ELSEVIER

Tetrahedron

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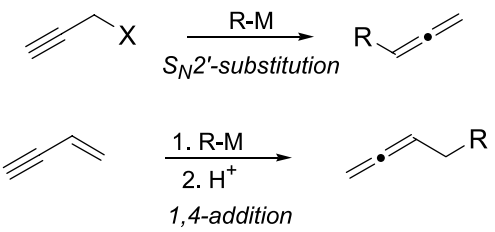
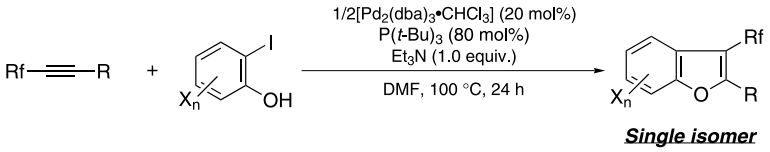
Contents

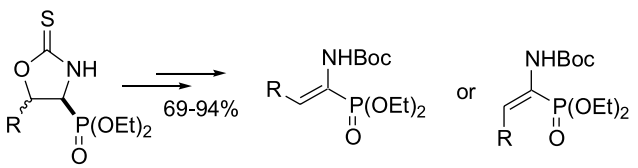
REPORT

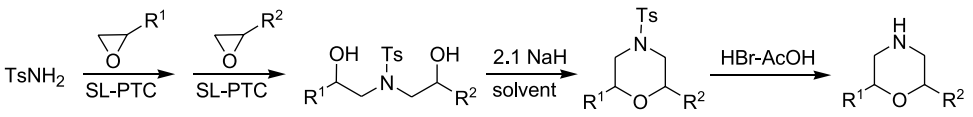


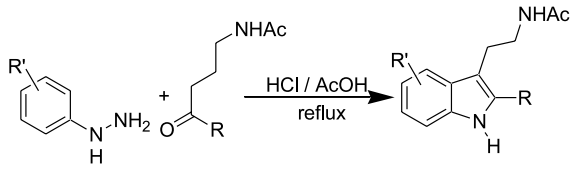
Various methods to synthesize allenes with organometallic reagents based on Li, Mg, Zn, Al, In, Ti, Cu and Sm are reviewed (ca. 240 refs.).

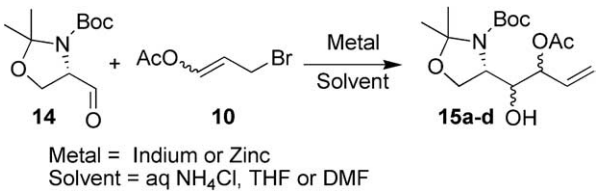
ARTICLES

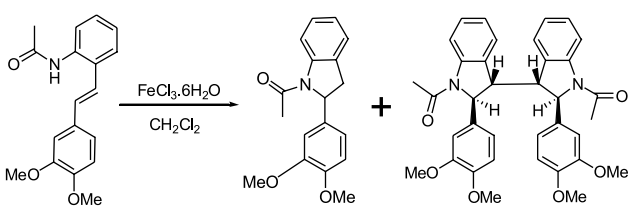


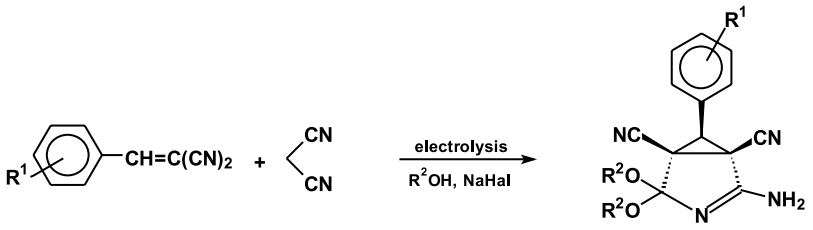


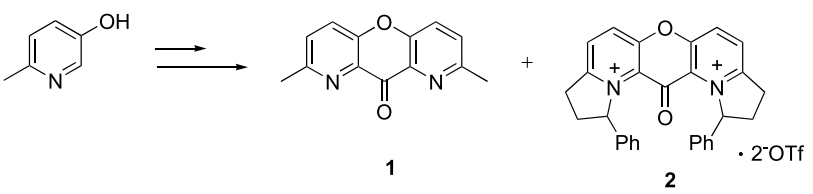


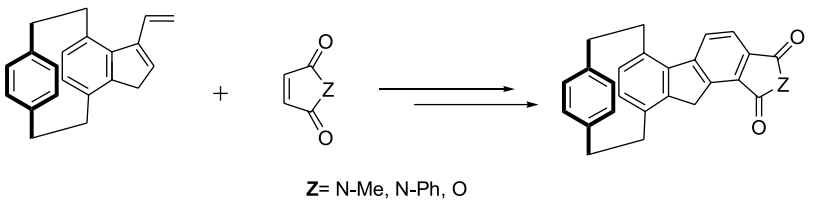












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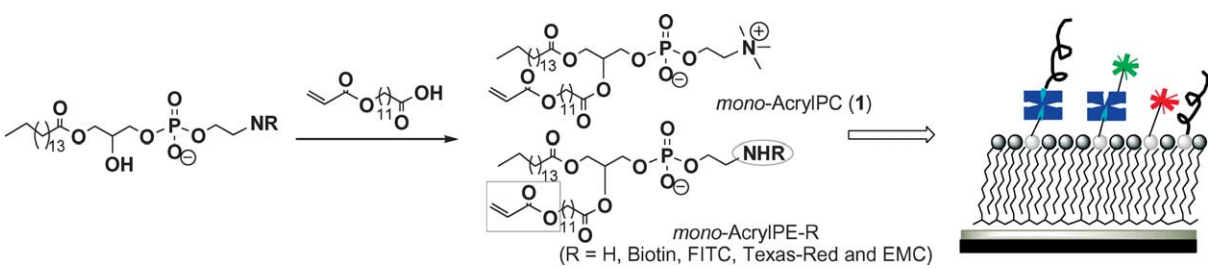
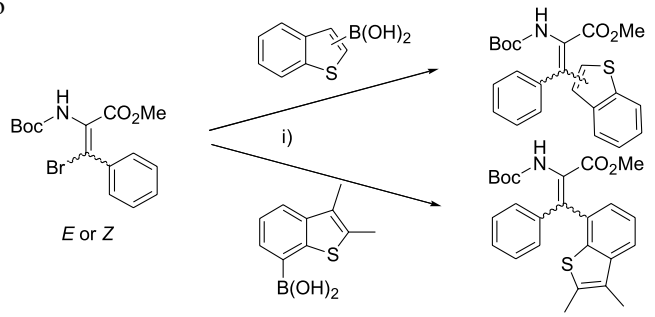
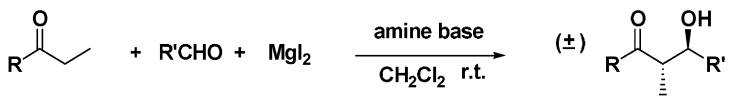
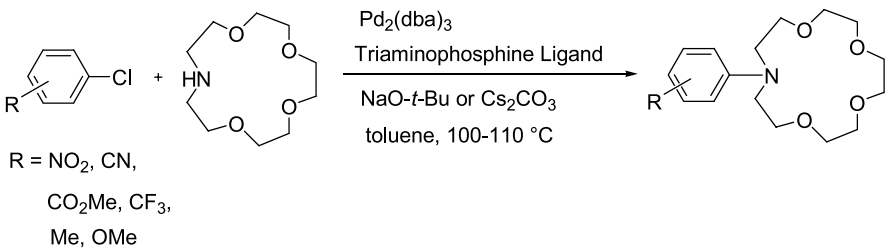
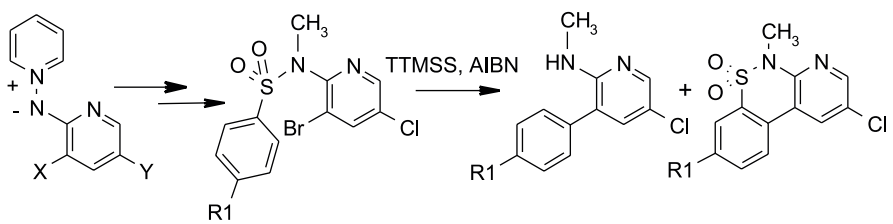
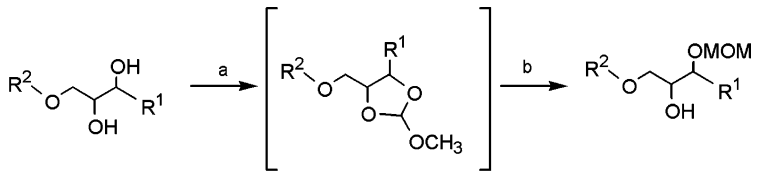




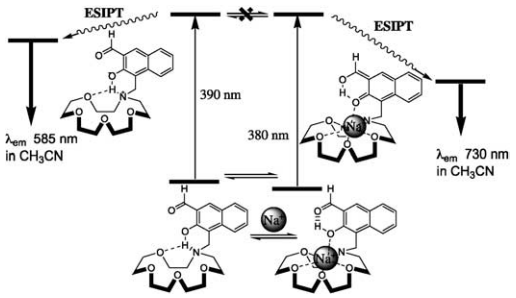


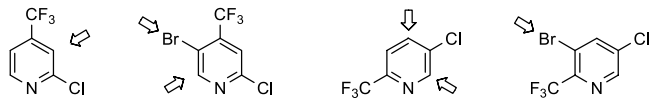


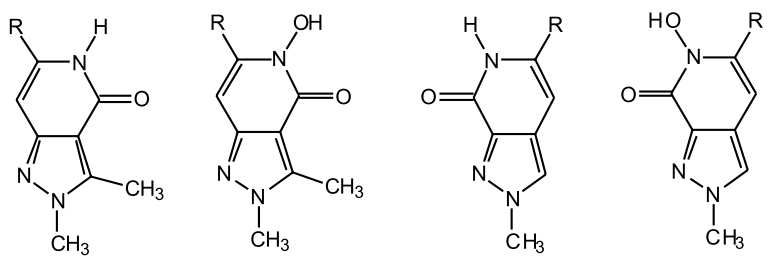


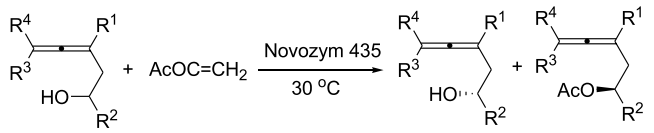


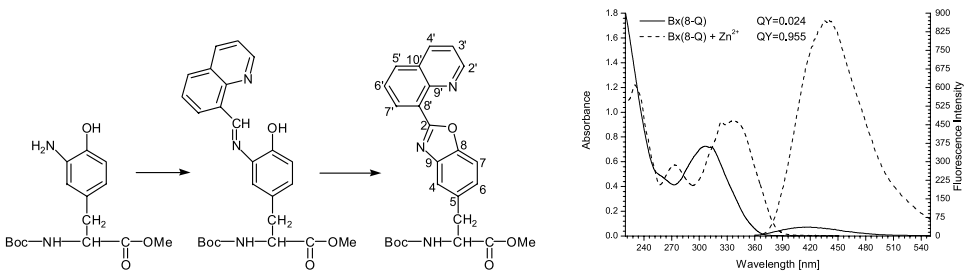
(a) trimethyl orthoformate, CH_2Cl_2, CAN, rt, 2 h; (b) DIBAL, -78 °C, 1 h, 0 °C, 10 min.



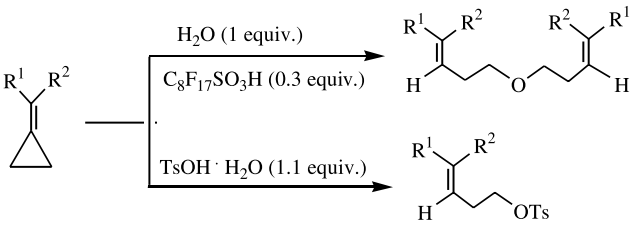


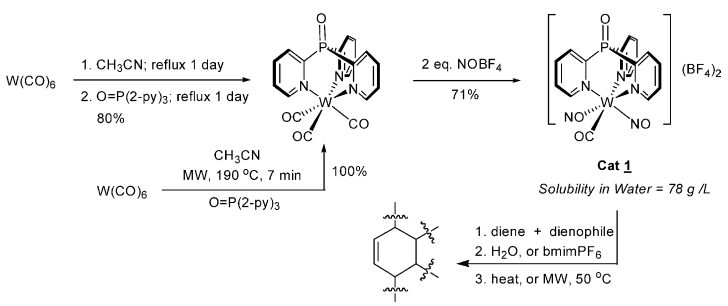


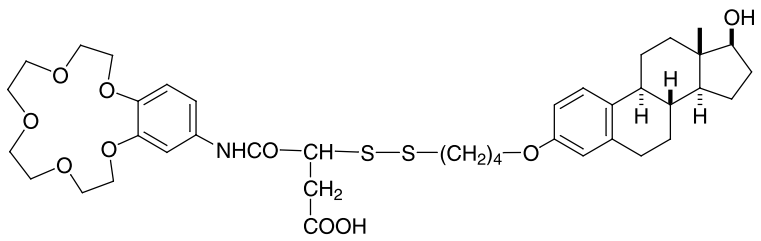


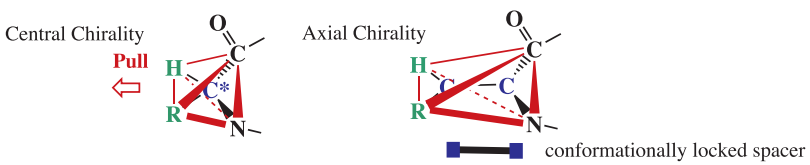


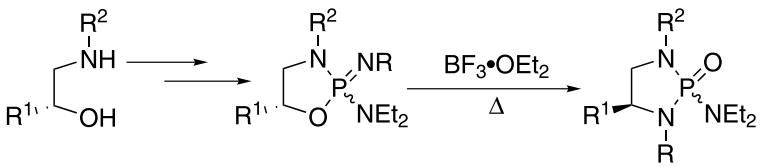
We report two different ring-opening patterns of methylenecyclopropanes (MCPs) in the presence of two Brønsted acids heptadecafluorooctane-1-sulfonic acid ($C_8F_{17}SO_3H$) and toluene *p*-sulfonic acid (TsOH): (a) the ring-opening of MCPs by H_2O and subsequent etherification give the corresponding homoallylic ethers in the presence of heptadecafluorooctane-1-sulfonic acid; (b) the direct ring-opening of MCPs by the Brønsted acid gives the corresponding homoallylic alcohol derivatives in the presence of toluene *p*-sulfonic acid.

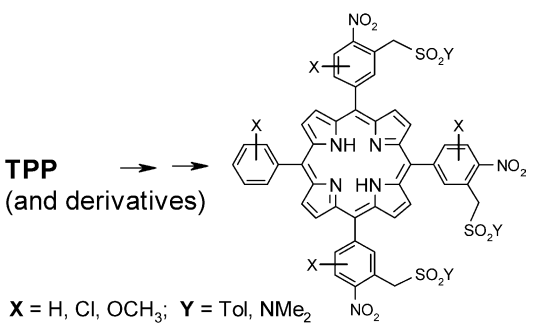












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*Corresponding author
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Synthesis of allenes with organometallic reagents

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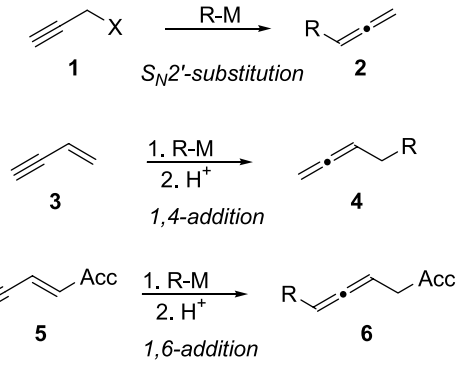
Contents

1. Introduction

The use of organometallic reagents for the synthesis of allenes is highly developed, and several fundamentally different methods are now well established. These include transition metal-catalyzed addition and substitution reactions, as well as isomerizations of alkynes to generate allenes with organometallic bases; furthermore, the preparation of allenes from allenyl/propargylmetal reagents and the well-known Doering–Moore–Skattebøl method for converting alkenes into allenes by addition of dihalocarbenes and subsequent insertion reaction should be mentioned here.[1] In contrast to these methods, this report deals with the use of stoichiometric amounts of non-allenic organometallic reagents for the generation of allenic target molecules starting from unsaturated electrophiles.

The fundamental reaction types suitable for metal-mediated syntheses of allenes **2**, **4** and **6** are outlined in Scheme 1 and comprise S_N2' nucleophilic substitution reactions of propargylic electrophiles **1**, as well as 1,4-additions to



Scheme 1.

Keywords: Allenes; Organometallic reagents; Axial chirality.
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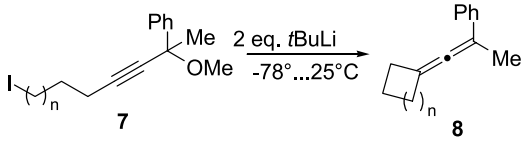
(unfunctionalized) enynes **3** and 1,6-addition reactions to acceptor-substituted enynes **5** (Scheme 1).

In these transformations, organocopper compounds are often the reagents of choice, although recently other metals such as aluminum, titanium, samarium and indium have proved to be highly useful. Since earlier achievements in this field have already been summarized extensively,[2] we will concentrate on the more recent contributions published after 1980. Rather than trying to be comprehensive, representative examples and references for the most important reaction types will be given.

2. Organolithium reagents

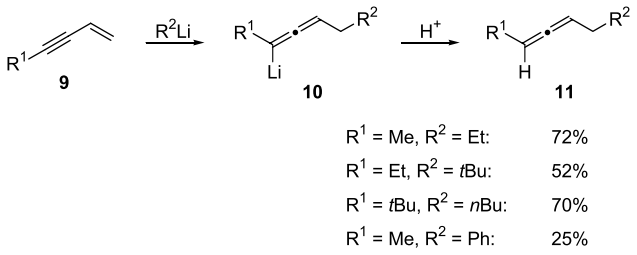
Basic organometallic reagents such as organolithium, organomagnesium, and organozinc compounds are indispensable in allene synthesis, where they either act as precursors for other organometallic reagents (e.g., cuprates; see below) or as nucleophiles in (transition) metal-catalyzed transformations (e.g., in palladium- or copper-catalyzed substitution reactions).[1,2] A significant number of methods for the generation of allenes is also available that rely on the direct use of these nucleophiles in addition or substitution reactions without the participation of other metals. It has to be noted, however, that, nowadays, these transformations are rarely applied, presumably due to their limited generality and functional group compatibility.

One of the very few examples of an S_N2' substitution reaction of propargylic electrophiles with organolithium reagents was reported by Bailey and Aspris (Scheme 2).[3] Iodine–lithium exchange of propargyl ethers **7** at low temperature led to the corresponding alkyllithium compounds which cyclized to furnish exocyclic allenes of the type **8** upon warming to room temperature. Four-, five- and six-membered rings were efficiently formed by *exo-dig* ring closure, whereas a substrate comprising a five-carbon tether furnished the corresponding seven-membered ring product with only 9% yield.



Scheme 2.

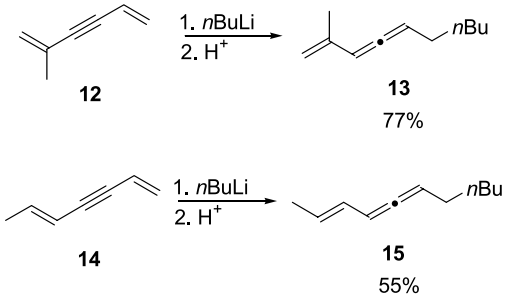
Moreover, organolithium compounds are the reagents of choice for the synthesis of allenes by 1,4-addition to conjugated enynes (cf. Scheme 1), and, in a comprehensive series of papers from the 1960s, a group of Russian authors has published various aspects of this chemistry.[4–8] It was found that aliphatic, aromatic, and heteroaromatic lithium reagents (as well as lithium phosphides[5]) react with enynes **9** regioselectively at the double bond terminus, leading to allenic lithium species **10**,[6] which were then regioselectively protonated to provide the allenes **11** (Scheme 3).[4]



Scheme 3.

This 1,4-addition reaction, however, competes with the anionic oligomerization/polymerization of the enyne precursor, so that the chemical yields of the allenes are sometimes only moderate.

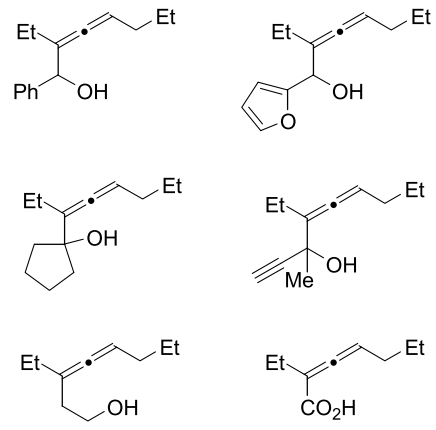
Unsymmetrical dienynes react regioselectively with organolithium compounds at the less substituted double bond (Scheme 4). Thus, the addition of *n*-butyllithium to 2-methylhexa-1,5-dien-3-yne (**12**) led after hydrolysis to the vinylallene **13**, whereas the corresponding carbolithiation of the linear isomer **14** furnished the product **15** with 55% yield.[7]



Scheme 4.

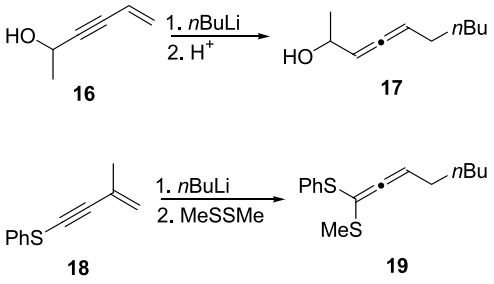
Besides protonation, a variety of other electrophiles have been employed for the trapping of allenyllithium intermediates **10**, for example, aldehydes, ketones and oxiranes, as well as carbon dioxide.[8] Scheme 5 shows a selection of functionalized allenes obtained by this method.

Enynes with oxygen or nitrogen substituents at the double bond react in an analogous manner.[9] With the regioisomeric 4-en-2-yn-1-ols (e.g., **16**) as substrates, however, the



Scheme 5.

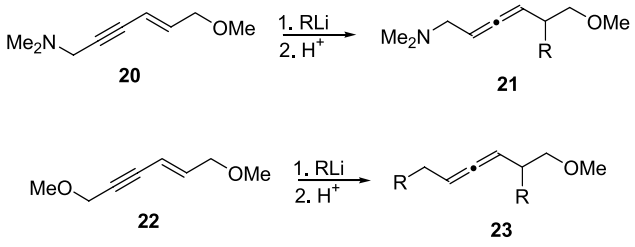
hydroxy group might direct the attack of the organolithium reagent towards the triple bond. In contrast to this expectation, the usual 1,4-addition reaction under C–C-bond formation at the olefinic terminus again prevailed, so that α-hydroxyallenes **17** emerged as the products (Scheme 6).[10] Accordingly, carbolithiation of 1-thio-3-en-1-ynes of the type **18** opened up an access to allenic dithioacetals (e.g., **19**) and related products.[11]



Scheme 6.

Miginiac et al.[12] examined the reaction of organolithium, Grignard, and organozinc reagents with conjugated enynes bearing various oxygen and nitrogen substituents at both termini (e.g., **20**). Usually, 1,4-addition with attack of the nucleophile at the C–C double bond was again observed, to give **21** (Scheme 7). In the case of the bis-ether **22** and similar substrates, however, two carbon groups from the nucleophile were incorporated into the product **23**, due to a 1,4-addition accompanied by a substitution reaction of the propargylic methoxy group.

A more recent application of this chemistry was reported by Oestreich and Hoppe[13] and involved the enantioselective

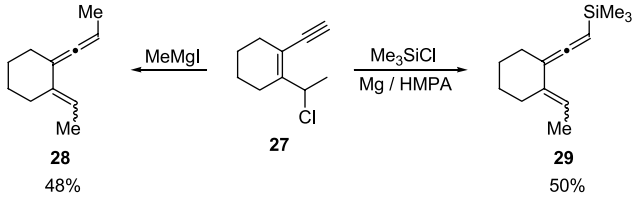


Scheme 7.

deprotonation of the enyne carbamate ester **24** with *s*-butyllithium in the presence of (−)-sparteine (Scheme 8). Removal of the pro-*S* hydrogen atom led to the corresponding organolithium intermediate, which then underwent a highly enantioselective intramolecular 1,4-addition to the enyne. Protonation of the resulting allenyllithium species **25** provided a 70:30-mixture of the two diastereomeric allenes **26**.

3. Grignard reagents

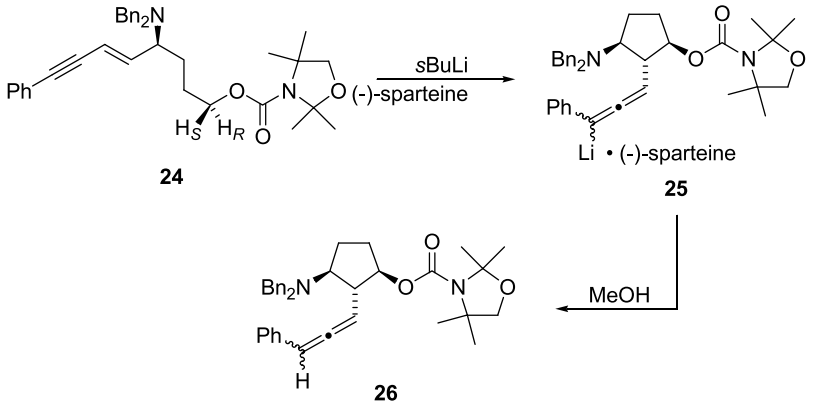
Apart from some examples of the 1,4-addition reaction of Grignard reagents to conjugated enynes,[12] such nucleophiles have only found application in allene synthesis (without the aid of additional metals) with regard to 1,5-substitution reactions of 1-chloro-2-en-4-ynes (e.g., **27**).[14] By treatment of these electrophiles with methylmagnesium iodide, Goré et al. and Dulcere et al. obtained the vinylallenes of the type **28** (Scheme 9). The method is not as general as the copper-mediated 1,5-substitution of enyne acetates (cf. Section 8.1), since other Grignard reagents completely failed to form the desired vinylallenes. The only notable exception is the generation of silyl allenes (e.g., **29**) from chloroenynes and trimethylsilylmagnesium chloride (or trimethylsilyllithium).[14d]



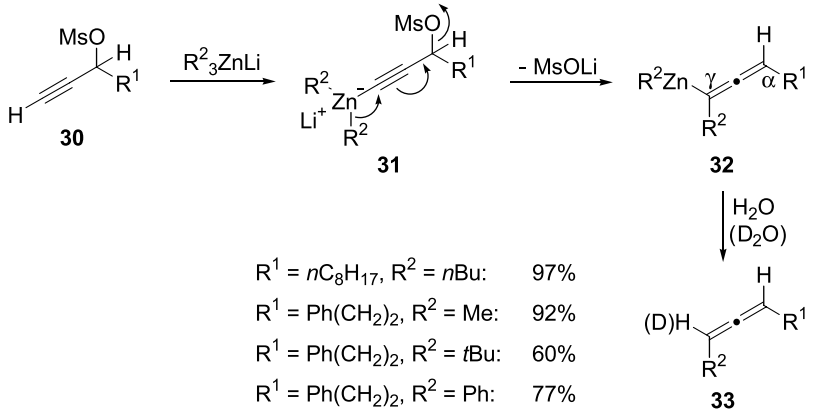
Scheme 9.

4. Organozinc reagents

The use of organozinc nucleophiles in allene synthesis is as limited as that of Grignard reagents. Harada et al.[15] reported the formation of allenes **33** by treatment of propargyl mesylates **30** (or the corresponding chlorides) with lithium triorganozincates (or silylzincates) and subsequent hydrolysis (Scheme 10). The reaction probably proceeded via



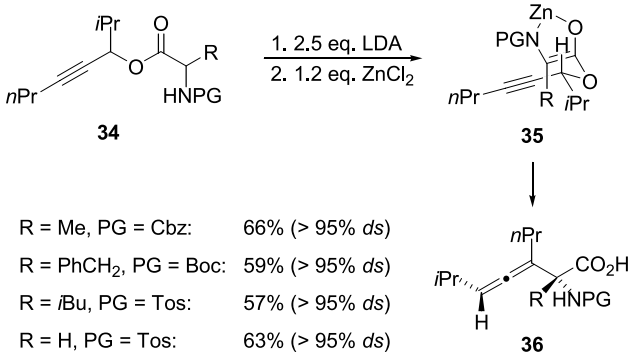
Scheme 8.



Scheme 10.

deprotonation of the alkyne and transfer of a carbon group from the zinc acetylides **31** to the triple bond, affording the allenylzinc species **32**. The presence of the latter intermediate was corroborated by incorporation of deuterium in the γ-position when D_2O was used for quenching. All of the other electrophiles examined, however, such as halogens, silyl halides, and carbonyl compounds, reacted preferably in the α-position of the allenylzinc intermediates **32**, furnishing the functionalized alkynes.

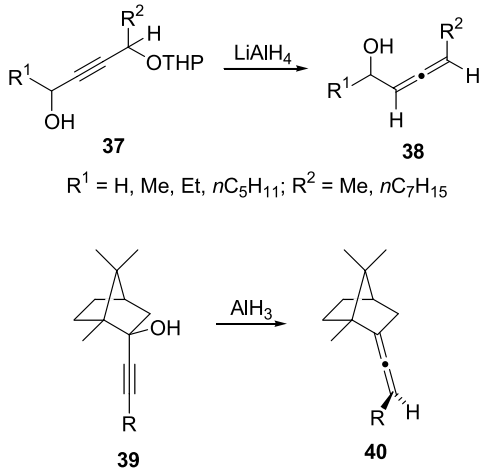
A second approach using organozinc compounds for the synthesis of allenes relies upon the chelate-controlled Claisen rearrangement of zinc ester enolates. Kazmaier et al.[16] have demonstrated that this route opens up an access to α-allenic α-amino acids, which are of interest as irreversible, mechanism-based inhibitors of vitamin B_6-dependent decarboxylases (cf. Section 8.2). Thus, the zinc enolates **35** of propargylic esters **34** (which are readily accessible by deprotonation of the latter esters with LDA and transmetalation with zinc chloride) underwent a highly *syn*-stereoselective rearrangement to the allenic amino acid derivatives **36** upon warming to room temperature (Scheme 11). Remarkably, both the chemical yield and the diastereoselectivity were found to be almost independent of the substitution pattern and the amino-protecting group used.



Scheme 11.

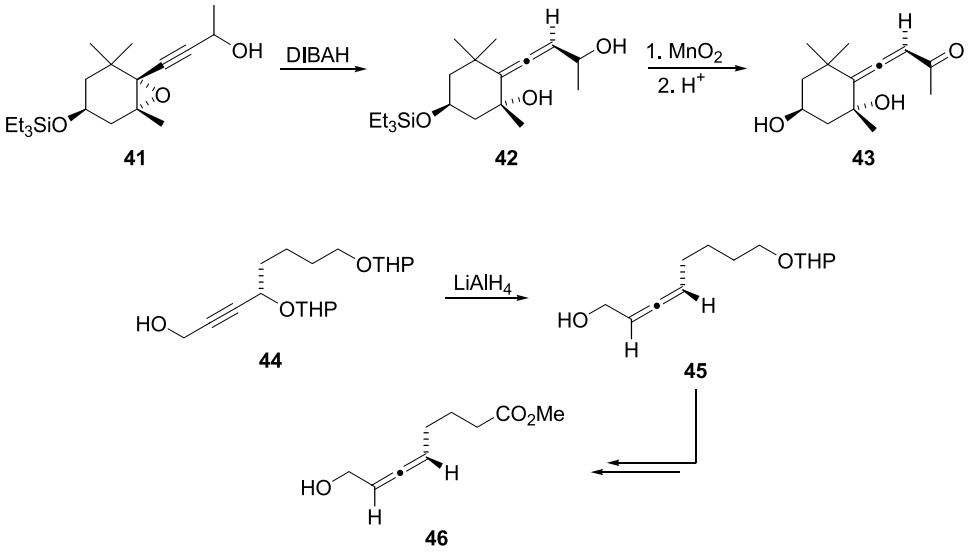
5. Aluminum reagents

The application of aluminum reagents in allene synthesis comprises mainly the formation of C–H bonds with aluminum hydrides, as well as the use of aluminum-based Lewis acids for C–C bond-formation processes. Various propargylic electrophiles such as alcohols, ethers, halides, and oxiranes can be reduced to the corresponding allenes with the aid of lithium aluminum hydride, diisobutylaluminum hydride (DIBAH) and other aluminum hydrides.[1,2] Depending on the substrate structure and the reducing agent, the transformation takes place either with *syn*- or with *anti*-stereoselectivity. More recent applications of the numerous examples of this chemistry include the synthesis of α-hydroxyallenes **38** from the mono-THP-ethers of bispropargylic alcohols **37**,[17] as well as the highly *anti*-stereoselective formation of various camphor-based allenes **40** via reduction of the propargylic alcohols **39** with AlH_3 (Scheme 12).[18] In the latter case, the alane did not only serve as the nucleophile, but also enabled the removal of the hydroxy group as an aluminum oxide.



Scheme 12.

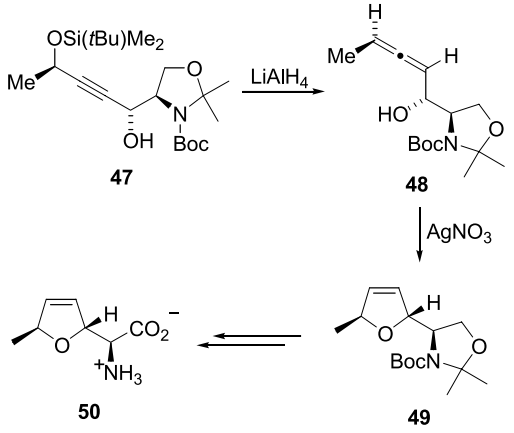
Due to its reliability, this method has frequently been applied in natural product synthesis. Thus, reduction of propargylic oxiranes of type **41** with diisobutylaluminum hydride (DIBAH) to give **42** allowed the formation of many allenic carotenoids and terpenoids, including the famous grasshopper ketone **43** (Scheme 13).[19,20] Moreover, as a result of a precoordination of the aluminum hydride to the



Scheme 13.

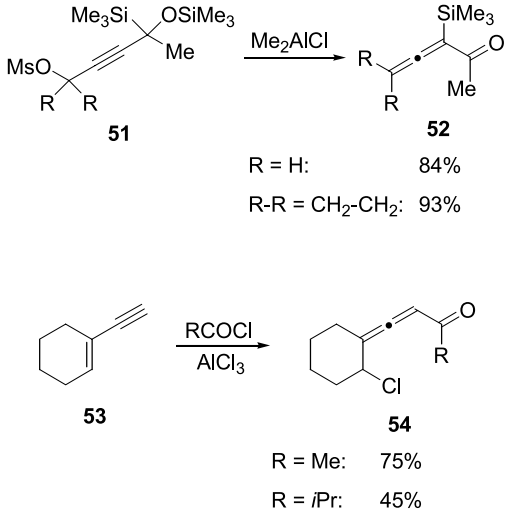
epoxide oxygen atom, these reductions took place with high *syn*-diastereoselectivity. In a similar fashion, reduction of the propargylic THP-ether **44** with $LiAlH_4$ again proceeded *syn*-selectively, furnishing the allenic alcohol **45**, a main precursor in the synthesis of the antifungal natural product, methyl (*R*)-8-hydroxyocta-5,6-dienoate (**46**).[21]

A further example of the reductive allene formation in the synthesis of a non-allenic natural product was recently reported by VanBrunt and Standaert (Scheme 14).[22] Treatment of the propargylic silyl ether **47** with $LiAlH_4$ led to the *syn*-stereoselective formation of the hydroxyallene **48**, albeit with an unsatisfactory chemical yield (25–50%). The latter allene was then transformed into the antibiotic amino acid, furanomycin (**50**), by silver-mediated cycloisomerization to the dihydrofuran **49** and elaboration of the side chain.



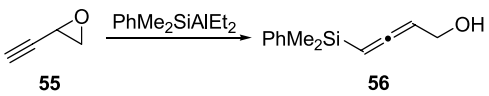
Scheme 14.

With regard to the use of aluminum-based Lewis acids for the synthesis of allenes, several examples of such transformations have been documented in recent years. Thus, the propargyl mesylates **51** were found to undergo a silyl migration to generate α-trimethylsilylallenones **52** upon treatment with dimethylaluminum chloride (Scheme 15),[23] while allenic ketones **54** were obtained through acylation of conjugated enynes **53** with acid chlorides in the presence of $AlCl_3$.[24] Although these allenic products were contaminated with variable amounts of the isomeric conjugated dienones, reasonably high chemical yields have been achieved in several cases.



Scheme 15.

An aluminum-mediated C–Si bond formation for the generation of allenes has been described by Trost et al.[25] Treatment of propargyl oxirane **55** with the silylaluminum reagent $PhMe_2SiAlEt_2$ led to a selective transfer of the silyl group to the electrophile, furnishing the silylated α-hydroxyallene **56** with 89% yield (Scheme 16). It seems reasonable to again assume that the aluminum reagent did not only serve as the nucleophile, but also as a Lewis acid to

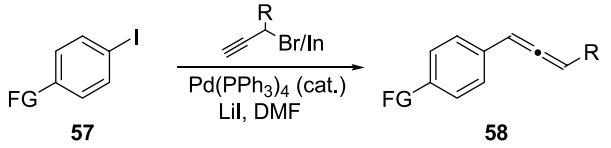


Scheme 16.

activate the oxirane for the subsequent S_N2' substitution reaction.

6. Organoindium reagents

A highly promising application of indium in the synthesis of (functionalized) allenes has recently been reported by Lee et al.[26] The palladium-catalyzed coupling reaction of allenylindium reagents (prepared in situ from propargyl bromides and indium) with various unsaturated halides (e.g., **57**) provided arylallenes of the type **58** with high chemical yields (Scheme 17). Due to its mildness, the reaction is compatible with various functional groups present in the coupling partner, and is not limited to aromatic and heteroaromatic halides, but proceeds equally well with alkenyl halides, iodoalkynes and even an imidoyl bromide.



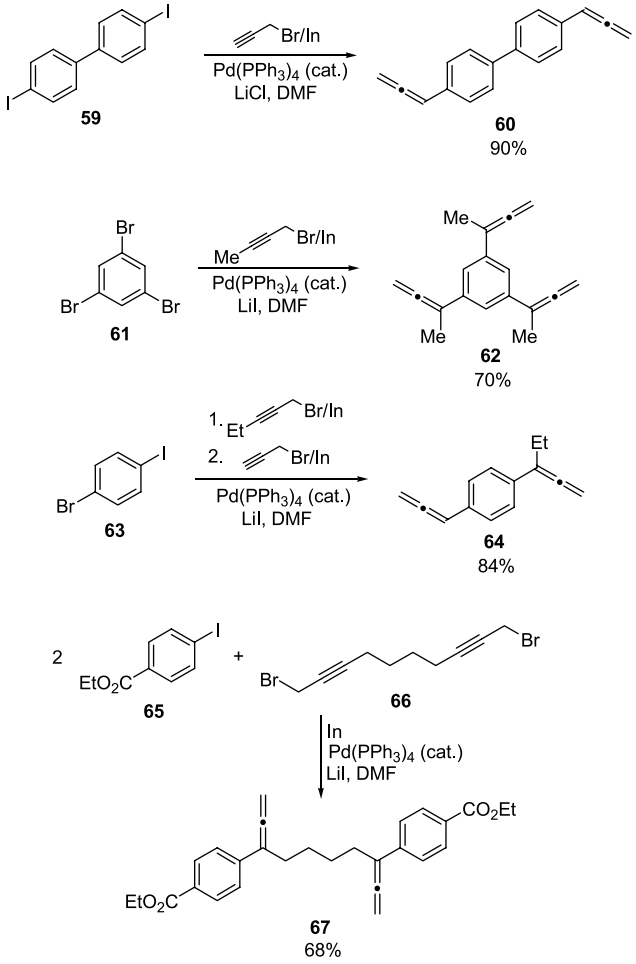
R = Me, FG = NO_2: 90%

R = H, FG = COMe: 87%

R = H, FG = MeO: 91%

R = Ph, FG = *n*Bu: 90%

Scheme 17.

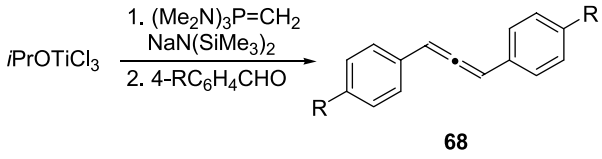


Scheme 18.

Furthermore, this protocol can be employed for the highly efficient introduction of two (**60**) and even three allene entities (**62**) into an aromatic 'workbench' **59** or **61** (Scheme 18). Thus, by starting with two different halides, for example, **63** (or with identical halides in different positions of a heteroaromatic substrate), two diverse allenic groups can be introduced by sequential coupling reactions to give bisallenes of the type **64**. Last, but not least, a structurally different bisallene **67** was also assembled via a two-fold coupling of the bis-propargyl bromide **66** with the functionalized aryl iodide **65**.[26]

7. Organotitanium reagents

The use of organotitanium compounds in the synthesis of allenes involves mainly Wittig-type olefination reactions of carbonyl compounds[27] with titanium ylides. The formation of allenes according to the scheme $C_1+C_1+C_1$ was described by Finn et al.,[28] who treated aromatic aldehydes with a mixed titanium/phosphorus ylide formed from *i*PrOTiCl$_3$, $(Me_2N)_3P{=}CH_2$ and an excess of sodium hexamethyldisilazide as base (Scheme 19). The symmetrical allenes **68** were obtained with moderate to good yield.



R = Me: 56%

R = MeO: 52%

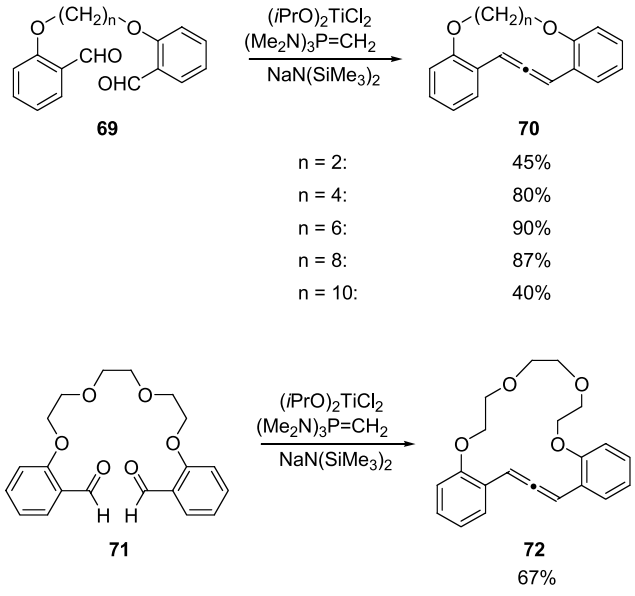
R = Me_2N: 32%

Scheme 19.

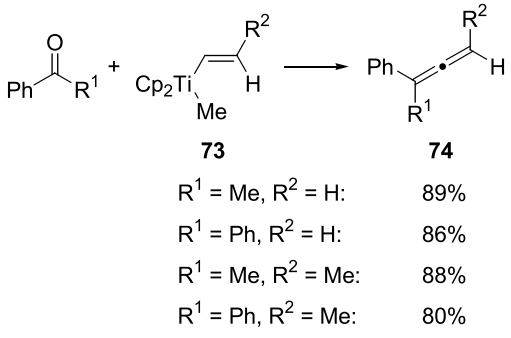
This route was also employed for the synthesis of macrocyclic allenes **70** via intramolecular coupling of aromatic dialdehydes **69**.[29] Depending on the ring size, chemical yields of up to 90% of the desired products were achieved (Scheme 20). The introduction of additional oxygen atoms into the tether, for example, **71**, did not diminish the efficiency of the protocol and therefore allowed an access to allenic crown ethers of the type **72**.

The alternative building scheme C_2+C_1 was used by Petasis and Hu,[30] who reacted various aldehydes and ketones with alkenyltitanocene derivatives **73** to obtain the corresponding allenes **74** with high chemical yields (Scheme 21). The reaction probably proceeds via titanocene vinylidene complexes, which can also be trapped with alkynes and isocyanides to afford allenylketene imines.[31]

This latter method can also be applied to aliphatic or α,β-unsaturated ketones, to diketones, and to aromatic or acetylenic aldehydes and tolerates a variety of functional

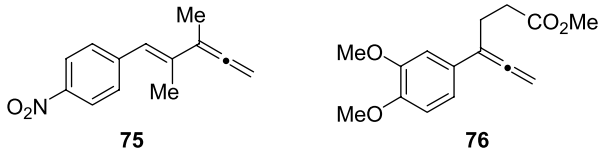


Scheme 20.



Scheme 21.

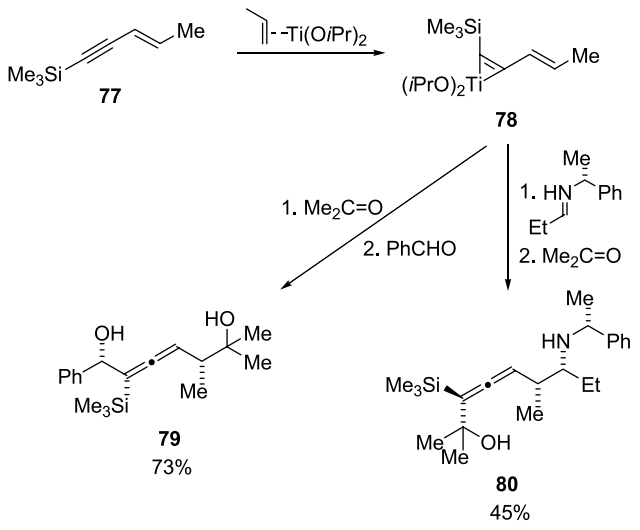
groups present in the substrate, as demonstrated by the efficient formation of allenes **75** and **76**, which bear an additional nitro and ester group, respectively (Scheme 22).[30]



Scheme 22.

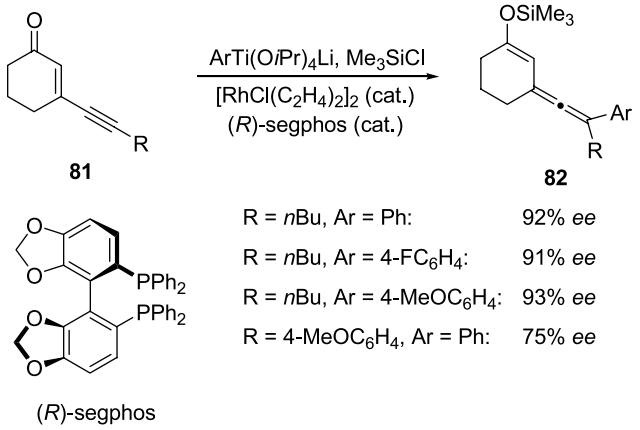
Conjugated enynes represent further useful substrates for the titanium-mediated synthesis of allenes. Sato et al.[32] have prepared titanium alkoxide complexes of the type **78** from enynes (e.g., **77**) and (η^2-propene)Ti(O*i*Pr)$_2$ and converted these into densely functionalized allenes (e.g., **79** and **80**) by sequential trapping with two electrophiles. In addition to protonating agents, aldehydes, ketones and imines can also be used for this purpose, allowing the highly regio- and diastereoselective formation of two further stereogenic centers besides the allenic chirality axis (Scheme 23).

A different approach towards titanium-mediated allene synthesis was used by Hayashi et al.,[33] who recently



Scheme 23.

reported rhodium-catalyzed enantioselective 1,6-addition reactions of aryltitanate reagents to 3-alkynyl-2-cycloalkenones **81** (Scheme 24). In the presence of chlorotrimethylsilane and (*R*)-segphos as the chiral ligand, allenic silyl enol ethers **82** were obtained with good to excellent enantioselectivities, and these can be converted further into allenic enol esters or triflates. In contrast to the corresponding copper-mediated 1,6-addition reactions (Section 8.2), these transformations probably proceed via alkenylrhodium species (formed by insertion of the C–C triple bond into a rhodium–aryl bond) and subsequent isomerization to the thermodynamically more stable oxa-π-allylrhodium intermediates.[33]

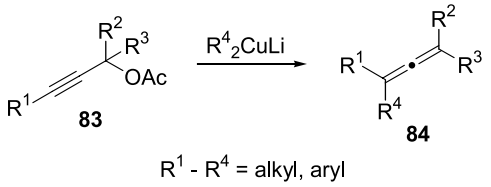


Scheme 24.

8. Organocopper reagents

8.1. Substitution reactions

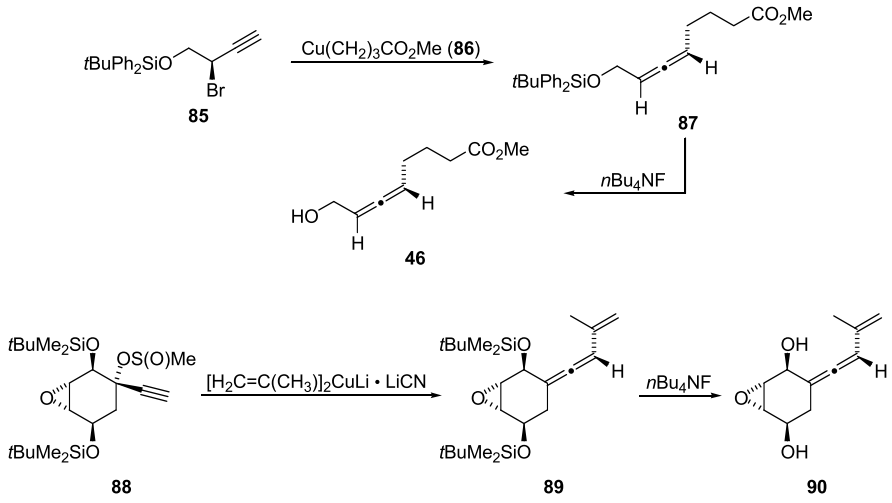
The first examples of allene syntheses using copper-mediated S_N2' substitution processes are documented for the reaction of propargylic acetates **83** with lithium dialkylcuprates, which led to the formation of allenes **84** with moderate to good chemical yields (Scheme 25).[34]



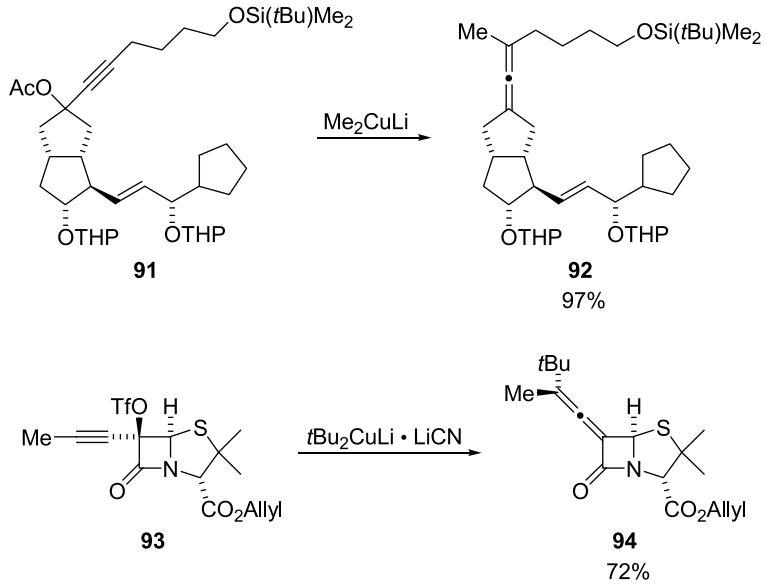
Scheme 25.

Since its discovery by Rona and Crabbé[34] in 1968, this method has developed into one of the most versatile and popular protocols for the synthesis of allenes.[1,2,35] One reason for its popularity is that many combinations of organocopper reagents and leaving groups result in clean conversions of the propargylic electrophiles into the desired allenes, which are often isolated in high chemical yield. Thus, besides acetates, benzoates and carbonates,[34–36] propargylic sulfonates,[37] ethers and acetals,[38] halides,[39] oxiranes[40] and even aziridines[40a,41] have been successfully employed as the substrates. With regard to the reagents, simple lithium diorganocuprates have been complemented inter alia by magnesium cuprates of different compositions,[42] as well as by functionalized cuprates derived from the corresponding Grignard and organozinc reagents.[43] Several applications of the method in natural product synthesis have been documented (Scheme 26). In one example, an alternative approach to the antifungal allene, methyl (*R*)-8-hydroxyocta-5,6-dienoate (**46**), takes advantage of the *anti*-selective S_N2' substitution of the propargyl bromide **85** with the functionalized copper reagent **86** to form **87**.[44] In a similar fashion, the propargylic sulfinate **88** was transformed into the exocyclic allene **89**, a precursor of the allenic fungal metabolite **90**.[45]

The S_N2' substitution process has likewise been highly relevant for the generation of pharmacologically active target molecules (Scheme 27), the methylated carbacyclin derivative **92**[36a] and the 6-alkylidenepenam **94**,[46] as well as the related 7-alkylidenecephalosporins,[47] being efficiently formed by cuprate-mediated S_N2' substitution reactions of



Scheme 26.



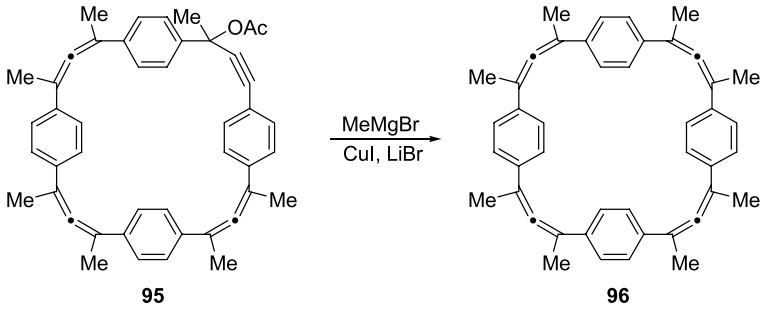
Scheme 27.

the corresponding propargylic derivatives **91** and **93**, respectively.

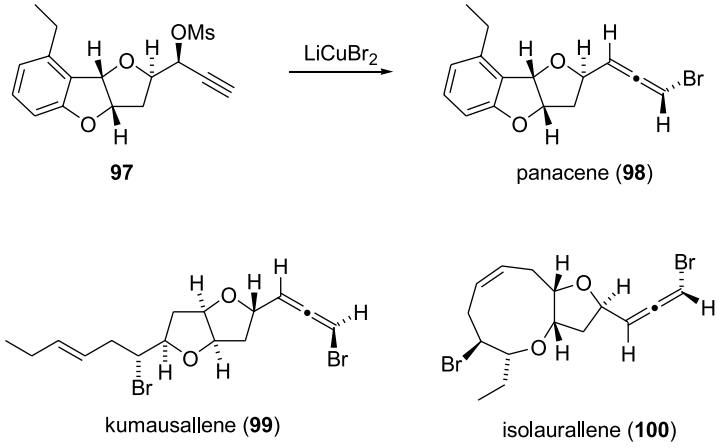
In the area of allenic non-natural product chemistry, the synthesis of the [3$_4$]allenophane **96** (Scheme 28) is particularly noteworthy, with all its four allenic bridges being formed through subsequent S_N2' substitution reactions of propargylic acetates (e.g., **95**) with a methylmagnesium cuprate.[48]

Furthermore, this copper-mediated S_N2' substitution reaction is not restricted to carbon–carbon bond formation, as can be seen from the synthesis of silylallenes,[49] stannylallenes[50] and bromoallenes[51] using propargylic electrophiles and the corresponding heterocuprates. The resulting allenes are often used as intermediates in target-oriented synthesis, for example, in cyclization and reduction reactions.[49–51] In particular, the S_N2' substitution of propargylic acetates with $LiCuBr_2$ has proved to be valuable for the synthesis of naturally occurring bromoallenes (Scheme 29).[20,52–54] In one example, treatment of the chiral propargyl mesylate **97** with lithium dibromocuprate afforded the tricyclic bromoallene, panacene (**98**),[52] and an analogous protocol was used in the synthesis of kumausallene (**99**) by Overman et al.,[53] as well as by Crimmins and co-workers in their synthesis of isolaurallene (**100**).[54]

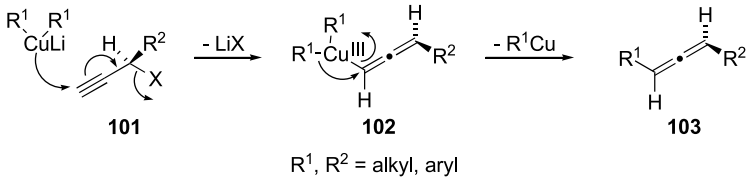
Many of these applications take advantage of the fact that the copper-promoted S_N2' substitution of propargylic electrophiles (in particular sulfonates) often proceeds with high *anti*-stereoselectivity (vide supra).[1,2,35,55] This efficient center-to-axis chirality transfer is rationalized by an interaction of a copper-centered d-orbital with the σ and π* orbitals of the substrate **101**. This leads to the formation of a σ-copper(III) species **102**, which finally undergoes a reductive elimination of an alkylcopper compound to furnish the *anti*-substitution product **103** (Scheme 30). Unfortunately, theoretical calculations, which have been highly useful for the mechanistic understanding of other



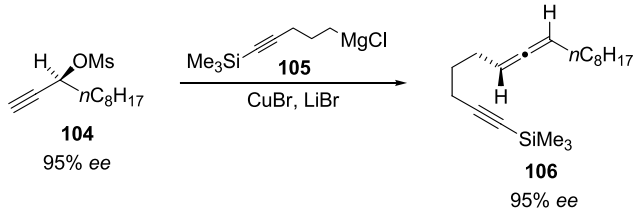
Scheme 28.



Scheme 29.



Scheme 30.



Scheme 31.

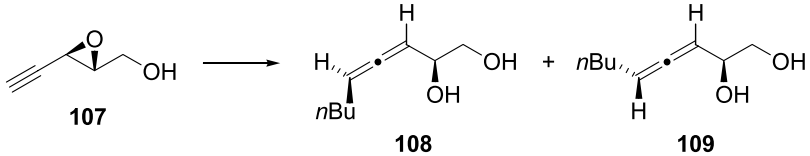
copper-mediated transformations,[56] have not yet been carried out for the S_N2' substitution of propargylic electrophiles.

Due to its reliability, the S_N2' substitution is often used in applications which require the highly enantioselective formation of the allene (vide supra); for example, Brummond et al.[55g] have prepared the yneallene **106** (a starting material for intramolecular allenic Pauson–Khand cycloadditions) through the *anti*-selective S_N2' substitution of the chiral propargylic mesylate **104** with a suitable magnesium cuprate prepared from the Grignard reagent **105** (Scheme 31).

For several reasons, propargyl oxiranes belong to the most interesting propargylic electrophiles among the many different kinds which can be employed in these transformations. Thus, the α-hydroxyallenes formed in the S_N2' substitution reaction contain not only one, but two functionalities which are highly useful for further synthetic manipulations and, due to the availability of enantiomerically pure or enriched oxiranes[57] by Katsuki–Sharpless,[58] Jacobsen,[59] or Shi epoxidation,[60] the corresponding α-hydroxyallenes can also be obtained easily in a stereochemically defined form. Finally, a particularly deep insight into the details of the reaction mechanism has been gained for this class of compounds.[40,61] Alexakis et al. revealed a strong halogen effect on the stereoselectivity (*anti* vs. *syn*) of the copper-*catalyzed* S_N2' substitution of propargylic oxiranes (and other ethers) with Grignard reagents, which was explained in terms of a competing addition–elimination mechanism.[38,40h–j] *syn*-Selective S_N2' substitutions of propargyl oxiranes can also be achieved with Grignard reagents under iron catalysis[62] and with aluminum hydrides (cf. Section 5) and, likewise, deviations from the preferred *anti*-selectivity can occur in the corresponding transformations with stoichiometric amounts of organocopper reagents, but for different reasons. Thus, in the first systematic study of the S_N2' substitution of a chiral propargyl epoxide **107** with organocuprates, Oehlschlager and Czyzewska[40e] found already in 1983 that *syn*/*anti* mixtures are formed in the absence of any additives. If, however, the reaction was carried out in the presence of dimethyl sulfide, high *anti*-stereoselectivities were obtained with both lithium and magnesium cuprates (Scheme 32).

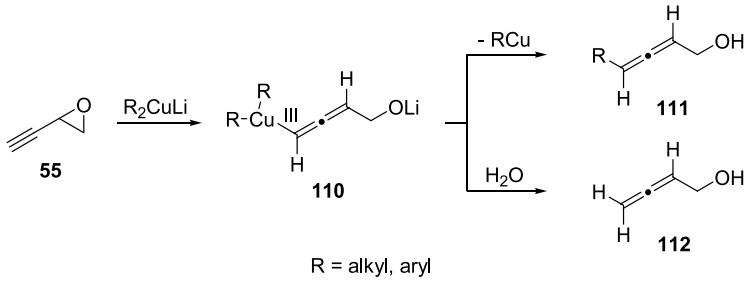
The reduced selectivity in the reaction with the pure cuprate is probably due to a racemization of the allene entity by the cuprate itself or by other reactive copper species present in the reaction mixture. Such racemizations of allenes have frequently been observed in copper-promoted substitution reactions of propargylic electrophiles[35a,35b,38b,63,64] and probably occur via single-electron transfer (SET) steps, even at rather low temperatures. If, for example, a 98:2-mixture of the allenes **109** and **108** is treated with lithium di-*n*-butylcuprate in diethyl ether for 2 hours, the *anti*/*syn* ratio decreases to 93:7 at −60 °C, and to 73:27 at −20 °C.[40e] In contrast, the thermal isomerization of allenes requires substantially higher activation barriers in the range of 35 to 47 kcal/mol,[65] explaining the fact that chiral allenes do not racemize thermally at room temperature. The tendency of organometallic reagents to racemize allenes is not restricted to organocopper compounds and can also be used to deracemize allenes (e.g., by employing chiral europium complexes[66]).

The effectiveness of dimethyl sulfide as an additive for the selective formation of the *anti*-product **109** from the propargyl epoxide **107** may be due to the formation of 'stabilized' copper species, which are less prone to undergo electron transfer processes. In this respect, other soft ligands which bind strongly to copper, in particular, phosphines and phosphites,[40h–j,61,64] have been used even more frequently. These additives also serve to suppress the formation of a common side product, that is, an allene containing a hydrogen atom instead of the carbon substituent which should have been delivered by the cuprate. The occurrence of such reduction products is also in accordance with the



nBu_2CuLi:	60 : 40
$nBu_2CuLi \cdot Me_2S$:	6 : 94
$nBu_2CuMgBr \cdot Me_2S$:	1 : 99

Scheme 32.

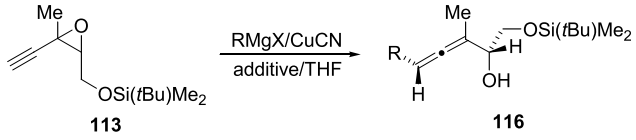


Scheme 33.

generally accepted mechanistic model (cf. Scheme 30), in which the copper(III) intermediate **110** resulting from the epoxide **55** may be sufficiently stable to 'survive' until work-up of the reaction mixture (or may undergo reductive elimination of R–R to give an allenic copper(I) compound), so that protonation leads to the reduction product **112**, besides the desired substitution product **111** (Scheme 33).[61]

The beneficial effect of added phosphine on the chemo- and stereoselectivity of the S_N2' substitution of propargyl oxiranes is demonstrated in the reaction of the substrate **113** with lithium dimethylcyanocuprate in diethyl ether (Scheme 34). In the absence of the phosphine ligand, reduction of the substrate prevailed, and attempts to shift the product ratio in favor of **115** by the addition of methyl iodide (which should alkylate the presumable intermediate **110**[40k]) had almost no effect. In contrast to this observation, the desired substitution product **115** was formed with good chemo- and *anti*-stereoselectivity when tri-*n*-butylphosphine was present in the reaction mixture.[61,67] Interestingly, this effect is strongly solvent dependent, since a complex product mixture was formed when THF was used instead of diethyl ether. With sulfur-containing copper sources such as the copper bromide–dimethyl sulfide complex or copper 2-thiophenecarboxylate, however, the addition of the phosphine caused the opposite effect, that is, exclusive formation of the reduced allene **114**. Thus, the course and outcome of the S_N2' substitution show a rather complex dependence on the reaction partners and conditions which needs to be further elucidated.

Whereas the S_N2' substitution of propargyl epoxides of the type **113** with lithium diorganocuprates proved to be rather capricious, the corresponding transformations with magnesium cuprates[68] proceed in a more predictable manner. Thus, treatment of the epoxide **113** in THF with the cuprates formed from 2 equiv of a Grignard reagent and 1 equiv of CuCN in the presence of 1 equiv of tri-*n*-butylphosphine or triethylphosphite consistently led to the exclusive formation of the desired S_N2' substitution products **116** with good chemical yields and high *anti*-diastereoselectivity (Scheme 35).[61,67]



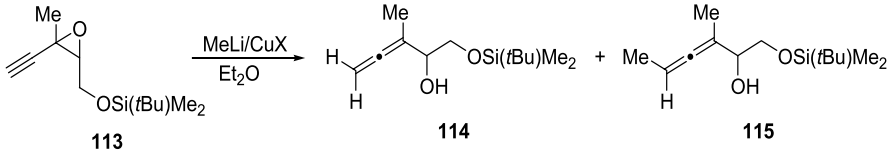
RMgX/additive		
MeMgBr/nBu$_3$P:	71%	(*ds* = 94 : 6)
tBuMgCl/(EtO)$_3$P:	82%	(*ds* > 95 : 5)
nHexMgBr/(EtO)$_3$P:	95%	(*ds* > 95 : 5)
iPrMgCl/(EtO)$_3$P:	76%	(*ds* > 95 : 5)
PhMgBr/nBu$_3$P:	84%	(*ds* = 95 : 5)

Scheme 35.

Most gratifyingly, these conditions are also applicable to functionalized magnesium reagents,[69] as demonstrated by the formation of the α-hydroxyallenes **117**–**120** from *cis*- or *trans*-**113** and the corresponding magnesium cuprates bearing substituted aryl groups (Scheme 36).[67]

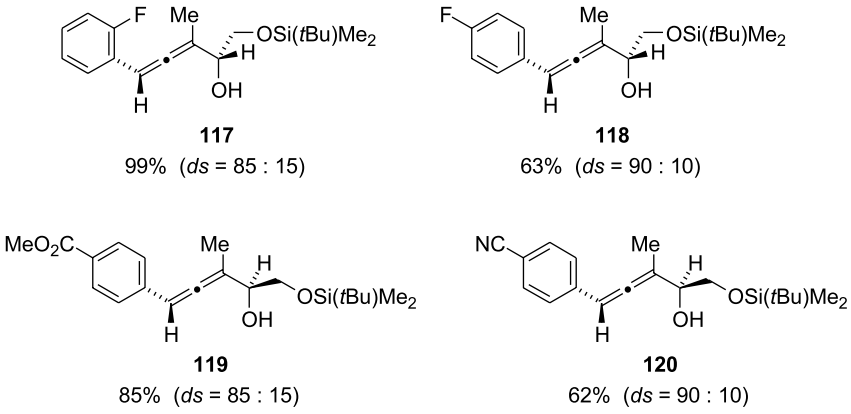
The related zinc cuprates formed from diorganozinc reagents and copper(I) cyanide also undergo smooth S_N2' substitution reactions with propargylic oxiranes in the presence of phosphines or phosphites (Scheme 37). These transformations can also be performed with catalytic amounts of the copper salt, since no direct reaction between the organozinc reagent and the substrate interferes,[67,70] and should therefore be applicable to functionalized organozinc compounds.

The occurrence of reduction products in S_N2' substitution

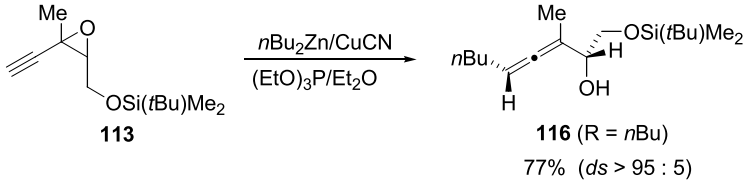


CuX = CuCN:	80 : 20
CuCN/nBu$_3$P:	4 : 96 (*anti:syn* = 85 : 15)
CuBr • SMe$_2$:	68 : 32
CuBr • SMe$_2$/nBu$_3$P:	> 99 : < 1

Scheme 34.

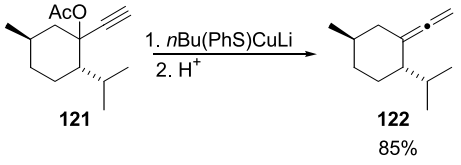


Scheme 36.



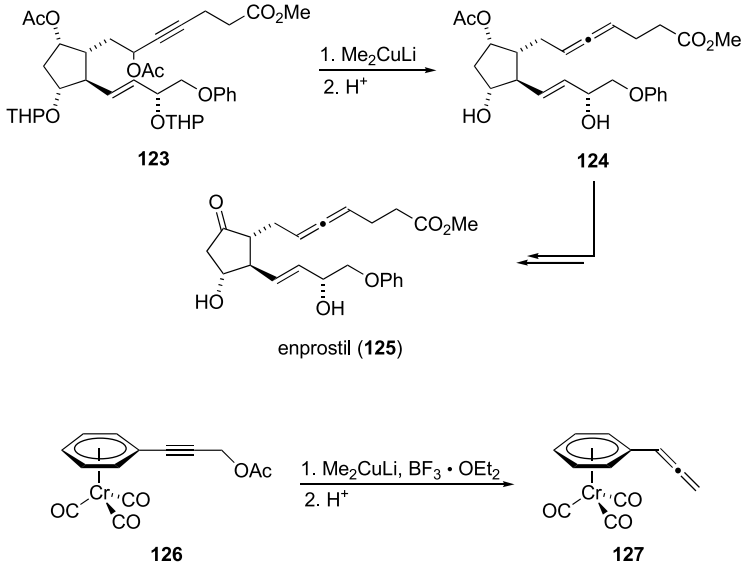
Scheme 37.

reactions of propargylic electrophiles with organocuprates is not limited to oxiranes[71,72] and can even be controlled in such a way that the reduced allenes are formed (almost) exclusively (vide supra). In one example, treatment of tertiary propargylic acetates (e.g., **121**) with lithium *n*-butyl(phenylthio)cuprate furnished the terminal allenes (e.g., **122**) in high yields (Scheme 38).[72] Presumably, the presence of the phenylthio group bound to copper again leads to a relative stabilization of the intermediate copper species (cf. Schemes 33 and 34) through its electron-donating ability.



Scheme 38.

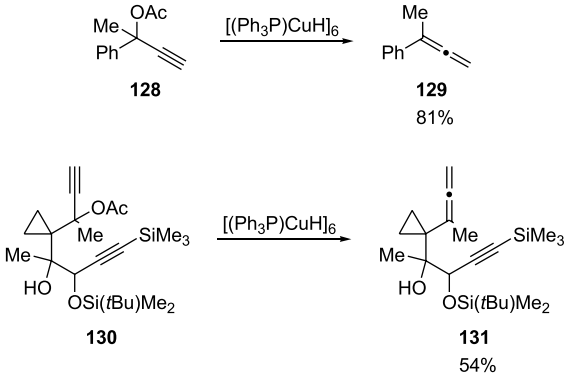
Interestingly, treatment of certain substrates with lithium dimethylcuprate already induced a selective reduction of the propargylic electrophile to an allene (Scheme 39). Thus, the precursor **124** of the allenic prostaglandin analogue, enprostil (**125**), a potent inhibitor of gastric acid secretion,[20] was obtained after the reaction of propargyl acetate **123** with Me_2CuLi and hydrolytic work-up.[73] A similar procedure



Scheme 39.

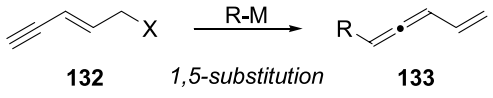
was applied by Müller et al.[74] to the synthesis of the chromotricarbonyl-complexed phenylallene **127**, starting from the precursor **126**. In the latter case, however, the addition of boron trifluoride etherate improved the yield of **127** from 37 to 74%.

Another, albeit less-frequently employed, option for a copper-mediated reduction of propargylic electrophiles to allenes relies upon the use of a copper hydride, for example, Stryker's reagent $[(Ph_3P)CuH]_6$. Whereas substrates without a leaving group lead to a reduction of the triple to a *cis* double bond, propargyl acetate **128** furnished allene the **129** in good yield (Scheme 40).[75] The method was applied by Brummond et al.[76] to the synthesis of the structurally complex precursor **131** for the potent antitumor agent, (±)-hydroxymethylacylfulvalene, from **130**.



Scheme 40.

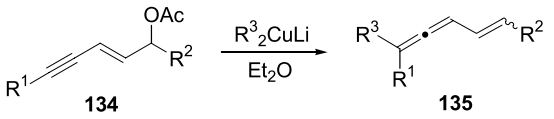
Introduction of a double bond between the triple bond and the leaving group leads to enyne electrophiles **132** which would give access to vinylallenes **133** if the attack of the nucleophile takes place at the triple bond in an S_N2'' (1,5) substitution reaction (Scheme 41). Besides the regioselectivity, two types of stereoselectivity have to be considered in this transformation, that is, the configuration of the olefinic double bond of the vinylallene and the (relative or absolute) configuration of the allenic chirality axis.



Scheme 41.

As described earlier (Section 3), the 1,5-substitution of 1-chloro-2-en-4-ynes (e.g., **27**) with Grignard reagents reported by Goré et al. and Dulcere et al.[14] does furnish vinylallenes, but lacks generality with regard to the nucleophile. In contrast to this work, the regioselective reaction of enyne acetates **134** with various lithium cuprates proceeds smoothly in diethyl ether, affording exclusively vinylallenes **135** with variable substituent patterns (Scheme 42).[77]

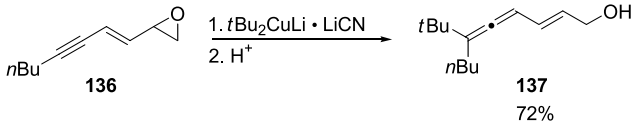
Although the resulting vinylallenes **135** were usually obtained as mixtures of the *E* and *Z* isomers, complete stereoselection with regard to the vinylic double bond was



$R^1 = R^2 = Me$, $R^3 = n$Bu: 90% (*E* : *Z* = 67 : 33)
$R^1 = R^2 = Me$, $R^3 = t$Bu: 93% (*E* : *Z* = 25 : 75)
$R^1 = Me_3Si$, $R^2 = Me$, $R^3 = t$Bu: 96% (*E* : *Z* = 40 : 60)
$R^1 = n$Bu, $R^2 = t$Bu, $R^3 = Me$: 92% (*E* : *Z* > 99 : 1)

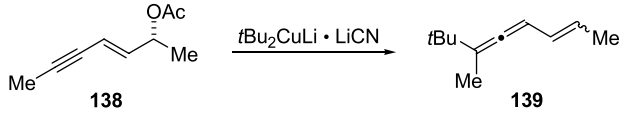
Scheme 42.

achieved in some cases. Besides enyne acetates, the corresponding oxiranes (e.g., **136**) also participate in the 1,5-substitution (Scheme 43) and are transformed into synthetically interesting hydroxy-substituted vinylallenes (e.g., **137**).[77] Moreover, these transformations can also be conducted under copper catalysis by simultaneous addition of the organolithium compound and the substrate to catalytic amounts of the cuprate.[77]



Scheme 43.

Initial attempts to perform the 1,5-substitution enantioselectively with chiral enyne acetates proceeded disappointingly. For example, treatment of the enantiomerically pure substrate **138** with the cyano-Gilman cuprate, tBu$_2$CuLi·LiCN, at −90 °C provided the vinylallene **139** as a 1:3-mixture of *E*/*Z* isomers with 20 and 74% *ee*, respectively (Scheme 44).[64] As previously described for the corresponding S_N2' substitution of propargylic electrophiles, this unsatisfactory stereoselection may be attributed to a racemization of the allene by the cuprate or other organometallic species present in the reaction mixture. Fortunately, the use of phosphines or phosphites as additive served again to improve the enantioselectivity up to a preparatively useful level (92%/93% *ee* in the case of **139**).[64]

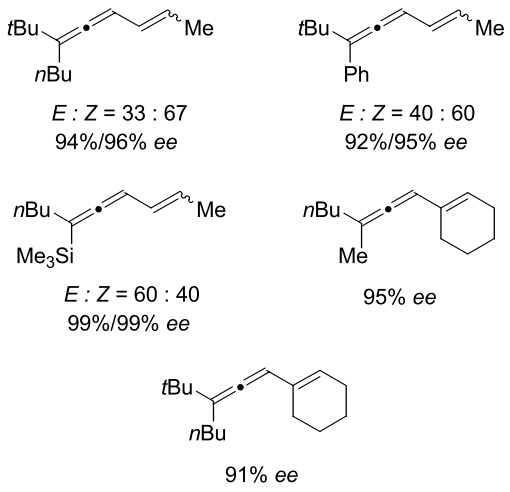


E : *Z* = 25 : 75

without additive: 20% *ee* (*E*), 74% *ee* (*Z*)
with 4 eq. of nBu$_3$P: 92% *ee* (*E*), 93% *ee* (*Z*)

Scheme 44.

Due to the distance between the stereogenic center and the position of the nucleophilic attack, the enantioselective 1,5-substitution of chiral enyne acetates constitutes one of the rare cases of remote stereocontrol in organocopper chemistry. Moreover, the method is not limited to the substrate **138**, but can also be applied to the synthesis of



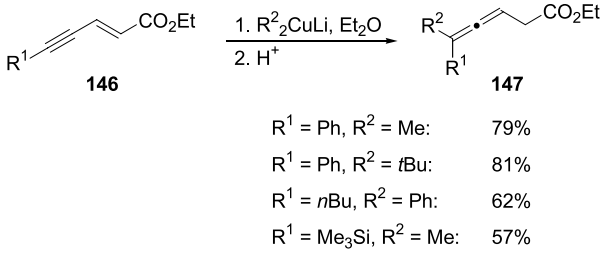
Scheme 45.

enantiomerically enriched or pure vinylallenes with variable substituent patterns (Scheme 45).[64]

8.2. Addition reactions

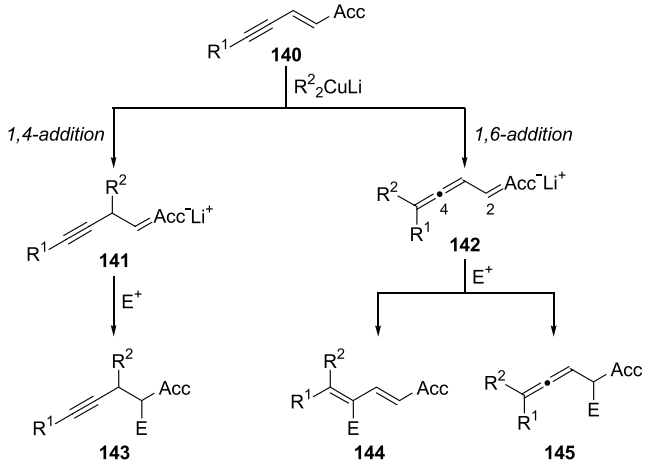
As for the substitution reactions summarized in the previous section, organocopper compounds also represent the reagents of choice for the synthesis of allenes by conjugate addition reactions.[78] The preferred substrates for this transformation are the conjugated enynes **140** with an activating acceptor substituent at the double bond, while the regioisomeric enynes with the acceptor group at the triple bond react with cuprates under 1,4-addition, leading to the conjugated dienes.[79] The outcome of the reaction, however, strongly depends on the regioselectivity of both the nucleophilic attack of the copper reagent (1,4-addition to **141**/**143** or 1,6-addition) and the electrophilic trapping of the enolate thus formed (Scheme 46). Due to the fact that the allenyl enolate **142** formed by 1,6-addition can furnish either a conjugated diene **144** or an allene **145** upon reaction with a soft electrophile and hence offers the possibility to create axial chirality, this transformation is of special interest from the preparative as well as the mechanistic point of view. Fortunately, the regio- and stereoselectivity of both steps can be controlled by the choice of the reactants, in particular by 'fine tuning' of the organocopper reagent and the electrophile.

The first copper-mediated addition reactions to enynes bearing an acceptor group at the double bond were reported by Hulce,[80] who found that 3-alkynyl-2-cycloalkenones react with cuprates regioselectively in a 1,6-addition. The allenyl enolates formed, however, were protonated at C-4 to provide conjugated dienes of type **144**. In contrast to this work, 2-en-4-ynoates **146**, which also react with the Gilman cuprate $Me_2CuLi \cdot LiI$ or cyano-Gilman reagents $R_2CuLi \cdot LiCN$ ($R \neq Me$) in diethyl ether in a 1,6-fashion, provided β-allenic esters **147** with variable substituents by regioselective protonation of the allenyl enolate (with dilute sulfuric acid) at C-2 (Scheme 47).[81–83] Gratifyingly, this 1,6-addition reaction can also be carried out with catalytic amounts of the cuprate[78a] or a copper arenethiolate[84] by simultaneous addition of the substrate and the organolithium reagent to the copper source.

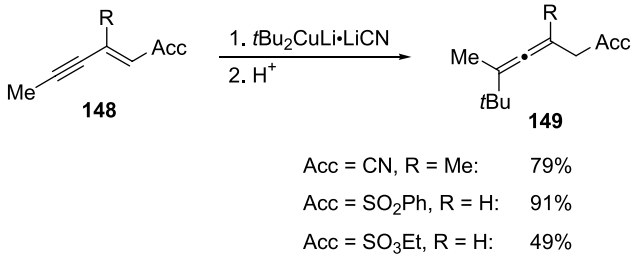


Scheme 47.

The nature of the acceptor substituent hardly affects the regioselectivity of the cuprate addition to acceptor-substituted enynes. Hence, enynes **148** comprising thioester, lactone, dioxanone, as well as keto, sulfonyl, sulfinyl, cyano, and oxazolidino, groups reacted in a 1,6-manner, furnishing functionalized allenes **149** (Scheme 48).[83] By contrast, 1-nitro-l-en-3-ynes were attacked at the C–C double bond with the formation of the corresponding 1,4-adducts. The differences in reactivity can be described qualitatively by the following reactivity scale: acceptor (Acc) = NO_2 > COR, CO_2R, COSR > CN, SO_3R, oxazolidino > SO_2R > SOR ≫ $CONR_2$. In order to achieve acceptable chemical



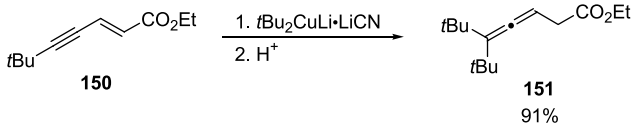
Scheme 46.



Scheme 48.

yields with the less-reactive Michael acceptors, for example, sulfones and sulfoxides, it is often necessary to use more reactive organocopper reagents (e.g., Me_3CuLi_2 instead of Me_2CuLi) or to activate the substrate by Lewis acid catalysis. Here, mild Lewis acids like Me_3SiI or Me_3SiOTf proved to be effective.[83] Unfortunately, enyne amides completely failed to form 1,6-adducts, even under these conditions.

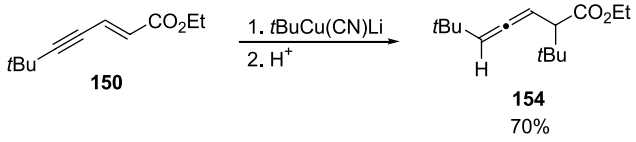
Remarkably, the regioselectivity of the cuprate addition to acceptor-substituted enynes is also insensitive to the steric properties of the substrate. Thus, enynes with *t*-butyl substituents at the triple bond (e.g., **150**) underwent 1,6-additions, even when the cuprate was also sterically demanding (Scheme 49).[82] The method is therefore highly suitable for the preparation of sterically encumbered allenes of the type **151**.



Scheme 49.

Unlike the substrate, the type of organocuprate used for the addition to acceptor-substituted enynes has a pronounced influence on the regiochemical course. While the Gilman cuprate $Me_2CuLi \cdot LiI$ or cyano-Gilman reagents $R_2CuLi \cdot LiCN$ ($R \neq Me$) readily underwent a 1,6-addition, the Yamamoto reagent $RCu \cdot BF_3$, as well as organocopper compounds RCu activated by Me_3SiI, furnished 1,4-adducts.[78a] Interestingly, the use of lithium di-*s*-butylcyanocuprate in diethyl ether predominantly led to the formation of reduced allenes as the major product (Scheme 50), treatment of 2-en-4-ynoate **150** with this reagent giving the 1,6-reduction product **152** with 51% yield, accompanied by 9% of the 1,6-adduct **153**.[85] Similar to the corresponding reduction of propargylic electrophiles with organocopper reagents (vide supra; Schemes 33 and 34), the formation of allene **152** may be attributed to the hydrolysis of a rather stable copper intermediate. In accordance with this assumption, two deuterium atoms were introduced into positions 2 and 5 of the allene when a deuterated proton source was used during work-up. In contrast, the 1,6-addition products of type **153** were the major products if THF instead of diethyl ether was used as the solvent.

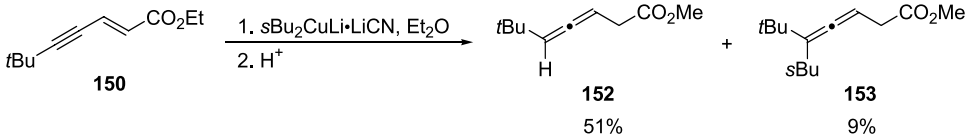
Lower-order cyanocuprates RCu(CN)Li again displayed a different behavior and, although they usually do not react with acceptor-substituted enynes, the cyanocuprate *t*Bu-Cu(CN)Li nevertheless underwent anti-Michael additions to 2-en-4-ynoates (e.g., **150**) and nitriles, affording allenes of type **154** (Scheme 51).[86] Unfortunately, an adequate interpretation of the abnormal behavior of this particular cuprate is still lacking.



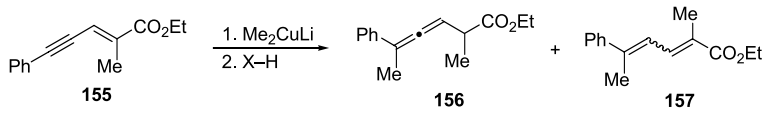
Scheme 51.

As already mentioned at the beginning of this section, allenes can only be obtained by 1,6-addition to acceptor-substituted enynes **140** if the intermediate allenyl enolate **142** reacts regioselectively with an electrophile at C-2 (or at the enolate oxygen atom to give an allenyl enol ether; see Scheme 46). Interestingly, the regioselectivity of the simplest trapping reaction, the protonation, depends on the steric and electronic properties of both the substrate and the proton source. Whereas the allenyl enolates obtained from 3-alkynyl-2-cycloalkenones provided conjugated dienones by protonation at C-4 (possibly via allenyl enols),[80] the corresponding ester enolates were usually found to be protonated at C-2 (Scheme 47), in particular when sterically demanding groups at C-5 blocked the attack of a proton source at C-4 (Scheme 49).[78,81–83] In the presence of a substituent at C-2 of the enolate (cf. substrate **155**), however, mixtures of both allenes **156** and conjugated dienes **157** were formed for steric reasons (Scheme 52). Fortunately, this problem can be solved by using weak organic acids as the proton source; in particular, pivalic acid at low temperature gave rise to the exclusive formation of the desired allenes of type **156**.[81]

In contrast to protonation, the regioselectivity of the reaction of other electrophiles with allenyl enolates derived from acceptor-substituted enynes is independent of the steric and electronic properties of the reaction partners.[78,83,87] As expected according to the HSAB principle, hard electrophiles such as silyl halides and triflates reacted at the enolate oxygen atom to form allenyl enol ethers, while soft electrophiles such as carbonyl compounds attacked at C-2 (see Scheme 53 for a selection of allenes obtained by



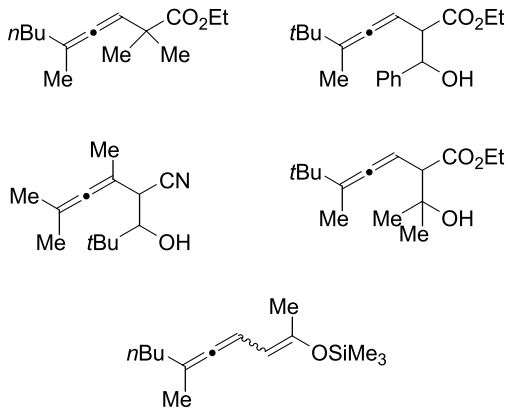
Scheme 50.



X–H = 2N H_2SO_4, 25°C: 50 : 50
AcOH, 25°C: 64 : 36
*t*BuCO_2H, 25°C: 82 : 18
*t*BuCO_2H, -80°C: > 99 : < 1

Scheme 52.

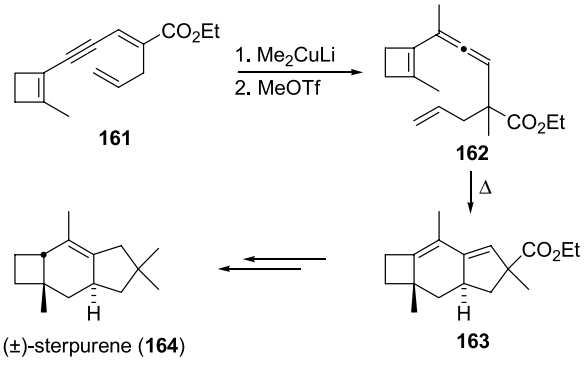
this method). Only allylic and propargylic halides reacted at C-4 of the allenyl enolate to give substituted conjugated dienes. Again, cyclic allenyl enolates obtained through 1,6-cuprate addition to 3-alkynyl-2-cycloalkenones showed a deviating behavior, treatment with iodomethane providing product mixtures derived from attack of the electrophile at C-2 and C-4, whereas the reaction with aldehydes and silyl halides taking place at C-4 exclusively.[88]



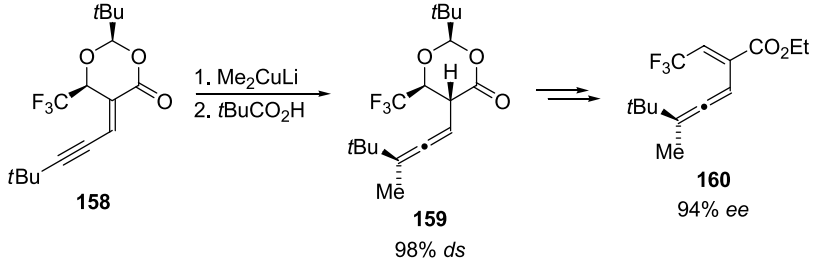
Scheme 53.

In order to control the configuration of the chirality axis of the resulting allenes, the 1,6-addition has to proceed diastereo- or enantioselectively. Among the many different chiral substrates examined, chiral 5-alkynylidene-1,3-dioxan-4-ones of the type **158** have proved to be particularly useful for diastereoselective 1,6-additions, since these Michael acceptors adopt a very rigid conformation. Due to the equatorial position of the *t*-butyl group, the trifluoromethyl residue shields the top face of the enyne moiety, exposing the underside of the molecule to be preferably attacked by the nucleophile (Scheme 54).[89] Therefore, reaction with lithium dimethylcuprate and pivalic acid gave the allene **159** with a diastereoselectivity of 98%, and the stereochemical information generated in this step remained intact during the subsequent conversion into the chiral vinylallene **160**. In contrast to this work, all attempts to establish an enantioselective 1,6-addition by treatment of acceptor-substituted enynes with various chirally modified organocopper reagents failed, due to the low reactivity of the latter compounds towards the Michael acceptors. As already mentioned, this problem was recently solved by Hayashi et al.,[33] who employed aryltitanates as nucleophiles in rhodium-catalyzed enantioselective 1,6-addition reactions to 2-en-4-ynones (see Section 7).

As was the case for the allene synthesis by copper-promoted S_N2' substitution reactions, the corresponding 1,6-addition to acceptor-substituted enynes has found several preparative applications.[78] In natural product synthesis, the method has been used to generate the insect pheromone, methyl 2,4,5-tetradecatrienoate, as well as the precursor **162** of the fungal metabolite, (±)-sterpurene (**164**), and its oxygenated metabolites (Scheme 55).[90] In the latter case, the reaction sequence started with the 1,6-addition of lithium dimethylcuprate to enynoate **161** and subsequent regioselective enolate trapping with methyl triflate. The vinylallene **162** formed underwent an intramolecular [4+2]-cycloaddition



Scheme 55.



Scheme 54.

to the tricyclic product **163**, which finally was converted into the target molecule **164**.

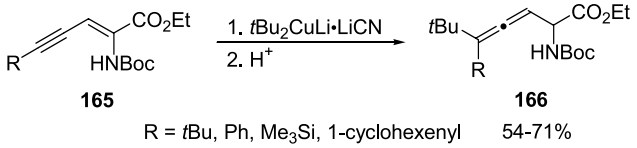
The Diels–Alder reaction outlined above is a typical example for the utilization of axially chiral allenes, accessible through 1,6-addition or other methods, to selectively generate new stereogenic centers. This transfer of chirality is also possible via intermolecular Diels–Alder reactions of vinylallenes,[91] aldol reactions of allenyl enolates,[55f] and Ireland–Claisen rearrangements of silyl allenylketene acetals.[92] Furthermore, it has been utilized recently in the diastereoselective oxidation of titanium allenyl enolates (formed by deprotonation of β-allenecarboxylates of the type **147** and transmetalation with titanocene dichloride) with dimethyl dioxirane (DMDO)[61,93] and in subsequent, acid- or gold-catalyzed cycloisomerization reactions of α-hydroxyallenes into 2,5-dihydrofurans.[61,93,94]

α-Allenic α-amino acids represent another type of heteroatom-substituted allenes which are of interest as irreversible, mechanism-based inhibitors of vitamin B_6-dependent decarboxylases. They are accessible via chelate-controlled Claisen rearrangement of zinc ester enolates (see Section 4) or by 1,6-cuprate addition to 2-amino-substituted enynes **165** (Scheme 56).[61] Due to the low reactivity of these Michael acceptors, however, the reaction succeeded only with the most reactive cuprate, that is, the *t*-butyl cyano-Gilman reagent $tBu_2CuLi \cdot LiCN$. Nevertheless, the addition products **166** were obtained with good chemical yields, and selective deprotection of either the ester or amino functionality under acidic conditions provided the desired target molecules.

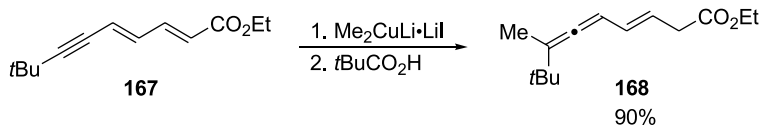
In view of the high value of the 1,6-cuprate addition to acceptor-substituted enynes for the synthesis of functionalized allenes, it seemed interesting to explore whether extended Michael acceptors with further C–C double bonds between the acceptor group and the triple bond can also be utilized for the formation of extended unsaturated allenic systems. Of course, the number of possible regioisomeric products rises with increasing length of the Michael acceptor. For example, the 2,4-dien-6-ynoate **167** can be attacked by an organocopper reagent at C-3, C-5, or C-7, and the latter possibility leads to a vinylogous allenyl enolate having four reactive positions for the subsequent trapping reaction (enolate oxygen, C-2, C-4 and C-6). Therefore, the high regioselectivity found for the reaction of **167** with lithium dimethylcuprate is striking, the cuprate attacking the triple bond exclusively, and protonation with pivalic acid occurring selectively at C-2 of the enolate, giving rise to the formation of the vinylallene **168** (a 1,8-addition product) as the only isolable regioisomer with 90% yield (Scheme 57).[91]

Analogously, the trienynoate **169** reacted in a 1,10-addition to give the 3,5,7,8-tetraenoate **170**, and the even higher unsaturated allene **172** was obtained from the Michael acceptor **171** containing four double bonds between the triple bond and the acceptor substituent (Scheme 58). In the latter case, however, the yield was only 26%; this is most probably due to the reduced thermal stability of the starting material and/or the addition product (the 1,12-adduct **172** was the only isolable reaction product, apart from polymeric compounds).[91]

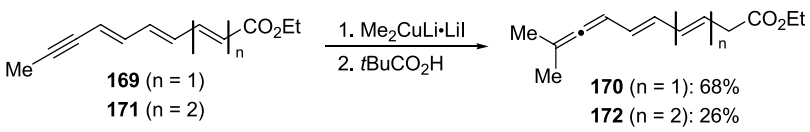
A mechanistic model for the 1,6-cuprate addition to acceptor-substituted enynes **173** has been developed on the basis of NMR spectroscopic investigations,[95] isotope effects,[96] and kinetic measurements.[97] Thorough ^{13}C NMR-spectroscopic studies have revealed that these addition reactions proceed via π-complexes **174** which are characterized by an interaction between the π-system of the C–C double bond and the nucleophilic copper atom (a soft–soft interaction in terms of the HSAB principle), as well as a second interaction between the hard lithium ion of the cuprate and the hard carbonyl oxygen atom (Scheme 59).[95] In particular, the use of ^{13}C-labeled substrates has shed light on the structure of the metal-containing part of these π-complexes, indicating, for example, that the cuprate does not interact with the triple bond of the enyne.[95b,c] Recently, ^{13}C kinetic isotope effects have been determined, which prove that the bond formation between C-5 of the acceptor-substituted enyne and the cuprate occurs in the rate-determining step.[96] Moreover, by means of kinetic measurements with a variety of different substrates, even the activation parameters for these transformations have been determined.[97] All these experimental results are in accordance with a model that comprises the formation of the σ-copper(III) species **175**, which should be in equilibrium



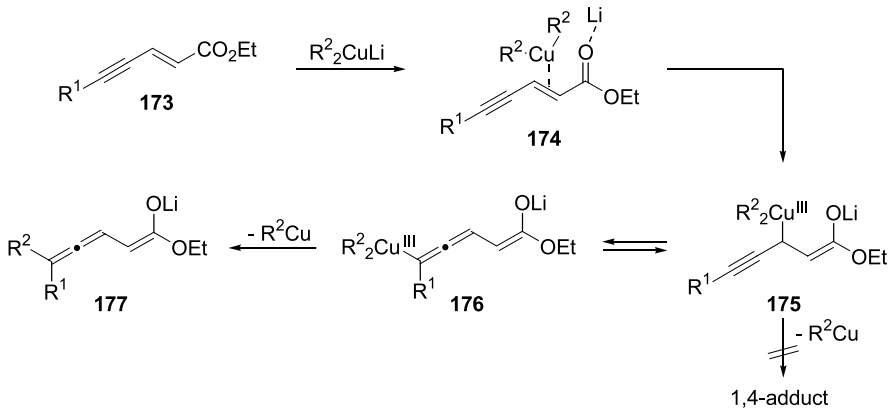
Scheme 56.



Scheme 57.



Scheme 58.



Scheme 59.

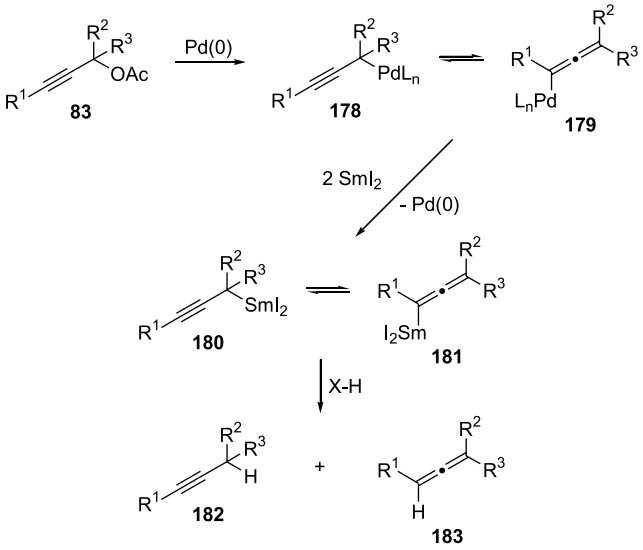
with the allenic copper(III) intermediate **176**. Both intermediates can undergo reductive elimination of an alkylcopper compound to produce the 1,4- and 1,6-adduct, respectively. The experimentally observed exclusive formation of the 1,6-addition product **177**, however, may indicate that the allenic copper species **176** undergoes a much faster reductive elimination than the intermediate **175**.

Similar models explain the 1,8-, 1,10-, and 1,12-addition reactions to the extended Michael acceptors **167**, **169**, and **171**, respectively (Schemes 57 and 58). Again, these transformations start with the formation of a cuprate π-complex at the double bond neighboring the acceptor group.[95a] Subsequently, an equilibrating mixture of σ-copper(III) intermediates is presumably formed, and the regioselectivity of the reaction may then be governed by the different relative rates of the reductive elimination step of these intermediates. Consequently, the exclusive formation of allenic products would be attributable to a comparatively fast reductive elimination of the corresponding allenic σ-copper(III) species.

9. Samarium reagents

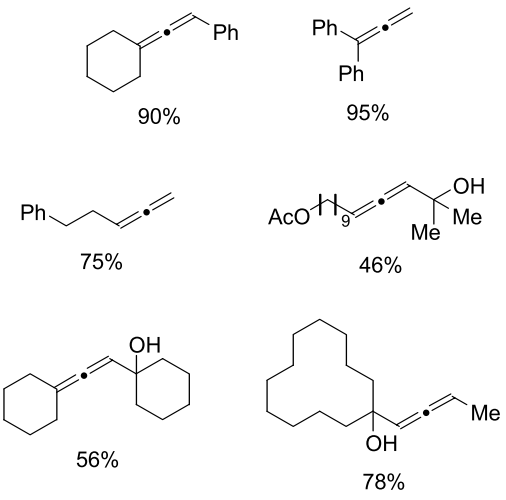
The use of samarium reagents for the synthesis of allenes was pioneered by Inanaga et al.,[98] who employed samarium diiodide in the palladium-catalyzed reduction of propargyl acetates **83**. The reaction probably takes place via an oxidative addition of Pd(0) to the substrate, resulting in an allenic palladium(II) intermediate **179**, which is in equilibrium with the corresponding propargylic palladium species **178** (Scheme 60). Subsequent transfer of two electrons from SmI_2 leads to the release of Pd(0) into the catalytic cycle and the formation of an allenic samarium(III) species **181** (which again exists in an equilibrium with the corresponding propargylic samarium intermediate **180**). Protonation then affords either an allene **183** or an alkyne **182**.

The regioselectivity of the protonation was found to depend on both the substrate structure and the protonating agent. Thus, whereas tertiary acetates furnished allenes with high selectivity, the less pronounced tendency of secondary acetates to give allenes was improved by using bulky protonating agents like *t*-butanol.[98] Only primary acetates afforded alkynes as the major product, regardless of the



Scheme 60.

proton source. A selection of allenes obtained by this method is shown in Scheme 61. Last, but not least, the intermediate samarium species **180/181** can also be trapped with carbonyl compounds.[99] Again, the C–C bond formation took place at the sterically less hindered site, so that



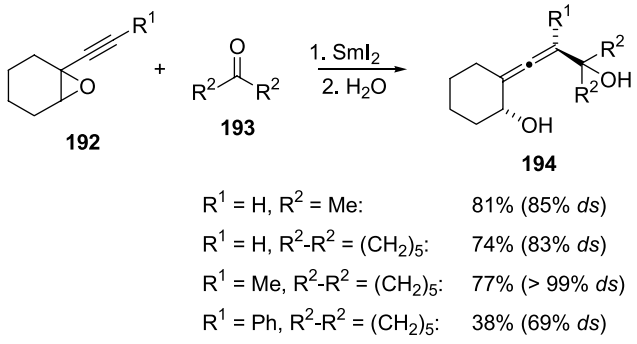
Scheme 61.

allenic alcohols were obtained from secondary and tertiary acetates, whereas primary acetates provided mainly the isomeric acetylenic products.

Mikami has extended the scope of this method considerably by using propargyl phosphates and chiral proton sources.[100] These substrates have been found to be advantageous, due to their high reactivity towards palladium and the extremely low nucleophilicity of the phosphate group.[101] In some cases, it was even possible to obtain allenes such as **185** from primary substrates, for example, ester **184** (Scheme 62).[102] A notable application of this transformation is the synthesis of the allenic isocarbacyclin derivative **187** from its precursor **186**.[103]

By employing chiral proton sources for the protonation of the intermediate samarium species **180/181**, highly enantioenriched allenes were accessible in some cases.[104] Thus, in the reaction of the propargylic phosphate **188**, (*R*,*R*)-1,2-diphenyl-1,2-ethandiol (**190**) and (*R*)-pantolactone (**191**) were found to give the highest selectivities, affording allene **189** with up to 95% *ee* (Scheme 63).

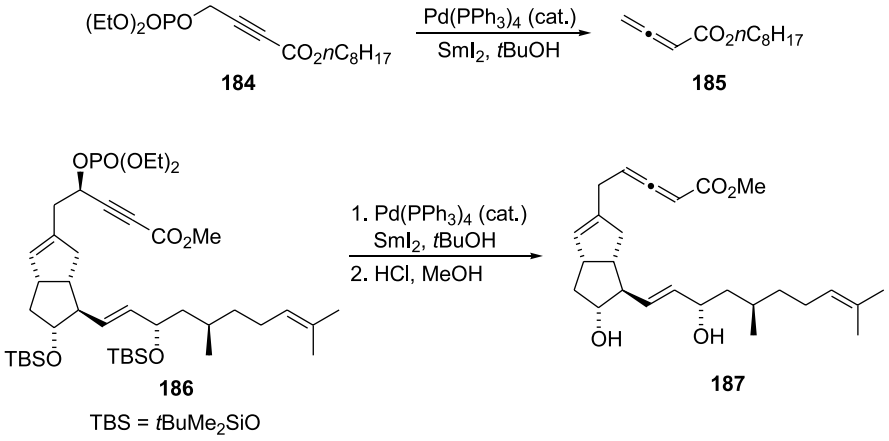
Moreover, propargylic oxiranes **192** were found to react with samarium diiodide and ketones **193** to form α,α′-dihydroxyallenes **194** with moderate to high *anti*-diastereoselectivities (Scheme 64). Aurrecoechea et al.[105] reported this reductive coupling to proceed smoothly in the absence of a palladium catalyst, that is, a direct electron transfer



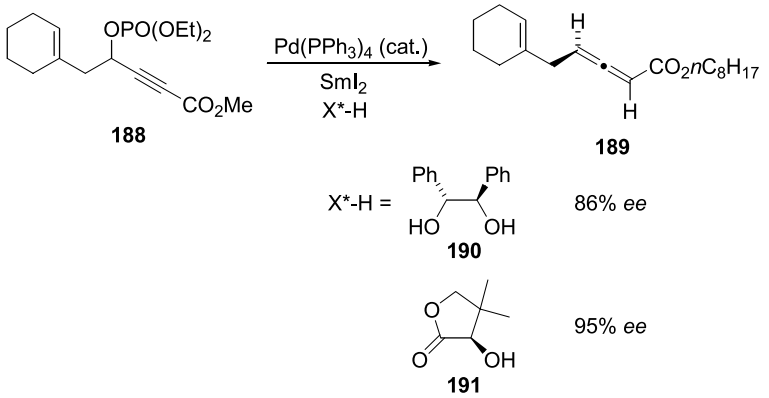
Scheme 64.

from the samarium(II) to the substrate has to take place in order to generate an allenyl/propargyl samarium intermediate of the type **180/181**, which is then regioselectively trapped by the electrophile.

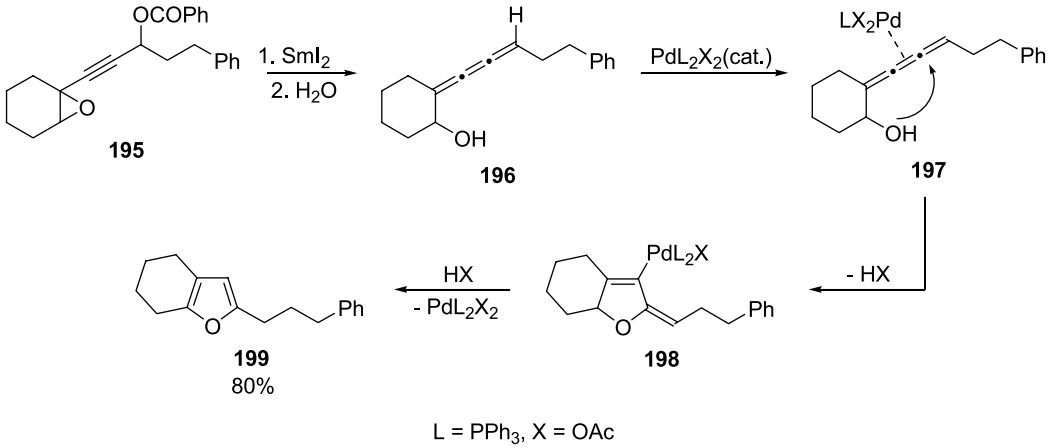
The analogous treatment of oxiranes bearing an additional leaving group at a second propargylic position (e.g., **195**) afforded rather unstable butatrienes of the type **196** through a SmI_2-promoted reduction–elimination sequence (Scheme 65).[106] Although some of these cumulenes had been isolated, they were usually cycloisomerized in situ to the trisubstituted furans (e.g., **199**) in the presence of a palladium(II) catalyst and acetic acid as the proton source. Presumably, these heterocyclic products are formed through



Scheme 62.



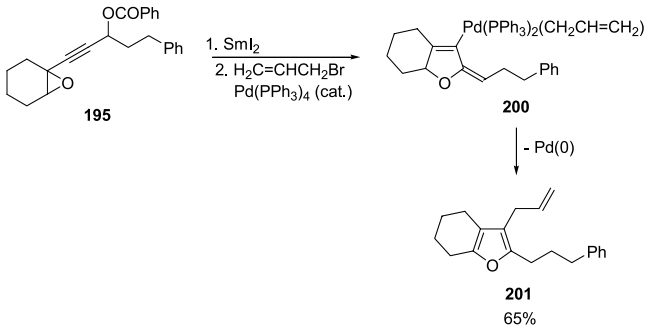
Scheme 63.



Scheme 65.

activation of the central butatriene double bond (**197**), followed by ring closure to the σ-palladium intermediate **198**, which upon protonation and tautomerization releases the palladium into the catalytic cycle.

Interestingly, if the cyclization was carried out in the presence of an aryl or allyl halide and a palladium(0) catalyst, an additional C–C-coupling step via the presumed intermediate **200** led to the formation of tetrasubstituted furans of the type **201** (Scheme 66).[107]



Scheme 66.

10. Conclusions

Over the years, organometallic reagents have become indispensable tools in allene synthesis. In many cases, protocols involving stoichiometric amounts of organometallic compounds are superior to similar catalytic procedures (if they exist) in terms of efficiency, selectivity and reliability. Whereas copper is still the metal of choice for the generation of allenes by C–C bond-forming addition and substitution reactions of multiply unsaturated substrates, it is now nicely supplemented by several other metals (e.g., titanium and indium), and future development of the latter reagents appears to be particularly promising. In the field of C–H bond formation, aluminum and samarium have proved to be prolific, whereas titanium-mediated olefination methods allow the efficient formation of allenes from smaller fragments. A crucial feature of many of these transformations is that they take place with high levels of regio- and steroselectivity, making them very attractive for target-oriented synthesis.

References and notes

1. *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004.
2. (a) *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980. (b) *The Chemistry of the Allenes*; Landor, S. R., Ed.; Academic: London, 1982. (c) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, 1984.
3. Bailey, W. F.; Aspris, P. H. *J. Org. Chem.* **1995**, *60*, 754–757.
4. (a) Kormer, V. A.; Petrov, A. A. *Zh. Obshch. Khim.* **1960**, *30*, 216–219. (b) Petrov, A. A.; Kormer, V. A.; Stadnichuk, M. D. *Zh. Obshch. Khim.* **1960**, *30*, 2243–2248. (c) Petrov, A. A.; Maretina, I. A.; Kormer, V. A. *Zh. Obshch. Khim.* **1963**, *33*, 413–415. (d) Cherkasov, L. N.; Kormer, V. A.; Bal'yan, K. V.; Petrov, A. A. *Zh. Org. Khim.* **1966**, *2*, 1573–1578. (e) Cherkasov, L. N.; Bal'yan, K. V.; Kormer, V. A. *Zh. Org. Khim.* **1966**, *2*, 1938–1942. (f) Cherkasov, L. N.; Bal'yan, K. V.; Kormer, V. A. *Zh. Org. Khim.* **1968**, *4*, 204–207. (g) Pis'mennaya, G. I.; Cherkasov, L. N.; Bal'yan, K. V. *Zh. Org. Khim.* **1972**, *8*, 905–907.
5. Petrov, A. A.; Kormer, V. A.; Savich, I. G. *Zh. Obshch. Khim.* **1960**, *30*, 1056.
6. (a) Petrov, A. A.; Kormer, V. A.; Savich, I. G. *Zh. Obshch. Khim.* **1960**, *3845*, 3846. (b) Kormer, V. A.; Petrov, A. A.; Savich, I. G.; Podporina, T. G. *Zh. Obshch. Khim.* **1962**, *32*, 318–319.
7. (a) Petrov, A. A.; Kormer, V. A.; Yakovleva, T. V. *Zh. Obshch. Khim.* **1960**, *2238*, 2243. (b) Petrov, A. A.; Porfir'eva, Y. I.; Kormer, V. A. *Zh. Obshch. Khim.* **1961**, *31*, 1518–1524.
8. (a) Perepelkin, O. V.; Cherkasov, L. N.; Kormer, V. A.; Bal'yan, K. V.; Petrov, A. A. *Zh. Obshch. Khim.* **1965**, *35*, 574–578. (b) Cherkasov, L. N.; Kormer, V. A.; Bal'yan, K. V.; Petrov, A. A. *Zh. Obshch. Khim.* **1965**, *35*, 616–617. (c) Perepelkin, O. V.; Kormer, V. A.; Bal'yan, K. V.; Petrov, A. A. *Zh. Obshch. Khim.* **1965**, *35*, 957–959. (d) Perepelkin, O. V.; Kormer, V. A.; Bal'yan, K. V.; Petrov, A. A. *Zh. Org. Khim.* **1965**, *1*, 1705–1706.
9. (a) Courtois, G.; Mauze, B.; Miginiac, L. *J. Organomet. Chem.* **1974**, *72*, 309–322. (b) Mesnard, D.; Miginiac, L. *J. Organomet. Chem.* **1976**, *117*, 99–115. (c) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1976**, *117*, 201–213.

(d) Mauze, B. *J. Organomet. Chem.* **1977**, *131*, 321–329. (e) Mauze, B. *J. Organomet. Chem.* **1977**, *134*, 1–13.
10. (a) Kormer, V. A.; Petrov, A. A. *Zh. Obshch. Khim.* **1960**, *30*, 3890–3894. (b) Cherkasov, L. N.; Bal'yan, K. V.; Kormer, V. A. *Zh. Org. Khim.* **1966**, *2*, 1934–1938.
11. (a) Radchenko, S. I.; Petrov, A. A. *Zh. Org. Khim.* **1965**, *1*, 993–996. (b) Radchenko, S. I.; Cherkasov, L. N.; Kupin, B. S.; Krivosheya, A. N. *Zh. Org. Khim.* **1970**, *1961*, 1964. (c) Radchenko, S. I.; Cherkasov, L. N.; Kupin, B. S.; Krivosheya, A. N. *Zh. Org. Khim.* **1971**, *7*, 104–106. (d) Guittet, E.; Bibang Bi Ekogha, C.; Julia, S. A. *Bull. Soc. Chim. Fr.* **1986**, 325–331.
12. (a) Mesnard, D.; Charpentier, J.-P.; Miginiac, L. *J. Organomet. Chem.* **1981**, *15*, 22. (b) Mesnard, D.; Charpentier, J.-P.; Miginiac, L. *J. Organomet. Chem.* **1981**, *214*, 23–29. (c) Mesnard, D.; Charpentier, J.-P.; Miginiac, L. *J. Organomet. Chem.* **1981**, *214*, 135–143.
13. Oestreich, M.; Hoppe, D. *Tetrahedron Lett.* **1999**, *40*, 1881–1884.
14. (a) Goré, J.; Dulcere, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 866–867. (b) Dulcere, J. P.; Goré, J.; Roumestant, M. L. *Bull. Soc. Chim. Fr.* **1974**, 1119–1123. (c) Bertrand, M.; Dulcere, J. P.; Gil, G.; Roumestant, M. L. *Tetrahedron Lett.* **1979**, *20*, 1845–1846. (d) Dulcere, J. P.; Grimaldi, J.; Santelli, M. *Tetrahedron Lett.* **1981**, *22*, 3179–3180.
15. (a) Katsuhira, T.; Harada, T.; Maejima, K.; Osada, A.; Oku, A. *J. Org. Chem.* **1993**, *58*, 6166–6168. (b) Harada, T.; Katsuhira, T.; Osada, A.; Iwazaki, K.; Maejima, K.; Oku, A. *J. Am. Chem. Soc.* **1996**, *118*, 11377–11390.
16. (a) Kazmaier, U.; Görbitz, C. H. *Synthesis* **1996**, 1489–1493. (b) Kazmaier, U. *Liebigs Ann./Recueil* **1997**, 285–295.
17. Horváth, A.; Bäckvall, J.-E. *J. Org. Chem.* **2001**, *66*, 8120–8126.
18. Hung, S.-C.; Wen, Y.-F.; Chang, J.-W.; Liao, C.-C.; Uang, B.-J. *J. Org. Chem.* **2002**, *67*, 1308–1313.
19. (a) Baumeler, A.; Brade, W.; Haag, A.; Eugster, C. H. *Helv. Chim. Acta* **1990**, *700*, 715. (b) Baumeler, A.; Eugster, C. H. *Helv. Chim. Acta* **1991**, *74*, 469–486. (c) Haugan, J. A. *Tetrahedron Lett.* **1996**, *37*, 3887–3890. (d) Haugan, J. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2731–2737. (e) Yamano, Y.; Watanabe, Y.; Watanabe, N.; Ito, M. *J. Chem. Soc., Perkin Trans.* **2002**, 2833–2844. (f) Furuichi, N.; Hara, H.; Osaki, T.; Mori, H.; Katsumura, S. *Angew. Chem.* **2002**, *114*, 1065–1068. *Angew. Chem. Int. Ed.* **2002**, *41*, 1023–1026.
20. Review: Hoffmann-Röder, A.; Krause, N. *Angew. Chem.* **2004**, *116*, 1216–1236. *Angew. Chem. Int. Ed.* **2004**, *43*, 1196–1216.
21. Huguet, J.; Reyes, M. d. C. *Tetrahedron Lett.* **1990**, *31*, 4279–4280.
22. VanBrunt, M. P.; Standaert, R. F. *Org. Lett.* **2000**, *2*, 705–708.
23. (a) Cunico, R. F. *Tetrahedron Lett.* **1994**, *35*, 2291–2294. (b) Cunico, R. F.; Zaporowski, L. F.; Rogers, M. *J. Org. Chem.* **1999**, *64*, 9307–9309.
24. Santelli-Rouvier, C.; Lefrère, S.; Mamai, M.; Santelli, M. *Tetrahedron Lett.* **1995**, *36*, 2459–2460.
25. Trost, B. M.; Tour, J. M. *J. Org. Chem.* **1989**, *54*, 484–486.
26. (a) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem.* **2002**, *114*, 4057–4059. *Angew. Chem. Int. Ed.* **2002**, *41*, 3901–3903. (b) See also: Lee, K.; Kim, H.; Miura, T.; Kiyota, K.; Kusama, H.; Kim, S.; Iwasawa, N.; Lee, P. H. *J. Am. Chem. Soc.* **2003**, *125*, 9682–9688.
27. The formation of allenes by Wittig or Horner–Wadsworth–Emmons-olefination of ketenes is well established.[1,2] For more recent examples, see: (a) Minami, T.; Okauchi, T.; Kouno, R. *Synthesis*, 349–357 (review). (b) Lang, R. W.; Kohl-Mines, E.; Hansen, H.-J. *Helv. Chim. Acta* **1985**, *68*, 2249–2253. (c) Kohl-Mines, E.; Hansen, H.-J. *Helv. Chim. Acta* **1985**, *68*, 2244–2248. (d) Lang, R. W.; Hansen, H.-J. In *Organic Syntheses*, *Collect. Vol. VIII*; Wiley: New York, 1993; pp 232–235. (e) Tanaka, K.; Otsubo, K.; Fuji, K. *Synlett*, 933–934. (f) Tanaka, K.; Otsubo, K.; Fuji, K. *Tetrahedron Lett.* **1996**, *35*, 3735–3738. (g) Kumar, K.; Kaur, S.; Ishar, M. P. S. *Synlett*, 1237–1238. (h) Yamazaki, J.; Watanabe, T.; Tanaka, K. *Tetrahedron: Asymmetry* **2001**, *12*, 669–675. (i) Inoue, H.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *Tetrahedron* **2002**, *58*, 83–90.
28. Hughes, K. A.; Dopico, P. G.; Sabat, M.; Finn, M. G. *Angew. Chem.* **1993**, *105*, 603–605. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 554–556. (b) Reynolds, K. A.; Dopico, P. G.; Sundermann, M. J.; Hughes, K. A.; Finn, M. G. *J. Org. Chem.* **1993**, *1298*, 1299.
29. Brody, M. S.; Williams, R. M.; Finn, M. G. *J. Am. Chem. Soc.* **1997**, *119*, 3429–3433.
30. Petasis, N. A.; Hu, Y.-H. *J. Org. Chem.* **1997**, *62*, 782–783.
31. Dennehy, R. D.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1992**, 35–36.
32. Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 7138–7139.
33. Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett.* **2004**, *6*, 305–307.
34. (a) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1968**, *90*, 4733–4734. (b) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289–3292.
35. Reviews: (a) Alexakis, A.; Mangeney, P.; Ghribi, A.; Marek, I.; Sedrani, R.; Guir, C.; Normant, J. F. *Pure Appl. Chem.* **1988**, *60*, 49–56. (b) Alexakis, A. *Pure Appl. Chem.* **1992**, *64*, 387–392. (c) Erdik, E. *Tetrahedron Lett.* **1992**, *48*, 9577–9648. (d) Elsevier, C. J. In *Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; (Houben-Weyl); Thieme: Stuttgart, 1995; Vol. E21a, pp 537–566.
36. (a) Djuric, S. W.; Miyano, M.; Clare, M.; Rydzewski, R. M. *Tetrahedron Lett.* **1987**, *28*, 299–302. (b) Mattay, J.; Conrads, M.; Runsink, J. *Synthesis* **1988**, 595–598. (c) Wu, K.-M.; Midland, M. M.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 4381–4392. (d) Kang, S.-K.; Kim, S.-G.; Cho, D.-G. *Tetrahedron: Asymmetry* **1992**, *3*, 1509–1510. (e) Corriu, R. J. P.; Huyn, V.; Iqbal, J.; Moreau, J. J. E.; Vernhet, C. *Tetrahedron* **1992**, *48*, 6231–6244. (f) Rey, J. G.; Rodríguez, J.; De Lera, A. R. *Tetrahedron Lett.* **1993**, *34*, 6293–6296. (g) Spino, C.; Thibault, C.; Gingras, S. *J. Org. Chem.* **1998**, *63*, 5283–5287.
37. (a) Bernard, D.; Doutheau, A.; Goré, J. *Tetrahedron* **1987**, *43*, 2721–2732. (b) Danheiser, R. L.; Tsai, Y.-M.; Fink, D. M. In *Organic Syntheses*, *Collect. Vol. VIII*; Wiley: New York, 1993; pp 471–474. (c) Gridnev, I.; Kanai, G.; Miyaura, N.; Suzuki, A. *J. Organomet. Chem.* **1994**, *481*, C4–C7. (d) Agami, C.; Couty, F.; Evano, G.; Mathieu, H. *Tetrahedron* **2000**, *56*, 367–376. (e) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tamaka, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem.* **2001**, *66*, 4904–4914.
38. (a) Marek, I.; Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 5499–5502. (b) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.*

1990, *112*, 8042–8047. (c) Marek, I.; Alexakis, A.; Mangeney, P.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1992**, *129*, 171–190.

39. (a) Burton, D. J.; Hartgraves, G. A.; Hsu, J. *Tetrahedron Lett.* **1990**, *31*, 3699–3702. (b) Hung, M. H. *Tetrahedron Lett.* **1990**, *31*, 3703–3706. (c) Yus, M.; Gomis, J. *Eur. J. Org. Chem.* **2003**, 2043–2048.
40. (a) Review: Chemla, F.; Ferreira, F. *Curr. Org. Chem.* **2002**, *6*, 539–570. (b) Cahiez, C.; Alexakis, A.; Normant, J. *Synthesis* **1978**, 528–530. (c) Tigchelaar, M.; Meijer, J.; Kleijn, H.; Bos, H. J. T.; Vermeer, P. *J. Organomet. Chem.* **1981**, *221*, 117–121. (d) Doutheau, A.; Saba, A.; Goré, J.; Quash, G. *Tetrahedron Lett.* **1982**, *23*, 2461–2464. (e) Oehlschlager, A. C.; Czyzewska, E. *Tetrahedron Lett.* **1983**, *24*, 5587–5590. (f) Kleijn, H.; Vermeer, P. *J. Org. Chem.* **1985**, *50*, 5143–5148. (g) Johnson, C. R.; Dhanoa, D. S. *J. Org. Chem.* **1987**, *52*, 1885–1888. (h) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1989**, *30*, 2387–2390. (i) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677–1696. (j) Alexakis, A. *Pure Appl. Chem.* **1992**, *64*, 387–392. (k) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180–7184. (l) Spino, C.; Frechette, S. *Tetrahedron Lett.* **2000**, *41*, 8033–8036.
41. (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 349–352. (b) Ohno, H.; Toda, A.; Fujii, N.; Takemoto, Y.; Tanaka, T.; Ibuka, T. *Tetrahedron* **2000**, *56*, 2811–2820.
42. (a) MacDonald, T. L.; Reagan, D. R. *J. Org. Chem.* **1980**, *45*, 4740–4747. (b) Jansen, A.; Krause, N. *Synthesis* **2002**, 1987–1992.
43. (a) Dunn, M. J.; Jackson, R. F. W. *Chem. Commun.* **1992**, 319–320. (b) Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Wishart, N.; Ellis, D.; Wythes, M. J. *Synlett* **1993**, 499–500. (c) Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210–2215. (d) Dunn, M. J.; Jackson, R. F. W. *Tetrahedron* **1997**, *53*, 13905–13914. (e) Jackson, R. F. W.; Fraser, J. L.; Wishart, N.; Porter, B.; Wythes, M. J. *J. Chem. Soc., Chem. Commun.* **1998**, 1903–1912. (f) Dieter, R. K.; Nice, L. E. *Tetrahedron Lett.* **1999**, *40*, 4293–4296. (g) Dieter, R. K.; Topping, C. M.; Chandupatla, K. R.; Lu, K. *J. Am. Chem. Soc.* **2001**, *123*, 5132–5133. (h) Dieter, R. K.; Watson, R. T.; Goswami, R. *Org. Lett.* **2004**, *6*, 253–256. (i) Parsons, P. J.; Gold, H.; Semple, G.; Montagnon, T. *Synlett* **2000**, 1184–1186. (j) Yokomatsu, T.; Ichimura, A.; Kato, J.; Shibuya, S. *Synlett* **2001**, 287–289. (k) Papillon, J. P. N.; Taylor, R. J. K. *Org. Lett.* **2002**, *4*, 119–122.
44. Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F. *J. Org. Chem.* **1991**, *56*, 1083–1088.
45. Gordon, J.; Tabacchi, R. *J. Org. Chem.* **1992**, *57*, 4728–4731.
46. (a) Buynak, J. D.; Borate, H. B.; Lamb, G. W.; Hurd, T.; Vallabh, J.; Matthew, J.; Lambert, J.; Siriwardane, U. *Tetrahedron Lett.* **1988**, *29*, 5053–5056. (b) Buynak, J. D.; Borate, H. B.; Lamb, G. W.; Khasnis, D. D.; Husting, C.; Isom, H.; Siriwardane, U. *J. Org. Chem.* **1993**, *58*, 1325–1335.
47. (a) Buynak, J. D.; Khasnis, D.; Bachmann, B.; Wu, K.; Lamb, G. *J. Am. Chem. Soc.* **1994**, *116*, 10955–10965. (b) Buynak, J. D.; Rao, A. S.; Ford, G. P.; Carver, C.; Adam, G.; Geng, B.; Bachmann, B.; Shobassy, S.; Lackey, S. *J. Med. Chem.* **1997**, *40*, 3423–3433.
48. Thorand, S.; Vögtle, F.; Krause, N. *Angew. Chem.* **1999**, *111*, 3929–3931. *Angew. Chem. Int. Ed.* **1999**, *38*, 3721–3723.
49. (a) Fleming, I.; Takai, K.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2269–2273. (b) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1994**, *116*, 9789–9790. (c) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905–10913. (d) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 5773–5784. (e) Weinreb, S. M.; Smith, D. T.; Jin, J. *Synthesis* **1998**, 509–521. (f) Aoyagi, S.; Hirashima, S.; Saito, K.; Kibiyashi, C. *J. Org. Chem.* **2002**, *67*, 5517–5526.
50. (a) Okamura, W. H.; Aurrecoechea, J. M.; Gibbs, R. A.; Norman, A. W. *J. Org. Chem.* **1989**, *54*, 4072–4083. (b) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**, *56*, 3210–3213. (c) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**, *56*, 6264–6266. (d) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1992**, *57*, 3387–3396.
51. (a) D'Aniello, F.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Tetrahedron Lett.* **1994**, *35*, 7775–7778. (b) D'Aniello, F.; Schoenfelder, A.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, *61*, 9631–9634. (c) Bernard, N.; Chemla, F.; Normant, J. F. *Tetrahedron Lett.* **1998**, *39*, 8837–8840. (d) Chemla, F.; Bernard, N.; Normant, J. F. *Eur. J. Org. Chem.* **1999**, 2067–2078. (e) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470–10471. (f) Löfstedt, J.; Franzén, J.; Bäckvall, J.-E. *J. Org. Chem.* **2001**, *66*, 8015–8020. (g) Ohno, H.; Hamaguchi, H.; Tanaka, T. *Org. Lett.* **2001**, *3*, 2269–2271. (h) Ohno, H.; Ando, K.; Hamaguchi, H.; Takeoka, Y.; Tanaka, T. *J. Am. Chem. Soc.* **2002**, *124*, 15266–15266.
52. Feldman, K. S.; Mechem, C. C.; Nader, L. *J. Am. Chem. Soc.* **1982**, *104*, 4011–4012.
53. Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468–2477.
54. (a) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533–1534. (b) Crimmins, M. T.; Emmitte, K. A.; Choy, A. L. *Tetrahedron* **2002**, *58*, 1817–1834. (c) See also: Saitoh, T.; Suzuki, T.; Sugimoto, M.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2003**, *44*, 3175–3178.
55. (a) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726–3730. (b) Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854–5855. (c) Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F. *J. Org. Chem.* **1991**, *56*, 1083–1088. (d) Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1993**, *115*, 7926–7927. (e) Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057–3083. (f) Laux, M.; Krause, N.; Koop, U. *Synlett* **1996**, 87–88. (g) Brummond, K. M.; Kerekes, A. D.; Wan, H. *J. Org. Chem.* **2002**, *67*, 5156–5163.
56. Nakamura, E.; Mori, S. *Angew. Chem.* **2000**, *112*, 3902–3924. *Angew. Chem. Int. Ed.* **2000**, *39*, 3750–3771. (b) Mori, S.; Nakamura, E. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 315–346.
57. Recent review: Bonini, C.; Righi, G. *Tetrahedron* **2002**, *58*, 4981–5021.
58. Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1–300 and references cited therein.
59. Jacobsen, E. N. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Oxford: Pergamon, 1995; Vol. 12, pp 1097–1136; and references cited therein.
60. Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435–2446 and references cited therein.

61. Krause, N.; Hoffmann-Röder, A.; Canisius, J. *Synthesis* **2002**, 1759–1774.
62. Fürstner, A.; Mendez, M. *Angew. Chem.* **2003**, *115*, 5513–5515. *Angew. Chem. Int. Ed.* **2003**, *42*, 5355–5357.
63. (a) Claesson, A.; Olsson, L. I. *J. Chem. Soc., Chem. Commun.* **1979**, 524–525. (b) Westmijze, H.; Nap, I.; Meijer, J.; Kleijn, H.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 154–157. (c) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726–3730. (d) Schurig, V.; Keller, F.; Reich, S.; Fluck, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3475–3480.
64. Krause, N.; Purpura, M. *Angew. Chem.* **2000**, *112*, 4512–4514. *Angew. Chem. Int. Ed.* **2000**, *39*, 4355–4356.
65. Roth, W. R.; Bastigkeit, T. *Liebigs Ann.* **1996**, 2171–2183.
66. Naruse, Y.; Watanabe, H.; Inagaki, S. *Tetrahedron: Asymmetry* **1992**, *3*, 603–606.
67. Hoffmann-Röder, A. PhD Thesis, Dortmund University, 2003.
68. Alexakis' method using Grignard reagents in the presence of catalytic amounts of copper salts[40h–j] cannot be used for substrates of type **113** since direct nucleophilic attack at the oxirane ring prevails.
69. Reviews: (a) Boudier, A.; Bromm, L. A.; Lotz, M.; Knochel, P. *Angew. Chem.* **2000**, *112*, 4584–4606. *Angew. Chem. Int. Ed.* **2000**, *39*, 4414–4435. (b) Rottländer, M.; Boymond, L.; Bérillon, L.; Lepretre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 767–770. (c) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem.* **2003**, *115*, 4438–4456. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302–4320.
70. Copper-catalyzed enantioselective S_N2' substitution of propargyl oxiranes in the presence of chiral phosphoramidites: Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Arnold, A.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 4893–4896.
71. Reich, H. J.; Eisenhart, E. K.; Whipple, W. L.; Kelly, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 6432–6442.
72. Nantz, M. H.; Bender, D. M.; Janaki, S. *Synthesis* **1993**, 577–578.
73. (a) Van Horn, A. R.; Garay, G.; Edwards, J. A. US Patent 4178457; *Chem. Abstr.* **1980**, *92*, 146339p.(b) Fried, J. H.; Muchowski, J. M.; Carpio, H. *Prostaglandins* **1977**, *14*, 807–811. (c) Baret, P.; Barreiro, E.; Greene, A. E.; Luché, J.-L.; Teixeira, M. A.; Crabbé, P. *Tetrahedron* **1979**, *35*, 2931–2938.
74. Ansorge, M.; Polborn, K.; Müller, T. J. J. *J. Organomet. Chem.* **2001**, *630*, 198–204.
75. Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 2397–2400.
76. Brummond, K. M.; Lu, J. *J. Am. Chem. Soc.* **1999**, *121*, 5087–5088.
77. Purpura, M.; Krause, N. *Eur. J. Org. Chem.* **1999**, 267–275.
78. Reviews: (a) Krause, N.; Gerold, A. *Angew. Chem.* **1997**, *109*, 194–213. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186–204. (b) Fredrick, M. A.; Hulce, M. *Tetrahedron* **1997**, *53*, 10197–10227. (c) Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1–11. (d) Krause, N.; Zelder, C. In *The Chemistry of Dienes and Polyenes*; Rappoport, Z., Ed.; Wiley: New York, 2000; Vol. 2, pp 645–691. (e) Krause, N.; Hoffmann-Röder, A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 145–166.
79. (a) Ernst, L.; Hopf, H.; Krause, N. *J. Org. Chem.* **1987**, *52*, 398–405. (b) Hopf, H.; Krause, N. In *Chemistry and Biology of Synthetic Retinoids*; Dawson, M. I., Okamura, W. H., Eds.; CRC: Boca Raton, FL, 1990; pp 177–199. (c) Bennani, Y. L. *J. Org. Chem.* **1996**, *61*, 3542–3544.
80. (a) Hulce, M. *Tetrahedron Lett.* **1988**, *29*, 5851–5854. (b) Lee, S.-H.; Hulce, M. *Tetrahedron Lett.* **1990**, *31*, 311–314. (c) Cheng, M.; Hulce, M. *J. Org. Chem.* **1990**, *55*, 964–975.
81. Krause, N. *Chem. Ber.* **1990**, *123*, 2173–2180.
82. Krause, N. *Chem. Ber.* **1991**, *124*, 2633–2635.
83. Hohmann, M.; Krause, N. *Chem. Ber.* **1995**, *128*, 851–860.
84. Haubrich, A.; Van Klaveren, M.; Van Koten, G.; Handke, G.; Krause, N. *J. Org. Chem.* **1993**, *58*, 5849–5852.
85. Krause, N.; Handke, G. *Tetrahedron Lett.* **1991**, *32*, 7229–7232.
86. Gerold, A.; Krause, N. *Chem. Ber.* **1994**, *127*, 1547–1549.
87. (a) Arndt, S.; Handke, G.; Krause, N. *Chem. Ber.* **1993**, *126*, 251–259. (b) Krause, N.; Arndt, S. *Chem. Ber.* **1993**, *126*, 261–263.
88. (a) Lee, S.-H.; Shih, M.; Hulce, M. *Tetrahedron Lett.* **1992**, *33*, 185–188. (b) Lee, S.-H.; Hulce, M. *Synlett* **1992**, 485–488.
89. (a) Handke, G.; Krause, N. *Tetrahedron Lett.* **1993**, *34*, 6037–6040. (b) Krause, N.; Handke, G.; Wecker, U. In *Stereoselective Reactions of Metal-Activated Molecules*; Werner, H., Sundermeyer, J., Eds.; Vieweg: Braunschweig, 1995; pp 153–155.
90. Krause, N. *Liebigs Ann. Chem.* **1993**, 521–525.
91. Koop, U.; Handke, G.; Krause, N. *Liebigs Ann.* **1996**, 1487–1499.
92. Becker, M.; Krause, N. *Liebigs Ann./Recueil* **1997**, 725–728.
93. Krause, N.; Laux, M.; Hoffmann-Röder, A. *Tetrahedron Lett.* **2000**, *41*, 9613–9616.
94. Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, 2537–2538.
95. (a) Krause, N. *J. Org. Chem.* **1992**, *57*, 3509–3512. (b) Krause, N.; Wagner, R.; Gerold, A. *J. Am. Chem. Soc.* **1994**, *116*, 381–382. (c) Canisius, J.; Mobley, T. A.; Berger, S.; Krause, N. *Chem. Eur. J.* **2001**, *7*, 2671–2675.
96. Uerdingen, M. PhD Thesis, Dortmund University, 2001.
97. Canisius, J.; Gerold, A.; Krause, N. *Angew. Chem.* **1999**, *111*, 1727–1730. *Angew. Chem. Int. Ed.* **1999**, *38*, 1644–1646.
98. (a) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5237–5240. (b) Inanaga, J.; Sugimoto, Y.; Hanamoto, T. *Tetrahedron Lett.* **1992**, *33*, 7035–7038.
99. Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 2275–2278.
100. Review: Mikami, K.; Yoshida, A. *Tetrahedron* **2001**, *57*, 889–898.
101. Mikami, K.; Yoshida, A.; Matsumoto, S.; Feng, F.; Matsumoto, Y.; Sugino, A.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1995**, *36*, 907–908.
102. Yoshida, A.; Mikami, K. *Synlett* **1997**, 1375–1376.
103. Mikami, K.; Yoshida, A.; Matsumoto, Y. *Tetrahedron Lett.* **1996**, *37*, 8515–8518.
104. Mikami, K.; Yoshida, A. *Angew. Chem.* **1997**, *109*, 892–894. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 858–860.
105. (a) Aurrecoechea, J. M.; Solay, M. *Tetrahedron Lett.* **1995**, *36*, 2501–2504. (b) Aurrecoechea, J. M.; Alonso, E.; Solay, M. *Tetrahedron* **1998**, *54*, 3833–3850.
106. Aurrecoechea, J. M.; Pérez, E.; Solay, M. *J. Org. Chem.* **2001**, *66*, 564–569.
107. (a) Aurrecoechea, J. M.; Pérez, E. *Tetrahedron Lett.* **2001**, *42*, 3839–3841. (b) Aurrecoechea, J. M.; Pérez, E. *Tetrahedron Lett.* **2003**, *44*, 3263–3266. (c) Aurrecoechea, J. M.; Pérez, E. *Tetrahedron* **2004**, *60*, 4139–4149.

Biographical sketch

Norbert Krause, born in 1959 in Wolfsburg, Germany, studied Chemistry at the Technical University of Braunschweig and obtained his PhD degree in 1986 under the guidance of H. Hopf with investigations on sterically and electronically modified retinoids. After one-year postdoctoral appointments with D. Seebach (ETH Zürich, Switzerland) and M. Saunders (Yale University, New Haven, USA), he obtained his habilitation for organic chemistry in the group of K. Hafner at the Technical University of Darmstadt in 1993. He became Associate Professor at the University of Bonn in 1994 and Full Professor at the University of Dortmund in 1998. His research interest comprise the development and mechanistic understanding of metal-promoted and -catalyzed reactions, their application to the synthesis of natural and non-natural target molecules, and stereoselective protonation reactions. These research activities have been recognized through the award of the 'Heinz-Maier-Leibnitz-Preis' (1991), the ADUC annual award for lecturers (1993), a Heisenberg scholarship (1994), and a 'Japan Society for the Promotion of Science (JSPS) Fellowship' (2003).

Anja Hoffmann-Röder, born in 1972 in Bonn, Germany, became laboratory technician at the Degussa AG and then studied Chemistry at the University of Bonn. She obtained her Diploma in 1999 with a Thesis on chiral allenophanes under the joint guidance of F. Vögtle and N. Krause. After moving to the University of Dortmund, she obtained her PhD degree in 2003 with N. Krause on research about stereoselective syntheses with copper, silver, and gold. In 2001–2003, she joined the groups of A. Alexakis (Geneva, Switzerland), Y. Yamamoto (Sendai, Japan), and P. Knochel (Munich) for scientific short-term missions which were sponsored by the European Community and the Japanese Ministry of Education, Culture, Sports, Science and Technology (Monbukagakusho). She is currently an Emmy-Noether fellow (sponsored by the Deutsche Forschungsgemeinschaft) in the group of F. Diederich (Zürich, Switzerland). Her studies and research activities were recognized through stipends of the Studienstiftung des Deutschen Volkes, the Fritz-ter-Meer foundation, and the Stiftung Stipendien-Fonds des Verbandes der Chemischen Industrie, as well as through the 'Heinrich-Hörlein-Gedächtnispreis' and a 'DSM Award for Chemistry and Technology 2003'.

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A first regioselective synthesis of 3-fluoroalkylated benzofurans via palladium-catalyzed annulation of fluorine-containing internal alkynes with variously substituted 2-iodophenol

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Abstract—The palladium-catalyzed annulation reaction of a variety of fluorine-containing internal alkynes with 2-iodophenol derivatives was investigated. The use of P(*t*-Bu)$_3$ as a ligand on palladium was found to be crucial in this annulation reaction, resulting in the exclusive formation of 3-fluoroalkylated benzofurans in high yields. ^{19}F NMR analysis of the reaction mixture revealed that the addition of phenol to the fluoroalkylated alkynes was followed by intramolecular Heck reaction, giving to the corresponding 3-fluoroalkylated benzofurans.

1. Introduction

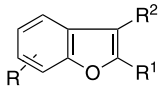
The benzofurans **1**, shown in Figure 1, are present in a wide variety of biologically active, naturally occurring compounds, and numerous approaches to their synthesis have been reported thus far.[1] However, the synthesis of functionalized benzofurans still stimulate a major challenge in organic synthesis. In particular, there have been only a few limited studies on the synthesis of fluoroalkylated benzofurans, despite of medicinal and pharmaceutical advantages imparted by fluorine atom(s).[2] Herein we wish to describe a first practical synthesis of 3-fluoroalkylated benzofurans by the palladium-catalyzed annulation of internal alkynes possessing a fluoroalkyl group.[3]

2. Results and discussion

The palladium-catalyzed reaction of trifluoro-methylated acetylene **2a** and 2-iodophenol **3** was chosen for our initial investigation of the annulation process[4] (Table 1). Thus, to a solution of 20 mol% of Pd(PPh$_3$)$_4$ and 1.0 equiv of Et$_3$N in DMF were added 1.0 equiv of **2a** and 2.0 equiv of 2-iodophenol, and the mixture was heated at 100 °C for 4 h. However, any trace of desired product was obtained (entry 1). Examination of base such as Na$_2$CO$_3$, KOAc, and K$_2$CO$_3$ brought about a dramatical change in the yield as shown in entries 2–4. Among such various bases, K$_2$CO$_3$ was found to be very effective, **1a** being afforded in 45% yield as a single isomer, together with 4% of the byproduct **4a** (vide supra) (entry 4). In this case, 2-CF$_3$-substituted benzofuran **5a** (Fig. 2) was not detected at all. The use of 5 equiv of K$_2$CO$_3$ caused a slight increase of the chemical yield (entry 5). We also examined various types of ligands on palladium as described in entries 6–14. Neither P(*n*-Bu)$_3$ nor P(OPh)$_3$ were suitable for the present reaction (entries 7 and 8). In sharp contrast, the bulky ligands such as PCy$_3$ and P(*o*-Tol)$_3$ led to good results to give **1a** in 44 and 52% yields, respectively (entries 9 and 10). It should be noted that the prolonged reaction time resulted in a slight increase of the yield in the case of P(*o*-Tol)$_3$ as a ligand (entry 11). P(*t*-Bu)$_3$ was also found to be effective, **1a** being given in 29% yield in 8 h though the reaction rate was somewhat lower than that in the case of PCy$_3$ and P(*o*-Tol)$_3$. Eventually, we found that the reaction in the presence of P(*t*-Bu)$_3$ for 24 h resulted in the exclusive formation of **1a** in 80% yield (entry 14).

With the optimized reaction conditions, we next investigated the annulation reaction of various types of alkynes with 2-iodophenol (Table 2).

As can be seen in entries 1–4, various fluoroalkylated alkynes could participate well in the annulation reaction.



1

Figure 1.

Keywords: Fluorine; Benzofurans.
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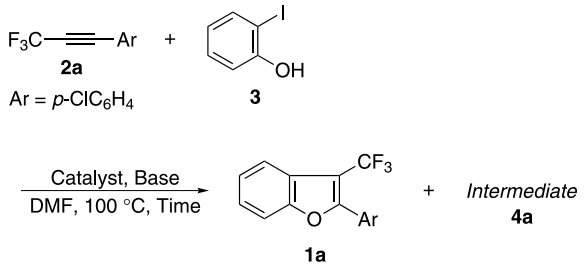
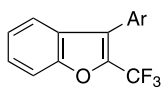
Table 1. Investigaton of the reaction conditions



Entry	Catalyst (20 mol%)	Base (equiv)	Time (h)	Yield[a] (%) of **1a**	Yield[a] (%) of **4a**
1	$Pd(PPh_3)_4$	Et_3N (1)	4	0	0
2	$Pd(PPh_3)_4$	KOAc (1)	4	5	10
3	$Pd(PPh_3)_4$	Na_2CO_3 (1)	4	19	24
4	$Pd(PPh_3)_4$	K_2CO_3 (1)	4	45	4
5	$Pd(PPh_3)_4$	K_2CO_3 (5)	4	52	0
6	$1/2[Pd_2(dba)_3\cdot CHCl_3]+4PPh_3$	K_2CO_3 (5)	4	1	80
7	$1/2[Pd_2(dba)_3\cdot CHCl_3]+4P(n\text{-}Bu)_3$	K_2CO_3 (5)	4	19	3
8	$1/2[Pd_2(dba)_3\cdot CHCl_3]+4P(OPh)_3$	K_2CO_3 (5)	4	6	43
9	$1/2[Pd_2(dba)3\cdot CHCl_3]+4PCy_3$	K_2CO_3 (5)	4	44	0
10	$1/2[Pd_2(dba)_3\cdot CHCl_3]+4P(o\text{-}Tol)_3$	K_2CO_3 (5)	4	52	18
11	$1/2[Pd_2(dba)_3\cdot CHCl_3]+4P(o\text{-}Tol)_3$	K_2CO_3 (5)	8	66	0
12	$1/2[Pd_2(dba)_3\cdot CHCl_3]+4P(t\text{-}Bu)_3$	K_2CO_3 (5)	4	10	83
13	$1/2[Pd_2(dba)_3\cdot CHCl_3]+4P(t\text{-}Bu)_3$	K_2CO_3 (5)	8	29	65
14	$1/2[Pd_2(dba)_3\cdot CHCl_3]+4P(t\text{-}Bu)_3$	K_2CO_3 (5)	24	80 (72)	0

[a] Determined by ^{19}F NMR. Value in parentheses is of isolated yield.

Thus, the alkynes bearing an electron-donating group (Me and MeO) or an electron-withdrawing group (CO_2Et) on the aromatic ring in **2** gave the corresponding benzofuran **1** in high yields. The reaction of the alkyne bearing a nitro group on an aromatic ring proceeded very sluggishly to give the desired compound **1** in very low yield (entry 5). Additionally, the use of the alkynes bearing an *ortho*-substituted aromatic ring or an alkyl side chain as R did not afford the benzofuran product at all (entries 6 and 8), whereas *meta*-substitution on an aromatic ring in **2** did not influence the reaction (entry 7). Changing a fluoroalkyl group from a CF_3 group to a CHF_2 group did not affect the efficiency of the reaction (entry 9). We also examined the reaction of **2a** with variously substituted 2-iodophenol derivatives as shown in entries 10–15. Introduction of various substituents (Cl, Me, Ph) into an aromatic ring at 4 position of **3** afforded various types of fluoroalkylated benzofurans in good to high yields (entries 10, 11, and 14). Additionally, the use of 3-iodo-2-naphthol instead of

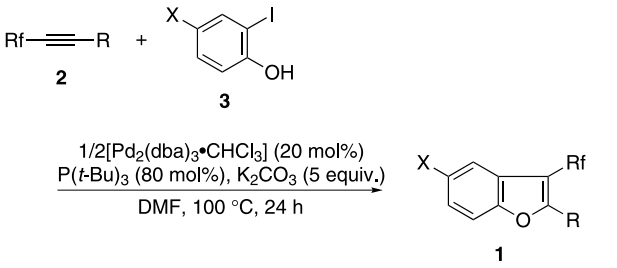


5a

Ar = *p*-ClC$_6$H$_4$

Figure 2.

Table 2. Annulation of fluoroalkylated alkynes with various 2-iodophenol derivatives



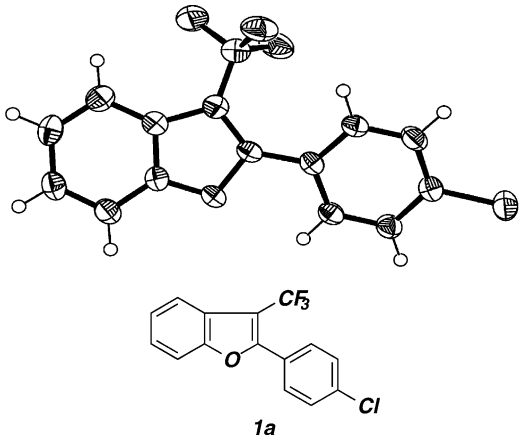
Entry	Rf	R	X	Product	Yield[a] (%) of **1**
1	CF_3	*p*-ClC_6H_4	H	**1a**	80 (72)
2	CF_3	*p*-MeC_6H_4	H	**1b**	74 (64)
3	CF_3	*p*-$MeOC_6H_4$	H	**1c**	84 (74)
4[b]	CF_3	*p*-$EtO_2CC_6H_4$	H	**1d**	75 (72)
5[c]	CF_3	*p*-$O_2NC_6H_4$	H		15
6[c]	CF_3	*o*-$ClCC_6H_4$	H		0
7[d]	CF_3	*m*-$ClCC_6H_4$	H	**1e**	87 (87)
8	CF_3	$C_6H_4(CH_2)_3$	H		0
9[c]	CHF_2	*p*-ClC_6H_4	H	**1f**	65 (52)
10	CF_3	*p*-ClC_6H_4	Cl	**1g**	78 (76)
11[d]	CF_3	*p*-ClC_6H_4	Me	**1h**	94 (94)
12	CF_3	*p*-ClC_6H_4	NO^2		6
13	CF_3	*p*-ClC_6H_4	CN		28
14	CF_3	*p*-ClC_6H_4	Ph	**1i**	75 (62)
15[d]	CF_3	*p*-ClC_6H_4	[e]	**1j**	60 (60)

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields.
[b] Stirred for 36 h.
[c] Stirred for 12 h.
[d] Stirred for 48 h.
[e] 3-Iodo-2-naphthol was employed instead of 2-iodophenol.

2-iodophenol did not influence the reaction, **1** being obtained in 60% yield. However, electron-withdrawing groups such as NO_2 and CN caused a significant decrease of the yield (entries 12 and 13). In all cases, any trace of 2-fluoroalkylated benzofuran derivatives was not detected at all.

3. Mechanistic study

The structure of the benzofuran **1a** was determined as 3-trifluoromethylated benzofuran, not 2-trifluoromethylated one, based on the X-ray crystallography of **1a**, as described in Figure 3. The stereochemical determination of the other



1a

Figure 3.

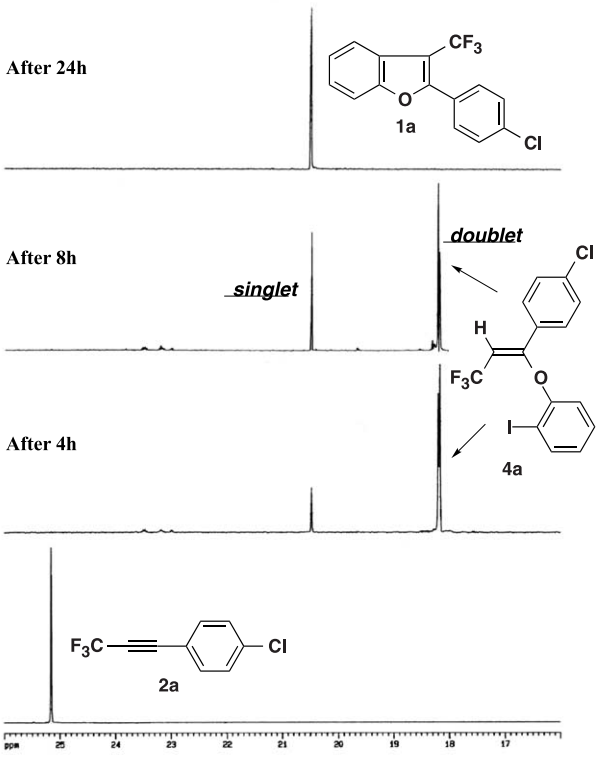
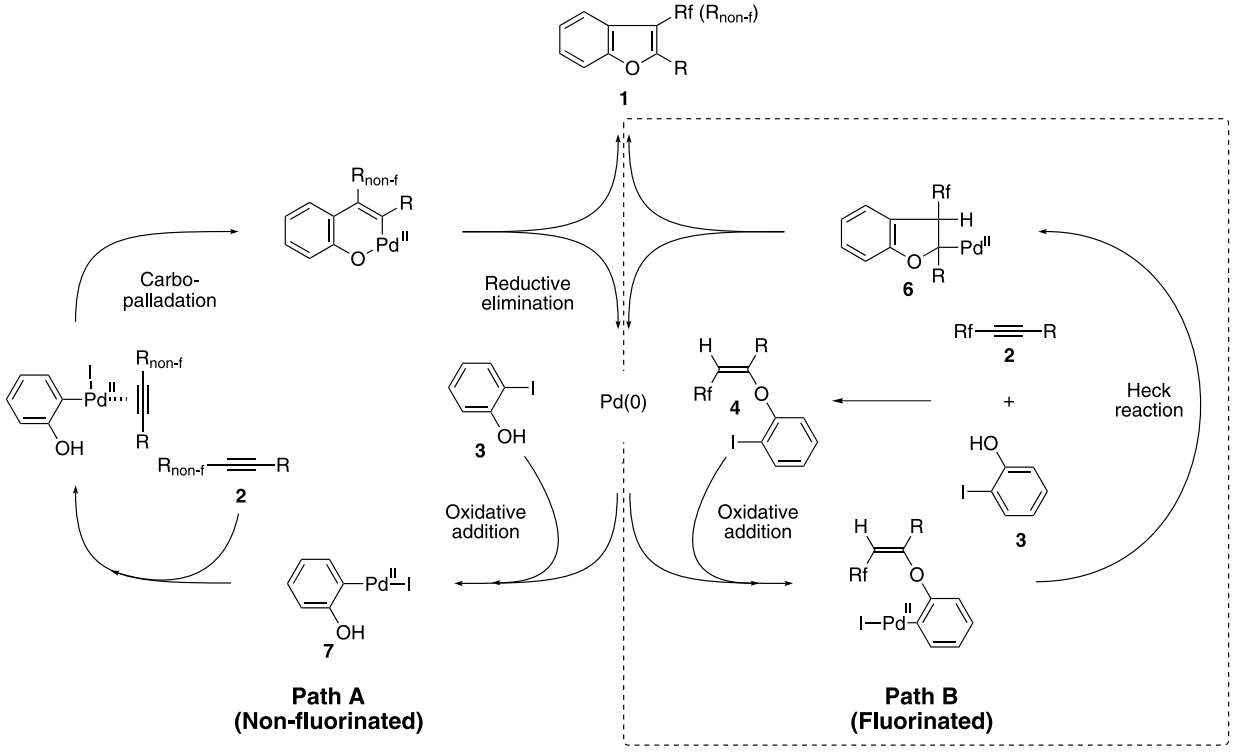


Figure 4. ^{19}F NMR analysis.

benzofurans **1** was made on the basis of the chemical shift of **1a** in ^{19}F NMR.

We also examined the reaction mechanism of the annulation by monitoring the reaction mixture using ^{19}F NMR (Fig. 4). Thus, **2a** was treated with 2.0 equiv of 2-iodophenol in the presence of palladium catalyst at 100 °C for 4 h or 8 h. ^{19}F NMR analyses indicated that the starting alkyne (^{19}F NMR δ 25.16 (s), referred C_6F_6) was completely consumed even after 4 h-stirring, and an intermediate was produced (^{19}F NMR δ 18.18 (d, $J=7.54$ Hz)) in 83% (after 4 h) or 65% yield (after 8 h), together with 10 or 29% of the desired product **1a** (^{19}F NMR δ 20.49 (s)). The resultant solution was allowed to be stirred at that temperature for additional 16 h. The peak for the intermediate in ^{19}F NMR disappeared completely and only the product peak was detected, strongly suggesting that the intermediate could be converted into the desired product **1a**. The intermediate was found to be relatively stable for silica gel. It could be isolated by a flash column chromatography and assigned as aryl vinyl ether derivative **4a** by ^{1}H and ^{13}C NMR analyses.[5] Accordingly, these results allow us to draw the reaction mechanism as described in Scheme 1.

In the initial step, Michael-type addition may proceed to form the aryl vinyl ether **4**, exclusively. The palladium(0) adds into **4** oxidatively, followed by intramolecular Heck reaction,[6] resulting in the formation of fluoroalkylated benzofuran **1** and the regeneration of Pd(0) (Path B). It is reported for the nonfluorinated substrates that the palladium complex **7** from the oxidative addition of Pd(0) into **3** undergoes the carbopalladation reaction, followed by oxygen displacement of iodide in the resulting palladium intermediate and the final reductive elimination, giving the final product **1** (Path A). Such a great difference in the reaction mechanism between the nonfluorinated and fluorinated alkynes may come from the difference of the electrophilicities of the alkynes.



Scheme 1.

4. Conclusion

In summary, we have disclosed a first highly regioselective annulation reaction of fluorine-containing alkynes with variously substituted 2-iodophenol derivatives. The reaction took place smoothly to give the corresponding 3-fluoroalkylated benzofurans as a single isomer in good to high yields. This reaction does not start from the oxidative addition of Pd(0) into 2-iodophenol derivatives, followed by carbopalladation, but starts from the addition of 2-iodophenol to the fluoroalkylated alkynes, followed by the intramolecular Heck reaction to afford 3-fluoroalkylated benzofurans **1**.

5. Experimental

5.1. General

^{1}H NMR spectra were measured with a Bruker DRX-500 (500.13 MHz) NMR spectrometer in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane (Me_4Si) as an internal reference. ^{13}C NMR spectra were recorded on a Bruker DRX-500 (125.77 MHz). A Bruker (282.4 MHz, FT) NMR spectrometer was used for determining ^{19}F NMR yield with internal C_6F_6. It was also used for determining regioselectivity and for taking ^{19}F NMR spectra in a $CDCl_3$ solution with internal $CFCl_3$. Infrared spectra (IR) were recorded on a Shimadzu FTIR-8200A (PC) spectrophotometer. Mass spectra (MS) were taken on a JEOL JMS-700.

5.2. Reagents

2-Iodophenol was commercially available from Wako chemicals Co. DMF was freshly distilled from calcium hydride (CaH_2). All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin layer chromatography (TLC) was done with Merck silica gel 60 F_{254} plates and column chromatography was carried out with Wako gel C-200.[1] The fluorine-containing alkynes **2** were readily prepared according to the literature.[3] The substituted *o*-iodophenols were synthesized from readily available phenols according to the method reported by Edgar and Falling.[7]

5.3. General procedure for the synthesis of benzofuran derivatives

$Pd_2(dba)_3\cdot CHCl_3$ (0.04 g, 0.048 mmol), P(*t*-butyl)$_3$ (10 wt% in hexane) (0.8 g, 0.395 mmol), K_2CO_3 (0.3 g, 2.44 mmol), the 2-iodophenol (0.214 g, 0.976 mmol), the alkyne (0.488 mmol), DMF (8.0 mL) were added to a flask equipped with a stirring bar. After being heated for 24 h at 100 °C, the mixture was quenched with $NaHCO_3$ aq. and extracted with Et_2O three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel using hexane to afford the corresponding benzofuran **1**.

5.3.1. 2-(4-Chlorophenyl)-3-(trifluoromethyl)benzofuran (1a). Yield 72%; a white solid; ^{1}H NMR ($CDCl_3$) δ 7.35 (1H, t, J=7.3 Hz), 7.40 (1H, t, J=7.4 Hz), 7.47 (2H, d, J=8.5 Hz), 7.55 (1H, d, J=8.2 Hz), 7.75 (3H, d, J=8.5 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 107.88 (q, J=37.35 Hz), 111.49, 120.76, 123.47 (q, J=267.76 Hz), 124.22, 125.44, 125.83, 127.15, 128.93, 129.82 (q, J=1.76 Hz), 136.54, 153.60, 154.48 (q, J=4.27 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −55.83 (3F, s) ppm; IR (KBr) 3150, 1602, 1492, 1390, 1236 cm^{-1}; HRMS Calcd for $C_{15}H_8ClF_3O$ 296.0216, Found 296.0211; Anal. Calcd for $C_{15}H_8ClF_3O$: C, 60.73; H, 2.72. Found: C, 60.40; H, 2.72; mp 79–81 °C.

5.3.2. 2-(Toluenyl)-3-(trifluoromethyl)benzofuran (1b). Yield 64%; a white solid; ^{1}H NMR ($CDCl_3$) δ 2.42 (3H, s), 7.30 (2H, d, J=8.05 Hz), 7.32–7.38 (2H, m), 7.53 (1H, d, J=7.95 Hz), 7.71 (2H, d, J=8.05 Hz), 7.74 (1H, d, J=7.45 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 21.47, 106.92 (q, J=37.34 Hz), 111.39, 120.57 (q, J=1.63 Hz), 123.69 (q, J=268.09 Hz), 123.96, 125.34, 125.70, 125.90, 128.49 (q, J=1.63 Hz), 129.30, 140.63, 153.49, 156.08 (q, J=4.5 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −55.75 (3F, s) ppm; IR (KBr) 2920, 1600, 1394, 1298 cm^{-1}; HRMS Calcd for $C_{16}H_{11}F_3O$ 276.0762, Found 276.0761; Anal. Calcd for $C_{16}H_{11}F_3O$: C, 69.56; H, 4.01. Found: C, 69.58; H, 4.17; mp 72–74 °C.

5.3.3. 2-(4-Methoxyphenyl)-3-(trifluoromethyl)benzofuran (1c). Yield 74%; a white solid; ^{1}H NMR ($CDCl_3$) δ 3.86 (3H, s), 7.00 (2H, d, J=8.8 Hz), 7.30–7.36 (2H, m), 7.52 (1H, d, J=7.85 Hz), 7.73 (1H, d, J=8.0 Hz), 7.76 (2H, d, J=8.75 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 55.34, 106.18 (q, J=37.34 Hz), 111.29, 114.05, 120.45, 121.14, 123.79 (q, J=267.97 Hz), 123.91, 125.15, 125.80, 130.09 (q, J=1.6 Hz), 153.35, 155.93 (q, J=4.65 Hz), 161.17 ppm; ^{19}F NMR ($CDCl_3$) δ−55.71 (3F, s) ppm; IR (KBr) 2912, 2841, 1614, 1394 cm^{-1}; HRMS Calcd for $C_{16}H_{11}F_3O_2$ 292.0711, Found 292.0712; Anal. Calcd for $C_{16}H_{11}F_3O_2$: C, 65,76; H, 3.79. Found: C, 65.02; H, 3.82; mp 41–43 °C.

5.3.4. 2-(4-Ethoxycarbonylphenyl)-3-(trifluoromethyl)-benzofuran (1d). Yield 72%; a white solid; ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t, J=7.15 Hz), 4.42 (2H, q, J=7.15 Hz), 7.36 (1H, t, J=8.05 Hz), 7.42 (1H, t, J=7.3 Hz), 7.57 (1H, d, J=8.2 Hz), 7.77 (1H, d, J=7.8 Hz), 7.90 (2H, d, J=8.4 Hz), 8.17 (2H, d, J=8.5 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 14.29, 61.30, 108.75 (q, J=37.47 Hz), 111.58, 120.90 (q, J=1.5 Hz), 123.39 (q, J=268.47 Hz), 124.30, 125.39, 126.09, 128.44 (q, J=1.7 Hz), 129.68, 131.80, 132.61, 153.78, 154.35 (q, J=4.6 Hz), 165.86 ppm; ^{19}F NMR ($CDCl_3$) δ −55.74 (3F, s) ppm; IR (KBr) 2987, 1724, 1612, 1411 cm^{-1}; HRMS Calcd for $C_{18}H_{13}F_3O_3$ 334.0817, Found 334.0817; Anal. Calcd for $C_{18}H_{13}F_3O_3$: C, 64.67; H, 3.92. Found: C, 63.95; H, 3.78; mp 92–94 °C.

5.3.5. 2-(3-Chlorophenyl)-3-(trifluoromethyl)benzofuran (1e). Yield 87%; a yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.36 (1H, t, J=7.9 Hz), 7.39–7.47 (3H, m), 7.55 (1H, d, J=8.2 Hz), 7.69 (1H, d, J=7.4 Hz), 7.76 (1H, d, J=8.0 Hz) 7.81 (1H, s) ppm; ^{13}C NMR ($CDCl_3$) δ 108.34 (q, J=37.22 Hz), 111.54, 120.84 (q, J=1.5 Hz), 123.37 (q, J=268.22 Hz), 124.27, 125.32, 125.99, 126.74 (q, J=1.7 Hz), 128.52, 129.85, 130.32, 130.34, 134.65, 153.65, 153.98 (q, J=4.6 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −55.79 (3F, s) ppm; IR (neat) 3047, 1778, 1614, 1587, 1452 cm^{-1}; HRMS Calcd for $C_{15}H_8ClF_3O$ 296.0266, Found 296.0211; Anal. Calcd for $C_{15}H_8ClF_3O$: C, 60.73; H, 2.72. Found: C, 60.38; H, 2.70.

5.3.6. 2-(4-Chlorophenyl)-3-(difluoromethyl)benzofuran (1f). Yield 52%; a white solid; ^{1}H NMR ($CDCl_3$) δ 6.93 (1H, t, J=54.41 Hz), 7.33 (1H, t, J=8.0 Hz), 7.38 (1H, d, J=7.5 Hz), 7.50 (2H, d, J=8.5 Hz), 7.54 (1H, d, J=8.0 Hz) 7.67 (2H, d, J=8.5 Hz), 7.85 (1H, d, J=7.5 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 111.06 (t, J=27.28 Hz), 111.39, 112.11 (t, J=232.26 Hz), 121.24, 123.86, 125.62, 125.71, 127.39, 129.09, 129.27, 130.53 (t, J=5.5 Hz), 136.26, 154.02 ppm; ^{19}F NMR ($CDCl_3$) δ −109.17 (2F, d, J=53.58 Hz)) ppm; IR (KBr) 2925, 1612, 1452, 1213 cm^{-1}; HRMS Calcd for $C_{15}H_9ClF_2O$ 278.0310, Found 278.0319; Anal. Calcd for $C_{15}H_9ClF_2O$: C, 64.65; H, 3.26. Found: C, 64.09; H, 3.38; mp 82–84 °C.

5.3.7. 2-(4-Chlorophenyl)-3-(trifluoromethyl)-5-chlorobenzofuran (1g). Yield 76%; a white solid; ^{1}H NMR ($CDCl_3$) δ 7.35 (1H, dd, J=9.0, 2.0 Hz), 7.45–7.48 (3H, m), 7.71 (1H, s), 7.73 (2H, d, J=8.5 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 107.49 (q, J=37.72 Hz), 112.52, 120.39 (q, J=2.1 Hz), 123.08 (q, J=268.47 Hz), 126.18, 126.60, 126.70 (q, J=1.3 Hz), 129.54, 129.79 (q, J=1.7 Hz), 130.04, 136.98, 151.92, 155.90 (q, J=4.5 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −55.88 (3F, s) ppm; IR (KBr) 3105, 2923, 1868, 1737, 1583, 1452 cm^{-1}; HRMS Calcd for $C_{15}H_7Cl_2F_3O$ 329.9826, Found 329.9832; Anal. Calcd for $C_{15}H_7Cl_2F_3O$: C, 54.41; H, 2.13. Found: C, 54.24; H, 2.25; mp 94–96 °C.

5.3.8. 2-(4-Chlorophenyl)-3-(trifluoromethyl)-5-methylbenzofuran (1h). Yield 94%; a white solid; ^{1}H NMR ($CDCl_3$) δ 2.48 (3H, s), 7.20 (1H, d, J=8.5 Hz), 7.42 (1H, d, J=8.5 Hz), 7.47 (2H, d, J=9.0 Hz), 7.53 (1H, s), 7.74 (2H, d, J=8.5 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 21.44, 107.44 (q, J=37.0 Hz), 120.41 (q, J=1.25 Hz), 123.51 (q, J=268.35 Hz), 125.50, 127.13, 127.32, 128.88, 129.78 (q, J=2.0 Hz), 133.91, 136.39, 152.09, 154.48 (q, J=4.7 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −55.81 (3F, s) ppm; IR (KBr) 2923, 2380, 1492, 1384 cm^{-1}; HRMS Calcd for $C_{16}H_{10}ClF_3O$ 310.0372, Found 310.0368; mp 96–98 °C.

5.3.9. 2-(4-Chlorophenyl)-3-(trifluoromethyl)-5-phenylbenzofuran (1i). Yield 62%; a white solid; ^{1}H NMR ($CDCl_3$) δ 7.37 (1H, t, J=7.2 Hz), 7.45–7.49 (4H, m), 7.58–7.63 (4H, m), 7.76 (2H, d, J=8.5 Hz), 7.92 (1H, s) ppm; ^{13}C NMR ($CDCl_3$) δ 108.01 (q, J=37.34 Hz), 111.62, 119.41 (q, J=1.5 Hz), 123.45 (q, J=267.84 Hz), 125.58, 125.97, 127.09, 127.34, 127.52, 128.86, 128.96, 129.83 (q, J=1.6 Hz), 136.63, 138.07, 140.97, 153.19, 155.10 (q, J=4.5 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −55.78 (3F, s) ppm; IR (KBr) 2923, 1614, 1450, 1386 cm^{-1}; HRMS Calcd for $C_{21}H_{12}ClF_3O$ 372.0529, Found 372.0532; Anal. Calcd for $C_{21}H_{12}ClF_3O$: C, 67.66; H, 3.24. Found: C, 67.34; H, 3.30; mp 181–183 °C.

5.3.10. Benzo-2-(4-chlorophenyl)-3-(trifluoromethyl)-benzofuran (1j). Yield 60%; a white solid; ^{1}H NMR ($CDCl_3$) δ 7.48 (2H, d, J=8.5 Hz), 7.55 (1H, t, J=8.0 Hz), 7.65–7.67 (4H, m), 7.85 (1H, d, J=9.0 Hz), 7.98 (1H, d, J=8.0 Hz), 8.42 (1H, d, J=8.5 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 108.95 (q, J=36.84 Hz), 119.44, 123.38 (q, J=267.72 Hz), 124.31 (q, J=4.7 Hz), 125.22, 126.70, 127.30, 127.95, 128.06, 128.61, 129.27, 130.96 (q, J=1.4 Hz), 131.20, 136.37, 152.49, 154.54 (q, J=4.5 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −54.99 (3F, s) ppm; IR (KBr) 3053, 2378, 1488, 1396 cm^{-1}; HRMS Calcd for $C_{19}H_{10}ClF_3O$ 346.0372, Found 346.0369; Anal. Calcd for $C_{19}H_{10}ClF_3O$: C, 65.82; H, 2.91. Found: C, 65.39; H, 2.77; mp 110–112 °C.

5.3.11. 1-(4-Chlorophenyl)-1-(2-iodophenoxy)-3,3,3-trifluoro-propene (4a). Yield 83% (Determined by ^{19}F NMR.); a brown oil; ^{1}H NMR ($CDCl_3$) δ 5.87 (1H, q, J=7.5 Hz), 6.60 (1H, d, J=7.5 Hz), 6.74 (1H, t, J=8.0 Hz), 7.11 (1H, t, J=8.0 Hz), 7.31 (2H, d, J=8.5 Hz), 7.42 (2H, d, J=8.5 Hz), 7.78 (1H, d, J=8.0 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 86.05, 105.96 (q, J=35.33 Hz), 116.12, 122.48 (q, J=270.11 Hz), 124.79, 128.39, 129.28, 129.40, 130.52, 136.90, 139.81, 154.83, 157.62 (q, J=5.6 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −58.36 (d, J=6.4 Hz) ppm; IR (neat) 2925 (w) 1668 (s), 1467 (s), 1263 (s), 1012 (m), 752 (s) cm^{-1}; HRMS Calcd for $C_{15}H_9ClF_3IO$ 424.5837, found 423.9343.

5.3.12. X-ray structural analysis of 1a. A colorless prismatic crystal of **1a** ($C_{15}H_8ClF_3O$) having approximate dimensions of 0.10×0.10×0.44 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Cu Kα radiation and a rotating anode generator. The number of measured reflections was 6716 (R_{int}=0.050), and the lattice parameters of C-centered monochlinic crystal (space group: C2/c(#14)) were as follows:

a=25.442(3) Å, b=4.8725(7) Å, c=20.897(3) Å, β=108.297(9)°, V=2459.6(6) Å

All calculation was performed by using the 'teXsan' crystallographic software package (Molecular Structure Corporation). The structure was solved by direct methods (SIR92) and expanded using Fourier techniques (DIRDIF94). After converged, final cycle of full-matrix least-squares refinement gave unweighted and weighted agreement factor (R and Rw) of 0.036 and 0.111, respectively.

References and notes

1. For the reviews, see: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198.
2. For the precedent work for the syntehsis of fluoroalkylated benzofurans, see: (a) Kiang, Z. X.; Qing, F.-L. *J. Fluorine Chem.* **2003**, *123*, 57–60. (b) Kaltenbronn, J. S.; Quin, J., III; Reisdorph, B. R.; Klutchko, S.; Reynolds, E. E.; Welch, K. M.; Flynn, M. A.; Doherty, A. M. *Eur. J. Med. Chem.* **1997**, *32*, 425–431. (c) Judd, D. B.; Dowle, M. D.; Middlemiss, D.; Scopes, D. I. C.; Ross, B. C.; Jack, T. I.; Pass, M.; Tranquillini, E.; Hobson, J. E.; Panchal, T. A.; Stuart, P. G.; Paton, J. M. S.; Hubbard, T.; Hilditch, A.; Drew, G. M.; Robertson, M. J.; Clark, K. L.; Travers, A.; Hunt, A. A. E.; Polley, J.; Eddershaw, P. J.; Bayliss, M. K.; Manchee, G. R.; Donnelly, M. D.; Walker, D. G.; Richard, S. A. *J. Med. Chem.* **1994**, *37*, 3108–3120. (d) Sawada, H.; Nakayama, M. *J. Fluroine Chem.* **1990**, *46*, 423–431. (e) Galllos, J. K.; Lianis, P. S.; Nicolaides, D. N. *J. Heterocyclic Chem.* **1989**, *26*, 1415–1420. (f) Kuckländer, U.;

Herweg-Wahl, U.; Poll, W.; Rickerich, L. *Chem. Ber.* **1988**, *121*, 1841–1845. (g) Onys'ko, P. P.; Proklina, N. V.; Prokopenko, V. P.; Gololobov, Y. G. *Zh. Org. Khim.* **1987**, *23*, 549–552. (h) Kobayashi, Y.; Kumadaki, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 661–664.

3. Konno, T.; Chae, J.; Kanda, M.; Nagai, G.; Tamura, K.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2003**, *59*, 7571–7580.
4. For the annulation reaction of the nonfluorinated substrates, see: Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271.
5. The similar addition reaction of phenol to fluorine-containing alkyne has been reported: Bumgardner, C. L.; Bunch, J. E.; Whangbo, M.-H. *Tetrahedron Lett.* **1986**, *27*, 1883–1886.
6. For reviews on the Heck reaction, see: (a) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7. (b) Meijere, A.; Meyer, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2411.
7. Edgar, K. J.; Falling, S. N. J. *Org. Chem.* **1990**, *55*, 5287–5291.

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A concise synthesis of diethyl 1-(*tert*-butoxycarbonylamino)-1-alkenylphosphonates

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Abstract—An efficient completely diastereoselective synthesis of (*Z*)- and (*E*)- *N*-Boc 1-aminoalkenylphosphonic acid diethyl esters from easily available 5-substituted (2-thioxo-oxazolidin-4-yl)phosphonic acid diethyl esters has been developed.

1. Introduction

For many years phosphonate analogues of α-amino acids have been a source of inspiration in bioorganic and medicinal chemistry due to their unique activities as peptidomimetics such as transition state-analogue inhibitors and haptens of catalytic antibodies,[1] to name just a few.

On the other hand, α-phosphonoenamides, which can be regarded as the analogues of α,β-dehydroamino acids are valuable synthons for the catalytic asymmetric hydrogenation[2] leading to optically active aminophosphonates.[3,4] Therefore, there is a need to develop efficient and stereoselective methods of syntheses of such building blocks.

Although a variety of approaches to α-aminophosphonates have been described,[1,5] the number of known β-alkyl/aryl substituted α-phosphonoenamides is limited, and only a few routes to such α-amino-α-alkenylphosphonates have been reported. Approaches towards these synthetic goals include; the reaction of α-oximinophosphonates with acetic anhydride and iron powder in acetic acid,[6] condensation of α-formylamino bisphosphonates with carbonyl compounds,[7] reaction of α-isocyanoalkylphosphonates with aldehydes and ketones followed by the elimination reaction of the oxazolines thus formed on treatment with potassium *tert*-butoxide,[8] chlorination of 2-benzoylamino-3-arylacrylic acids followed by the Arbuzov type reaction with trialkyl phosphites and subsequent in situ decarboxylation.[9] Unfortunately, all of these transformations[10] suffer from low or no stereoselectivity, except the last one for which complete *E*-diastereoselectivity was observed.[9] However, this methodology is limited to the aromatic derivatives only.

Herein we report[11] our investigations within this area, utilizing appropriately substituted oxazolidine-2-thiones, that under the action of potassium *tert*-butoxide undergo the transformation to a range of α-phosphonoenamides.

2. Results and discussion

Recently, we described an efficient, three-step transformation of easily available diethyl isothiocyanomethylphosphonate[12] **1** into *N*-Boc 1-amino-2-hydroxyalkylphosphonic acid diethyl esters.[13] The key intermediates of this transformation are 5-substituted (2-thioxo-oxazolidin-4-yl)phosphonic acid diethyl esters **2/3**, which were formed in diastereoselective manner from metallated isothiocyanate **1** and appropriate aldehydes. It should be emphasized here that these diastereomeric oxazolidine-2-thiones **2/3** can be easily separated by flash chromatography or even crystallization into the single *cis*- and *trans*- isomers **2** and **3**.[13]

We present here a new methodology for the synthesis of α-phosphonoenamides.[11] For this purpose we make use of diethyl 5-substituted (2-thioxo-oxazolidin-4-yl)phosphonates[13] **2/3**, mentioned above, as starting material. Our initial studies concentrated on the optimization of the conditions of elimination. Diethyl 5-phenyl (2-thioxo-oxazolidin-4-yl) phosphonates **2a/3a** were chosen as the model compounds. Thus, according to Scheme 1, oxazolidine-2-thiones **2a/3a** were converted into *N*-Boc derivatives **4a/5a**, following the literature protocol,[14] and were subject, without isolation, to the action of base. The results are presented in Table 1.

No progress of reaction was observed when *N*-methylmorpholine or DBU was used as a base. Positive results were

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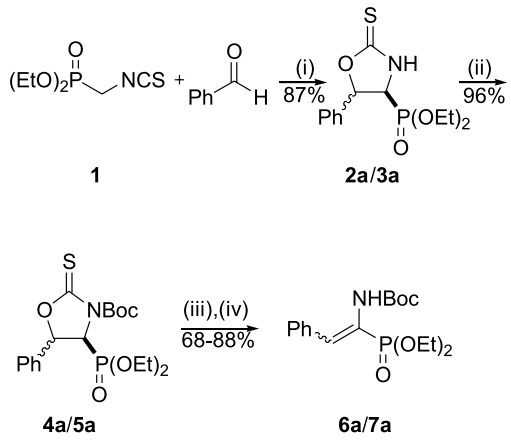


Scheme 1. Reagents and conditions: (i) NaH or *t*-BuOK, THF, see Ref. 13 for details; (ii) Boc_2O, DMAP, see Ref. 13 for details; (iii) Base, THF, −78 °C or rt, 0.5–24 h; (iv) $KHSO_4$ aq, −78 °C or rt.

unsaturated intermediates formed during the elimination can be responsible for these results.[†] Similar isomerization was also observed by Hoppe and Follmann[15] in the synthesis of α,β-dehydroamino acids from appropriate oxazolidine-2-thiones. When sodium hydride was substituted for potassium *tert*-butoxide, a catalytic amount of crown ether (15-crown-5, 10 mol%) was required for the elimination to occur. However, isomerization also took place under those conditions (Table 1, entry 4).

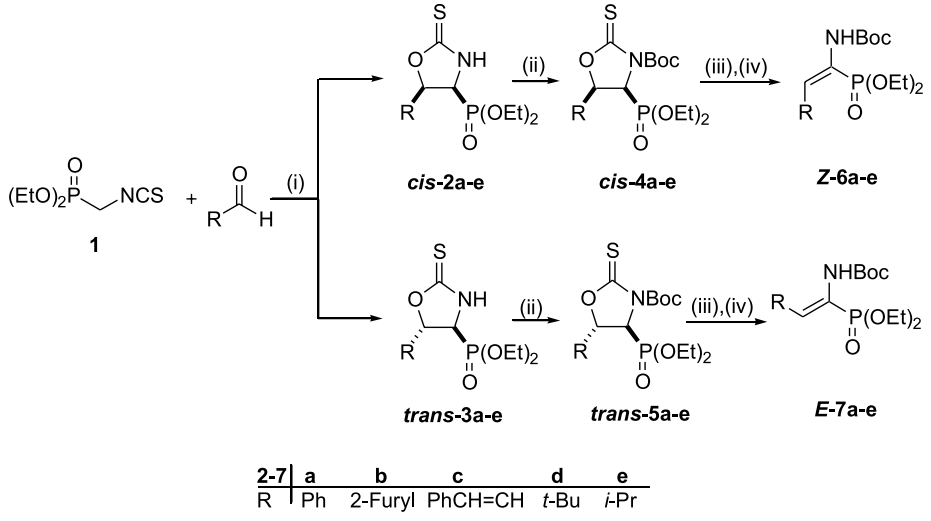
On the other hand, the data given in Table 1 (entry 5) clearly indicate that performing the reaction of the oxazolidine-2-thiones **4a/5a** with 2 equiv of potassium *tert*-butoxide, at −78 °C for half an hour gave the desired **6a/7a** with high yield and in stereospecific manner.

All of the other eliminations were executed in compliance with this optimized protocol. Thus, according to Scheme 2,

Table 1. Diethyl (1-*tert*-butoxycarbonylamino-2-phenyl-vinyl)phosphonates **6a/7a**

Entry	Compounds	R	Substrate **2a/3a** (*cis*:*trans*)	Reaction conditions time (h), temperature (°C)	Base[a]	Product **6a/7a** (*Z*:*E*)	Yield (%)
1	**6a/7a**	Ph	44:56	1, rt	*t*-BuOK (2 equiv)[b]	54:46	70
2			44:56	24, rt	*t*-BuOK (2 equiv)	37:63	68
3			100:0	24, rt	*t*-BuOK (2 equiv)	87:13	80
4			75:25	24, rt	NaH, 15-C-5[c] (2 equiv)	84:16	75
5			44:56	0.5, −78	*t*-BuOK (2 equiv)	44:56	77

[a] Only oxazolidine-2-thione **4a/5a** was regenerated when NMM or DBU were used as bases.
[b] When less than 2 equiv of potassium *tert*-butoxide was applied a significant amount of **4a/5a** was present in the reaction mixture.
[c] 15-Crown-5 (1,4,7,10,13-pentaoxacyclopentadecane).



Scheme 2. Reagents and conditions: (i) for details, see Ref. 13; (ii) Ref. 13: Boc_2O (1.15 equiv), DMAP (0.2 equiv), CH_2Cl_2, rt, 2 h; (iii) *t*-BuOK (2 equiv), THF, −78 °C, 0.5 h; (iv) $KHSO_4$ aq, −78 °C to rt.

obtained when strong base, such as potassium *tert*-butoxide was applied for elimination. At first the elimination was performed at room temperature (Table 1, entries 1, 2 and 3 respectively) using 2 equiv of potassium *tert*-butoxide. However, under those conditions the changes of the ratios of the products **6a/7a** in relation to the starting oxazolidine-2-thiones **2a/3a** were observed. The reversible Michael's addition of nucleophiles present in the reaction mixture, such as *t*-butoxide and/or *O*-*tert*-butyl thiocarbonate, to

[†] Unfortunately, further studies on equilibration cannot be continued because the conditions required for this process to occur also make the reagents conducive towards monodealkylation, giving a considerable amount of *O*-ethyl 5-phenyl (2-thioxo-oxazolidin-4-yl)phosphonic acid (17%, after 3 days at rt).

Table 2. Diethyl 1-(*tert*-butoxycarbonylamino)-1-alkenylphosphonates **6/7** prepared

Entry	Compounds **6/7**	R	Substrate **2/3** *cis*:*trans*[a]	Product **6/7** *Z*:*E*[a]	Yield[b] (%)
1	**6a**	Ph	100:0	100:0[c]	88
2	**6a/7a**	Ph	34:66	33:67	77[d]
3	**7b**	2-Furyl	0:100	0:100[c]	69
4	**6b/7b**	2-Furyl	89:11	90:10	70[d]
5	**6c/7c**	PhCH=CH	64:36	64:36	77[d]
6	**7d**	*t*-Bu[e]	0:100	0:100[c]	94
7	**6e/7e**	*i*-Pr	59:41	60:40	71[d]
8	**6e**	*i*-Pr	100:0	100:0[c]	94

[a] Diastereomer ratios measured by ^{31}P NMR.
[b] Yields of isolated products **6/7** based on oxazolidine-2-thiones **2/3**.
[c] Only one diastereomer could be observed in the ^{31}P and ^{1}H NMR spectrum of the crude reaction mixture.
[d] Yields of separated single *Z*-**6** or *E*-**7** diastereomers are given in Section 4.
[e] When the oxo analog, diethyl *N*-Boc *trans*-(2-oxo-5-*tert*-butyloxazolidin-4-yl)phosphonate was treated with *t*-BuOK (2 equiv) at rt for 2 h the appropriate enamide **7d**, contaminated with unidentified organophosphorus compounds, was formed in 70% yield, as estimated by ^{1}H and ^{31}P NMR.

a range of representative diethyl 5-substituted (2-thioxo-oxazolidin-4-yl)phosphonates **2/3** derived from parent aldehydes, after conversion into *N*-Boc **4/5**, underwent elimination under the action of 2 equiv of potassium *t*-butoxide at −78 °C. Elimination was completed within half an hour and gave the desired diethyl 1-(*tert*-butoxycarbonylamino)-1-alkenylphosphonates **6/7** with high isolated yields (for details, see Table 2). Finally, above-mentioned transformations occurred with complete diastereoselectivity. Thus, *cis*-oxazolidine-2-thiones **2** afforded *Z*-enamides **6** whereas the diastereomeric *E*-**7** were formed from *trans*-**3**. When the reaction was carried out on the mixture of *cis*- and *trans*-oxazolidine-2-thiones **2/3**, resulting α-phosphono-enamides **6/7** could be easily separated by flash chromatography into single *Z*-**6** and *E*-**7** diastereomers (Table 2, entries 2, 4, 5 and 7). The above-mentioned conversion was conducted without isolation of the intermediate *N*-Boc derivatives **4/5**.

The assignment of the stereochemistry of the double bond in α-phosphonenamides **6** and **7** was based on the values of vicinal coupling constants carbon–phosphorus atom ($^{3}J_{CP}$) and vinyl proton–phosphorus atom ($^{3}J_{HP}$), respectively. The ^{31}P NMR chemical shifts and selected diagnostic heteronuclear couplings constants of the *N*-Boc 1-aminoalkenylphosphonates **6** and **7** are summarized in Table 3.

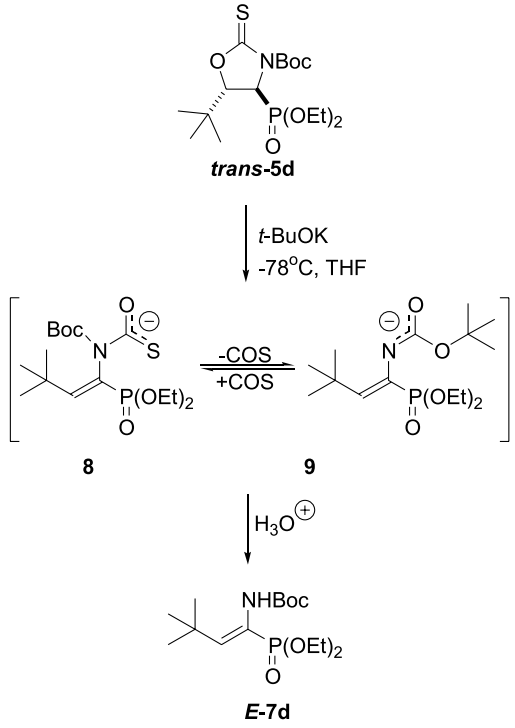
Table 3. ^{31}P NMR chemical shifts (δ) and selected heteronuclear vicinal coupling constants (J) of α-phosphonoenamides **6** and **7**

Entry	Compounds **6/7**	R	^{31}P NMR, δ (ppm)	^{13}C NMR $^{3}J_{CP}$ (Hz)	^{1}H NMR $^{3}J_{HP}$ (Hz)
1	*Z*-**6a**	Ph	13.45	5.84	41.20
2	*E*-**7a**	Ph	15.00	19.00	16.15
3	*Z*-**6b**	2-Furyl	13.20	6.95	39.20
4	*E*-**7b**	2-Furyl	14.76	21.95	15.20
5	*Z*-**6c**	PhCH=CH	14.17	6.92	40.00
6	*E*-**7c**	PhCH=CH	14.89	17.86	—[a]
7	*E*-**7d**	*t*-Bu	15.71	15.65	16.75
8	*Z*-**6e**	*i*-Pr	15.17	4.80	42.50
9	*E*-**7e**	*i*-Pr	14.96	13.90	14.75

[a] Overlapped with other signals.

Thus, the values of $^{3}J_{CP}$ for diethyl (*Z*)-1-(*tert*-butoxycarbonylamino)-1-alkenylphosphonates **6** are smaller (J= 5–7 Hz) than the ones for *E*-diastereomers **7** (J=14–22 Hz). The reverse relation is observed when it comes to $^{3}J_{HP}$. For *Z*-isomers **7** vicinal coupling constants $^{3}J_{HP}$ are around 40 Hz, whereas the *E*-isomers **6** is characterized by the value in the range of 14–17 Hz. These results stand in agreement with literature data.[3b,7,8b,16]

Complete stereoselectivity of the conversion of diethyl 5-substituted (2-thioxo-oxazolidin-4-yl)phosphonates **2/3** into diethyl 1-(*tert*-butoxycarbonylamino)-1-alkenylphosphonates **6/7**, can be explained by a concerted E2 elimination.[17] Such an elimination mechanism was proposed previously by Hoppe and Follmann[15] in the base induced ring cleavage of 3-alkoxycarbonyl-2-thioxo-4-oxazolidinecarboxylates to α-(alkoxycarbonylamino)acrylic acid esters. The highly probable pathway of this olefin-forming elimination, shown on the model analog **5d**, is presented in Scheme 3.



Scheme 3.

Stereochemistry of the elimination suggest that *N*-Boc oxazolidine-2-thione **5d** underwent concerted elimination under the action of potassium *tert*-butoxide to give unsaturated intermediate **8**, which could be in equilibrium with **9**, and carbon oxysulfide.‡ Next, the intermediates **8** and **9** underwent the conversion into the final product *E*-**7d** upon protonation. ^{31}P and ^{1}H NMR spectroscopy and trapping experiments were applied to account for the formation of some intermediate products. All of the ^{1}H

‡ At this stage of investigations we have no experimental proof confirming such equilibrium. However, this assumption stands in agreement with literature data where similar equilibrium was postulated in the base induced ring cleavage of 3-alkoxycarbonyl-2-thioxo-4-oxazolidinecarboxylates.[15]

and ^{31}P NMR measurements were taken in THF-d_8 within the temperature interval from −70 °C to room temperature.

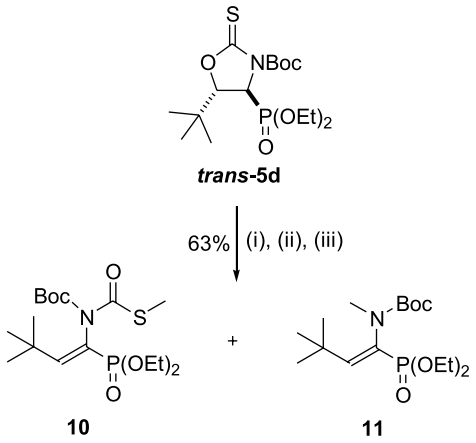
Thus, the ^{31}P NMR (proton decoupled) spectrum taken at −70 °C, after mixing the starting **5d** with potassium *t*-butoxide, indicated quantitative transformation of **5d** (δ_p=18.95 ppm at −60 °C) into at least three new major species, with chemical shifts δ_p=22.42, 22.48 and 22.90 ppm respectively. On raising the temperature to −50 °C, a new broad signal at δ_p=21.20 ppm appeared. When the temperature of the sample was gradually raised to −30 °C, the signal at δ_p=21.12 ppm became the major one. At room temperature major signal appeared at δ_p=20.83 ppm.[§]

On the basis of these data, we can conclude that at these temperatures the metallated **7d**[¶] is present in the reaction mixture. Quenching of the reaction mixture with water resulted in the formation of the final **7d** with the chemical shift at δ_p=16.21 ppm.

Another noteworthy observation was made analyzing ^1H NMR spectra. ^1H NMR spectrum measured at −70 °C showed, in the vinyl region, broad unsymmetrical signal at 5.32–5.49 ppm. At −50 °C this signal split up into broad doublet at δ_H=5.33 ppm with distinct vicinal proton–phosphorus atom coupling constant ($^3J_{HP}$) around 15.5 Hz, and partially overlapped unsymmetrical multiplets around 5.36–5.45 ppm, respectively. Upon raising the temperature to −30 °C, the spectrum remained unchanged. In turn, in the ^1H NMR spectrum taken at room temperature only the doublet of the vinyl proton at δ_H=5.34 ppm ($^3J_{HP}$=17.50 Hz) was observed.[‖]

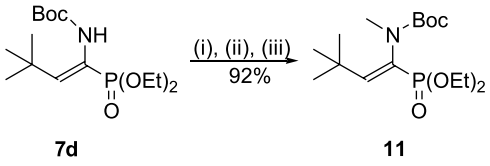
Concluding, these spectral data provide evidence for the presence of unsaturated intermediates formed in the first step of this olefin-forming elimination and were consistent with the reaction pathway presented in Scheme 3. The additional proof of our suggestions was provided by trapping experiment with iodomethane.

Thus, according to Scheme 4, *N*-Boc oxazolidine-2-thione **5d** was subject to the standard elimination under the conditions described earlier. Next, the reaction mixture was quenched at −78 °C with iodomethane and the temperature of the sample was gradually raised to room temperature. As a result of the methylation, a mixture of methyl thiocarbamate **10** and the *N*-methyl *N*-Boc 1-aminoalkenylphosphonate **11** were formed in a 41:59 ratio. Purification allowed isolation of the separable products **10** and **11** in 33 and 30% yield, respectively (63% overall). Their structures were unequivocally confirmed by ^{31}P, ^{13}C, ^1H NMR, mass spectrometry and elemental analyses. The enamide **11** consists of two rotamers in ratio 68:32 (δ_p=16.07 and 15.60 ppm, respectively) as estimated by ^{31}P NMR. Studies on evaluation of the rotational barrier are in progress and will be published in due course.



Scheme 4. Reagent and conditions: (i) *t*-BuOK (2 equiv), THF, −78 °C, 0.5 h; (ii) MeI (8 equiv), THF, −78 °C to rt, 2 h; (iii) $KHSO_4$ aq, rt.

In addition, according to Scheme 5, *N*-methyl α-phosphonoenamide **11** was achieved in 92% yield, by direct methylation of the diethyl (1-*tert*-butoxycarbonylamino-3,3-dimethyl-but-1-enyl)phosphonate **7d** by iodomethane, in the presence of potassium *tert*-butoxide as a base. The ratio of rotamers in product **11**, prepared on independent route, was the same as in the trapping experiment.



Scheme 5. Reagent and conditions: (i) *t*-BuOK (2 equiv), THF, −78 °C, 0.5 h; (ii) MeI (8 equiv), THF, −78 °C to rt, 2 h; (iii) $KHSO_4$ aq, rt.

3. Conclusions

In summary, the protocol described here provides new and simple access to *N*-Boc protected 1-aminoalkenylphosphonates starting from the appropriate 5-substituted (2-thioxo-oxazolidin-4-yl)phosphonic acid diethyl esters. The transformations occurred under very mild conditions and led to the desired α-phosphonoenamides with good to excellent yields. Elimination is stereospecific. Thus, (*Z*)-*N*-Boc 1-aminoalkenylphosphonates were formed from *cis*-5-substituted (2-thioxo-oxazolidin-4-yl)phosphonates, whereas the diastereomeric *trans*-oxazolidine-2-thiones gave *E*-enamides. Some intermediates formed during the olefin-forming elimination were identified by NMR and trapping experiment.

4. Experimental

NMR spectra were recorded on a Bruker Avance DPX 250 instrument at 250.13 MHz for ^1H NMR, 62.90 MHz for ^{13}C NMR and 101.3 MHz for ^{31}P NMR in $CDCl_3$ or THF-d_8 solution, using tetramethylsilane as internal and 85% H_3PO_4 as external standard. Positive chemical shifts are downfield

[§] The differences of the chemical shifts of the NMR spectra can be associated with temperatures of the measurement. Residual signal from the solvent at δ_H=3.58 ppm was used as internal reference for ^1H NMR.

[¶] The ^{31}P NMR taken for metallated **7d**, prepared on independent way from **7d** and potassium *t*-butoxide, gave singlet at δ_P=20.93 ppm at room temperature.

[‖] The ^1H NMR spectra taken in $CDCl_3$ (TMS int.), after the standard work-up, gave the doublet of vinyl proton at δ_H=6.53 ppm ($^3J_{HP}$=17.50 Hz).

from external 85% H_3PO_4 for ^{31}P NMR spectra. Chemical shifts (δ) are indicated in ppm and coupling constants (J) in Hz. Elemental analyses were performed on a NA 2500 CE Elemental Analyser.

Low-resolution mass spectra (m/z) were recorded either on a Finnigan MAT 95 spectrometer (CI, isobutane) or on APO Electron (Ukraine) model MI 12001E spectrometer equipped with a FAB ion source (thioglycerol matrix). IR spectra were measured on a Specord M80 (Zeiss) instrument and are reported in wavenumbers (cm^{-1}). Flash chromatography was performed with glass column packed with Baker silica gel (30–60 μm). Eluents: $CHCl_3$/aceton 9:1 (A); $CHCl_3$/aceton 14:1 (B); $CHCl_3$/aceton 12:1 (C); AcOEt/hexane 3:1 (D). Melting points were determined in open capillaries and are uncorrected. All reagents were purchased from Fluka and used without further purification. Diethyl isothiocyanomethylphosphonate **1** was prepared as described previously[12] from diethyl 1-azidoalkylphoposphonate,[18] triphenylphosphine and CS_2.

4.1. Diethyl 1-(*N*-*tert*-butoxycarbonylamino)-1-alkenylphosphonates (6a–e/7a–e). General procedure

To the solution of oxazolidine-2-thione **2/3** (1 mmol) in dry CH_2Cl_2 (20 mL), di-*tert*-butoxycarbonate (1.15 mmol, 0.251 g) and DMAP (0.20 mmol, 0.025 g) were added. After stirring at room temperature for 1 h, the solution was diluted with CH_2Cl_2 (30 mL). The solution was washed with 5% $KHSO_4$ (2×5 mL), water (2×5 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the rest of the volatile material was removed at 30 °C/0.1 Torr. To the solution of *N*-Boc-oxazolidine-2-thione **4/5** (1 mmol) in dry THF (15 mL) cooled to −78 °C potassium *tert*-butoxide (2 mmol, 0.224 g) in one portion was added. The reaction was carried out at −78 °C for 0.5 h. Then, the mixture was quenched with 5% $KHSO_4$ (aq) and allowed to warm to room temperature. The solvent was evaporated under reduced pressure, and the residue was partitioned between CH_2Cl_2 (50 mL) and 5% $KHSO_4$ (3 mL). The organic layer was separated, washed with 5% $KHSO_4$ (2×3 mL), water (2×3 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the rest of the volatile material removed at 30 °C/0.1 Torr. Where necessary diastereomeric **6/7** were separated by flash chromatography, using appropriate eluents.

4.1.1. Diethyl (*Z*)-(1-*tert*-butoxycarbonylamino-2-phenyl-vinyl)phosphonate (6a). Yield: 88%; colorless solid, mp 70–72 °C; R_f=0.59 (A); ^{1}H NMR: δ=1.14 (dt, $^3J_{HH}$=7.05 Hz, $^4J_{HP}$=0.60 Hz, 6H, 2CH_3), 1.51 (s, (9H, 3CH_3)), 3.84–4.11 (m, 4H, 2CH_2O), 6.95 (bd, $^3J_{HP}$=7.30 Hz, 1H, N*H*), 7.22–7.44 (m, 5H$_{arom}$), 7.94 (d, $^3J_{HP}$=41.20 Hz, 1H, =C*H*); ^{13}C NMR: δ=15.65 (d, $^3J_{CP}$=6.95 Hz, 2CH_3), 28.09 (s, 3CH_3), 62.45 (d, $^2J_{CP}$=5.45 Hz, 2CH_2O), 80.43 (s, *C*), 124.40 (d, $^1J_{CP}$=197.65 Hz, P–*C*), 127.24, 127.43 (2s, 3CH_{arom}), 127.68 (d, $^2J_{CP}$=10.20 Hz, =CH), 128.82 (d, $^4J_{CP}$=1.60 Hz, 2CH_{arom}), 135.10 (d, $^3J_{CP}$=5.85 Hz, C_{arom}), 152.84 (d, $^3J_{CP}$=14.45 Hz, *C*=O); ^{31}P NMR: δ=13.45; IR (film): ν=3288, 2976, 1712, 1368, 1252, 1156, 1020; MS (CI) m/z (%): 356 (100). Anal. Calcd for $C_{17}H_{26}NO_5P$ (355.38): C: 57.46; H: 7.37; N: 3.94. Found: C: 57.64; H: 7.55; N: 3.80.

4.1.2. Diethyl (*E*)-(1-*tert*-butoxycarbonylamino-2-phenyl-vinyl)phosphonate (7a). Yield: 48%; colorless solid, mp 125–127 °C; R_f=0.36 (A); ^{1}H NMR: δ=1.35 (t, $^3J_{HH}$=7.08 Hz, 6H, 2CH_3), 1.33 (s, 9H, 3CH_3), 4.09–4.23 (m, 4H, 2CH_2O), 5.83 (bs, 1H, N*H*), 7.19 (d, $^3J_{HP}$=16.15 Hz, 1H, =C*H*), 7.28–7.57 (m, 5H$_{arom}$); ^{13}C NMR: δ=16.19 (d, $^3J_{CP}$=6.50 Hz, 2CH_3), 27.86 (s, 3CH_3), 62.38 (d, $^2J_{CP}$=5.05 Hz, 2CH_2O), 80.67 (s, C), 122.74 (d, $^1J_{CP}$=209.45 Hz, P–*C*), 128.29, 129.10, 129.35 (3s, 5CH_{arom}), 134.22 (d, $^3J_{CP}$=19.00 Hz, C_{arom}), 137.92 (d, $^2J_{CP}$=24.10 Hz, =*C*H), 152.15 (bs, *C*=O); ^{31}P NMR: δ=15.00; IR (film): ν=3160, 2976, 1720, 1244, 1160, 1028; MS (CI) m/z (%): 356 (100). Anal. Calcd for $C_{17}H_{26}NO_5P$ (355.38): C: 57.46; H: 7.37; N: 3.94. Found: C: 57.56; H: 7.49; N: 3.76.

4.1.3. Diethyl (*Z*)-(1-*tert*-butoxycarbonylamino-2-furan-2-yl-vinyl)-phosphonate (6b). Yield: 60%; yellow solid, mp=44–46 °C; R_f=0.54 (C); ^{1}H NMR: δ=1.27 (dt, $^3J_{HH}$=7.05 Hz, $^4J_{HP}$=0.70 Hz, 6H, 2CH_3), 1.49 (s, 9H, 3CH_3), 3.98–4.22 (m, 4H, 2CH_2O), 6.40 (dd, $^3J_{HH}$=3.40 Hz, $^3J_{HH}$=1.75 Hz, 1H$_{arom}$), 6.67 (dd, $^3J_{HH}$=3.40 Hz, $^4J_{HH}$=0.60 Hz, 1H$_{arom}$), 7.08 (bd, $^3J_{HP}$=7.85 Hz, 1H, N*H*), 7.40 (dd, $^3J_{HH}$=1.75 Hz, $^4J_{HH}$=0.6 Hz, 1H$_{arom}$), 7.86 (d, $^3J_{HP}$=39.20 Hz, 1H, =C*H*); ^{13}C NMR: δ=15.76 (d, $^3J_{CP}$=6.80 Hz, 2CH_3), 27.97 (s, 3CH_3), 62.63 (d, $^2J_{CP}$=4.95 Hz, 2CH_2O), 80.48 (s, *C*), 111.30 (s, CH_{arom}), 111.53 (s, CH_{arom}), 114.08 (d, $^2J_{CP}$=7.40 Hz, =*C*H), 121.45 (d, $^1J_{CP}$=195.65 Hz, P–*C*=), 142.25 (s, C_{arom}), 149.35 (d, $^3J_{CP}$=6.95 Hz, C_{arom}), 152.48 (d, $^3J_{CP}$=14.95 Hz, *C*=O, 1C); ^{31}P NMR: δ=13.20; IR (film): ν=3384, 2984, 1720, 1508, 1368, 1252, 1160, 1020; MS (CI) m/z (%): 346 (100). Anal. Calcd for $C_{15}H_{24}NO_6P$ (345.34): C: 52.17; H: 7.00; N: 4.06. Found: C: 52.47; H: 7.24; N: 3.89.

4.1.4. Diethyl (*E*)-(1-*tert*-butoxycarbonylamino-2-furan-2-yl-vinyl)-phosphonate (7b). Yield: 69%; yellow solid, mp=120–122 °C; R_f=0.22 (C); ^{1}H NMR: δ=1.34 (dt, $^3J_{HH}$=7.05 Hz, $^4J_{HP}$=0.5 Hz, 6H, 2CH_3), 1.44 (s, 9H, 3CH_3), 4.08–4.22 (m, 4H, 2CH_2O), 6.04 (bd, $^3J_{HP}$=4.20 Hz, 1H, N*H*), 6.46 (dd, $^3J_{HH}$=3.40 Hz, $^3J_{HH}$=1.75 Hz, 1H$_{arom}$), 6.60 (d, $^3J_{HH}$=3.40 Hz, 1H$_{arom}$), 7.04 (d, $^3J_{HP}$=15.20 Hz, 1H, =C*H*), 7.48 (bd, $^3J_{HH}$=1.75 Hz, 1H$_{arom}$); ^{13}C NMR: δ=16.12 (d, $^3J_{CP}$=6.65 Hz, 2CH_3), 27.95 (s, 3CH_3), 62.35 (d, $^2J_{CP}$=5.10 Hz, 2CH_2O), 80.45 (s, *C*), 111.75 (s, CH_{arom}), 114.60 (s, CH_{arom}), 120.00 (d, $^1J_{CP}$=213.40 Hz, P–*C*=), 124.70 (d, $^2J_{CP}$=25.70 Hz, =*C*H), 143.80 (s, CH_{arom}), 149.75 (d, $^3J_{CP}$=21.95 Hz, C_{arom}), 152.40 (d, $^3J_{CP}$=3.00 Hz, *C*=O); ^{31}P NMR: δ=14.76; IR (film): ν=2976, 1720, 1512, 1252, 1160, 1024; MS (CI) m/z (%): 346 (100). Anal. Calcd for $C_{15}H_{24}NO_6P$ (345.34): C: 52.17; H: 7.00; N: 4.06. Found: C: 52.05; H: 6.78; N: 4.15.

4.1.5. Diethyl (*Z*)-(1-*tert*-butoxycarbonylamino-4-phenyl-buta-1,3-dienyl)-phosphonate (6c). Yield: 50%; yellow oil; R_f=0.63 (B); ^{1}H NMR: δ=1.36 (dt, $^3J_{HH}$=7.05 Hz, $^4J_{HP}$=0.50 Hz, 6H, 2CH_3), 1.49 (s, 9H, 3CH_3), 4.02–4.26 (m, 4H, 2CH_2O), 6.66 (d, $^3J_{HH}$=15.25 Hz, 1H, Ph–C*H*=),

6.85 (bd, $^3J_{HP}$=8.35 Hz, 1H, N*H*), 7.20–7.43 (m, 5H$_{arom}$), 7.34 (dd, $^3J_{HH}$=15.25 Hz, $^3J_{HH}$=11.80 Hz, 1H, =C*H*), 7.70 (dd, $^3J_{HP}$=40.00 Hz, $^3J_{HH}$=11.80 Hz, 1H, =C*H*); ^{13}C NMR: δ=15.18 (d, $^3J_{CP}$=6.60 Hz, 2*C*H$_3$), 27.22 (s, 3*C*H$_3$), 61.78 (d, $^2J_{CP}$=4.60 Hz, 2*C*H$_2$O), 79.80 (s, *C*), 123.14 (d, $^1J_{CP}$=194.40 Hz, P*C*), 123.63 (d, $^3J_{CP}$=6.90 Hz, *C*H=), 125.62, 126.84, 127.66 (3s, 5*C*H$_{arom}$), 126.00 (d, $^2J_{CP}$=9.45 Hz, =*C*H), 134.40 (d, $^5J_{CP}$=1.90 Hz, *C*$_{arom}$), 136.22 (s, *C*HPh), 151.70 (d, $^3J_{CP}$=15.40 Hz, *C*=O); ^{31}P NMR: δ=14.17; IR (film): ν=2984, 1724, 1504, 1252, 1156, 1020; MS (CI) *m*/*z* (%): 382 (100). Anal. Calcd for $C_{19}H_{28}NO_5P$ (381.41): C: 59.83; H: 7.40; N: 3.67. Found: C: 60.12; H: 7.55; N: 3.51.

4.1.6. Diethyl (*E*)-(1-*tert*-butoxycarbonylamino-4-phenyl-buta-1,3-dienyl)-phosphonate (7c). Yield: 27%; yellow oil; R_f=0.33 (B); ^{1}H NMR: δ=1.34 (dt, $^3J_{HH}$=7.05 Hz, $^4J_{HP}$=0.55 Hz, 6H, 2C*H*$_3$), 1.49 (s, 9H, 3C*H*$_3$), 4.05–4.20 (m, 4H, 2C*H*$_2$O), 5.75 (bs, 1H, N*H*), 6.80–7.05 (m, 3H, C*H*=C*H*–C*H*=), 7.24–7.46 (m, 5H$_{arom}$); ^{13}C NMR: δ=16.03 (d, $^3J_{CP}$=6.50 Hz, 2*C*H$_3$), 27.89 (s, 3*C*H$_3$), 62.15 (d, $^2J_{CP}$=5.10 Hz, 2*C*H$_2$O), 80.46 (s, *C*), 122.08 (d, $^1J_{CP}$=211.05 Hz, P*C*), 122.60 (d, $^3J_{CP}$=17.85 Hz, *C*H=), 126.88, 128.45, 128.53 (3s, 5*C*H$_{arom}$), 136.15 (d, $^5J_{CP}$=1.90 Hz, *C*$_{arom}$), 138.30 (d, $^2J_{CP}$=23.15 Hz, =*C*H), 138.46 (s, *C*HPh), 152.94 (d, $^3J_{CP}$=4.55 Hz, *C*=O); IR (film): ν=2984, 1716, 1244, 1164, 1024; MS (CI) *m*/*z* (%): 382 (100). Anal. Calcd for $C_{19}H_{28}NO_5P$ (381.41): C: 59.83; H: 7.40; N: 3.67. Found: C: 59.70; H: 7.21; N: 3.65.

4.1.7. Diethyl (*E*)-(1-*tert*-butoxycarbonylamino-3,3-dimethyl-but-1-enyl)-phosphonate (7d). Yield: 94%; colorless oil; ^{1}H NMR: δ=1.11 (s, 9H, 3C*H*$_3$), 1.25 (t, $^3J_{HH}$=7.00 Hz, 6H, 2C*H*$_3$), 1.40 (s, 9H, 3C*H*$_3$), 3.97–4.14 (m, 4H, C*H*$_2$O), 5.17 (bs, 1H, N*H*), 6.46 (d, $^3J_{HP}$=16.75 Hz, 1H, *t*-Bu–C*H*); ^{13}C NMR: δ=16.22 (d, $^3J_{CP}$=6.65 Hz, 2*C*H$_3$), 28.18, 28.98 (2s, 2(*C*H$_3$)$_3$), 35.00 (d, $^3J_{CP}$=15.65 Hz, *C*), 62.14 (d, $^2J_{CP}$=5.05 Hz, 2*C*H$_2$O), 80.13 (s, *C*=O), 120.96 (d, $^1J_{CP}$=213.45 Hz, *C*–P), 153.91 (d, $^3J_{CP}$=14.40 Hz, *C*=O), 155.98 (d, $^2J_{CP}$=23.75 Hz, *C*H); ^{31}P NMR: δ=15.71; IR (film): ν=3216, 2968, 1724, 1480, 1368, 1248, 1196, 1164, 1024; MS (FAB) *m*/*z* (%): 336 (32), 280 (100). Anal. Calcd for $C_{15}H_{30}NO_5P$ (335.38): C: 53.72; H: 9.02; N: 4.18. Found: C: 53.46; H: 8.79; N: 4.30.

4.1.8. Diethyl (*Z*)-(1-*tert*-butoxycarbonylamino-3-methyl-but-1-enyl)-phosphonate (6e). Yield: 94%; colorless solid, mp=60–62 °C; R_f=0.58 (A); ^{1}H NMR: δ=1.02 (d, $^3J_{HH}$=6.50 Hz, 6H, 2C*H*$_3$), 1.34 (t, $^3J_{HH}$=7.00 Hz, 6H, 2C*H*$_3$), 1.45 (s, 9H, 3C*H*$_3$), 2.95 (dheptet, $^3J_{HH}$=11.60 Hz, $^3J_{HH}$=6.50 Hz, 1H, C*H*), 4.00–4.20 (m, 4H, 2C*H*$_2$O), 6.47 (bd, $^3J_{HP}$=4.25 Hz, 1H, N*H*), 6.65 (dd, $^3J_{HP}$=42.50 Hz, $^3J_{HH}$=11.60 Hz, 1H, =C*H*); ^{13}C NMR: δ=16.11 (d, $^3J_{CP}$=6.85 Hz, 2*C*H$_3$), 22.95 (d, $^4J_{CP}$=1.50 Hz, 2*C*H$_3$), 28.20 (s, 3*C*H$_3$), 28.28 (d, $^3J_{CP}$=4.80 Hz, *C*H), 62.30 (d, $^2J_{CP}$=4.95 Hz, 2*C*H$_2$O), 80.00 (s, *C*), 121.25 (d, $^1J_{CP}$=199.25 Hz, *C*–P), 138.17 (bs, =*C*H), 153.10 (d, $^3J_{CP}$=14.40 Hz, *C*=O); ^{31}P NMR: δ=15.17; IR (film): ν=3392, 2968, 1724, 1512, 1368, 1248, 1160, 1016; MS (CI) *m*/*z* (%): 322 (14). Anal. Calcd for $C_{14}H_{28}NO_5P$ (321.36): C: 52.33; H: 8.78; N: 4.36. Found: C: 52.56; H: 9.00; N: 4.28.

4.1.9. Diethyl (*E*)-(1-*tert*-butoxycarbonylamino-3-methyl-but-1-enyl)-phosphonate (7e). Yield: 26%; colorless oil; R_f=0.37 (A); ^{1}H NMR: δ=1.05 (d, $^3J_{HH}$=6.65 Hz, 6H, 2C*H*$_3$), 1.32 (t, $^3J_{HH}$=7.05 Hz, 6H, 2C*H*$_3$), 1.46 (s, 9H, 3C*H*$_3$), 2.72 (ddheptet, $^3J_{HH}$=10.10 Hz, $^3J_{HH}$=6.65 Hz, $^4J_{HP}$=2.20 Hz, 1H, C*H*), 4.02–4.11 (m, 4H, 2CH$_2$O), 5.46 (bs, 1H, NH), 6.35 (dd, $^3J_{HP}$=14.75 Hz, $^3J_{HH}$=10.10 Hz, 1H, =CH); ^{13}C NMR: δ=16.12 (d, $^3J_{CP}$=6.55 Hz, 2*C*H$_3$), 21.30 (s, 2*C*H$_3$), 27.61 (d, $^3J_{CP}$=13.90 Hz, *C*H), 28.03 (s, 3*C*H$_3$), 62.08 (d, $^2J_{CP}$=5.15 Hz, 2*C*H$_2$O), 80.08 (s, *C*), 120.96 (d, $^1J_{CP}$=206.75 Hz, *C*–P), 152.47 (d, $^2J_{CP}$=21.50 Hz, =*C*H), 153.17 (s, *C*=O); ^{31}P NMR: δ=14.96; IR (film): ν=3216, 2984, 1720, 1480, 1368, 1248, 1168, 1028; MS (CI) *m*/*z* (%): 322 (14). Anal. Calcd for $C_{14}H_{28}NO_5P$ (321.36): C: 52.33; H: 8.78; N: 4.36. Found: C: 52.45; H: 8.91; N: 4.28.

4.2. Trapping experiment

To the solution of *N*-Boc-oxazolidine-2-thione **5d** (0.5 mmol, 0.17 g) in THF (15 mL) cooled to −78 °C *t*-BuOK (0.75 mmol, 0.08 g) in one portion was added. After 10 min at −78 °C iodomethane (4 mmol, 0.57 g) was added to the reaction mixture. Then the reaction mixture was allowed to warm to rt. After 2 h at rt, the reaction mixture was quenched with 5% $KHSO_4$ (aq), the solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 (50 mL) and 5% $KHSO_4$ (2 mL). The organic layer was separated, washed with 5% $KHSO_4$ (2 mL), water (2×2 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the rest of the volatile material was removed at 30 °C/0.1 Torr. The mixture of crude products was separated by flash chromatography.

4.2.1. Diethyl (*E*)-[1-(*tert*-butoxycarbonyl-1-methylsulfanylcarbonyl)-amino)-3,3-dimethyl-but-1-enyl]-phosphonate (10). Yield: 33%; colorless oil; R_f=0.39 (C); ^{1}H NMR: δ=1.10 (s, 9H, 3C*H*$_3$), 1.28, 1.33 (2dt, $^3J_{HH}$=7.05 Hz, $^4J_{HP}$=0.70 Hz, 2C*H*$_3$), 1.53 (s, 9H, 3C*H*$_3$), 2.29 (s, 3H, C*H*$_3$S), 3.98–4.18 (m, 4H, 2C*H*$_2$O), 6.61 (d, $^3J_{HP}$=16.65 Hz, 1H, *t*-Bu–C*H*); ^{13}C NMR: δ=14.00 (s, *C*H$_3$–S), 16.06 (d, $^3J_{CP}$=7.2 Hz, *C*H$_3$), 16.39 (d, $^3J_{CP}$=6.10 Hz, *C*H$_3$), 27.87 (s, 3*C*H$_3$), 28.41 (d, $^4J_{CP}$=1.35 Hz, 3*C*H$_3$), 35.47 (d, $^3J_{CP}$=14.95 Hz, *C*), 62.02 (d, $^2J_{CP}$=6.29 Hz, *C*H$_2$O), 62.37 (d, $^2J_{CP}$=5.06 Hz, *C*H$_2$O), 84.17 (s, *C*), 123.25 (d, $^1J_{CP}$=221.65 Hz, *C*–P), 151.55 (s, *C*=O), 156.18 (d, $^2J_{CP}$=20.9 Hz, =H*C*–*t*-Bu), 170.97 (s, *C*–S); ^{31}P NMR: 13.70; IR (film): ν=2976, 1736, 1664, 1368, 1304, 1284, 1256, 1216, 1152, 1024; MS (CI) *m*/*z* (%): 410 (100). Anal. Calcd for $C_{17}H_{32}O_6PNS$ (409.49): C: 49.86; H: 7.88; N: 3.42; S: 7.83. Found: C: 49.71; H: 7.65; N: 3.56; N: 7.98.

4.2.2. Diethyl (*E*)-[1-(*tert*-butoxycarbonyl-methylamino)-3,3-dimethyl-but-1-enyl]-phosphonate (11). Yield: 30%; colorless oil; R_f=0.26 (D); the mixture of rotamers described in Sections 4.2.2.1 and 4.2.2.2 are in the ratio 68:32. IR (film): ν=2976, 1704, 1480, 1368, 1348, 1252, 1156, 1024; MS (CI) *m*/*z* (%) 350 (100). Anal. Calcd for $C_{16}H_{32}NO_5P$ (349.41): C: 55.00; H: 9.23; N: 4.01; Found: C: 55.27; H: 9.46; N: 4.29.

4.2.2.1. Major rotamer. ^{1}H NMR: δ=1.07 (s, 9H, 3CH_3), 1.26, 1.27 (2t, $^{3}J_{HH}$=7.10 Hz, 6H, 2CH_3), 1.38 (s, 9H, 3CH_3), 2.89 (d, $^{4}J_{HP}$=0.80 Hz, 3H, CH_3N), 3.99–4.09 (m, 4H, 2CH_2O), 6.33 (d, $^{3}J_{HP}$=16.55 Hz, 1H, *t*-Bu–C*H*=); ^{13}C NMR: δ=16.30 (d, $^{3}J_{CP}$=6.60 Hz, *C*H$_3$), 16.40 (d, $^{3}J_{CP}$=6.40 Hz, *C*H$_3$), 28.29 (s, 3*C*H$_3$), 28.85 (d, $^{4}J_{CP}$=1.61 Hz, 3*C*H$_3$), 34.91 (d, $^{3}J_{CP}$=15.90 Hz, *C*), 37.04 (s, *C*H$_3$–N), 61.64 (d, $^{2}J_{CP}$=6.19 Hz, *C*H$_2$O), 61.92 (d, $^{2}J_{CP}$=6.00 Hz, *C*H$_2$O), 80.24 (s, *C*), 128.21 (d, $^{1}J_{CP}$=213.05 Hz, *C*–P), 154.22 (d, $^{2}J_{CP}$=26.85 Hz, =H*C*–*t*-Bu), 154.48 (s, *C*=O); ^{31}P NMR: δ=15.60.

4.2.2.2. Minor rotamer. ^{1}H NMR: δ=1.07 (s, 9H, 3CH_3), 1.26, 1.27 (2t, $^{3}J_{HH}$=7.10 Hz, 6H, 2CH_3), 1.38 (s, 9H, 3CH_3), 2.89 (d, $^{4}J_{HP}$=0.80 Hz, 3H, CH_3N), 3.99–4.09 (m, 4H, 2CH_2O), 6.49 (d, $^{3}J_{HP}$=16.30 Hz, 1H, *t*-Bu–C*H*=); ^{13}C NMR: δ=16.07 (d, $^{3}J_{CP}$=7.40 Hz, *C*H$_3$), 16.30 (d, $^{3}J_{CP}$=6.60 Hz, *C*H$_3$), 28.17 (s, 3*C*H$_3$), 28.77 (d, $^{4}J_{CP}$=1.60 Hz, 3*C*H$_3$), 34.81 (d, $^{3}J_{CP}$=15.70 Hz, *C*), 37.63 (s, *C*H$_3$–N), 61.55 (d, $^{2}J_{CP}$=6.30 Hz, *C*H$_2$O), 62.35 (d, $^{2}J_{CP}$=4.40 Hz, *C*H$_2$O), 79.78 (s, *C*), 127.93 (d, $^{1}J_{CP}$=210.30 Hz, *C*–P), 154.22 (d, $^{2}J_{CP}$=26.85 Hz, =H*C*–*t*-Bu), 154.48 (s, *C*=O); ^{31}P NMR: δ=16.17.

4.3. Diethyl (*E*)-(1-*tert*-butoxycarbonyl-methyl-amino-3,3-dimethyl-but-1-enyl)-phosphonate (11)

To the solution of diethyl (*E*)-(1-*tert*-butoxycarbonylamino-3,3-dimethyl-but-1-enyl)-phosphonate (**7d**) (0.17 g, 0.5 mmol) in THF (15 mL) cooled to −78 °C, *t*-BuOK (0.75 mmol, 0.08 g) was added in one portion. After 10 min at −78 °C, iodomethane (4 mmol, 0.57 g) was added to the reaction mixture. Then the reaction mixture was allowed to warm to room temperature for 2 h and quenched with 5% $KHSO_4$ (aq). The solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 (50 mL) and 5% $KHSO_4$ (2 mL). The organic layer was separated, washed with 5% $KHSO_4$ (2 mL), water (2× 2 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the rest of the volatile material was removed at 30 °C/0.1 Torr to give 0.16 g of analytically pure **11** in 92% yield. The ratio of rotamers and their spectral data are in accordance with those given in Section 4.2.2.

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References and notes

1. *Aminophosphonic and Aminophosphinic Acids Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; Wiley: Chichester, 2000.
2. For recent reviews on catalytic asymmetric hydrogenation, see: (a) Crépy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79–101. (b) Crépy, K. V. L.; Imamoto, T. *Top. Curr. Chem.* **2003**, *229*, 1–40.
3. (a) Schmidt, U.; Oehme, G.; Krause, H. W. *Synth. Commun.* **1996**, *26*, 777–781. (b) Schmidt, U.; Krause, H. W.; Oehme, G.; Michalik, M.; Fischer, C. *Chirality* **1998**, *10*, 564–572. (c) Grassert, I.; Schmidt, U.; Ziegler, S.; Fischer, C.; Oehme, G. *Tetrahedron: Asymmetry* **1998**, *9*, 4193–4202.
4. Burk, M. J.; Stammers, T. A.; Straub, J. A. *Org. Lett.* **1999**, *1*, 387–390.
5. Edmundson, R. S. In *The Synthesis of Functionalized Phosphinic and Phosphonic Acid and their Derivatives. Part B: Diazo, Nitro and Amino Functionalized Acids*; Hartley, F. R., Ed.; The Chemistry of Organophosphorus Compounds; Wiley: Chichester, 1996; Vol. 4, pp 312–374.
6. Quiclet-Sire, B.; Zard, S. Z.; Zhang, H. *J. Organomet. Chem.* **2002**, *643–644*, 404–408.
7. Schöllkopf, U.; Hoppe, I.; Thiele, A. *Liebigs Ann. Chem.* **1985**, 555–559.
8. (a) Schöllkopf, U.; Schröder, R. *Tetrahedron Lett.* **1973**, 633–636. (b) Schöllkopf, U.; Schröder, R. *Liebigs Ann. Chem.* **1974**, 44–53.
9. Brovarets, V. S.; Zyus, K. V.; Budnik, L. V.; Solodenko, V. A.; Drach, B. S. *Zh. Obshch. Khim.* **1993**, *63*, 1259–1265.
10. As reported in Ref. 4, the condensation of dimethyl propionylphosphonate with benzylcarbamate afforded dimethyl (*Z*)-(1-benzyloxycarbonylamino-propenyl)phosphonate, in poor 11% yield.
11. Gajda, T.; Błażewska, K. *Presented in Part at the 16th International Conference on Phosphorus Chemistry*; Birmingham: Great Britain, 2004; p 39.
12. Sikora, D.; Gajda, T. *Phosphorus Sulfur Silicon* **2000**, *157*, 201–210.
13. Błażewska, K.; Sikora, D.; Gajda, T. *Tetrahedron Lett.* **2003**, *44*, 4747–4750.
14. Schmidt, U.; Leitenberger, V.; Griesser, H.; Schmidt, J.; Meyer, R. *Synthesis* **1992**, 1248–1254.
15. Hoppe, D.; Follmann, R. *Chem. Ber.* **1976**, *109*, 3062–3078.
16. (a) Schöllkopf, U.; Schröder, R.; Gerhart, F.; Hoppe, D. *Liebigs Ann. Chem.* **1972**, 116–129. (b) Mikołajczyk, M.; Grzejszczak, S.; Midura, W.; Zatorski, A. *Synthesis* **1976**, 396–398. (c) Zoń, J. *Synthesis* **1981**, 324. (d) Costisella, B.; Keitel, I.; Gross, H. *Tetrahedron* **1981**, *37*, 1227–1232. (e) Öhler, E.; Zbiral, E. *Chem. Ber.* **1991**, *124*, 175–184. (f) Öhler, E.; Kotzinger, S. *Synthesis* **1993**, 497–502. (g) Bentrude, W. G.; Setzer, W. N. In *Stereospecificity in ^{31}P-Element Couplings Proton–Phosphorus Couplings*; Verkade, J. G., Quin, L. D., Eds.; ^{31}P NMR in Stereochemical Analysis; VCH: Deerfield Beach, FL, 1987; p 379. (h) Quin, L. D. In *Stereospecificity in ^{31}P-Element Couplings Carbon–Phosphorus Couplings*; Verkade, J. G., Quin, L. D., Eds.; ^{31}P NMR in Stereochemical Analysis; VCH: Deerfield Beach, FL, 1987; p 401.
17. Sicher, J. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 200–214.
18. Gajda, T.; Matusiak, M. *Synthesis* **1992**, 367–368.

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Synthesis of 2,6-disubstituted morpholines through regioselective oxiranes ring opening by tosylamide under PTC conditions

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Abstract—Symmetric and non-symmetric 2,6-disubstituted morpholines were synthesized through regioselective nucleophilic ring opening of oxiranes with tosylamide under solid–liquid phase transfer catalysis (SL-PTC) conditions followed by cyclization of the tosylamido diols thus obtained and final deprotection of the corresponding *N*-tosyl morpholines. The morpholines prepared are interesting building blocks in the synthesis of pharmaceuticals and agrochemicals.

1. Introduction

Substituted morpholines have attracted considerable interest due to their presence in a number of therapeutically and biologically active compounds[1] or chiral reagents.[2] In particular, the 2,6-dimethylmorpholine skeleton is of paramount importance for the construction of a large class of agrochemical fungicides and bactericides.[3–11] Furthermore, the C_2-symmetric (2*R*,6*R*)-2,6-dimethylmorpholine has been prepared and then incorporated in Fisher-type aminocarbene complexes, behaving as an excellent chiral auxiliary.[12,13] Several 2,6-disubstituted morpholine derivatives are used as antitumor agents,[14] mild diuretics and anorectics.[15] This class of morpholines has been also employed as CO_2, H_2S, and COS adsorbents in the purification of liquids and gases,[16] and as fuel additives to provide fast-burning.[17] Finally, some morpholine derivatives have found applications as polymerization catalysts[18] and additives for inks.[19]

In spite of their industrial importance, few general preparations of 2,6-disubstituted morpholines are reported in the literature: (i) the dialkylation of a primary amine with an oxirane;[20] (ii) the reaction of a sulfonamide with excess chlorohydrin.[21,22] The amino or amido diols thus obtained have been cyclized to the corresponding morpholines in the presence of a base[23] or cyclodehydrated using concentrated sulfuric acid.[24] Alternatively, substituted morpholines have been prepared by a catalyzed vapor phase reaction of a dialkylene glycol with an aminating agent in the presence of hydrogen.[25]

This paper describes the synthesis of 2,6-disubstituted morpholines through the phase transfer (PT) catalyzed dialkylation of 4-toluenesulfonamide (**1**) by oxiranes **2** (Scheme 1), followed by cyclization of the tosylamido diols **4–7** thus obtained (Schemes 2 and 3), and final deprotection of the *N*-tosyl morpholines **10–13** to produce the target compounds **15** (Scheme 4). This procedure is regioselective and of general application, both for symmetric and non-symmetric morpholines.

2. Results and discussion

2.1. Oxirane ring opening by tosylamide

2.1.1. Preparation of symmetric tosylamido diols. In a previous paper,[26] we reported the preparation of β-tosylamido alcohols **3**, realized through ring opening of epoxides **2** with excess tosylamide (**1**), under solid–liquid PT catalysis (SL-PTC) conditions (Scheme 1, path a). As well as the mono-*N*-alkylation products **3**, small quantities of the *N*-dialkylated by-products **4**, **5** were isolated.

The direct dialkylation of **1** under analogous SL-PTC conditions with excess **2** (Scheme 1, path c), gave excellent yields (75–95%) (Table 1) of the (50:50) diastereoisomeric mixture **4**, **5** of the symmetric tosylamido diols, which could

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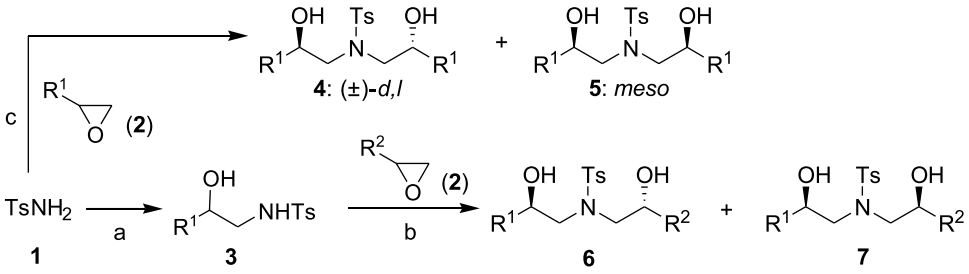


	2a	2b	2c	2d	2e	2f
R^1, R^2	C_6H_{13}	$PhOCH_2$	Ph	$AllylOCH_2$	$MeOCH_2$	t-$BuOCH_2$

	3a	3b	3c	3d
R^1	$PhOCH_2$	Ph	$AllylOCH_2$	$MeOCH_2$

	4,5a	4,5b	4,5c
R^1	C_6H_{13}	$PhOCH_2$	Ph

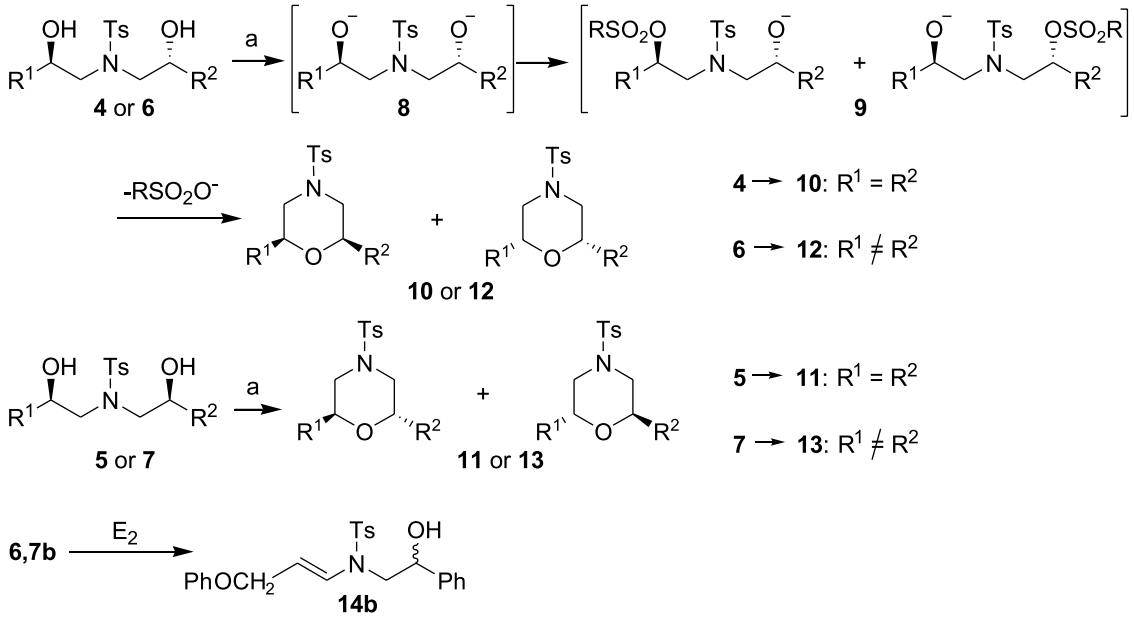
	6,7a	6,7b	6,7c	6,7d	6,7e
R^1	$PhOCH_2$	$PhOCH_2$	$PhOCH_2$	$AllylOCH_2$	$MeOCH_2$
R^2	C_6H_{13}	Ph	t-$BuOCH_2$	t-$BuOCH_2$	$PhOCH_2$

Scheme 1. (a) **1** (1 mol), **2** (0.5 mol), K_2CO_3 (0.05 mol), TEBA (0.05 mol), dioxane, 90 °C; (b) **2** (1.1 mol), **3** (1 mol), M_2CO_3 (0.1 mol), TEBA (0.1 mol), dioxane, 90 °C (or DME, 80 °C); (c) **1** (1 mol), **2** (3 mol), M_2CO_3 (0.1 mol), TEBA (0.1 mol), dioxane, 90 °C (or DME, 80 °C).

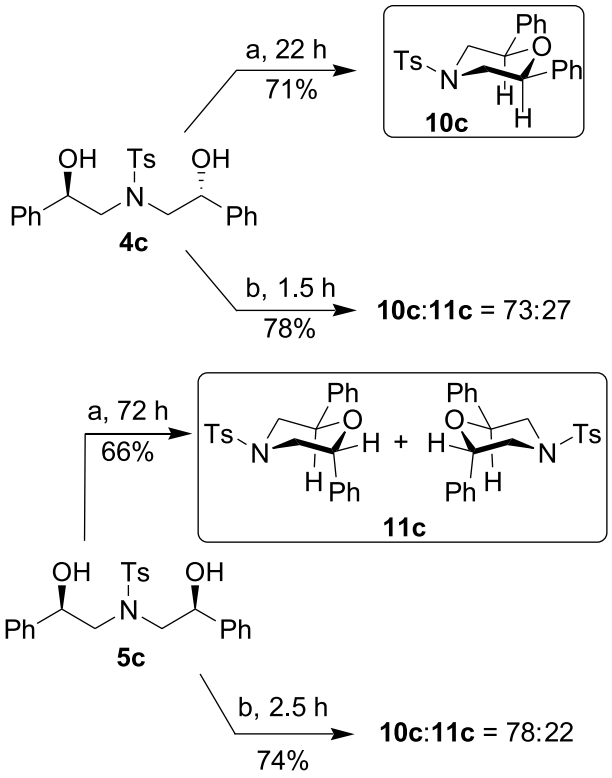
be easily separated by column chromatography to give the pure (±)-*d*,*l* **4** and *meso* **5** isomers.

The efficiency of the different alkaline metal carbonates M_2CO_3, used in catalytic amounts,[24] is related to the nature of the substituent on the oxirane ring: sodium carbonate is the most active base in the case of 1,2-epoxyoctane (**2a**) and 1,2-epoxy-3-phenoxypropane (**2b**), while cesium carbonate is more effective with styrene oxide (**2c**) (Table 1). Most probably, as confirmed by the results concerning the preparation of non-symmetric amido diols **6**, **7** described later, the base–epoxide relationship is the determinant factor for the in situ alkylation of the intermediate amido alcohol **3**.

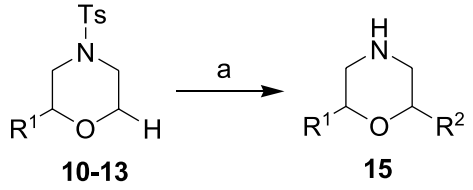
2.1.2. Preparation of non-symmetric tosylamido diols. The synthesis of non-symmetric tosylamido diols **6** and **7** involves a two-step alkylation protocol. After the preparation of the β-tosylamido alcohol **3** (Table 2, Step 1), this intermediate was reacted under SL-PTC conditions with a second epoxide **2** ($R^2 \neq R^1$) (Scheme 1, path b; Table 2, step 2). From the (1:1) diastereoisomeric mixture **6**, **7** formed under these conditions, the pure tosylamido diols **6** and **7**



Scheme 2. (a) **4**–**7** (1 mol), NaH (2.1 mol), RSO_2X (Tf_2O or TsCl, 1 mol), solvent, 0–25 °C. R^1 and R^2 substituents are described in Scheme 1.



Scheme 3. (a) NaH (2.1 mol), TsCl (1 mol), DCM, 40 °C; (b) NaH (2.1 mol), Tf_2O (1 mol), DCM, 25 °C.



Scheme 4. (a) 40% HBr–AcOH (PhOH), 25–80 °C.

Table 1. Preparation of symmetric tosylamido diols **4**, **5** under SL-PTC conditions[a]

	R^1	*t* (h)	Products			
				(%)[b]		(%)[b]
2a	C_6H_{13}[c]	10	**4a**	47	**5a**	48
2b	$PhOCH_2$[c]	6	**4b**	45	**5b**	45
2c	Ph[d]	6	**4c**	38	**5c**	37

[a] Scheme 1, path c. Reaction conditions: $TsNH_2$ (**1**) (1 mol), oxirane **2** (3 mol), TEBA (0.1 mol), Na_2CO_3 (0.1 mol).
[b] Isolated yields, after column chromatography.
[c] In DME at 80 °C.
[d] In the presence of Cs_2CO_3 (0.1 mol), in dioxane at 90 °C.

were separated by column chromatography. As found in the synthesis of symmetric amido diols **4**, **5**, in the alkylation of **3** the choice of the base is crucial (Table 2). As expected, in an attempt to prepare **6**, **7** by using equimolar amounts of oxiranes **2b** and **2c**, by operating in a one-pot reaction conditions, a complex mixture of the possible symmetric and non-symmetric amido diols was obtained.

2.2. Cyclization of tosylamido diols to 2,6-dialkyl-*N*-tosyl-morpholines

Poor results were obtained in the cyclization of diols **4**–**7** to *N*-tosyl-morpholines **10**–**13** by using literature methods of direct dehydration,[23,24] therefore, a detailed study for the best cyclization conditions of the isolated stereoisomers **4**–**7** was undertaken (Scheme 2).

The best results were obtained by generating the oxydianion **8** in the presence of excess NaH in dichloromethane (DCM) or 1,2-dimethoxyethane (DME), and promoting the cyclization through the in situ formation of the two possible mono-triflates **9** with (trifluoromethane)sulfonic anhydride (Tf_2O). Cyclization of the intermediate **9** proceeds through an intramolecular nucleophilic displacemement with stereoselective inversion of configuration at the reactive center. Furthermore, the *O*-triflation of **8** was not a regioselective process and, as a result, racemic morpholines were formed.

In the cyclization of symmetric tosylamido diols **4a**,**b** and **5b** (Table 3), the use of tosyl chloride (entries 1, 4, 6) instead of Tf_2O resulted in longer reaction times and lower yields of *N*-tosyl morpholines **10a**,**b** and **11b**. In the case of symmetric diols derived from 2-phenyl-oxirane (**2c**), it was found that the formation of *meso* morpholine **10c**, the less hindered isomer, bearing equatorial phenyl groups, proceeded with a higher reaction rate than the formation of *d*,*l* isomer **11c** (Table 3, entries 8–11).

In particular, starting from **4c**, in the presence of TsCl, **10c** was isolated as a sole product in 71% yield (entry 8), whilst by using Tf_2O a mixture of **10c**:**11c** (entry 9), which consisted mainly of *meso* **10c**, was produced (Scheme 3). In the same way, the activation of **5c** with tosyl chloride afforded the corresponding *d*,*l* **11c** (entry 10), whereas with Tf_2O an analogous mixture of **10c**:**11c** (entry 11) was obtained. When the mono-*O*-tosylate **9** (Scheme 2, R = Tol) is the intermediate, the nucleophilic substitution proceeds through a bimolecular mechanism, with complete inversion of the carbon atom, while in the case of the mono-*O*-triflate **9** (Scheme 2, R = CF_3), which bears a better leaving group, a unimolecular mechanism, via a carbocation, is responsible for the major formation of **10c**.

A similar behavior was found in the cyclization reactions of non-symmetric tosylamido diols **6**, **7** (Table 4) and TsCl was used as an activating agent when a phenyl group is present, as in diols **6**, **7b** (entries 3, 4).

2.3. *N*-Detosylation of *N*-tosyl-morpholines to 2,6-dialkyl-morpholines

The 2,6-disubstituted morpholines **15** (Scheme 4) can be obtained by deprotection of the corresponding *N*-tosyl morpholines **10**–**13** by reaction with 40% HBr–AcOH (Table 5).[27] In the case of the morpholines **10b**,**c**, **11b** and **12**, **13c** (entries 3–7), that contain phenyl and phenoxymethyl groups, the reactions were conducted in the presence of phenol as bromine scavenger, to avoid aromatic bromination of the products.

Table 2. Preparation of non-symmetric tosylamido diols **6**, **7** under SL-PTC conditions

Step 1[a]		*t* (h)	Product		Step 2[b]		Base	*t* (h)	Products			
Epoxide	R^1		**3**	(%)[c]	Epoxide	R^2			**6**, **7**	(%)[c]		(%)[c]
2b	$PhOCH_2$	2	**3a**	91	**2a**	C_6H_{13}	K_2CO_3	11	**6a**	35	**7a**	35
2b	$PhOCH_2$	2	**3a**	91	**2c**	Ph	Cs_2CO_3	22	**6b**	36	**7b**	36
2c	Ph	6	**3b**	93	**2b**	$PhOCH_2$	Na_2CO_3	6	**6b**	33	**7b**	32
2b	$PhOCH_2$	2	**3a**	91	**2f**	*t*-$BuOCH_2$	Na_2CO_3	48	**6**, **7c**	70[d]	—	—
2d	$AllylOCH_2$	2	**3c**	79	**2f**	*t*-$BuOCH_2$	Na_2CO_3	20	**6**, **7d**	70[d]	—	—
2e	$MeOCH_2$	2	**3d**	83	**2b**	$PhOCH_2$	Na_2CO_3	20	**6**, **7e**	82[d]	—	—

[a] Scheme 1, path a. Reaction conditions: $TsNH_2$ (**1**) (1 mol), epoxide **2** (0.5 mol), TEBA (0.05 mol), K_2CO_3 (0.05 mol), dioxane, 90 °C.
[b] Scheme 1, path b. Reaction conditions: epoxide **2** (1.1 mol), tosylamido alcohol **3** (1 mol), TEBA (0.1 mol), M_2CO_3 (0.1 mol), dioxane, 90 °C.
[c] Isolated yields.
[d] Isolated as (50:50) inseparable mixture of the diastereoisomers **6** and **7**.

Table 3. Cyclization of symmetric tosylamido diols **4** and **5** to *N*-tosyl morpholines **10** and **11**[a]

Entry		Method[b]	*t* (h)	Product	(%)[c]
1	**4a**	A	13	**10a**	55
2	**4a**	B	6	**10a**	78
3	**5a**	C	6	**11a**	80
4	**4b**	A	48	**10b**	72
5	**4b**	B	13	**10b**	77
6	**5b**	A[d]	23	**11b**	75
7	**5b**	B[d]	6	**11b**	80
8	**4c**	D[d]	22	**10c**	71
9	**4c**	B[d]	1.5	**10c**	57
				11c	21
10	**5c**	D[d]	72	**11c**	66
11	**5c**	B[d]	2.5	**10c**	58
				11c	16

[a] Reaction conditions: tosylamido diol **4**, **5** (1 mol), NaH (2.1 mol), RSO_2X (1 mol)—solvent, 0–25 °C.
[b] A: TsCl–DME; B: Tf_2O–DCM; C: Tf_2O–DME; D: TsCl–DCM, 25 °C.
[c] Isolated yields.
[d] At 40 °C.

Table 4. Cyclization of non-symmetric tosylamido diols **6**, **7** to *N*-tosyl morpholines **12** and **13**[a]

Entry		Method[b]	*t* (h)	Product	(%)[c]
1	**6a**	B	2	**12a**	85
2	**7a**	B	7	**13a**	77
3	**6b**	D	54	**12b**	46[d]
4	**7b**	D	28	**13b**	65[e]
5	**7b**	B	5	**13b**	54[f]
6	**6c**, **7c**[g]	B	5	**12c**	74[h]
				13c	64[i]
7	**6d**, **7d**[g]	D	28	**12d**	70[h]
				13d	59[i]
8	**6e**, **7e**[g]	B	5	**12e**	57[h]
				13e	53[i]

[a] Reaction conditions: tosylamido diol **6**, **7** (1 mol), NaH (2.1 mol), RSO_2X (1 mol)—solvent, 25 °C.
[b] B: Tf_2O–DCM; D: TsCl–DCM.
[c] Isolated yields.
[d] Together with **13b** (7%).
[e] Together with **12b** (3%) and **14b** (14%).
[f] Together with **12b** (25%).
[g] Starting from the corresponding (50:50) diastereoisomeric mixture **6**, **7**.
[h] Isolated yield calculated from the molar amount of the corresponding tosylamido diol **6**.
[i] Isolated yield calculated from the molar amount of the corresponding tosylamido diol **7**.

Table 5. Deprotection of *N*-tosyl morpholines **10–13**

Entry	Substrate	Method[a]	*t* (h)	Product	(%)[b]
1	**10a**	A	2	**15a**	65
2	**11a**	B	4	**15b**	63
3	**10b**	C	4	**15c**	75
4	**11b**	C	4	**15d**	75
5	**10c**	D	9	**15e**	61
6	**12a**	D	24	**15f**	74
7	**13a**	D	24	**15g**	67

[a] **10–13** (1 mol); A: 40% HBr–AcOH (30 mol), 60 °C; B: 40% HBr–AcOH (30 mol), 80 °C; C: 40% HBr–AcOH (30 mol), PhOH (3 mol), 60 °C; D: 40% HBr–AcOH (30 mol), PhOH (3 mol), 25 °C.
[b] Isolated yields.

3. Conclusions

In conclusion, in this work we have outlined a viable synthesis of 2,6-disubstituted morpholines **15** through the regioselective ring opening of a pair of easily accessible, appropriately substituted epoxides **2** with $TsNH_2$ **1**, employing SL-PTC conditions. The strategy described here, involving the cyclization of the tosyl amido diols **4–7** thus obtained, followed by deprotection of the corresponding *N*-tosyl morpholines **10–13**, enabled us to prepare a variety of 2,6-disubstituted morpholines **15**, which are tools of great interest as building blocks in the synthesis of pharmaceuticals and agrochemicals. Moreover, the inexpensive, readily available and environmentally friendly reagents add attractiveness to this method.

4. Experimental

4.1. General informations

Melting points were determined on a Büchi 535 apparatus and are corrected. ^1H NMR spectra were recorded on a Bruker AC 300 spectrometer operating at 300.133 MHz; TMS was used as an external reference; δ values are in ppm and *J* values are in Hz. Reagent-grade commercially available reagents and solvents were used and dried, when required, before use. Petroleum ether (PE) having a boiling range of 40–60 °C was used in the chromatographic purifications. Epoxides **2a–f** are commercially available. Alkaline metal carbonates were dried by heating at 140 °C

under vacuum (0.05 mmHg) for 6 h. Analytical TLC was performed using Merck pre-coated silica gel F_{254} plates.

4.2. General method for the preparation of β-tosylamido alcohols 3

A heterogeneous mixture of $TsNH_2$ (**1**) (342 mg, 2 mmol), TEBA (23 mg, 0.1 mmol) and epoxide **2** (1 mmol) solution in anhydrous dioxane (0.5 mL) and anhydrous K_2CO_3 (14 mg, 0.1 mmol), was magnetically stirred at 90 °C until no starting material **1** was detectable (TLC analysis). After cooling, the crude product was diluted with DCM (10 mL), filtered through celite, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (230–400 mesh). Starting epoxide **2**, reaction time, chromatographic eluant, yield and physical, spectroscopic and analytical data of amido alcohols **3a**–**d** are as follows.

4.2.1. *N*-(2-Hydroxy-3-phenoxy-propyl)-4-methyl-benzenesulfonamide (3a). 2-Phenoxymethyl-oxirane (**2b**); 2 h; AcOEt–PE 1:1. **3a**, 292.5 mg, 91%; white solid, mp 63 °C (lit.,[26] 64–66 °C); ν_{max} (Nujol) 3479, 3245, 1599, 1586, 1499, 1417, 1332, 1310, 1253, 1154, 1078, 1046, 1023, 952, 813, 750 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.75 (2H, d, $J=8.3$ Hz, *Ts*), 7.32–7.25 (4H, m, *Ar*), 6.97 (1H, t, $J=7.4$ Hz, *Ph*), 6.85 (2H, d, $J=8.1$ Hz, *Ph*), 5.12 (1H, t, $J=6.3$ Hz, N*H*), 4.11–4.07 (1H, m, C*H*OH), 3.96–3.91 (2H, m, CH_2OPh), 3.25 (1H, ddd, $J=3.9$, 7.0, 13.2 Hz, CH_aH_bN), 3.13–3.05 (1H, m, CH_aH_bN), 2.64 (1H, d, $J=4.6$ Hz, O*H*), 2.43 (3H, s, Ar*Me*). Anal. calcd for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N, 4.36. Found: C, 59.80; H, 5.93; N, 4.39.

4.2.2. *N*-(2-Hydroxy-2-phenyl-ethyl)-4-methyl-benzenesulfonamide (3b). 2-Phenyl-oxirane (**2c**); 6 h; Et_2O–PE 1:1. **3b**, 271.0 mg, 93%; white solid, mp 105–106 °C (lit.,[26] 107–108 °C); ν_{max} (Nujol) 3401, 3149, 1918, 1662, 1598, 1318, 1148, 1098, 1088, 1065 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72 (2H, d, $J=8.3$ Hz, *Ts*), 7.34–7.23 (8H, m, *Ar*+N*H*), 5.01–4.99 (1H, m, C*H*OH), 3.05 (1H, dd, $J=3.6$, 8.6 Hz, CH_aH_bN), 3.01 (1H, dd, $J=4.6$, 8.5 Hz, CH_aH_bN), 2.42 (3H, s, Ar*Me*), 2.31 (1H, d, $J=3.5$ Hz, O*H*). Anal. calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N 4.81. Found: C, 61.91; H, 5.92; N, 4.78.

4.2.3. *N*-(3-Allyloxy-2-hydroxy-propyl)-4-methyl-benzenesulfonamide (3c). 2-Allyloxymethyl-oxirane (**2f**); 2 h; AcOEt–PE 1:2. **3c**, 225.4 mg, 79%; wax; ν_{max} (Nujol) 3470, 3280, 2974, 1728, 1599, 1340, 1160, 1090, 994 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.71 (2H, d, $J=8.1$ Hz, *Ts*), 7.27 (2H, d, $J=8.1$ Hz, *Ts*), 5.88–5.75 (1H, m, =C*H*CH_2O), 5.37 (1H, t, $J=6.0$ Hz, N*H*), 5.24–5.13 (2H, m, CH_2=), 3.93 (2H, d, $J=5.2$ Hz, =CHCH_2O), 3.88–3.81 (1H, m, C*H*OH), 3.44–3.34 (2H, m, CH_2OAll), 3.12–3.04 (1H, m, CH_aH_bNH), 2.95–2.87 (1H, m, CH_aH_bNH), 2.90 (1H, bs, O*H*) 2.39 (3H, s, Ar*Me*). Anal. calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.81; H, 6.67; N, 4.81.

4.2.4. *N*-(2-Hydroxy-3-methoxy-propyl)-4-methyl-benzenesulfonamide (3d). 2-Methoxymethyl-oxirane (**2e**); 2 h; AcOEt–PE 1:1. **3d**, 215.2 mg, 83%; wax; ν_{max} (Nujol) 3392, 3284, 1926, 1662, 1598, 1332, 1162, 1222, 1055, 952, 901, 862, 816, 708, 662 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.73 (2H, d, $J=8.1$ Hz, *Ts*), 7.29 (2H, d, $J=8.1$ Hz, *Ts*), 5.11 (1H, t, $J=5.9$ Hz, N*H*), 3.87–3.80 (1H, m, C*H*OH), 3.42–3.35 (2H, m, CH_2OMe), 3.33 (3H, s, O*Me*), 3.14–3.06 (1H, m, CH_aH_bNH), 2.96–2.88 (1H, m, CH_aH_b-NH), 2.70 (1H, bs, O*H*), 2.41 (3H, s, Ar*Me*). Anal. calcd for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.40. Found: C, 50.89; H, 6.60; N, 5.46.

4.3. General method for the preparation of symmetric tosylamido diols 4 and 5

A heterogeneous mixture of $TsNH_2$ (**1**) (171 mg, 1 mmol), TEBA (23 mg, 0.1 mmol), epoxide **2** (3 mmol) solution in anhydrous dimethoxyethane or dioxane (0.75 mL) and anhydrous alkaline carbonate (0.1 mmol), was magnetically stirred at 80–90 °C until no starting material **1** was detectable (TLC analysis). After the usual workup, as described for the preparation of tosylamido alcohols **3**, the residue was purified by flash column chromatography on silica gel (230–400 mesh). Starting epoxide **2**, solvent, temperature, base, reaction time, chromatographic eluant, yield and physical, spectroscopic and analytical data of amido diols **4** and **5** are as follows.

4.3.1. Tosylamido diols 4a and 5a. 2-Hexyl-oxirane (**2a**); dimethoxyethane; 80 °C; Na_2CO_3; 10 h; Et_2O–PE 1:3. **4a**, 201.0 mg, 47%; white solid, mp 61–62 °C; ν_{max} (Nujol) 3392, 1909, 1737, 1600, 1494, 1343, 1158, 1099, 848, 764, 666 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.68 (2H, d, $J=8.2$ Hz, *Ts*), 7.32 (2H, d, $J=8.2$ Hz, *Ts*), 3.93–3.89 (2H, m, 2C*H*OH), 3.23 (2H, bs, 2O*H*), 3.02–2.99 (4H, m, 2CH_2N), 2.42 (3H, s, Ar*Me*), 1.43–1.27 (20H, m, 2C_5H_{10}), 0.86 (6H, t, $J=6.9$ Hz, 2*Me*). Anal. calcd for $C_{23}H_{41}NO_4S$: C, 64.60; H, 9.66; N, 3.28. Found: C, 64.71; H, 9.70, N, 3.26. **5a**, 205.3 mg, 48%; white solid, mp 86–87 °C; ν_{max} (Nujol) 3400–3200 (br), 1934, 1820, 1734, 1660, 1597, 1494, 1340, 1162, 1088, 848, 818, 726, 648 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.68 (2H, d, $J=8.2$ Hz, *Ts*), 7.33 (2H, d, $J=8.2$ Hz, *Ts*), 4.02–3.98 (2H, m, 2C*H*OH), 3.68 (2H, bs, 2O*H*), 3.37 (2H, dd, $J=14.7$, 2.4 Hz, 2CH_aCH_bN), 2.76 (2H, dd, $J=14.7$, 9.8 Hz, 2CH_aCH_bN), 2.43 (3H, s, Ar*Me*), 1.37–1.27 (20H, m, 2C_5H_{10}), 0.87 (6H, t, $J=6.9$ Hz, 2*Me*). Anal. calcd for $C_{23}H_{41}NO_4S$: C, 64.60; H, 9.66; N, 3.28. Found: C, 64.68; H, 9.72; N, 3.20.

4.3.2. Tosylamido diols 4b and 5b. 2-Phenoxymethyl-oxirane (**2b**); dimethoxyethane; 80 °C; Na_2CO_3; 6 h; Et_2O–PE 1:1. **4b**, 212.2 mg, 45%; white solid, mp 75 °C; ν_{max} (Nujol) 3369 (br), 1598, 1587, 1335, 1248, 1146, 1087, 942, 917, 809, 751 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72 (2H, d, $J=8.2$ Hz, *Ts*), 7.35–7.24 (6H, m, *Ar*), 6.97 (2H, t, $J=7.4$ Hz, *Ph*), 6.89 (4H, d, $J=8.1$ Hz, *Ph*), 4.38–4.31 (2H, m, 2C*H*OH), 4.02 (4H, d, $J=5.2$ Hz, 2CH_2OPh), 3.48 (2H, d, $J=4.5$ Hz, 2O*H*), 3.36 (4H, d, $J=5.7$ Hz, 2CH_2N), 2.42 (3H, s, Ar*Me*). Anal. calcd for $C_{25}H_{29}NO_6S$: C, 63.67; H, 6.20; N, 2.97. Found: C, 63.60; H, 6.26; N, 3.00. **5b**, 212.2 mg, 45%; white solid, mp 112 °C; ν_{max} (Nujol) 3233 (br), 1597, 1587, 1494, 1342, 1249, 1161, 1040, 993, 922, 813, 751 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72 (2H, d, $J=8.2$ Hz, *Ts*), 7.33–7.24 (6H, m, *Ar*), 6.96 (2H, t, $J=7.3$ Hz, *Ph*), 6.89 (4H, d, $J=8.2$ Hz, *Ph*), 4.43–4.37 (2H, m, 2C*H*OH), 4.00 (4H, d, $J=5.2$ Hz, 2CH_2OPh), 3.66 (2H,

bs, 2O*H*), 3.60 (2H, dd, $J=15.0$, 2.9 Hz, 2CH_aH_bN), 3.20 (2H, dd, $J=15.0$, 8.6 Hz, 2CH_aH$_b$N), 2.42 (3H, s, Ar*Me*). Anal. calcd for $C_{25}H_{29}NO_6S$: C, 63.67; H, 6.20; N, 2.97. Found: C, 63.56; H, 6.25; N, 2.93.

4.3.3. Tosylamido diols 4c and 5c. 2-Phenyl-oxirane (**2c**); dioxane; 90 °C; Cs_2CO_3; 6 h; Et_2O–PE 2:3. **4c**, 156.4 mg, 38%; white solid, mp 82–83 °C; ν_{max} (Nujol) 3294 (br), 1730, 1599, 1343, 1158, 1065, 952, 844, 811 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.68 (2H, d, $J=8.3$ Hz, *Ts*), 7.43–7.25 (12H, m, *Ar*), 5.13 (2H, dd, $J=10.0$, 3.0 Hz, 2C*H*OH), 3.44 (2H, d, $J=3.0$ Hz, 2O*H*), 3.33 (2H, dd, $J=14.7$, 10.0 Hz, 2C$H_a$$H_b$N), 3.17 (2H, dd, $J=14.7$, 3.0 Hz, 2CH_aH$_b$N), 2.38 (3H, s, Ar*Me*). Anal. calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.40. Found: C, 67.18; H, 6.18; N, 3.33. **5c**, 152.2 mg, 37%; white solid, mp 166–168 °C; ν_{max} (Nujol) 3310, 3196, 1733, 1599, 1344, 1154, 1088, 1056, 991, 869, 814 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.67 (2H, d, $J=8.3$ Hz, *Ts*), 7.44–7.25 (12H, m, *Ar*), 5.24 (2H, dd, $J=9.8$, 2.5 Hz, 2C*H*OH), 3.60 (2H, dd, $J=15.0$, 2.5 Hz, 2C$H_a$$H_b$-N), 4.16 (2H, bs, 2O*H*), 2.99 (2H, dd, $J=15.0$, 9.8 Hz, 2CH_aH$_b$N), 2.38 (3H, s, Ar*Me*). Anal. calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.40. Found: C, 67.20, H, 6.08; N, 3.46.

4.4. General method for the preparation of non-symmetric tosylamido diols 6 and 7

A heterogeneous mixture of tosylamido alcohol **3** (1 mmol), TEBA (23 mg, 0.1 mmol), epoxide **2** (1.1 mmol) solution in anhydrous dioxane (1.5 mL) and anhydrous alkaline carbonate (0.1 mmol), was magnetically stirred at 90 °C until no starting material **1** was detectable (TLC analysis). After the usual workup, the residue was purified by flash column chromatography on silica gel (230–400 mesh). Starting oxirane **2**, tosylamido alcohol **3**, base, reaction time, chromatographic eluant, yield and physical, spectroscopic and analytical data of non-symmetric tosylamido diols **6** and **7** are as follows.

4.4.1. Tosylamido diols 6a and 7a. 2-Hexyl-oxirane (**2a**), **3a**; K_2CO_3; 11 h; AcOEt–PE 1:6. **6a**, 157.4 mg, 35%; white solid, mp 67–69 °C; ν_{max} (Nujol) 3316, 3258, 1918, 1733, 1602, 1589, 1500, 1343, 1247, 1158, 1042, 980, 911, 816, 752, 655 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.70 (2H, d, $J=$ 8.2 Hz, *Ts*), 7.35–7.25 (4H, m, *Ar*), 6.95 (1H, t, $J=7.3$ Hz, *Ph*), 6.89 (2H, d, $J=8.1$ Hz, *Ph*), 4.36–4.29 (1H, m, C$H_{c'}$OH), 4.05–4.00 (2H, m, CH_2OPh), 3.95 (1H, m, CH_cOH), 3.62 (1H, bs, O*H*), 3.35 (1H, dd, $J=14.7$, 8.0 Hz, C$H_{a'}H_{b'}$N), 3.26 (1H, dd, $J=14.7$, 3.4 Hz, C$H_{a'}$H$_{b'}$-N), 3.19 (1H, bs, O*H*), 3.12 (1H, dd, $J=14.4$, 3.7 Hz, C$H_a$$H_b$N), 3.05 (1H, dd, $J=14.4$, 8.2 Hz, CH_aH$_b$N), 2.43 (3H, s, Ar*Me*), 1.43–1.25 (10H, m, C_5H_{10}), 0.88 (3H, t, $J=$ 6.9 Hz, *Me*). Anal. calcd for $C_{24}H_{35}NO_5S$: C, 64.11; H, 7.85; N, 3.12. Found: C, 63.10; H, 7.90; N, 3.07. **7a**, 157.4 mg, 35%; white solid, mp 88–89 °C; ν_{max} (Nujol) 3320, 3272, 1912, 1730, 1600, 1590, 1504, 1350, 1252, 1156, 988, 912, 756 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.69 (2H, d, $J=8.3$ Hz, *Ts*), 7.32–7.24 (4H, m, *Ar*), 6.95 (1H, t, $J=$ 7.3 Hz, *Ph*), 6.88 (2H, d, $J=8.0$ Hz, *Ph*), 4.38–4.23 (1H, m, C$H_{c'}$OH), 4.20 (1H, bs, O*H*), 4.03–3.99 (1H, m, CH_cOH), 3.99–3.92 (2H, m, CH_2OPh), 3.65 (1H, bs, O*H*), 3.62 (1H, dd, $J=14.9$, 2.7 Hz, C$H_{a'}H_{b'}$N), 3.38 (1H, dd, $J=14.7$, 2.3 Hz, C$H_a$$H_b$N), 3.08 (1H, dd, $J=14.9$, 8.8 Hz, C$H_{a'}$H$_{b'}$-N), 2.87 (1H, dd, $J=14.7$, 9.6 Hz, CH_aH$_b$N), 2.42 (3H, s, Ar*Me*), 1.41–1.26 (10H, m, C_5H_{10}), 0.87 (3H, t, $J=6.9$ Hz, *Me*). Anal. calcd for $C_{24}H_{35}NO_5S$: C, 64.11; H, 7.85; N, 3.12. Found: C, 64.22; H, 7.90; N, 3.16.

4.4.2. Tosylamido diols 6b and 7b. Phenyl-oxirane (**2c**), **3a**; Cs_2CO_3; 22 h; methyl-*tert*-butyl ether–PE 2:3. **6b**, 159.0 mg, 36%; white solid, mp 104–106 °C; ν_{max} (Nujol) 3552, 3320, 1733, 1599, 1590, 1344, 1246, 1154, 963, 812, 754, 660 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.69 (2H, d, $J=$ 8.2 Hz, *Ts*), 7.40–7.25 (9H, m, *Ar*), 6.97 (1H, t, $J=7.3$ Hz, *Ph*), 6.91 (2H, d, $J=8.0$ Hz, *Ph*), 5.15 (1H, dd, $J=2.9$, 9.6 Hz, C*H*Ph), 4.36–4.32 (1H, m, C*H*CH$_2$OPh), 4.06 (2H, d, $J=5.2$ Hz, CH_2OPh), 3.48 (1H, dd, $J=8.1$, 14.0 Hz, C$H_a$$H_b$N), 3.44 (2H, bs, 2O*H*), 3.34–3.25 (2H, m, CH_2N), 3.21–3.17 (1H, m, CH_aH$_b$N), 2.40 (3H, s, Ar*Me*). Anal. calcd for $C_{24}H_{27}NO_5S$: C, 65.28; H, 6.16; N, 3.17. Found: C, 63.80; H, 6.70; N, 3.06. **7b**, 159.0 mg, 36%; white solid, mp 93.5–95.5 °C; ν_{max} (Nujol) 3540, 3332, 1730, 1602, 1594, 1350, 1260, 1156, 964, 820, 758, 662 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.70 (2H, d, $J=8.2$ Hz, *Ts*), 7.40–7.24 (9H, m, *Ar*), 7.00–6.89 (3H, m, *Ph*), 5.21 (1H, dd, $J=9.7$, 2.5 Hz, C*H*Ph), 4.52–4.42 (1H, m, C*H*CH$_2$OPh), 4.00 (2H, d, $J=5.3$ Hz, CH_2OPh), 3.66 (1H, dd, $J=15.0$, 2.7 Hz, C$H_{a'}H_{b'}$N), 3.53 (1H, dd, $J=14.7$, 2.5 Hz, CH_aH$_b$N), 3.12 (1H, dd, $J=14.7$, 8.7 Hz, C$H_{a'}$H$_{b'}$N), 3.10 (1H, dd, $J=14.7$, 9.7 Hz, CH_aH$_b$N), 2.62 (2H, bs, 2O*H*), 2.41 (3H, s, Ar*Me*). Anal. calcd for $C_{24}H_{27}NO_5S$: C, 65.28; H, 6.16; N, 3.17. Found: C, 64.90; H, 6.40; N, 3.12.

4.4.3. Tosylamido diols 6c, 7c. 2-*tert*-Butoxymethyl-oxirane (**2f**), **3a**; Na_2CO_3; 48 h; AcOEt–PE 1:3. **6c**, **7c** (50:50), 316.1 mg, 70%; colourless oil; ν_{max} (neat) 3391 (br), 3064, 3041, 2975, 2926, 2877, 1928, 1736, 1599, 1494, 1456, 1390, 1348, 1305, 1246, 1168, 1089, 974, 816, 755, 692, 665 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.70 (2H-**6c**+2H-**7c**, d, $J=8.8$ Hz, *Ts*), 7.31–7.23 (4H-**6c**+4H-**7c**, m, *Ar*), 6.94 (1H-**6c**+1H-**7c**, t, $J=7.3$ Hz, *Ph*), 6.88 (2H-**6c**+2H-**7c**, d, $J=7.3$ Hz, *Ph*), 4.39–4.32 (1H-**7c**, m, C*H*CH$_2$OPh), 4.30–4.25 (1H-**6c**, m, C*H*CH$_2$OPh), 4.16–3.92 (3H-**6c**+ 3H-**7c**, m, 2CH_2OPh+2C*H*CH$_2$OBu^t), 3.76 (2H-**6c**+2H-**7c**, bs, 4O*H*), 3.62 (2H-**7c**, dd, $J=14.7$, 2.9 Hz, 2C$H_a$$H_b$N), 3.47 (2H-**6c**, dd, $J=14.7$, 2.9 Hz, 2CH_aH$_b$N), 3.44–3.14 (2H-**6c**+2H-**7c**, m, 2CH_2OBu^t), 3.10 (2H-**6c**, dd, $J=14.7$, 8.8 Hz, 2CH_aH$_b$N), 3.03 (2H-**7c**, dd, $J=14.7$, 8.8 Hz, 2CH_aH$_b$N), 2.41 (3H-**6c**+3H-**7c**, s, 2Ar*Me*), 1.17 (9H, s, CMe_3), 1.16 (9H, s, CMe_3). Anal. calcd for $C_{23}H_{33}NO_6S$: C, 61.17; H, 7.37; N, 3.10. Found: C, 60.98; H, 7.21; N, 3.12.

4.4.4. Tosylamido diols 6d, 7d. 2-*tert*-Butoxymethyl-oxirane (**2f**), **3c**; Na_2CO_3; 20 h; AcOEt–PE 1:8. **6d**, **7d** (45:55); 290.9 mg, 70%, wax; ν_{max} (Nujol) 3402 (br), 2975, 1727, 1646, 1599, 1494, 1391, 1342, 1290, 1195, 1163, 1089, 996, 925, 816, 753, 659 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.70 (2H-**6d**+2H-**7d**, d, $J=8.1$ Hz, 2*Ts*), 7.31 (2H-**6d**+ 2H-**7d**, d, $J=8.1$ Hz, 2*Ts*), 5.95–5.82 (1H-**6d**+1H-**7d**, m, 2C*H*=CH$_2$), 5.29–5.16 (2H-**6d**+2H-**7d**, m, 2CH_2=), 4.17–4.14 (1H-**7d**, m, C*H*CH$_2$OAll), 4.09–4.06 (1H-**6d**, m, C*H*CH$_2$OAll), 4.01 (2H-**6d**+2H-**7d**, dd, $J=2.9$, 15.4 Hz, 2OCH_2CH=CH$_2$), 3.84 (2H, bs, 2O*H*), 3.70 (2H, bs, 2O*H*), 3.47 (2H-**6d**+2H-**7d**, d, $J=5.1$ Hz, 2CH_2-OAll), 3.21 (2H-**6d**+2H-**7d**, d, $J=5.5$ Hz, 2CH_2OBu^t),

3.53–3.12 (5H-**6d**+3H-**7d**, m, (C*H*CH$_2$OBu^t+2C*H*$_2$N)+(CH$_a$*H*$_b$N+CH$_{a'}$*H*$_{b'}$N+C*H*CH$_2$OBu^t), 3.05–2.97 (1H-**7d**, m, C*H*$_{a'}$H$_{b'}$N), 3.04–2.96 (1H-**7d**, m, C*H*$_a$H$_b$N), 2.42 (3H-**6d**+3H-**7d**, s, 2Ar*Me*), 1.18 (9H, s, C*Me*$_3$), 1.17 (9H, s, C*Me*$_3$). Anal. calcd for $C_{20}H_{33}NO_6S$: C, 57.81; H, 8.00; N, 3.37. Found: C, 57.67; H, 8.09; N, 3.31.

4.4.5. Tosylamido diols 6e, 7e. 2-Phenoxymethyl-oxirane (**2b**), **3d**; Na_2CO_3; 20 h; AcOEt–PE 2:3. **6e**, **7e** (50:50), 335.8 mg, 82%; colourless oil; ν_{max} (neat) 3392 (br), 3064, 2925, 1599, 1588, 1494, 1455, 1338, 1246, 1160, 1089, 995, 816, 757, 693, 658 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.71 (2H-**6e**+2H-**7e**, d, J=8.3 Hz, *Ts*), 7.34–7.24 (4H-**6e**+4H-**7e**, m, *Ar*), 6.96 (1H-**6e**+1H-**7e**, t, J=7.3 Hz, *Ph*), 6.89 (2H-**6e**+2H-**7e**, d, J=7.9 Hz, *Ph*), 4.54 (2H-**6e**+2H-**7e**, bs, 4O*H*), 4.43–4.25 (1H-**6e**+1H-**7e**, m, 2C*H*OH), 4.22–4.03 (1H-**6e**+1H-**7e**, m, 2C*H*OH), 4.02–3.96 (2H-**6e**+2H-**7e**, m, 2C*H*$_2$OPh), 3.63–3.51 (2H-**7e**, m, CH$_a$*H*$_b$N+CH$_{a'}$*H*$_{b'}$N), 3.48–3.42 (2H-**6e**+2H-**7e**, m, 2C*H*$_2$OMe), 3.38 (3H, s, O*Me*), 3.37 (3H, s, O*Me*), 3.34–3.22 (4H-**6e**, m, 2C*H*$_2$N), 3.19–2.98 (2H-**7e**, m, C*H*$_a$H$_b$N+C*H*$_{a'}$H$_{b'}$N), 2.43 (3H-**6e**+3H-**7e**, s, 2Ar*Me*). Anal. calcd for $C_{20}H_{27}NO_6S$: C, 58.66; H, 6.65; N, 3.42. Found: C, 58.72; H, 6.44; N, 3.32.

4.5. General method for the preparation of 2,6-dialkyl-4-(toluene-4-sulfonyl)-morpholines 10–13

In a flame-dried round bottomed flask, 60% sodium hydride (84 mg, 2.1 mmol) was rinsed with anhydrous *n*-pentane (3×0.5 mL). A tosylamido diol **4–7** (1 mmol) solution in anhydrous dichloromethane or dimethoxyethane (5 mL) was cooled at 0 °C and then added to the NaH by syringe, under nitrogen atmosphere. The reaction mixture was stirred at 0 °C until hydrogen evolution ended. A solution of tosyl chloride (TsCl, 1 mmol) or trifuoromethanesulfonic anhydride (Tf_2O, 1 mmol) in dichloromethane (DCM, 5 mL) or dimethoxyethane (DME, 5 mL) was added to the reaction mixture and the stirring was continued at 25–40 °C until disappearance of the starting diol **4–7** (TLC analysis). After cooling, H_2O (2 mL) was added, DCM was evaporated under reduced pressure and the residue was extracted with AcOEt (4×10 mL). The organic phase was dried over sodium sulfate, the solvent was evaporated to dryness under vacuum and the crude was purified by flash column chromatography on silica gel (230–400 mesh). Starting tosylamido diol **4–7**, cyclization agent (TsCl or Tf_2O), solvent, temperature, reaction time, chromatographic eluant, yield and physical, spectroscopic and analytical data are as follows.

4.5.1. Morpholine 10a. Tosylamido diol **4a**; Tf_2O; DCM; 25 °C; 6 h; Et_2O–PE 1:18. **10a**, 319.5 mg, 78%; white solid, mp 56 °C; ν_{max} (Nujol) 1922, 1666, 1600, 1493, 1348, 1170, 1128, 1094, 1000, 956, 816, 784, 663, 619 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.61 (2H, d, J=8.2 Hz, *Ts*), 7.32 (2H, d, J=8.2 Hz, *Ts*), 3.54 (2H, d, J=10.8 Hz, 2CH$_a$*H*$_b$N), 3.50–3.44 (2H, m, 2C*H*O), 2.43 (3H, s, Ar*Me*), 1.92 (2H, dd, J=10.8, 10.8 Hz, 2C*H*$_a$H$_b$N), 1.54–1.25 (20H, m, 2C$_5$*H*$_{10}$), 0.87 (6H, t, J=6.9 Hz, 2*Me*). Anal. calcd for $C_{23}H_{39}NO_3S$: C, 67.44; H, 9.60; N, 3.42. Found: C, 67.20; H, 9.68; N, 3.41.

4.5.2. Morpholine 11a. Tosylamido diol **5a**; Tf_2O; DME; 25 °C; 6 h; AcOEt–PE 1:20. **11a**, 327.7 mg, 80%; white solid, mp 40–41 °C; ν_{max} (Nujol) 1600, 1364, 1170, 1092, 949, 814, 677 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.60 (2H, d, J=8.2 Hz, *Ts*), 7.32 (2H, d, J=8.2 Hz, *Ts*), 3.79–3.73 (2H, m, 2C*H*O), 2.98 (2H, dd, J=11.2, 3.3 Hz, 2CH$_a$*H*$_b$N), 2.67 (2H, dd, J=11.2, 5.8 Hz, 2C*H*$_a$H$_b$N), 2.43 (3H, s, Ar*Me*), 1.65–1.27 (20H, m, 2C$_5$*H*$_{10}$), 0.87 (6H, t, J=6.9 Hz, 2*Me*). Anal. calcd for $C_{23}H_{39}NO_3S$: C, 67.44; H, 9.60; N, 3.42. Found: C, 67.12; H, 9.52; N, 3.40.

4.5.3. Morpholine 10b. Tosylamido diol **4b**; Tf_2O; DCM; 25 °C; 13 h; AcOEt–PE 1:10. **10b**, 349.2 mg, 77%; white solid, 125–127 °C; ν_{max} (Nujol) 1599, 1586, 1494, 1341, 1254, 1211, 1160, 1119, 1052, 1036, 999, 814, 753, 692, 666 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.66 (2H, d, J=8.2 Hz, *Ts*), 7.36–7.25 (6H, m, *Ar*), 6.96 (2H, t, J=7.3 Hz, *Ph*), 6.87 (4H, d, J=8.1 Hz, *Ph*), 4.08–4.04 (4H, m, 2C*H*O+C*H*$_2$OPh), 3.92–3.87 (4H, m, 2CH$_a$*H*$_b$N+C*H*$_2$OPh), 2.44 (3H, s, Ar*Me*), 2.26 (2H, dd, J=10.8, 10.8 Hz, 2C*H*$_a$H$_b$N). Anal. calcd for $C_{25}H_{27}NO_5S$: C, 66.20; H, 6.00; N, 3.09. Found: C, 66.11; H, 5.98; N, 3.06.

4.5.4. Morpholine 11b. Tosylamido diol **5b**; Tf_2O; DCM; 40 °C; 6 h; AcOEt–PE 1:8. **11b**, 362.8 mg, 80%; white solid, mp 143–145 °C; ν_{max} (Nujol) 1601, 1582, 1492, 1341, 1252, 1160, 1120, 1050, 998, 814, 754, 690, 666 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.65 (2H, d, J=8.2 Hz, *Ts*), 7.34–7.27 (6H, m, *Ar*), 6.97 (2H, t, J=7.3 Hz, *Ph*), 6.89 (4H, d, J=8.0 Hz, *Ph*), 4.28–4.25 (2H, m, 2C*H*O), 4.13 (2H, dd, J=9.6, 5.4 Hz, CH$_{a'}$*H*$_{b'}$OPh), 4.11 (2H, dd, J=9.6, 6.4 Hz, C*H*$_{a'}$H$_{b'}$OPh), 3.25 (2H, dd, J=11.6, 3.3 Hz, 2CH$_a$*H*$_b$N), 3.04 (2H, dd, J=11.6, 5.7 Hz, 2C*H*$_a$H$_b$N), 2.43 (3H, s, Ar*Me*). Anal. calcd for $C_{25}H_{27}NO_5S$: C, 66.20; H, 6.00; N, 3.09. Found: C, 66.31; H, 6.07; N, 3.05.

4.5.5. Morpholine 10c. Tosylamido diol **4c**; TsCl; DCM; 40 °C; 22 h; Et_2O–PE 1:3. **10c**, 279.4 mg, 71%; white solid, mp 128–130 °C; ν_{max} (Nujol) 1960, 1821, 1732, 1597, 1494, 1341, 1228, 1166, 1068, 962, 814, 776, cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.59 (2H, d, J=8.2 Hz, *Ts*), 7.47–7.27 (12H, m, *Ar*), 4.85 (2H, dd, J=10.6, 2.5 Hz, 2C*H*O), 3.89 (2H, dd, J=10.6, 2.5 Hz, 2CH$_a$*H*$_b$N), 2.41 (3H, s, Ar*Me*), 2.28 (2H, dd, J=10.6, 10.6 Hz, 2C*H*$_a$H$_b$N). Anal. calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56. Found: C, 70.09; H, 5.60; N, 3.61.

4.5.6. Morpholine 11c. Tosylamido diol **5c**; TsCl; DCM; 40 °C; 72 h; Et_2O–PE 1:3. **11c**, 259.7 mg, 66%; wax; ν_{max} (Nujol) 1962, 1823, 1732, 1596, 1495, 1342, 1306, 1230, 1167, 1089, 1065, 961, 926, 815, 774, 702, 692, 651 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.65 (2H, d, J=8.2 Hz, *Ts*), 7.46–7.30 (12H, m, *Ar*), 4.90 (2H, dd, J=5.7, 3.7 Hz, 2C*H*O), 3.35 (2H, dd, J=11.6, 5.7 Hz, 2CH$_a$*H*$_b$N), 3.27 (2H, dd, J=11.6, 3.7 Hz, 2C*H*$_a$H$_b$N), 2.45 (3H, s, Ar*Me*). Anal. calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56. Found: C, 70.33; H, 5.90; N, 3.60.

4.5.7. Morpholine 12a. Tosylamido diol **6a**; Tf_2O; DCM; 25 °C; 2 h; Et_2O–PE 1:1. **12a**, 366.8 mg, 85%; colourless oil; ν_{max} (neat) 1661, 1600, 1496, 1378, 1302, 1245, 1169, 1121, 1094, 815, 754, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.64 (2H, d, J=8.2 Hz, *Ts*), 7.33 (2H, d, J=8.2 Hz, *Ts*), 7.30–7.24 (2H, m, *Ph*), 6.95 (1H, t, J=7.3 Hz, *Ph*), 6.87 (2H, d, J=8.2 Hz, *Ph*), 4.05–4.00 (1H, m, C*H*O), 4.00–3.92

(1H, m, C*H*O), 3.86–3.81 (2H, m, CH_2OPh), 3.63–3.57 (2H, m, CH$_a$$H_b$N+CH$_{a'}$$H_{b'}$N), 2.43 (3H, s, Ar*Me*), 2.16 (1H, dd, *J*=10.8, 10.4 Hz, C$H_{a'}$H$_{b'}$N), 2.00 (1H, dd, *J*=11.2, 11.2 Hz, CH_aH$_b$N), 1.49–1.25 (10H, m, C_5H_{10}), 0.87 (3H, t, *J*=7.0 Hz, *Me*). Anal. calcd for $C_{24}H_{33}NO_4S$: C, 66.79; H, 7.71; N, 3.25. Found: C, 66.64; H, 7.78; N, 3.20.

4.5.8. Morpholine 13a. Tosylamido diol **7a**; Tf_2O; DCM; 25 °C; 7 h; AcOEt–PE 1:9. **13a**, 332.3 mg, 77%; colourless oil; ν_{max} (neat) 1662, 1598, 1588, 1496, 1376, 1300, 1244, 1168, 1120, 1093, 812, 754, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (2H, d, *J*=8.2 Hz, *Ts*), 7.33–7.24 (4H, m, *Ar*), 6.96 (1H, t, *J*=7.3 Hz, *Ph*), 6.87 (2H, d, *J*=8.2 Hz, *Ph*), 4.20–4.17 (1H, m, C*H*CH$_2$OPh), 4.12 (1H, dd, *J*=9.4, 5.4 Hz, CH$_a$$H_b$OPh), 4.02 (1H, dd, *J*=9.4, 6.4 Hz, CH_aH$_b$-OPh), 3.84–3.81 (1H, m, C*H*C_6H_{13}), 3.15 (1H, dd, *J*=11.4, 3.3 Hz, CH$_{a'}$$H_{b'}$N), 3.08 (1H, dd, *J*=11.4, 3.3 Hz, CH$_a$$H_b$-N), 2.98 (1H, dd, *J*=11.4, 5.5 Hz, C$H_{a'}$H$_{b'}$N), 2.73 (1H, dd, *J*=11.4, 6.0 Hz, CH_aH$_b$N), 2.42 (3H, s, Ar*Me*), 1.70–1.66 (2H, m, CHCH_2), 1.37–1.22 (8H, m, C_4H_8), 0.87 (3H, t, *J*=6.9 Hz, *Me*). Anal. calcd for $C_{24}H_{33}NO_4S$: C, 66.79; H, 7.71; N, 3.25. Found: C, 66.90; H, 7.78; N, 3.20.

4.5.9. Morpholine 12b. Tosylamido diol **6b**; TsCl; DCM; 25 °C; 54 h; AcOEt–PE 1:7. **12b**, 194.8 mg, 46%; white solid, mp 124–126 °C; ν_{max} (Nujol) 1598, 1586, 1492, 1344, 1238, 1166, 1122, 1066, 1052, 966, 774, 756 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (2H, d, *J*=8.2 Hz, *Ts*), 7.37–7.25 (9H, m, *Ar*), 6.97 (1H, t, *J*=7.3 Hz, *Ph*), 6.89 (2H, d, *J*=8.2 Hz, *Ph*), 4.73 (1H, dd, *J*=10.5, 2.4 Hz, C*H*Ph), 4.20–4.12 (1H+1H, m, C*H*CH$_2$OPh+CH$_a$$H_b$N), 3.99–3.93 (2H, m, C$H_2$OPh), 3.82 (1H, d, *J*=11.0 Hz, CH$_{a'}$$H_{b'}$N), 2.43 (3H, s, Ar*Me*), 2.32 (1H, dd, *J*=10.5, 10.5 Hz, CH_aH$_b$N), 2.22 (1H, dd, *J*=11.0, 11.0 Hz, C$H_{a'}$H$_{b'}$N). Anal. calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 67.92; H, 5.91; N, 3.23. Together with **13b** (29.6 mg, 7%).

4.5.10. Morpholine 13b. Tosylamido diol **7b**; TsCl; DCM; 25 °C; 28 h; AcOEt–PE 1:7. **13b**, 275.3 mg, 65%; white solid, mp 146–148 °C; ν_{max} (Nujol) 1598, 1587, 1493, 1345, 1236, 1167, 1131, 1122, 1065, 1051, 968, 813, 776, 757, 682 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.64 (2H, d, *J*=8.2 Hz, *Ts*), 7.44–7.24 (9H, m, *Ar*), 6.96 (1H, t, *J*=7.3 Hz, *Ph*), 6.90 (2H, d, *J*=8.2 Hz, *Ph*), 4.95 (1H, dd, *J*=6.9, 3.2 Hz, C*H*Ph), 4.24–4.18 (1H, m, C*H*CH$_2$OPh), 4.21–4.18 (2H, m, CH_2OPh), 3.41 (1H, dd, *J*=11.8, 3.2 Hz, CH$_a$$H_b$N), 3.29 (1H, dd, *J*=11.5, 3.9 Hz, CH$_{a'}$$H_{b'}$N), 3.10 (1H, dd, *J*=11.5, 2.6 Hz, C$H_{a'}$H$_{b'}$N), 3.06 (1H, dd, *J*=11.8, 6.9 Hz, CH_aH$_b$-N), 2.43 (3H, s, Ar*Me*). Anal. calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 68.20; H, 5.92; N, 3.42. Together with **12b** (12.7 mg, 3%) and **14b** (59.3 mg, 14%). Vinyl tosylamide **14b**; wax; ν_{max} (Nujol) 3320, 3040, 1734, 1600, 1588, 1345, 1246, 1156, 964, 814, 756, 660 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.64 (2H, d, *J*=8.2 Hz, *Ts*), 7.44–7.24 (9H, m, *Ar*), 6.96 (1H, t, *J*=7.3 Hz, *Ph*), 6.90 (2H, d, *J*=8.2 Hz, *Ph*), 5.97 (1H, dt, *J*=6.2, 6.2 Hz, C*H*=CHN), 5.48 (1H, d, *J*=7.7 Hz, CH=C*H*N), 4.88–4.73 (3H, m, CH_2-OPh+C*H*Ph), 3.42–3.34 (1H+1H, m, OH+CH$_a$$H_b$N), 3.15–3.07 (1H, m, C$H_aH_b$N), 2.40 (3H, s, Ar*Me*). Anal. calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 68.21; H, 5.89; N, 3.08.

4.5.11. Morpholines 12c and 13c. Tosylamido diols **6c**, **7c** (50:50); Tf_2O; DCM; 25 °C; 5 h; AcOEt–PE 1:10. **12c**, 320.8 mg, 74%; wax; ν_{max} (Nujol) 1599, 1580, 1346, 1247, 1167, 1120, 1087, 814, 756 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.65 (2H, d, *J*=8.4 Hz, *Ts*), 7.35–7.24 (4H, m, *Ar*), 6.95 (1H, t, *J*=7.4 Hz, *Ph*), 6.86 (2H, d, *J*=7.7 Hz, *Ph*), 4.10–3.96 (1H+1H, m, 2C*H*O), 3.86–3.73 (4H, m, CH_2OPh+CH_2OBu^t), 3.47 (1H, dd, *J*=11.0, 4.8 Hz, CH$_a$$H_b$N), 3.23 (1H, dd, *J*=11.0, 7.0 Hz, CH$_{a'}$$H_{b'}$N), 2.44 (3H, s, Ar*Me*), 2.20 (1H, dd, *J*=11.0, 11.0 Hz, C$H_{a'}$H$_{b'}$N), 2.09 (1H, dd, *J*=11.0, 11.0 Hz, CH_aH$_b$N), 1.15 (9H, s, CMe_3). Anal. calcd for $C_{23}H_{31}NO_5S$: C, 63.72; H, 7.21; N, 3.23. Found: C, 63.42; H, 7.18; N, 3.20.

Compound **13c**. 277.5 mg, 64%; wax; ν_{max} (Nujol) 1600, 1576, 1346, 1246, 1168, 1120, 1086, 816, 758 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.63 (2H, d, *J*=8.1 Hz, *Ts*), 7.34–7.25 (4H, m, *Ar*), 6.96 (1H, t, *J*=7.4 Hz, *Ph*), 6.88 (2H, d, *J*=7.7 Hz, *Ph*), 4.22–4.17 (1H, m, C*H*CH$_2$OPh), 4.14–4.08 (1H, m, C*H*CH$_2$OBu^t), 4.00–3.89 (2H, m, CH_2OPh), 3.54 (2H, d, *J*=6.2 Hz, CH_2OBu^t), 3.31 (1H, dd, *J*=11.4, 2.9 Hz, CH$_{a'}$$H_{b'}$N), 3.07 (1H, dd, *J*=11.4, 4.8 Hz, CH$_a$$H_b$-N), 2.99 (1H, dd, *J*=11.4, 3.6 Hz, CH_aH$_b$N), 2.83 (1H, dd, *J*=11.4, 6.2 Hz, C$H_{a'}$H$_{b'}$N), 2.43 (3H, s, Ar*Me*), 1.19 (9H, s, CMe_3). Anal. calcd for $C_{23}H_{31}NO_5S$: C, 63.72; H, 7.21; N, 3.23. Found: C, 63.82; H, 7.24; N, 3.18.

4.5.12. Morpholines 12d and 13d. Tosylamido diols **6d**, **7d** (45:55); TsCl; DCM; 25 °C; 28 h; AcOEt–PE 1:8. **12d**, 278.3 mg, 70%; colourless oil; ν_{max} (neat), 3066, 2975, 2922, 2872, 1730, 1646, 1598, 1494, 1455, 1348, 1195, 1168, 1088, 996, 816, 787, 664 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.64 (2H, d, *J*=8.1 Hz, *Ts*), 7.33 (2H, d, *J*=8.1 Hz, *Ts*), 5.91–5.78 (1H, m, C*H*=CH$_2$), 5.26–5.16 (2H, m, CH_2=), 3.96 (2H, d, *J*=5.5 Hz, OCH_2CH=CH$_2$), 3.78–3.64 (4H, m, 2CH_2O), 3.53–3.43 (2H, m, C*H*O), 3.39 (1H, dd, *J*=11.0, 5.2 Hz, CH$_a$$H_b$N), 3.18 (1H, dd, *J*=11.0, 7.4 Hz, CH$_{a'}$$H_{b'}$N), 2.43 (3H, s, Ar*Me*), 2.14 (1H, dd, *J*=11.0, 11.0 Hz, C$H_{a'}$H$_{b'}$N), 2.03 (1H, dd, *J*=10.7, 10.7 Hz, CH_aH$_b$N), 1.14 (9H, s, CMe_3). Anal. calcd for $C_{20}H_{31}NO_5S$: C, 60.43; H, 7.86; N, 3.52. Found: C, 60.56; H, 7.78; N, 3.53.

Compound **13d**. 234.5 mg, 59%; colourless oil; ν_{max} (neat) 3526 (br), 3068, 2972, 2923, 2870, 1726, 1646, 1594, 1494, 1456, 1344, 1170, 1094, 994, 814, 785, 664 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (2H, d, *J*=8.1 Hz, *Ts*), 7.33 (2H, d, *J*=8.1 Hz, *Ts*), 5.93–5.78 (1H, m, C*H*=CH$_2$), 5.28–5.17 (2H, m, CH_2=), 3.98 (2H, d, *J*=5.9 Hz, OCH_2CH=CH$_2$), 3.89–3.87 (1H, m, C*H*O), 3.58–3.43 (5H, m, C*H*O+2CH_2O), 3.15 (1H, dd, *J*=11.4, 2.9 Hz, CH$_a$$H_b$N), 3.03 (1H, dd, *J*=11.4, 4.8 Hz, CH$_{a'}$$H_{b'}$N), 2.94 (1H, dd, *J*=11.4, 3.7 Hz, C$H_{a'}$H$_{b'}$N), 2.74 (1H, dd, *J*=11.4, 7.0 Hz, CH_aH$_b$-N), 2.43 (3H, s, Ar*Me*), 1.15 (9H, s, CMe_3). Anal. calcd for $C_{20}H_{31}NO_5S$: C, 60.43; H, 7.86; N, 3.52. Found: C, 60.60; H, 7.81; N, 3.44.

4.5.13. Morpholines 12e and 13e. Tosylamido diols **6e**, **7e** (50:50); Tf_2O; DCM; 25 °C; 5 h; AcOEt–PE 1:15. **12e**, 223.1 mg, 57%; colourless oil; ν_{max} (neat) 3063, 3040, 2917, 2850, 2057, 1929, 1746, 1599, 1494, 1456, 1347, 1245, 1168, 1000, 816, 757, 687 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.64 (2H, d, *J*=8.1 Hz, *Ts*), 7.35–7.24 (4H, m, *Ar*), 6.95 (1H, t, *J*=7.4 Hz, *Ph*), 6.86 (2H, d, *J*=8.1 Hz, *Ph*),

4.08–4.01 (1H, m, C*H*CH_2OPh), 4.00–3.98 (1H, m, C*H*CH_2OMe), 3.87–3.85 (2H, m, CH_2OPh), 3.84–3.82 (1H, m, CH_aH_bN), 3.68 (1H, dd, J=11.0, 1.0 Hz, $CH_{a'}H_{b'}$N), 3.43 (2H, dd, J=4.4, 1.5 Hz, CH_2OMe), 3.34 (3H, s, O*Me*), 2.44 (3H, s, Ar*Me*), 2.23 (1H, dd, J=11.0, 11.0 Hz, $CH_{a'}H_{b'}$N), 2.21 (1H, dd, J=11.0, 11.0 Hz, CH_aH_bN). Anal. calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.42; H, 6.32; N, 3.53.

Compound **13e**. 207.5 mg, 53%; colourless oil; ν_{max} (neat) 3064, 3042, 2918, 2848, 2058, 1927, 1746, 1600, 1496, 1456, 1350, 1244, 1169, 1000, 814, 758, 686 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.63 (2H, d, J=8.1 Hz, *Ts*), 7.34–7.25 (4H, m, *Ar*), 6.96 (1H, t, J=7.4 Hz, *Ph*), 6.89 (2H, d, J=8.1 Hz, *Ph*), 4.25–4.20 (1H, m, C*H*CH_2OMe), 4.18–4.15 (1H, m, C*H*CH_2OPh), 4.07–4.02 (2H, m, CH_2OPh), 3.60 (1H, dd, J=10.3, 5.1 Hz, $CH_{a'}H_{b'}$N), 3.51 (1H, dd, J=10.3, 5.1 Hz, $CH_{a'}H_{b'}$N), 3.37 (3H, s, O*Me*), 3.15 (2H, d, J=11.7 Hz, CH_2OMe), 3.06 (1H, dd, J=11.7, 5.1 Hz, CH_aH_bN), 2.88 (1H, dd, J=11.7, 6.6 Hz, CH_aH_bN), 2.43 (3H, s, Ar*Me*). Anal. calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.28; H, 6.52; N, 3.52.

4.6. General method for the preparation of 2,6-dialkylmorpholines 15

A mixture of *N*-tosyl morpholine **10–13** (1 mmol), 30% HBr–AcOH (6 mL, 30 mmol) and, if it is the case, phenol (0.28 g, 3 mmol) was magnetically stirred at 25–80 °C until no starting material was detectable (TLC analysis). After cooling, the reaction mixture was poured into ice (20 g), NaOH pellets were added until pH 8 was reached and the aqueous phase was extracted with AcOEt (4×10 mL); the organic phase was dried over sodium sulfate, evaporated under vacuum and purified by flash column chromatography on silica gel (230–400 mesh). Starting *N*-tosyl morpholine **10–13**, reaction time, chromatographic eluant, yield and physical, spectroscopic and analytical data of morpholines **15** are as follows.

4.6.1. Morpholine 15a. *N*-tosyl morpholine **10a**; 60 °C; 2 h; MeOH–CH_2Cl_2 1:20. **15a**, 166.0 mg, 65%; wax; ν_{max} (Nujol) 3350, 1920, 1668, 1600, 1497, 1168, 1096, 1000, 816, 784, 663, 619 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.82 (1H, bs, N*H*), 3.71–3.66 (2H, m, 2C*H*O), 3.14 (2H, dd, J=11.4, 1.2 Hz, $2CH_aH_b$N), 2.56 (2H, dd, J=11.4, 11.4 Hz, $2CH_aH_b$N), 1.45–1.26 (20H, m, $2C_5H_{10}$), 0.87 (6H, t, J=6.9 Hz, 2*Me*). Anal. calcd for $C_{16}H_{33}NO$: C, 75.23; H, 13.02; N, 5.48. Found: C, 75.11; H, 13.00; N, 5.51.

4.6.2. Morpholine 15b. *N*-tosyl morpholine **11a**; 80 °C; 4 h; MeOH–CH_2Cl 1:30. **15b**, 160.9 mg, 63%; wax; ν_{max} (Nujol) 3320, 1602, 1168, 1090, 949, 810, 678 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.82 (1H, bs, N*H*), 3.94–3.87 (2H, m, 2C*H*O), 3.17 (2H, dd, J=12.6, 3.6 Hz, $2CH_aH_b$N), 2.86 (2H, dd, J=12.6, 6.1 Hz, $2CH_aH_b$N), 1.86–1.77 (2H, m, CH_2CH), 1.51–1.39 (2H, m, $CHCH_2CH_2$), 1.36–1.27 (16H, m, $2C_2H_4$), 0.86 (6H, t, J=6.9 Hz, 2*Me*). Anal. calcd for $C_{16}H_{33}NO$: C, 75.23; H, 13.02; N, 5.48. Found: C, 75.34; H, 13.10; N, 5.40.

4.6.3. Morpholine 15c. *N*-tosyl morpholine **10b**; 60 °C; 4 h; MeOH–CH_2Cl_2 1:30. **15c**, 224.5 mg, 75%; wax; ν_{max} (Nujol) 3340, 1600, 1586, 1494, 1250, 1162, 1119, 1054, 1036, 813, 755, 694 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–6.76 (10H, m, *Ph*), 4.09–3.85 (6H, m, $2CH_2OPh+2CHO$), 3.14–3.06 (2H, m, $2CH_aH_b$N), 2.75–2.66 (2H, m, $2CH_aH_b$N), 1.80 (1H, bs, N*H*). Anal. calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.33; H, 7.04; N, 4.72.

4.6.4. Morpholine 15d. *N*-tosyl morpholine **11b**; 60 °C; 4 h; MeOH–CH_2Cl_2 1:20. **15d**, 224.5 mg, 75%; white solid, mp 75–77 °C; ν_{max} (Nujol) 3348, 1600, 1584, 1491, 1252, 1160, 1120, 1050, 816, 756, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.31–7.25 (4H, m, *Ph*), 6.98–6.91 (6H, m, *Ph*), 4.18–4.16 (2H, m, 2C*H*O), 4.20–4.10 (4H, m, $2CH_2OPh$), 3.12 (2H, dd, J=12.2, 3.0 Hz, $2CH_aH_b$N), 2.93 (2H, dd, J=12.2, 4.5 Hz, $2CH_aH_b$N), 2.21 (1H, bs, N*H*). Anal. calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.10; H, 7.04; N, 4.63.

4.6.5. Morpholine 15e. *N*-tosyl morpholine **10c**; 25 °C; 9 h; MeOH–CH_2Cl_2 1:30. **15e**, 146.0 mg, 61%; wax; ν_{max} (Nujol) 3344, 1962, 1820, 1734, 1597, 1496, 1226, 1164, 1068, 964, 812, 774, cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.46–7.25 (10H, m, *Ph*), 4.71 (2H, dd, J=10.5, 2.4 Hz, 2C*H*O), 3.13 (2H, dd, J=12.7, 2.4 Hz, $2CH_aH_b$N), 2.80 (2H, dd, J=12.7, 10.5 Hz, $2CH_aH_b$N), 2.00 (1H, bs, N*H*). Anal. calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.06; N, 5.85. Found: C, 80.42; H, 7.02; N, 5.78.

4.6.6. Morpholine 15f. *N*-tosyl morpholine **12a**; 25 °C; 24 h; MeOH–CH_2Cl_2 1:14. **15f**, 205.3 mg, 74%; colourless oil; ν_{max} (neat) 3342, 1662, 1599, 1586, 1498, 1300, 1244, 1166, 1122, 814, 754 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29–7.24 (2H, m, *Ph*), 6.94–6.87 (3H, m, *Ph*), 4.04 (1H, dd, J=8.6, 4.2 Hz, CH_aH_bOPh), 4.00–3.91 (1H, m, C*H*CH_2OPh), 3.89 (1H, dd, J=8.6, 5.3 Hz, CH_aH_bOPh), 3.62–3.50 (1H, m, C*H*C_6H_{13}), 3.19 (1H, dd, J=11.4, 11.4 Hz, CH_aH_bN), 2.99 (1H, dd, J=11.2, 11.2 Hz, $CH_{a'}H_{b'}$N), 2.95 (1H, bs, N*H*), 2.72 (1H, dd, J=11.2, 11.2 Hz, $CH_{a'}H_{b'}$N), 2.55 (1H, dd, J=11.4, 11.4 Hz, CH_aH_bN), 1.49–1.25 (10H, m, C_5H_{10}), 0.87 (3H, t, J=6.9 Hz, *Me*). Anal. calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.72; H, 9.76; N 5.12.

4.6.7. Morpholine 15g. *N*-tosyl morpholine **13a**; 25 °C; 24 h; MeOH–CH_2Cl_2 1:36. **15g**, 185.9 mg, 67%; colourless oil; ν_{max} (neat) 3338, 1660, 1599, 1588, 1494, 1302, 1245, 1166, 1118, 1095, 813, 756, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.28–7.23 (2H, m, *Ph*), 6.95–6.90 (3H, m, *Ph*), 4.13 (2H, d, J=5.7 Hz, CH_2OPh), 4.09–4.02 (1H, m, C*H*CH_2OPh), 3.76–3.69 (1H, m, C*H*C_6H_{13}), 3.04 (1H, dd, J=12.4, 3.5 Hz, $CH_{a'}H_{b'}$N), 2.96 (1H, dd, J=12.2, 3.3 Hz, CH_aH_bN), 2.87 (1H, dd, J=12.4, 4.9 Hz, $CH_{a'}H_{b'}$N), 2.61 (1H, dd, J=12.2, 6.4 Hz, CH_aH_bN), 2.01 (1H, bs, N*H*), 1.70–1.25 (10H, m, C_5H_{10}), 0.87 (3H, t, J=6.9 Hz, *Me*). Anal. calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.72; H, 9.75; N, 5.02.

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References and notes

1. Lanman, B. A.; Myers, A. G. *Org. Lett.* **2004**, *6*, 1045–1047.
2. Dave, R.; Sasaki, N. A. *Org. Lett.* **2004**, *6*, 15–18.
3. Meki, N.; Takano, J. JP 01254680; *Chem. Abstr.* **1990**, *112*, 179000.
4. Antony, V. M.; Worthington, P. A. EP 253498; *Chem. Abstr.* **1988**, *109*, 6529.
5. Camaggi, G.; Filippini, L.; Gusmeroli, M.; Riva, R.; Garavaglia, C.; Mirenna, L. EP 521465; *Chem. Abstr.* **1993**, *118*, 212675.
6. Carson, C. M.; Copping, L. G.; Ehr, R. J.; Gitlitz, M. H.; McNeil, M. W.; Street, P. F. S.; Liebeschuetz, M. H. EP 313353; *Chem. Abstr.* **1989**, *111*, 154100.
7. Meki, N.; Takano, H. EP 262870; *Chem. Abstr.* **1989**, *110*, 192837.
8. Worthing, C. R. *The Pesticide Manual*, 7th ed.; British Crop Protection Council: 1983; pp 265, 550.
9. Wegler, R. In *Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel*; Springer: Berlin, 1970; Vol. 2, p 123.
10. Wegler, R. In *Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel*; Springer: Berlin, 1977; Vol. 4, p 219.
11. Bowers, W. S.; Ebing, W.; Fukuto, T. R.; Martin, D. In *Chemistry of Plant Protection*; Springer: Berlin, 1986; Vol. 1, pp 55–56.
12. Licandro, E.; Maiorana, S.; Papagni, A.; Pryce, M.; Zanotti-Gerosa, A.; Riva, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1891–1894.
13. Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, S.; Zanotti-Gerosa, A. *J. Organomet. Chem.* **1995**, *486*, 279–282.
14. Hikichi, M.; Yokokura, T.; Furuta, T.; Yaegashi, T. JP 62135472; *Chem. Abstr.* **1987**, *107*, 198358.
15. GB 831933; *Chem. Abstr.* **1961**, *55*, 2697.
16. Sharma, M. M. BE 660875; *Chem. Abstr.* **1966**, *64*, 33470.
17. Scott, C. R.; Ayers, A. L.; Mahan, J. E. US 2771737; *Chem. Abstr.* **1957**, *51*, 19438.
18. Kotaka, N.; Saito, R.; Motokawa, N. JP 02111765; *Chem. Abstr.* **1990**, *113*, 132199.
19. Tanaka, K. JP 01313576; *Chem. Abstr.* **1990**, *112*, 237012.
20. Sanne, W.; Koenig, K. H.; Pommer, H.; Stummeyer, H. BE 614214; *Chem. Abstr.* **1963**, *58*, 27366.
21. Payman, J. B., Piggot, H. A. GB 298336; *Chem. Abstr.* **1929**, *23*, 22918.
22. Payman, J. B.; Piggot, H. A. US 1859527; *Chem. Abstr.* **1932**, *26*, 36615.
23. Bettoni, G.; Franchini, C.; Perrone, R.; Tortorella, V. *Tetrahedron* **1980**, *36*, 409–415.
24. Hernestam, S. *J. Heterocycl. Chem.* **1983**, *20*, 1681–1685.
25. Langdon, W. K.; Ernest, J.; Levis, W. W., Jr. GB 835717; *Chem. Abstr.* **1961**, *55*, 13519.
26. Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Tetrahedron* **1999**, *55*, 6387–6394.
27. Li, G.; Sharpless, K. B. *Acta Chem. Scand.* **1996**, *50*, 649–651.

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Convenient synthesis of melatonin analogues: 2- and 3-substituted -*N*-acetylindolylalkylamines

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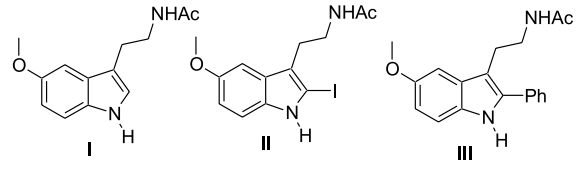
Abstract—A new method for the synthesis of 2- and 3-substituted indolylalkylamides, derivatives of melatonin, from arylhydrazines and amidoketones by the Fischer reaction was elaborated. The amidoketones can be easily prepared from cyclic imines by reaction with acylpyridinium chloride. This method is a one-step synchronous creation of the selected alkylamide fragment and the indole core. Variation of the arylhydrazines create the desired substituents in the carbocycle of indolylalkylamides and suitable choice of amidoketone can direct the amidoalkyl chain to the 2- or 3-position of the indole.

1. Introduction

Melatonin **I** (5-methoxy-*N*-acetyltryptamine) is a hormone which regulates a number of neuroendocrine and physiological processes. Seasonal changes in various aspects of physiology in photoperiodic species, such as sheep and hamsters, are controlled by actions of melatonin. Melatonin administration can also entrain the circadian clock by a direct action on the CNS. Many studies have also indicated an influence on immune function and antioxidant actions.

Melatonin is a derivative of indolylalkylamines, which have importance as a main structural unit of indole alkaloids which contain many biologically active substances and remedies.[1] Recently, derivatives of 2-substituted tryptamines have attracted a lot of attention because of their high selectivity for serotonin,[2] melatonin[3] and gonadotropin releasing hormone[4] receptors. Substitution at the 2-position of the indole ring of melatonin also increases affinity and potency; in part because steric effects restrict the flexible C-3 side-chain allowing easier docking at the active site of the receptor. For example, 2-position substitution improves affinity at both melatonin receptor subtypes ML1 and ML2; 2-iodomelatonin **II** and 2-phenylmelatonin **III** show a ~10-fold improvement in affinity ($K_i \sim 60$ pM) over melatonin itself. Other analogues which have been used to characterise melatonin binding sites are 6-chloromelatonin, an agonist and *N*-acetyltryptamine, a partial agonist (Scheme 1).[5]



Scheme 1.

Four general approaches exist to *N*-acylindolylalkylamines. The first is an acylation of a previously synthesized indolylalkylamines.[6] The second consists in attaching the acylamine fragment to the indole core.[7] The third involves multi-step modification of the 3-indole substituent into the acylamine chain.[8] The forth lies in the synchronous creation of the selected acylamine fragment and the indole core and is the method of choice because it should provide a shortened and simplified procedure.

To fulfil such an approach there is the Fischer reaction. It has been applied to the synthesis of 2-unsubstituted indolylalkylamides from amidoaldehydes (with the aminogroup protected by Phth-,[9] Boc-[10] or Cbz[11]-group). Reaction of cyclic amidoketones (with Phth-,[12] carbamoyl-,[13] benzoyl-[14] or acetyl-[15] protective group) with arylhydrazines leads to indoles condensed with saturated cycle (with nitrogen atom in cycle or attached to it). It should be noted that in most cases protective groups remained intact during the Fischer reaction so it is the main way for the direct synthesis of melatonin derivatives.

Keywords: Melatonin; Cyclic imines; Amidoketones; Arylhydrazines; Fischer reaction; Indoles.
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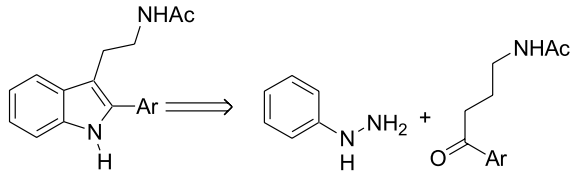
Recently,[16] we elaborated an easy and scaleable procedure for the synthesis of previously unknown 2-arylindolylalkylamines from arylhydrazones of 6-aminohexanones, which readily undergo Fischer rearrangement in glacial acetic acid. On the basis of this work we developed a new and effective synthesis of melatonin analogues from derivatives of aminoketones.

2. Results and discussion

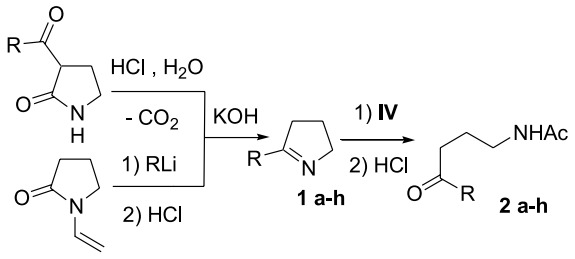
We proposed that arylketones with a *N*-acyl group should give rise to 2-aryl substituted indolylalkylamides in the Fischer reaction (Scheme 2).



Scheme 2.

At the first step we aimed at developing a convenient synthesis of arylketones with a *N*-acyl group from aminoketones. We chose α-acyllactams as the starting materials for synthesis of the aminocarbonyl compounds on the basis of literature analysis: they can be obtained by Claisen condensation of an *N*-protected lactam and ester. Recently we thoroughly investigated this condensation of the 5-, 6- and 7-membered lactams with various esters.[17] On the basis of NMR spectra we have found out that in the case of 5-membered 3-acyllactams, acidic hydrolysis and decarboxylation[18] leads to mixture of cyclic imines and aminoketones. Thus, the reaction mixture was basified by 50% KOH and pure cyclic imines were obtained. In the case of readily available organolithium derivatives or acidic-sensitive substituents reaction of organolithium reagents with *N*-vinylpyrrolidone was used,[19–24] and it was also basified to give the cyclic imines.

There are rare examples of acylation of cyclic imines to amidoketones,[20,25,26] but none lead to satisfactory results. So we developed a new method of acylation using *N*-acetylpyridinium chloride **IV**. The results are shown in Scheme 3 and Table 1.

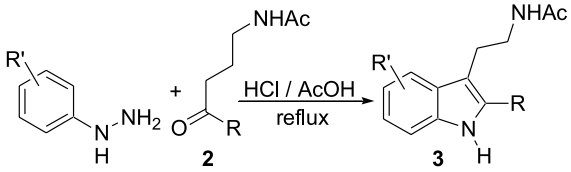


Scheme 3.

Table 1. Synthesis of 2-substituted cyclic imines **1a–c** (from 3-acyllactams), imines **1d–h** (by reaction of *N*-vinyllpirrolidone with RLi) and synthesis of amidoketones **2a–h**

R	Imine, yield, %	Amidoketone, yield, %
C_6H_5	**1a**, 89	**2a**, 91
$C_6H_5CH_2$	**1b**, 85	**2b**, 86
Me	**1c**, 70	**2c**, 75
4-Me–C_6H_4	**1d**, 65	**2d**, 95
2,4-MeO–C_6H_3	**1e**, 60	**2e**, 70
2-Thienyl	**1f**, 65	**2f**, 87
2-Furyl	**1g**, 65	**2g**, 80
n-Bu	**1h**, 50	**2h**, 85

We introduced amidoketones **2** in the Fischer reaction and the corresponding indolylalkylamides **3** and **4** were obtained in good to near quantitative yields using acetic acid saturated with gaseous HCl as catalyst (Scheme 4 and Table 2).



Scheme 4.

Table 2. Synthesis of 2-substituted *N*-acetyltryptamines **3a**, **d–g**, **i–m**

N-Acetyl-tryptamine	R	R′	Yield, %
3a	C_6H_5	H	93
3d	4-Me–C_6H_4	H	95
3e	2,4-MeO–C_6H_3	H	65
3f	2-Thienyl	H	66
3g	2-Furyl	H	43[a]
3i	C_6H_5	5-F	64
3j	C_6H_5	5-Cl	87
3k	C_6H_5	5-Br	80
3l	C_6H_5	5-MeO	85[b]
3m	C_6H_5	7-Et	84

[a] Ethyl ester of polyphosphoric acid (PPE, 3 equiv), 1 h, 85 °C.
[b] Glacial AcOH, reflux, 10 min.

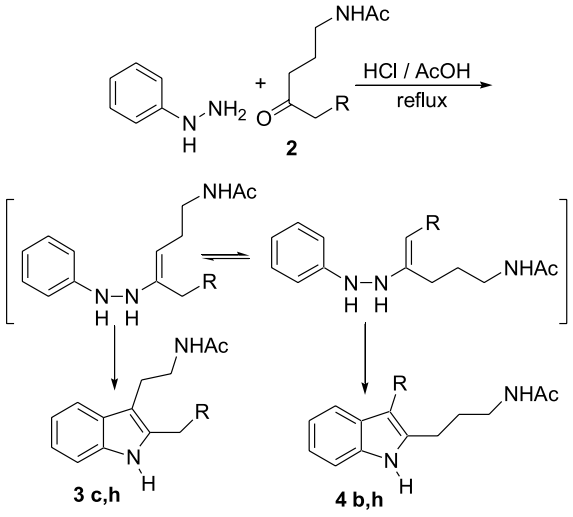
To investigate the scope of the method and the effect of substituents on the yield of the Fischer reaction, various arylhydrazines with donor and acceptor groups were synthesized.[27] It was found that in all cases *N*-acetyltryptamines were isolated in good to high yields. Generally no restriction of hydrazine or ketone structure for this approach was found. Yields are quite good except in the case of amidoketone **2g** with a furyl substituent, when this conditions of Fischer rearragement lead to tar formation. Thus, we selected a more soft catalyst, namely ethyl ester of polyphosphoric acid[28] (PPE, 3 equiv), to give 2-furyl-*N*-acetyltryptamine **3g**. 2-Phenylmelatonin was obtained in high yield from 4-methoxyphenylhydrazone of amidoketone **2a** by refluxing it for 10 min in pure acetic acid.

Amidoketones with two CH_2 units at carbonyl group has two ways for Fischer indolyzation. Thus, it opens possibilities to synthesize two different classes of

indolylalkylamides, containing an amidoalkyl chain in the 2- or 3-position of the indole core. To investigate the effect of substituents on the regioselectivity of the Fischer rearrangement, we synthesized compounds **2b**, **2c** and **2h**.

Reaction of **2b** with phenylhydrazine gives rises only to *N*-acetylizohomotryptamine **4b** with a Ph group in the 3-position of the indole core. We explain that regioselectivity due to stabilization of enehydrazine by mesomeric conjugation of ene-bond with the aromatic core. In the case of amidoketone **2c** also only **3c** was obtained, because one enehydrazine is more stable thermodynamically in comparison with the other terminal enhydrazine, so this factor is decisive for direction of the reaction to proceed.

4-Oxooctyl-*N*-acetamide **2h** reacted with phenylhydrazine giving a mixture of **3h** (2-butyl-*N*-acetyltryptamine) and **4h** (3-propyl-*N*-acetylizohomotryptamine) in 1:2 ratio, both of which can be easily separated by flash chromatography (Scheme 5 and Table 3).



Scheme 5.

Table 3. Direction of indolyzation of amidoketones **2b**, **2c** and **2h**

N-Acetylindolylalkylamine	R	Yield, %
4b	Ph	93
3c	H	77
3h/4h	Pr	90 (1/2)

The reaction of amidoketones with two alkyl substituents at the carbonyl group allows preparation of previously unknown 3-subsituted *N*-acetylizohomotryptamines and shows that preferable direction of indolyzation depends on the stability of the intermediate enehydrazines.

3. Conclusion

We have described a new method for the synthesis of 2- and 3-substituted indolylalkylamides, derivatives of melatonin, from arylhydrazines and amidoketones by the Fischer reaction. The amidoketones can be easily prepared from cyclic imines by reaction with acylpyridinium chloride. It should be noted especially, that our method is a one-step synchronous creation of the selected acylamine fragment and the indole core. Variation of the arylhydrazines creates the desired substituents in the carbocycle of indolylalkylamides and suitable choice of amidoketone directs the amidoalkyl chain to the 2- or 3-position of the indole.

4. Experimental

4.1. General

TLC was performed with 'Silufol UV-254' plates, and flash chromatography was carried out with silica gel (63–200 mesh), using EtOAc/CH_2Cl_2 in 1:2 proportions. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions (if not mentioned otherwise) were respectively recorded at 400 and 100 MHz, TMS was used as internal standard. IR spectra were recorded in thin layer for liquid and in nujol for solid substances.

4.2. General procedure for the synthesis of *N*-(4-oxo-4-substituted butyl)-acetamides

To a well stirred solution of 1.6 mL (20 mmol) pyridine in 20 mL abs. CH_2Cl_2 solution of 0.71 mL (0.8 g, 10 mol) AcCl in 10 mL abs. CH_2Cl_2 was slowly added and mixture was stirred an additional 15 min.

To a suspension of *N*-acetylpyridinium chloride obtained solution of 10 mmol cyclic imine **1a–h** in 25 mL abs. CH_2Cl_2 was added dropwise with stirring. After addition reaction mixture was stirred until *N*-acetylpyridinium salt was dissolved totally and then an additional 10 min.

To a clear solution obtained 20 mL 5% HCl was added with intensive stirring and after 15 min of it organic layer was separated, washed with water (2×20 mL), dried with Na_2SO_4 and evaporated. The residue was triturated with hexanes giving amidoketones **2a–h**.

4.2.1. *N*-(4-Oxo-4-phenylbutyl)acetamide (2a). White crystal solid, 1.87 g, yield 91%, mp 95 °C. IR, (ν, cm^{-1}): 1640 (O=CNH), 1680 (PhC=O). ^1H NMR δ 1.93 (s, 3H), 1.96 (tt, J=6.7, 5.9 Hz, 2H), 3.03 (t, J=6.7 Hz, 2H), 3.32 (dt, J=6.7, 5.9 Hz, 2H), 5.93 (bs, 1H), 7.44 (t, J=7.6 Hz, 2H), 7.55 (t, J=7.6 Hz, 1H), 7.93 (d, J=7.6 Hz, 2H). ^{13}C NMR δ 23.3, 23.7, 36.0, 39.3, 128.0 (2C), 128.6 (2C), 133.2, 136.6, 169.0, 200.0. Calcd for $C_{12}H_{15}NO_2$, C 70.40, H 7.28; found C 70.22, H 7.37.

4.2.2. *N*-(4-Oxo-5-phenylpentyl)acetamide (2b). Brown crystal solid, 1.89 g, yield 86%, mp 43–44 °C. IR, (ν, cm^{-1}): 1640 (O=CNH), 1700 ($PhCH_2C$=O). ^1H NMR δ 1.72 (tt, J=6.7 Hz, 2H), 1.87 (s, 3H), 2.5 (t, J=6.7 Hz, 2H), 3.14 (dt, J=6.7 Hz, 2H), 3.67 (s, 2H), 5.8 (bs, 1H), 7.18 (d, J=7.0 Hz, 2H), 7.25 (tt, J=7.3, 7.0 Hz, 1H), 7.31 (t, J=7.3 Hz, 2H). ^{13}C NMR δ 23.1, 23.2, 38.9, 39.2, 50.1, 127.0, 128.7 (2C), 129.3 (2C), 134.0, 170.2, 208.2. Calcd for $C_{13}H_{17}NO_2$ C 72.21, H 7.81; found C 72.29, H 7.81.

4.2.3. *N*-(4-Oxopentyl)acetamide (2c). Red crystal solid, 1.07 g, yield 75%, mp 48–50 °C. IR, (ν, cm^{-1}): 1630 (O═CN), 1700 (CH_3C═O). ^1H NMR δ 1.71 (tt, J=7.0, 6.7 Hz, 2H), 1.9 (s, 3H), 2.1 (s, 3H), 2.45 (t, J=7.0 Hz, 2H), 3.16 (dt, J=6.7, 5.9 Hz, 2H), 6.2 (bs, 1H). ^{13}C NMR δ 23.0, 23.3, 30.0, 39.9, 40.9, 170.4, 208.7. Calcd for $C_7H_{13}NO_2$, C 58.72, H 9.15; found C 58.31, H 8.91.

4.2.4. *N*-(4-Oxo-4-(4-methylphenyl)-butyl)acetamide (2d). Yellowish crystal solid, 2.08 g, yield 95%, mp 118–120 °C. IR, (ν, cm^{-1}): 1630 (O═CNH), 1665 (ArC═O). ^1H NMR δ 1.92 (s, 3H), 1.93 (tt, J=7.0, 6.7 Hz, 2H), 2.38 (s, 3H), 3.0 (t, J=7.0 Hz, 2H), 3.35 (dt, J=6.7, 5.9 Hz, 2H), 6.00 (bs, 1H), 7.23 (d, J=8.1 Hz, 2H), 7.82 (d, J=8.1 Hz, 2H). ^{13}C δ NMR 21.5, 23.3, 23.7, 36.0, 39.3, 128.0 (2C), 129.3 (2C), 134.2, 144.0, 170.0, 200.0. Calcd for $C_{13}H_{17}NO_2$, C 72.21, H 7.81; found C 72.41, H 7.95.

4.2.5. *N*-(4-Oxo-4-(2,4-dimethoxyphenyl)butyl)acetamide (2e). Brown crystal solid, 1.86 g, yield 70%, mp 78–80 °C. IR, (ν, cm^{-1}): 1640 (O═CNH), 1680 (ArC═O). ^1H NMR δ 1.87 (tt, J=7.0, 6.7 Hz, 2H), 1.92 (s, 3H), 2.98 (t, J=7.0 Hz, 2H), 3.26 (dt, J=6.7, 5.6 Hz, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 6.07 (bs, 1H), 6.42 (d, J=2.3 Hz, 1H), 6.49 (dd, J=8.8, 2.3 Hz, 1H), 7.76 (d, J=8.8 Hz, 1H). ^{13}C NMR δ 23.3, 23.7, 39.7, 41.3, 55.4, 55.5, 98.3, 105.2, 120.7, 132.5, 160.7, 164.5, 170.3, 200.0. Calcd for $C_{14}H_{19}NO_4$ C 63.38, H 7.22; found C 62.84, H 7.25.

4.2.6. *N*-(4-Oxo-4-thien-2-ylbutyl)acetamide (2f). White crystal solid, 1.84 g, yield 87%, mp 72 °C. IR, (ν, cm^{-1}): 1640 (O═CNH), 1660 (thienyl-CO). ^1H NMR δ 1.67 (tt, J=7.0, 6.7 Hz, 2H), 1.82 (s, 3H), 2.45 (t, J=6.7 Hz, 2H), 3.09 (dt, J=6.7, 5.9 Hz, 2H), 5.75 (bs, 1H), 7.08–7.27 (m, 3H). ^{13}C NMR δ 23.3, 23.7, 36.0, 39.3, 128.0, 131.8, 133.5, 143.8, 170.0, 192.0. Calcd for $C_{10}H_{13}NO_2S$, C 56.85, H 6.20; found C 56.65, H 6.07.

4.2.7. *N*-[4-(2-Furyl)-4-oxobutyl]acetamide (2g). Grey crystal solid, 1.56 g, yield 80%, mp 66–68 °C. IR, (ν, cm^{-1}): 1640 (O═CNH), 1655 (furyl-C═O). ^1H NMR δ 1.91 (tt, J=7.0, 6.7 Hz, 2H), 1.92 (s, 3H), 2.87 (t, J=7.0 Hz, 2H), 3.29 (dt, J=6.7, 5.9 Hz, 2H), 6.07 (bs, 1H), 6.50 (dd, J=3.5, 1.8 Hz, 1H), 7.17 (dd, J=3.5, 0.6 Hz, 1H), 7.55 (dd, J=1.8, 0.6 Hz, 1H). ^{13}C NMR δ 23.3, 23.7, 36.0, 39.3, 112.0, 146.5, 117.3, 152.5, 170.0, 189.0. Calcd for $C_{10}H_{13}NO_3$, C 61.53, H 6.71; found C 61.36, H 6.62.

4.2.8. *N*-(4-Oxooctyl)acetamide (2h). Brownish crystal solid, 1.57 g, yield 85%, mp 65–67 °C. IR, (ν, cm^{-1}): 1640 (O═CN), 1695 (CH_2C═O). ^1H NMR δ 0.84 (t, J=7.3 Hz, 3H), 1.24 (dt, J=7.6, 7.3 Hz, 2H), 1.48 (tt, J=7.6, 7.3 Hz, 2H), 1.72 (tt, J=7.0, 6.7 Hz, 2H), 1.91 (s, 3H), 2.35 (t, J=7.3 Hz, 2H), 2.42 (t, J=7.0 Hz, 2H), 3.17 (dt, J=6.7, 5.9 Hz, 2H), 6.16 (bs, 1H). ^{13}C NMR δ 13.7, 22.2, 23.1, 23.2, 25.8, 39.2, 40.0, 42.5, 170.3, 211.2. Calcd for $C_{10}H_{19}NO_2$, C 64.83, H 10.34; found C 64.56, H 10.20.

4.3. General procedure for the synthesis of *N*-acetylindolylalkylamines

Mixture of 11 mmol arylhydrazine (salt or free base), 10 mmol *N*-(4-oxo-4-substituted butyl)acetamide in 20 mL acetic acid, saturated with gaseous HCl at 20 °C, was quickly warmed to boiling. When all solids were dissolved refluxing was continued for 5 min. Then reaction mixture was evaporated and distributed between water and CH_2Cl_2. Organic phase was washed with water (2×20 mL) and evaporated. The flash chromatography of the residue afforded the products.

4.3.1. *N*-[2-(2-Phenyl-1*H*-indol-3-yl)ethyl]acetamide (3a). Cream crystal solid, 2.59 g, yield 93%, mp 114–116 °C. R_f (EtOAc)=0.45. IR, (ν, cm^{-1}): 1620 (O═CNH). ^1H NMR δ 1.73 (s, 3H), 3.11 (t, J=6.7 Hz, 2H), 3.52 (dt, J=6.7, 6.2 Hz, 2H), 5.53 (bs, 1H), 7.14 (t, J=7.0 Hz, 1H), 7.21 (t, J=7.0 Hz, 1H), 7.35 (t, J=7.3 Hz, 1H), 7.38 (d, J=8.1 Hz, 1H), 7.45 (t, J=7.3 Hz, 2H), 7.56 (d, J=7.3 Hz, 2H), 7.62 (d, J=8.1 Hz, 1H), 8.48 (bs, 1H). ^{13}C NMR δ 23.1, 24.4, 40.1, 109.6, 111.0, 118.8, 119.8, 122.3, 127.7, 127.9 (2C), 128.9 (2C), 132.9, 133.2, 135.3, 135.9, 170.1. Calcd for $C_{18}H_{18}N_2O$, C 77.67, H 6.52; found C 77.67, H 6.50.

4.3.2. *N*-[3-(3-Phenyl-1*H*-indol-2-yl)propyl]acetamide (4b). Grey crystal solid, 2.75 g, yield 93%, mp 123 °C. R_f (EtOAc)=0.6. IR, (ν, cm^{-1}): 1620 (O═CNH). ^1H NMR δ 1.72 (tt, J=6.5, 6.2 Hz, 2H), 1.84 (s, 3H), 2.76 (t, J=6.5 Hz, 2H), 3.19 (dt, J=6.5, 6.2 Hz, 2H), 5.63 (bs, 1H), 7.01 (t, J=7.0 Hz, 1H), 7.09 (t, J=7.0 Hz, 1H), 7.23 (t, J=7.0 Hz, 1H), 7.37 (m, 5H), 7.55 (d, J=7.9 Hz, 1H), 9.70 (bs, 1H). ^{13}C NMR δ 22.3, 23.0, 30.2, 38.3, 111.0, 114.0, 118.6, 116.6, 121.4, 125.8, 127.6, 128.6 (2C), 129.6 (2C), 135.1, 135.4, 135.6, 171.5. Calcd for $C_{19}H_{20}N_2O$, C 78.05, H 6.89; found C 77.93, H 6.86.

4.3.3. *N*-[2-(2-Methyl-1*H*-indol-3-yl)ethyl]acetamide (3c). Yellowish solid, 1.67 g, yield 77%, mp 83–85 °C. R_f (EtOAc)=0.4. IR, (ν, cm^{-1}): 1620 (O═CNH). ^1H NMR δ 1.88 (s, 3H), 2.36 (s, 3H), 2.90 (t, J=6.7 Hz, 2H), 3.48 (dt, J=6.7, 6.2 Hz, 2H), 5.57 (bs, 1H), 7.06 (t, J=7.3 Hz, 1H), 7.11 (t, J=7.3 Hz, 1H), 7.26 (d, J=7.3 Hz, 1H), 7.47 (d, J=7.3 Hz, 1H), 8.14 (bs, 1H). ^{13}C NMR δ 11.5, 23.3, 24.1, 40.0, 108.4, 110.3, 117.7, 119.3, 121.1, 128.6, 131.9, 135.3, 170.0. Calcd for $C_{13}H_{16}N_2O$, C 72.19, H 7.46; found C 72.09, 7.13 H.

4.3.4. *N*-{2-[2-(4-Methylphenyl)-1*H*-indol-3-yl]ethyl} acetamide (3d). White crystal solid, 2.78 g, yield 95%, mp 165–166 °C. R_f (EtOAc)=0.5. IR, (ν, cm^{-1}): 1620 (O═CNH). IR, (ν, cm^{-1}): 1620 (O═CNH). ^1H NMR δ 1.76 (s, 3H), 2.4 (s, 3H), 3.11 (t, J=6.7 Hz, 2H), 3.54 (dt, J=6.7, 6.2 Hz, 2H), 5.44 (bs, 1H), 7.14 (t, J=7.0 Hz, 1H), 7.21 (t, J=7.0 Hz, 1H), 7.28 (d, J=8.1 Hz, 2H), 7.38 (d, J=8.1 Hz, 1H), 7.44 (d, J=8.1 Hz, 2H), 7.62 (d, J=8.1 Hz, 1H), 8.16 (bs, 1H). ^{13}C NMR δ 21.2, 23.2, 24.4, 40.2, 109.5, 110.9, 118.8, 119.8, 122.3, 127.8 (2C), 129.1, 129.7 (2C), 130.0, 135.4, 135.8, 137.9, 170.0. Calcd for $C_{19}H_{20}N_2O$, C 78.05, H 6.89; found C 78.01, H 6.89.

4.3.5. *N*-{2-[2-(2,4-Dimethoxyphenyl)-1*H*-indol-3-yl]ethyl}acetamide (3e). Yellowish crystal solid, 2.2 g, yield 65%, mp 161–163 °C. R_f (EtOAc)=0.5. IR, (ν, cm^{-1}): 1620 (O═CNH). ^1H NMR δ 1.76 (s, 3H), 3.0 (t, J=6.4 Hz, 2H), 3.50 (dt, J=6.4, 6.2 Hz, 2H), 3.82 (s, 3H), 3.85 (s, 3H), 5.52 (bs, 1H), 6.58–6.61 (m, 2H), 7.11 (t, J=7.5 Hz, 1H),

7.18 (t, J=7.5 Hz, 1H), 7.37 (dd, J=8.0, 5.0 Hz, 2H) 7.61 (d, J=7.5 Hz, 1H), 8.47 (bs, 1H). ^{13}C NMR δ 23.1, 24.5, 39.7, 55.5, 55.6, 99.2, 104.9, 109.9, 110.7, 113.9, 118.5, 119.3, 121.9, 128.2, 132.0, 132.5, 135.6, 158.1, 161.0, 169.9. Calcd for $C_{20}H_{22}N_2O_3$, C 70.99, H 6.55; found C 70.81, H 6.57.

4.3.6. *N*-{2-[2-(2-Thienyl)-1*H*-indol-3-yl]ethyl}acetamide (3f). Cream crystal solid, 1.88 g, yield 66%, mp 113–116 °C. R_f (EtOAc)=0.55. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.81 (s, 3H), 3.17 (t, J=6.5 Hz, 2H), 3.51 (q, J=6.5 Hz, 2H), 5.57 (bs, 1H), 7.12 (m, 2H), 7.21 (t, J=7.0 Hz, 1H), 7.29 (d, J=4.3 Hz, 1H), 7.33 (d, J=4.3 Hz, 1H), 7.36 (d, J=8.1 Hz, 1H), 7.58 (d, J=8.1 Hz, 1H), 8.45 (bs, 1H). ^{13}C NMR δ 23.2, 24.7, 39.9, 110.5, 110.9, 118.8, 120.0, 122.9, 124.9, 125.3, 127.8, 129.1, 129.2, 134.4, 135.9 170.3. Calcd for $C_{16}H_{16}N_2OS$, C 67.58, H 5.67; found C 67.71, H 5.71.

4.3.7. *N*-[2-(2-Butyl-1*H*-indol-3-yl)ethyl]acetamide (3h). Yellowish oil, 0.78 g, yield 30%. R_f (EtOAc)=0.7. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 0.94 (t, J=7.3 Hz, 3H), 1.39 (m, 2H), 1.64 (m, 2H), 1.89 (s, 3H), 2.72 (t, J=7.6 Hz, 2H), 2.91 (t, J=6.7 Hz, 2H), 3.51 (dt, J=6.7, 6.2 Hz, 2H), 5.54 (bs, 1H), 7.07 (td, J=7.0, 1.2 Hz, 1H), 7.13 (td, J=7.0, 1.2 Hz, 1H), 7.28 (dd, J=7.0, 1.2 Hz, 1H), 7.5 (dd, J=7.0, 1.2 Hz, 1H), 8.02 (bs, 1H). ^{13}C NMR δ 14.3, 22.3, 23.2, 24.2, 26.3, 30.4, 38.6, 110.6, 111.5, 118.2, 118.5, 120.6, 128.5, 134.5, 135.3, 171.2. Calcd for $C_{16}H_{22}N_2O$, C 74.38, H 8.58; found C 74.28, H 8.47.

4.3.8. *N*-[3-(3-Propyl-1*H*-indol-2-yl)propyl]acetamide (4h). White solid, 1.55 g, yield 60%, mp 120 °C. R_f (EtOAc)=0.4. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 0.96 (t, J=7 Hz, 3H), 1.64 (m, 2H), 1.78 (m, 2H), 1.98 (s, 3H), 2.66 (t, J=6.5 Hz, 2H), 2.72 (m, 2H), 3.32 (dt, J=6.5, 6.2 Hz, 2H), 5.95 (bs, 1H), 7.02–7.15 (m, 2H), 7.32 (d, J=7.9 Hz, 1H), 7.51 (d, J=7.9 Hz, 1H), 9.35 (bs, 1H). ^{13}C NMR δ 14.2, 19.5, 23.0, 23.5, 27.6.2, 30.3, 41.2, 111.5, 114.4, 118.7, 119.2, 120.6, 130.8, 132.6, 135.2, 171.5. Calcd for $C_{16}H_{22}N_2O$, C 74.38, H 8.58; found C 74.33, H 8.45.

4.3.9. *N*-[2-(5-Fluoro-2-phenyl-1*H*-indol-3-yl)ethyl]acetamide (3i). Yellow crystals, 1.90 g, yield 64%, mp 147–149 °C. R_f (EtOAc)=0.62. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.71 (s, 3H), 3.06 (t, J=6.7 Hz, 2H), 3.49 (dt, J=6.7 Hz, 2H), 5.48 (bs, 1H), 6.94 (td, J=8.7, 2.5 Hz, 1H), 7.24–7.30 (m, 2H), 7.37 (t, J=7.3 Hz, 1H), 7.46 (t, J=7.3 Hz, 2H), 7.55 (d, J=7.3 Hz, 2H), 8.22 (bs, 1H). ^{13}C NMR (DMSO-d^6) δ 22.6, 25.0, 40.1, 103.2 (d, J=23.4 Hz), 109.3 (d, J=4.4 Hz), 109.6 (d, J=26.4 Hz), 112.12 (d, J=10.2 Hz), 127.6, 127.8 (2C), 128.7 (2C), 129.1 (d, J=10.3 Hz), 132.5, 132.6, 136.6, 156.9 (d, J=231.3 Hz), 169.2. Calcd for $C_{18}H_{17}N_2OF$, C 72.95, H 5.78; found C 72.79, H 5.73.

4.3.10. *N*-[2-(5-Chloro-2-phenyl-1*H*-indol-3-yl)ethyl]acetamide (3j). Brownish cubic crystals, 2.72 g, yield 87%, mp 147–149 °C. R_f (EtOAc)=0.4. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.76 (s, 3H), 3.05 (t, J=6.7 Hz, 2H), 3.48 (dt, J=6.7, 6.2 Hz, 2H), 5.50 (bs, 1H), 7.14 (dd, J=8.5, 1.5 Hz, 1H), 7.28 (d, J=8.5 Hz, 1H), 7.36 (t, J=7.5 Hz, 1H), 7.44 (t, J=7.5 Hz, 2H), 7.35 (t, J=7.5 Hz, 2H), 7.52 (m, 1H), 7.57 (dd, J=7.5, 1.5 Hz, 1H), 8.48 (bs, 1H). ^{13}C NMR δ 23.1, 24.4, 40.2, 109.6, 112.0, 118.3, 122.6, 125.5, 128.0 (2C), 128.2, 129.1 (2C), 130.2, 132.4, 134.2, 136.7, 170.1. Calcd for $C_{18}H_{17}N_2OCl$, C 69.12, H 5.48; found C 68.82, H 5.35.

4.3.11. *N*-[2-(5-Bromo-2-phenyl-1*H*-indol-3-yl)ethyl]acetamide (3k). Reddish crystal solid, 2.86 g, yield 80%, mp 113–115 °C. R_f (EtOAc)=0.4. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.76 (s, 3H), 3.03 (t, J=6.7 Hz, 2H), 3.47 (dt, J=6.7, 6.2 Hz, 2H), 5.55 (bs, 1H), 7.25 (m, 2H), 7.35 (d, J=7.3 Hz, 1H), 7.43 (t, J=7.3 Hz, 2H), 7.53 (d, J=7.3 Hz, 2H), 7.71 (s, 1H), 8.66 (bs, 1H). ^{13}C NMR δ 23.1, 24.4, 40.2, 109.4, 112.5, 112.9, 121.4, 125.1, 128.0 (2CH), 128.15, 129.0 (2CH), 130.8, 132.4, 135.4, 136.6, 170.3. Calcd for $C_{18}H_{17}BrN_2O$, C 60.52, H 4.80; found C 61.07, H 4.76.

4.3.12. *N*-[2-(7-Ethyl-2-phenyl-1*H*-indol-3-yl)ethyl]acetamide (3m). Brown crystal solid, 2.57 g, yield 84%, mp 147–149 °C. R_f (EtOAc)=0.5. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.39 (t, J=7.6 Hz, 3H), 1.74 (s, 3H), 2.91 (q, J=7.6 Hz, 2H), 3.10 (t, J=6.7 Hz, 2H), 3.53 (dt, J=6.7, 6.2 Hz, 2H), 5.52 (bs, 1H), 7.08–7.14 (m, 2H), 7.37 (m, 1H), 7.44–4.51 (m, 3H), 7.58 (m, 2H), 8.27 (bs, 1H). ^{13}C NMR δ 13.8, 23.1, 24.0, 24.5, 40.1, 110.3, 116.6, 120.2, 121.0, 126.5, 127.8, 128.1 (2C), 128.7, 129.0 (2C), 133.1, 134.7, 135.1, 170.0. Calcd for $C_{20}H_{22}N_2O$, C 78.40, H 7.24; found C 78.23, H 7.12.

4.4. Synthesis of *N*-[2-(5-methoxy-2-phenyl-1*H*-indol-3-yl)ethyl]acetamide (3l)

Mixture of 502 mg of 4-methoxyphenylhydrazine oxalate (2.2 mmol) and 411 mg of *N*-(4-oxo-4-phenylbutyl)acetamide (**2a**) (2 mmol) was refluxed in 20 mL of EtOH for 20 min. After evaporation the residue was refluxed in 15 mL of glacial AcOH for 10 min. Then reaction mixture was evaporated and distributed between water and CH_2Cl_2. Organic phase was washed with water (2×20 mL) and evaporated. The flash chromatography of the residue afforded the product as amorphous solid, 0.52 g, yield 85%. R_f (EtOAc)=0.4. All spectral data of the compound is identical to the literature.[29]

4.5. Synthesis of *N*-{2-[2-(2-furyl)-1*H*-indol-3-yl]ethyl}acetamide (3g)

Mixture of 380 mg 4-oxo-4-furylbutyl-*N*-acetamide (**2g**) (2 mmol), 216 mg (2 mmol) phenylhydrazine and 2.4 g (6 mmol) ethyl ester of polyphosphoric acid was warmed on the water bath at 85 °C for 1 h. Then reaction mixture was evaporated and distributed between water and CH_2Cl_2. Organic phase was washed with water (2×20 mL) and evaporated. The flash chromatography of the residue afforded the product as yellowish oil, 0.23 g, yield 43%. R_f (EtOAc)=0.55. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.82 (s, 3H), 3.17 (t, J=6.7 Hz, 2H), 3.55 (dt, J=6.7, 6.5 Hz, 2H), 5.80 (bs, 1H), 6.48 (dd, J=3.2, 1.8 Hz, 1H), 6.75 (d, J=3.2 Hz 1H), 7.09 (t, J=7.0 Hz, 1H), 7.18 (t, J=7.0 Hz, 1H), 7.35 (d, J=8.1 Hz, 1H), 7.44 (d, J=1.8 Hz, 1H), 7.55 (d, J=8.1 Hz, 1H), 9.0 (bs, 1H). ^{13}C NMR δ 23.2, 24.5, 39.7, 106.5, 109.4, 110.9, 111.9, 118.5, 119.7,

122.6, 126.2, 128.8, 137.8, 141.5, 147.4, 170.4. Calcd for $C_{16}H_{16}N_2O_2$, C 71.62, H 6.01; found C 71.35, H 6.07.

References and notes

1. (a) Glennon, R. A.; Jacyno, J. M.; Young, R.; McKenney, J. D.; Nelson, D. *J. Med. Chem.* **1984**, *27*, 41. (b) Person, H.; Pardo, M. D. A.; Founcaud, A. *Tetrahedron Lett.* **1979**, *21*, 281.
2. (a) Stevenson, G. I.; Smith, A. L.; Lewis, S.; Michie, S. G.; Neduvelil, J. G.; Patel, S.; Marwood, R.; Patel, S.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2697. (b) Glennon, R. A.; Lee, M.; Rangisetty, J. B.; Dukat, M.; Roth, B. L.; Savage, J. E.; McBride, A.; Rausen, L.; Hufeisen, S.; Lee, D. K. H. *J. Med. Chem.* **2000**, *43*, 1011.
3. Mor, M.; Spadoni, G.; Giacomo, B. D.; Diamantini, G.; Bedini, A.; Tarzia, G.; Plazzi, P. V.; Rivara, S.; Nonno, R.; Lucini, V.; Pannacci, M.; Fraschini, F.; Stankov, B. M. *Bioorg. Med. Chem.* **2001**, *9*, 1045.
4. Walsh, T. F.; Toupence, R. B.; Ujjainwalla, F.; Young, J. R.; Goulet, M. T. *Tetrahedron* **2001**, *57*, 5233.
5. Molinari, R. *Eur. J. Pharmacol.* **1996**, *301*, 159.
6. (a) Thomson, D. W.; Commeureuc, A. G. J.; Berlin, S.; Murphy, J. A. *Synth. Commun.* **2003**, *33*(20), 3631. (b) Revial, G.; Jabin, I.; Lim, S.; Pfau, M. *J. Org. Chem.* **2002**, *67*(7), 2252. (c) Chung, I. H.; Cha, K. S.; Seo, J. H.; Kim, J. H.; Chung, B. Y.; Kim, C. S. *Heterocycles* **2000**, *53*(3), 529.
7. (a) Snyder, M. *J. Am. Chem. Soc.* **1955**, *77*, 1257. (b) Legters, J.; Willems, G. H.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas.* **1992**, *111*(2), 59. (c) Konda-Yamada, Y.; Okada, C.; Yoshida, K.; Umeda, Y.; Arima, S.; Sato, N.; Kai, T.; Takayanagi, H.; Harigaya, Y. *Tetrahedron* **2002**, *58*(39), 7851.
8. (a) Kirkup, M. P.; Moore, R. E. *Tetrahedron Lett.* **1983**, *24*(20), 2087. (b) Huebner, A. *J. Am. Chem. Soc.* **1953**, *75*, 5887. (c) Repke, D. B.; Ferguson, W. J.; Bates, D. K. *J. Heterocycl. Chem.* **1981**, *18*, 175. (d) Gatta, F.; Misiti, D. *J. Heterocycl. Chem.* **1987**, *24*, 1183.
9. Vinogradov, H. L.; Suvorov, N. N. *Chim. Heterocycl. Soed.* **1984**, *9*, 1206.
10. Gorohovsky, S.; Meir, S.; Shkoulev, V.; Byk, G.; Gellerman, G. *Synlett* **2003**, *10*, 1411.
11. Jandu, K. S.; Barret, V.; Brockwell, M.; Cambridge, D.; Farrant, D. R.; Foster, C.; Giles, H.; Glen, R.; Hill, A. P.; Hobbs, H.; Honey, A.; Martin, G. R.; Salmon, J.; Smith, D.; Woolard, P.; Sekwood, D. L. *J. Med. Chem.* **2001**, *44*, 681.
12. (a) Brennan, J. P.; Saxton, J. E. *Tetrahedron* **1987**, *43*(1), 191. (b) Glennon, R. A.; Hong, S. S.; Bondarev, M.; Law, H.; Dukat, M.; Rakhit, S.; Power, P.; Fan, E.; Kinneau, D.; Kamboj, R.; Teiler, M.; Herrick-Davis, K.; Smith, C. *J. Med. Chem.* **1996**, *39*, 314. (c) Barf, T.; Wikstrom, H.; Pauwels, P. J.; Palmier, C.; Tardif, S.; Lundmark, M.; Sundell, S. *Bioorg. Med. Chem.* **1998**, *6*, 1469.
13. Cloudsdale, I. S.; Kluge, A. F.; McClure, N. L. *J. Org. Chem.* **1982**, *47*(6), 919.
14. Gennet, D.; Michel, P.; Rassat, A. *Synthesis* **2000**, 3, 447.
15. Bird, C. W.; Wee, G. H. *Tetrahedron* **1985**, *41*(10), 2019.
16. Nenajdenko, V. G.; Zakurdaev, E. P.; Balenkova, E. S. *Tetrahedron Lett.* **2002**, *43*(47), 8449.
17. Nenajdenko, V. G.; Gololobov, A. M.; Zakurdaev, E. P.; Balenkova, E. S. *Russ. Chem. Bull.* **2003**, *252*(11), 2473.
18. Sorgi, K. L.; Maryanoff, A. C.; McComsey, D. F.; Maryanoff, B. E. *Org. Synth.* **1998**, *75*, 215.
19. Seeman, J. I. *Synthesis* **1977**, 498.
20. Bielawski, J.; Brandage, S.; Lindblom, L. *J. Heterocycl. Chem.* **1978**, *15*(1), 97.
21. Feringa, B.; Jansen, J. *Tetrahedron Lett.* **1986**, *27*(4), 507.
22. Hua, D.; Shon, W. M.; Narashima, S. *J. Org. Chem.* **1990**, *55*, 3682.
23. Koldobsky, A. B.; Vakhmistrov, V. E.; Solodova, E. V.; Shilova, O. S.; Kalinin, V. N. *Izv. Acad. Nauk.* **2002**, *387*(1), 61.
24. Giovanni, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228.
25. Belleau, B. *Can. J. Chem.* **1957**, *35*, 651.
26. Poisel, H.; Schmidt, U. *Chem. Ber.* **1975**, *108*, 2917.
27. Barclay, B. M.; Campbell, N. *J. Chem. Soc.* **1945**, *8*, 530.
28. Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*, Wiley: New York, 1967; Vol. 1, p 892.
29. Garratt, P. J.; Jones, R.; Tocher, D. A. *J. Med. Chem.* **1995**, *38*, 1132.

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An environmentally friendly α-hydroxyallylation reaction of the Garner aldehyde: a comparative assessment of alternative Barbier conditions

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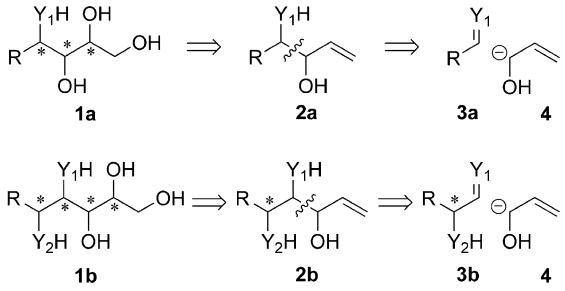
Abstract—The reaction of 3-bromo-propenyl acetate with the Garner aldehyde promoted by zinc or indium metal is studied in different solvents; besides the stereoselectivity, attention is focused on a comparative environmental assessment of different experiments carried out in NH_4Cl, THF or DMF, using green chemistry metrics and a qualitative analysis of environmental risks.

1. Introduction

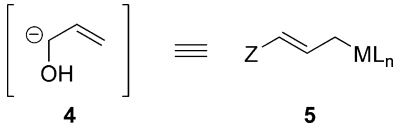
The total synthesis of sugars, azasugars and other families of natural products containing densely functionalised appendages such as sugars, sphingosines etc., solicits the development of simple and effective methodologies able to approach structures like **1**, which contains a sequence of consecutive functionalised stereocentres. Our retrosynthetic strategy to **1** is depicted in Scheme 1. Thanks to the number of regio- and stereochemically controlled functionalisation reactions of carbon–carbon double bonds, alk-1-en-3,4-diols **2** are recognized as attractive precursors of **1**. Thus, we focused our attention on the disconnective approach to **2** based on the formal α-hydroxyallylation of a carbonyl compound **3a** (Y_1 = O) or to an imine derivative (Y_1 = NR).



Scheme 1. Y_1 and Y_2 = O or NH.

Of course, if the carbonyl compound or azomethine derivative possess a stereogenic heterosubstituted carbon in the α-position (structure **3b**), the stereotetrad **1b** becomes accessible.

A number of synthetic equivalents of the formal synthon **4** are available in the literature; they correspond to γ-heterosubstituted allylic organometallic species of general structure **5**[1] (Scheme 2), as shown by the representative list depicted in Table 1. Complexes **5** are divided in two groups, depending on simple diastereoselectivity exhibited in the addition to aldehydes.



Scheme 2.

Most of γ-heterosubstituted allylic organometallic species **5** are prepared according to a standard lithiation/transmetallation protocol (Scheme 3): a suitable precursor **6** is metallated in anhydrous THF at low temperature with an alkyllithium derivative, then the required metal halide is added to the intermediate allyl lithium **7**.

This two-step protocol is affected by high economic and environmental costs associated with the use of an expensive base, the need to adopt strictly controlled conditions (anhydrous solvent, inert atmosphere) and the need to cool

Keywords: α-Hydroxylation; Garner aldehyde; Barbier-type reactions; Indium; Zinc; Green chemistry metrics.
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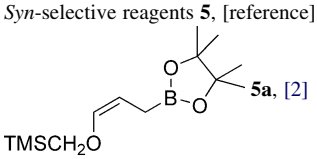
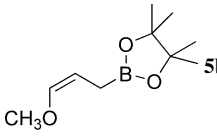
Table 1. Selected γ-heterofunctionalized allylic organometallic reagents **5**

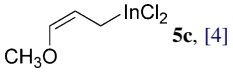
Syn-selective reagents **5**, [reference]



5a, [2]



5b, [3]



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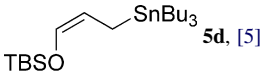

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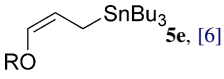

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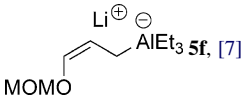
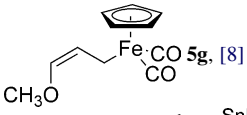
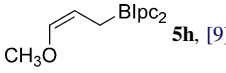


5f, [7]



5g, [8]



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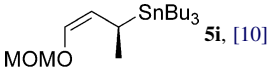

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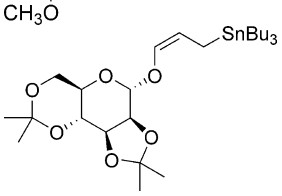

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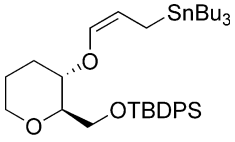
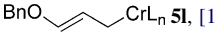
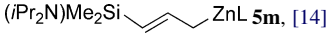


5k, [12]

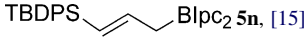
Anti-selective reagents **5**, [reference]



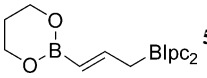
5l, [13]



5m, [14]



5n, [15]



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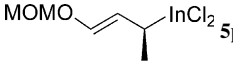
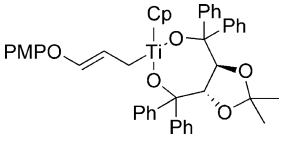


5p, [17]



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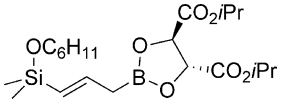
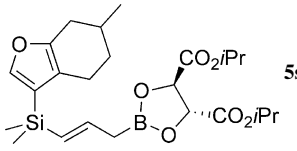
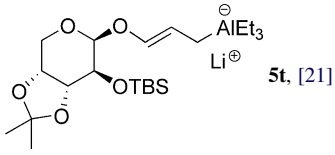


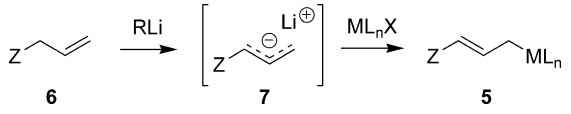
5r, [19]



5s, [20]



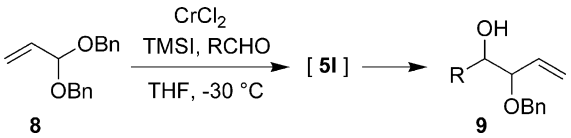
5t, [21]



Scheme 3. Z=protected OH, R_3Si, R_2B.

to low temperature, an operation which involves energy consumption. All these aspects make it difficult scaling up the overall process.

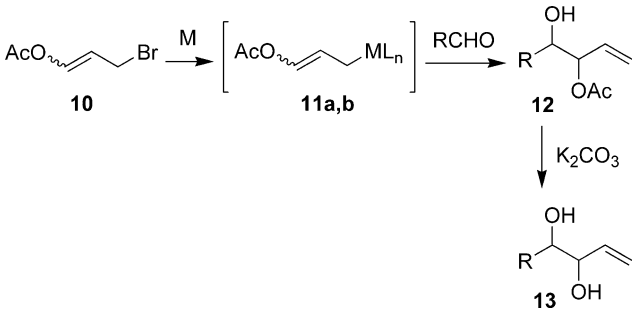
Chromium derivative **5l**, on the other hand, involves a more simple one-pot preparation: acrolein acetal **8** is reacted with Cr(II) and trimethylsilyl iodide (TMSI) in the presence of an aldehyde, so that, as soon as **5l** is formed, it is trapped by the carbonyl compound to give **9** (Scheme 4).[13a] Drawbacks, again in terms of economic and environmental point of views, are represented by the necessity to use 1 equiv of costly and unstable TMSI and an excess (3 equiv) of the eco-toxic salt, chromium(II) chloride.



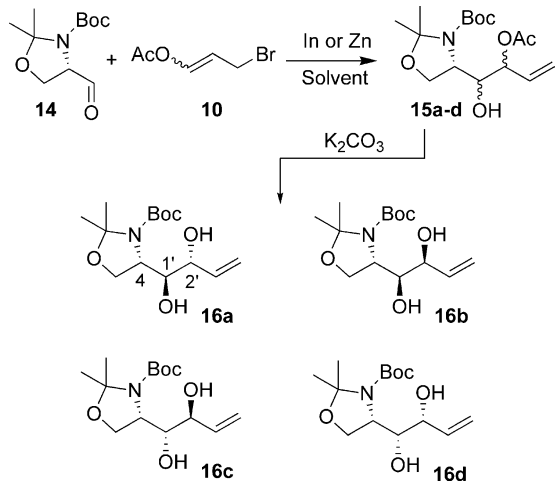
Scheme 4.

This reaction recently was greatly improved by adopting a catalytic cycle based on the redox Mn(0)/Cr(II) couple, where Cr is used in catalytic amount (7%) and TMSI is generated in situ from TMSCl and NaI.[22]

In the last years, with the aim to design less expensive and more environmental benign routes to γ-heterosubstituted allylic organometallic species **5**, we proposed to the attention of chemists 3-bromopropenyl acetate **10**. The oxidative addition of Zn or In metal to the C–Br bond of **10** (Scheme 5) opens a route to a new class of γ-heterofunctionalised metal



Scheme 5. a: M=In, b: M=Zn.



Scheme 6.

complexes **5**, namely 3-acetoxy-allylic indium and zinc species **11a** and **11b**.[23]

The reaction is carried out at 0 °C in commercial grade (99%) THF, DMF, THF/DMSO mixtures, or even in aqueous solutions of ammonium chloride, and makes use of metals with low eco-toxicity. All these aspects together imply a benefit in terms of economy and ecology with respect to previous processes reported in Schemes 3 and 4.

At last, as refers to the reaction of **11** with carbonyl compounds, two protocols were developed: (i) a Grignard two-step protocol where **11** is prepared in an organic solvent before the carbonyl compound is added, as represented in Scheme 5, (ii) a Barbier one-pot protocol in which **11** is prepared in the presence of the carbonyl compound. Excellent conversions are obtained after 30 min, even though a longer reaction time is seldom adopted to optimize chemical yields of adduct **12**.

Here we wish to report a new case study, the hydroxyallylation of Garner aldehyde[24] **14** using **11a** or **11b** under Barbier conditions in different solvents. For each condition an assessment on the basis of green chemistry metrics and of a qualitative analysis of environmental risks is presented.

2. Results and discussion

2.1. Hydroxyallylation of Garner aldehyde

In a preliminary communication, the reaction of 3-bromopropenyl acetate (**10**) with the Garner aldehyde **14** promoted by In(0), was reported.[25] A Grignard protocol had been adopted, the organoindium species had been preformed in THF, then it had been allowed to react with **14** to give **15a** in 66% yield. An overall reaction time of 8 h was required. The usefulness of intermediates **15** as precursors of azasugars or sphingosines is apparent, since they allow, for example, to incorporate the stereodefined four-carbon unit $HOCH_2$–*$CHNH_2$–*CHOH–*CHOH– into a target molecule. In the same communication,[25] an application of **15a** to the synthesis of 1,4-dideoxy-1,4-L-iminoribitol, an azasugar displaying inhibitory activity towards glycosidases, was reported as an example of chemical and structural potentiality of this intermediate.

Now we present an optimisation study of the hydroxyallylation of **14** with **10** in terms of chemical yield, simple and facial stereoselectivity and overall reaction time. In particular, the last goal was achieved by testing a number of Barbier protocols in which **10** and **14** are exposed to zinc or indium powder in different reaction media. A mixture of monoacetylated diols **15a–d** are formed which can be later on quantitatively converted into the corresponding diols **16a–d** upon alkaline hydrolysis (K_2CO_3 in $MeOH/H_2O$) (Scheme 6).

Three different types of reaction media were examined, THF, DMF and aq solutions of NH_4Cl at two different concentrations. The use of aq solutions of NH_4Cl instead of simple water is strongly recommended for both metals. Using zinc, aq NH_4Cl promotes the activation of the metal via surface corrosion;[26] it is well known, indeed, that aq NH_4Cl is the solvent of choice in the Luche version[27] of the classical Barbier allylation of carbonyl compounds. On the other hand, a buffered aq solution is also required when indium is used. When indium reacts with allylic halides in pure water, the pH drops to 2–3[28] and these conditions promote hydrolysis of the enolester functionality of **10**.

Results using indium and zinc in the three media are summarised and compared in Table 2. All the reactions are carried out at 0 °C mixing **14** and **10** in a 1:1.5 molar ratio and using 2 equiv of zinc or 1.2 equiv of indium. As a first effect, very good yields are observed in runs 2, 4, 6 and 7 with reaction times 2 to 8-fold shorter than that previously reported under Grignard conditions.[25]

As refers to stereochemistry, among four possible isomers **16a–d**, adduct **16a** is always the most abundant stereoisomer produced. This was not unexpected, since the $C_{1'}$–$C_{2'}$ *anti* diastereoselectivity is exactly that anticipated on the basis of previous results with prochiral saturated aldehydes, both in aq NH_4Cl and in THF.[23a–c] As refers to

Table 2. α-Hydroxyallylation reactions of Garner aldehyde **14** using 3-bromopropenyl acetate **10** in the presence of zinc or indium

Run	M	Reaction medium	*t* (h)	**16** overall yield (%)	**16a**	**16b**	**16c**	**16d**
1	Zn	NH_4Cl 0.5 M	2	51	65	16	17	2
2	Zn	NH_4Cl 7 M	1	83	58	25	11	6
3	Zn	THF	2.5	50	95	5	—	—
4	Zn	DMF	3	78	90	10	—	—
5	In	NH_4Cl 7 M	3	54	87	13	—	—
6	In	THF	4	95	85	9	6	—
7	In	DMF	3	88	97	3	—	—

π-facial diastereoselectivity, expressed by the C_4–$C_{1'}$ stereorelationship, an *anti* stereopreference is more often observed in the addition of organometallic compounds to **14**.[24]

Zinc afforded the best results in terms of overall yield in 7 M NH_4Cl and in DMF, while in terms of overall stereocontrol, runs 3 and 4 in organic solvents are by far the most selective (80–90% de). Indium, widely used in Barbier allylation of carbonyl compounds with allylic halides in water,[29] offers in saturated NH_4Cl its worst performance (run 5) as already observed in our preliminary studies,[23a,c] while THF and DMF are superior solvents in terms of stereoselectivity, the latter (run 7) affording the highest level of de (94%). Thus, water, the best green solvent 'par excellence',[29b,c,30] represents the worst reaction medium on the basis of efficiency criteria, namely chemical yield and stereoselectivity.

2.2. Comparative assessment of runs 1–7 (Table 2) on economic and environmental grounds

In order to compare runs 1–7 in terms of their economic and environmental rating, green reaction metrics are applied to each run, then the best reaction conditions are compared in terms of safety and environmental risks associated to them.

2.2.1. Costs. Costs of chemicals and their role are collected in Table 3. Molecules which transfer atoms to the target molecule (TM) structure are defined as starting materials (SM); any other reactant, promoter, ligand etc. is defined as reactant (R). Solvents are divided in reaction solvents (S) and extraction solvents (ES).

Table 3. Commercial prices of chemicals used[a]

Chemical (role)	€ (per gram)	Chemical (role)	€ (per gram)
10 (SM)	6[b]	THF (S)	0.059
14 (SM)	100[b]	DMF (S)	0.047
Zn (R)	0.10	H_2O (S)[c]	0.008
In (R)	5.30	Ether (ES)	0.051
NH_4Cl (S)	0.026	Ethyl acetate (ES)	0.025

[a] Unless otherwise stated, prices were taken from 2003–4 Fluka and Aldrich fine chemicals catalogues. See Materials in Section 4.
[b] Evaluated on the basis of reagent costs, time required and distillation costs needed for the preparation of **10** (Ref. 23c) and **14** (Refs. 24 and 25).
[c] HPLC grade water.

Reactions costs related to energy consumption and time are not considered to be relevant, while disposal costs (values refer to the 2004 Italian market) are as follows: (i) incineration of the organic phase: 0.3 €/L; (ii) treatment in an industrial waste water treatment plant of the aq phase containing In or Zn (max concentration accepted 1 g/L), and in some cases ammonium chloride: 0.07 €/L. Possible costs associated to the recovery of metal from the aqueous phase and to the recovery of solvents from the residual organic phase have been not been quantified, but they are supposed to be higher in terms of energy and time than incineration or disposal costs.

2.2.2. Green metrics. Atom economy[31] (AE) and environmental impact factor[32] (*E*) have been proposed in the last decade as a measure of environmental sustainability in terms of minimisation of the theoretical waste amount. Given the balanced stoichiometric Eq. 1:

$$\sum n_i \mathrm{SM}_i + \sum m_i \mathrm{R}_i \rightarrow y\mathrm{TM} + \sum k_i \mathrm{C}_i \tag{1}$$

where *n*, *m*, *k* and *y* are stoichiometric coefficients, and C any co-product formed, definitions of AE and of *E* are expressed by Eqs. 2 and 3:

$$\mathrm{AE} = \frac{y \cdot \mathrm{MW_{TM}}}{\sum(n_i \cdot \mathrm{MW_{SM_i}}) + \sum(m_i \cdot \mathrm{MW_{R_i}})} \tag{2}$$

$$E = \frac{\sum(k_i \cdot \mathrm{MW_{C_i}})}{y \cdot \mathrm{MW_{TM}}} \tag{3}$$

Thus, ideal conditions should be characterised by 100% AE and 0% *E*, as happens in an addition or rearrangement reaction affording a single product. AE and *E* are correlated by Eq. 4:

$$\mathrm{AE} = \frac{1}{1+E} \tag{4}$$

which also predicts that, when AE=*E*, their value is 0.618. Thus, environmental acceptable reactions are considered those processes having AE>*E*, that means %AE >61.8.

If stoichiometric reactions relative to the acetoxyallylation of Garner aldehyde using zinc (Eq. 5) or indium (Eq. 6) are considered, AE and *E* can be easily reckoned. In the first case AE=0.670 and *E*=0.493, while in the case of indium AE=0.655 and *E*=0.527.

$$\underset{(229.3)}{\mathbf{14}} + \underset{(179.0)}{\mathbf{10}} + \underset{(65.4)}{\mathrm{Zn}} + \underset{(18.2)}{\mathrm{H_2O}} \rightarrow \underset{(329.4)}{\mathbf{15}} + \underset{(162.3)}{\mathrm{ZnBrOH}} \tag{5}$$

$$\underset{(229.3)}{3\cdot\mathbf{14}} + \underset{(179.0)}{3\cdot\mathbf{10}} + \underset{(114.8)}{2\cdot\mathrm{In}} + \underset{(18.2)}{3\cdot\mathrm{H_2O}} \rightarrow \underset{(329.4)}{3\cdot\mathbf{15}} + \underset{(520.37)}{\mathrm{In_2Br_3(OH)_3}} \tag{6}$$

Decreasing in AE when zinc is replaced with heavier indium, is partially balanced by the different stoichiometric ratios required by divalent Zn and trivalent In. These AE values reflect an intrinsic limitation of organometallic additions to carbonyl compounds where a metal salt is ineluctably formed as co-product! However, both reactions 5 and 6 can be considered environmental acceptable since their % AEs are higher than 61.8.

AE and *E* are theoretical measures of the chemical and environmental efficiency of a chemical reaction, only based on stoichiometric equation; they do not consider solvents, possible excess of a reagent, formation of unwanted products or stereoisomers, etc. Thus, further indexes of critical mass intensity[33] are required in order to parametrise Eqs. 5 and 6 if isomer **15a** is considered the desired TM, while **15b–d** are considered co-products (C). These indexes are mass intensity (MI), reaction mass efficiency (RME) and carbon efficiency (CE) which are defined according to Eqs. 7–9.

$$\mathbf{MI} = \frac{\text{sum of masses of SMs, reagents, catalysts, solvents etc.}}{\text{isolated mass of TM}} \tag{7}$$

$$\mathbf{RME} = \frac{\text{isolated mass of TM}}{\text{sum of masses of all SMs}} \quad (8)$$

$$\mathbf{CE} = \frac{\text{carbon mass in isolated TM}}{\text{sum of carbon masses of all SMs}} \quad (9)$$

While, ideally, MI should approach 1, RME and CE should be maximised to 100%. The cost of 1 g of TM **15a**, and values of MI, RME and CE are collected in Table 4 for run 2 of Table 2.

Table 4. Main costs and mass indexes for run 2 of Table 2, which affords **15a** in 48% yield

Chemical (role)	Amount charged per batch (g)	Chemicals cost (€)
10 (SM)	0.215	1.29
14 (SM)	0.229	22.90
Zn (R)	0.131	0.01
H_20 (R)	0.180	—
H_20 (S)	3.130	0.02
NH_4Cl (S)	1.870	0.05
Ether (ES)	14.50	0.74
	Overall cost per batch	25.04

MI[a]	RME (%)	CE (%)	Overall cost of **15a**[b] (€/g)
35.3	26.7	45.2	158.4

[a] Extraction solvent is not considered.
[b] Yield of **15a** is 0.158 g.

Table 4 clearly puts in evidence the dominant role of Garner aldehyde **14** in determining the overall cost per batch (91%), followed by 3-bromopropenyl acetate (6.4%) and extraction solvent (2.8%). Improvement in terms of overall cost, hence, identifies in the optimisation of the preparation of **14** the fundamental demand.

Mass intensity MI = 1 represents an ideal solvent-free reaction with 100% AE and 100% yield. MI of the order of 35 demonstrates that a large contribution to MI is due to reaction solvent; if solvent was removed, MI should decrease to 3.74. Actually, when the hydroxyallylation of Garner aldehyde using **10**, Zn dust and solid NH_4Cl under solvent-free conditions[34] was checked, it resulted in an uncontrollable exothermic reaction with a rapid formation of a black tar. If the extraction solvent is considered, MI jumps to 127.1, thus stressing the role of reaction and work-up solvents in waste accumulation. Solvents, even though available at low costs, have an important life cycle impact considering their manufacture, transport, use and final disposal;[35] thus MI clearly solicits to pursue solvent reduction, particularly, but not only, in the work-up process (scientists involved in industrial process development every day cope with this problem). The last indexes RME and CE portray the efficiency of a process better than AE. Indeed, RME and CE take into account not only the concept of AE, but also the yield and the actual molar quantities of the starting materials. In conclusion, in order to compare different processes by a green point of view, these set of indexes looks as a more useful tool. Cost and efficiency measurements for runs 1–7 are compared in Table 5.

Since most of experimental conditions are identical (reaction scale, molar ratios, quantity of reaction and work-up solvents), data in Table 5 quantitatively reflect the zinc and indium efficiency in the three media chosen.

The best yields obtained with In in organic solvents (runs 7 and 8) markedly determine the lowest costs and MI indexes, as well as the highest values of the two efficiency parameters RME and CE. The cost/batch ranges from 25 to 26 €, confirming the strong levelling effect of **14** on the reaction cost. Even though indium used in this work has a price 50 fold higher than zinc, it affects the overall cost/batch by 0.7 € only. Thus, if the analysis is limited to economy and mass intensity measurements, runs 7, 6 and 4 are the best ones within this set of experiments, in this decreasing ranking order.

If solvent and disposal costs do not impact the process economy, by an environmental point of view they represent a main issue; indeed, modern green chemistry philosophy takes into account all the externalities coupled to: (i) chemicals involved, particularly solvents (environmental impact of their manufacture), (ii) overall energy consumption, (iii) thermal hazard, (iv) waste recycling or disposal, and (v) risk of dispersion of chemicals in the environment. In the last decade, chemists have been feeling the urgency, on one hand, to plan new chemistry and/or to redesign old chemistry according to the general green chemistry guidelines even for lab scale processes,[36] on the other, to parametrise the level of sustainability in quantitative terms.[37] Since the most promising results have been obtained in THF and DMF (Table 5, runs 4,6,7), here we analyse, on a qualitative basis, the major environmental impacts of these two reaction media.

(i) *Physico-chemical hazards*. Possibility that a harmful event such as fire, explosion and so on occurs, is strictly related to physical properties such as boiling point, flash point, vapour pressure and explosion limits. Comparison of the corresponding values for THF and

Table 5. Cost and mass metrics for runs 1–7 of Table 2

Run	**15a** Y (%)	**15a** cost (€/g)	MI	RME (%)	CE (%)
1	33	230.1	51.29	18.33	31.06
2	48	158.4	35.26	26.67	45.18
3	48	159.6	31.75	26.67	45.18
4	70	109.3	22.96	38.89	65.88
5	47	166.4	36.06	25.81	44.24
6	81	97.3	18.84	44.48	76.24
7	85	92.5	18.94	46.67	80.00

DMF, clearly indicates THF as much more hazardous than DMF.

(ii) *Risk of dispersion in the atmosphere*. The higher value of the THF Henry's constant ($k_H = 7.5$ Pa m^3 mol^{-1}) with respect to DMF ($k_H = 7.5 \times 10^{-3}$ Pa m^3 mol^{-1})[38] testifies the higher probability for THF to be released to the air with consequence also on smog forming processes, which require the presence of volatile organic compounds.

(iii) *Bioaccumulation*. Octanol/water partitioning constants (expressed as $\log K_{ow}$) are useful parameters to anticipate solute behaviour in water. 1-Octanol is an amphiphilic molecule with a solvating ability not unlike that of humic acids in soils and in suspended colloids, as well as that of lipophilic biological membranes. In case of THF $\log K_{ow} = 0.29$[39], while for DMF $\log K_{ow} = -1.01$;[40] these values tell us that: (i) neither THF nor DMF are expected to adsorb to suspended organic matter in water bodies, and that they will have very high mobility in soil, even in humic acid-rich soils, and (ii) neither THF nor DMF are expected to bioaccumulate in aquatic biota. Indeed, typical of high solid-phase association as well as of the high bioaccumulation factors of PCBs, PAHs, etc. are $\log K_{ow}$'s values >3[41]

(iv) *Biodegradation*. THF is biodegraded under aerobic conditions only,[42] while DMF is degraded both aerobically and anaerobically by various micro-organisms over a wide range of concentrations.[43]

(v) *Eco-toxicology*. A very useful database of ecotoxicological studies of THF and DMF towards a number of organisms is available from Pesticide Action Network North America (PAN).[44] Both chemicals do not exhibit strong toxicity, however LC_{50} values towards blue-green algae of DMF is twice the value of THF (mean toxic dose, mg/l: THF 225, DMF 472).

(vi) *Human health impact*. Both THF and DMF, are considered slightly toxic chemicals for humans, and no evidence is so far available to classify them as carcinogens, developmental or reproductive toxins or endocrine disruptors.[44] LD_{50} s from experiments with rats are very similar: LD_{50} (oral administration, mg/kg body weight): DMF 2800,[45] THF 2816.[46] Among the six environmental issues examined, four of them remark a clear preference for DMF; besides to present very limited risks of explosion and of dispersion into the atmosphere by virtue of its physico-chemical properties, DMF, when released in a water body, does not bioaccumulate in organisms, is biodegradable in any environmental condition (aerobic and anaerobic), and displays the lowest eco-toxic effects towards blue-green algae.[44] On the other hand, both solvents deserve comparable attention as refers to impact on human health.

3. Conclusions

The synthesis of (2*S*,3*S*,4*R*)-2-amino-hex-5-en,1,3,4-triol derivative **16a** has been documented via Barbier addition of 3-bromopropenyl acetate **10** to the Garner aldehyde **14**, according to an original protocol developed in our lab which exploits either zinc or indium metal. This approach to alk-1-en-3,4-diols, presently, performs as the most convenient α-hydroxyallylation of carbonyl compounds in terms of both economic and environmental criteria, with respect to alternative allylic complexes reported in Table 1. Chemical versatility of **16a** is apparent, since it can be manipulated at the double bond terminus, thus opening routes to 2-deoxy-2-amino pentoses upon ozonization, to 2-deoxy-2-amino hexose upon dihydroxylation, to disubstituted olefins via cross-methatesis, etc. The great flexibility of 3-halopropenyl esters allow us to exploit a wide range of solvents, such as THF, DMF, and aq NH_4Cl. We attempted an economic and environmental comparison among all the experiments conducted (Table 2). By an economic and a mass efficiency point of view, the best performances were furnished by indium in DMF and THF (runs 6 and 7, Table 2), while comparison of environmental impacts qualitatively confirms DMF as better than THF.

4. Experimental

4.1. Materials

Tetrahydrofuran (THF) over molecular sieves (water content less than 0.005%), and *N*,*N*-dimethylformamide (DMF) over molecular sieves (water content less than 0.01%), are purchased from Fluka. Zinc dust (<10 micron, >98%) and indium powder (99%) are purchased from Aldrich. Garner aldehyde was prepared following both Dondoni[47] and Taylor[48] procedures, at a cost about 50% inferior than its commercial price (Aldrich: 1 g, 208.5 €/g). The preparation of 3-bromopropenyl acetate follows the procedure previously reported.[23c]

4.2. Hydroxyallylation of Garner aldehyde in aqueous solvents, typical procedure A

Garner aldehyde (**14**, 0.23 g, 1 mmol), 3-bromo-propenyl acetate (**10**, 0.18 mL, 1.5 mmol) and the metal (zinc: 0.13 g, 2 mmol or indium: 0.14 g, 1.2 mmol) were subsequently added at 0 °C to 5 mL of the desired NH_4Cl solution. The reaction mixture is stirred at 0 °C and monitored by TLC and GC. The heterogeneous solution is extracted with diethyl ether or ethyl acetate (2×10 mL). The combined organic layers are dried (Na_2SO_4) and evaporated to dryness to afford the acetylated diols **15a–d**. HPLC-MS analysis of the crude reaction mixture (column: Zorbax C-8, elution: 5 min isocratic H_2O/CH_3CN 70:30 v/v, gradient ramp up to H_2O/CH_3CN = 20:80 v/v in 10 min, flow: 0.5 mL/min): *m/z*: 597.4 $[2M+Na]^+$, 326.2 $[M+K]^+$, 310.2 $[M+Na]^+$.

4.3. Hydroxyallylation of Garner aldehyde in organic solvents, typical procedure B

Garner aldehyde (**14**, 0.23 g, 1 mmol), 3-bromo-propenyl acetate (**10**, 0.18 mL, 1.5 mmol) and the metal (zinc: 0.13 g, 2 mmol or indium: 0.14 g, 1.2 mmol) were subsequently added at 0 °C to 5 mL of the desired organic solvent. The reaction mixture is stirred at 0 °C and monitored by TLC and GC. Water is added (1 mL) then the aqueous layer is extracted with diethyl ether or ethyl acetate (2–10 mL). The combined organic layers are dried (Na_2SO_4) and evaporated to dryness to afford the acetylated diols **15a–d**.

4.3.1. Synthesis of *tert*-butyl 4-[(1,2-dihydroxybut-3-enyl)]-2,2-dimethyloxazolidine-3-carboxylate 16a–d, typical procedure. The crude reaction mixture obtained by Procedure A or B was dissolved in MeOH/H_2O (5 mL, 4:1 v/v), K_2CO_3 (0.276 g, 2 mmol) was added and the reaction mixture was stirred at rt for 1.5 h. MeOH was removed at reduced pressure and the aqueous layer was extracted with ether. The combined organic layers were dried (Na_2SO_4) and solvents were evaporated at reduced pressure. GC–MS analysis of the crude reaction mixture (column: HP-5MS cross-linked 5% phenyl-methyl silicone glass capillary column, 0.25 μm film thickness, elution program: temperature was held at 50 °C for the first 2 min and was then ramped to 250 °C at 10 °C min^{-1}) revealed the presence of four peaks (t_R=18.2, 18.8, 19.1, 19.2 min) with closely related mass spectra and corresponding to the diols **16a–d**. Purification by flash-chromatography on silica (cyclohexane/ethyl acetate 85:15, triethylamine 1% v/v) afforded a first fraction containing a mixture of minor diastereoisomers **16c**,**d** followed by two more fractions containing almost pure **16b** and **16a**, respectively (chemical purity >95% by ^{1}H NMR). Absolute (4*S*)-[(1*S*,2*R*)] stereochemistry of **16a** was unambiguously assigned by us in a previous work by chemical correlation;[25] (4*S*)-[(1*S*,2*S*)] stereochemistry was assigned to **16b** by comparison of its ^{13}C NMR spectrum with that reported in the literature.[49] **16a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43 (s, 3H), 1.48 (s, 9H), 1.50 (s, 3H), 3.40–3.58 (m, 1H), 3.62–3.76 (m, 1H), 3.80–4.08 (m, 2H), 4.12–4.30 (m, 1H), 5.10–5.42 (m, 2H), 5.95 (ddd, J=4.5/10.8/16.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.2, 26.9, 28.3, 58.6, 65.1, 74.4, 74.6, 81.2, 93.9, 114.8, 136.8, 153.7. GC–MS (70 eV) *m*/*z* (%):272 (0.5, [M^+-15]), 231 (7), 216 (4), 200 (11), 174 (14), 172 (12), 155 (6), 144 (12), 116 (47), 100 (25), 87 (5), 57 (100).

16b: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.48 (s, 3H), 1.50 (s, 9H), 1.51 (s, 3H), 3.57 (t, J=4.5 Hz, 1H), 3.87–3.90 (m, 1H), 3.96–4.07 (m, 2H), 4.25–4.35 (m, 1H), 5.24–5.41 (m, 2H), 6.02 (ddd, J=6.0/10.5/16.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 26.5, 28.2, 57.5, 66.2, 73.0, 81.8, 94.3, 116.7, 136.9, 155.0. GC–MS (70 eV) *m*/*z* (%): 272 (0.4, [M^+-15]), 231 (9), 216 (5), 200 (10), 174 (14), 172 (13), 155 (8), 144 (14), 116 (45), 100 (23), 87 (10), 57 (100).

Stereochemistry to **16c** and **16d**, unseparable by flash-chromatography, was assigned on the basis of the known stereochemical bias in nucleophilic additions to the Garner aldehyde[24]. **16c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.50 (broad s, 3H+9H), 1.52 (s, 3H), 3.31–3.46 (m, 1H), 3.88 (dd, J= 5.2/9.2 Hz, 1H), 3.98 (dd, J=5.3/9.0 Hz, 1H), 4.11–4.16 (m, 2H), 5.26 (dt, J=1.1/10.7 Hz, 1H), 5.43 (dt, J=1.2/17.2 Hz, 1H), 5.93 (ddd, J=4.4/10.7/17.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.1, 27.6, 28.3, 59.0, 65.9, 69.8, 73.8, 81.8, 94.0, 116.1, 136.8, 154.7. GC–MS (70 eV) *m*/*z* (%):272 (0.5, [M^+-15]), 231 (7), 216 (5), 200 (12), 174 (13), 172 (12), 155 (6), 144 (14), 116 (46), 100 (23), 87 (6), 57 (100).

16d: GC–MS (70 eV) *m*/*z* (%):272 (0.4, [M^+-15]), 231 (6), 216 (5), 200 (13), 174 (11), 172 (10), 155 (8), 144 (13), 116 (45), 100 (27), 87 (5), 57 (100).

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References and notes

1. Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665.
2. (a) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1981**, *22*, 5263. (b) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann. Chem.* **1987**, 881.
3. Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984.
4. Hirashita, T.; Kamei, T.; Horie, T.; Yamamura, H.; Kaway, M.; Araki, S. *J. Org. Chem.* **1999**, *64*, 172.
5. Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139.
6. (a) Watrelot-Bourdeau, S.; Parrain, J.-L.; Quintard, J.-P. *J. Org. Chem.* **1997**, *62*, 8261. (b) Micalizio, G. C.; Roush, W. R. *Tetrahedron Lett.* **1999**, *40*, 3351. (c) Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. *J. Org. Chem.* **2000**, *65*, 8730.
7. Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Organomet. Chem.* **1985**, *285*, 31.
8. Jiang, S.; Agoston, G. E.; Chen, T.; Cabal, M. P.; Turos, E. *Organometallics* **1995**, *14*, 4697.
9. (a) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535. (b) Ganesh, P.; Nicholas, K. M. *J. Org. Chem.* **1997**, *62*, 1737.
10. Keck, G. E.; Savin, K. A.; Cressman, E. N.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889.
11. Roush, W. R.; VanNieuwenhze, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 8536.
12. Kadota, I.; Kobayashi, K.; Okano, H.; Asao, N.; Yamamoto, Y. *Bull. Soc. Chim. Fr.* **1995**, *132*, 615.
13. (a) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5263. (b) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275.
14. Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987**, *52*, 957.
15. Heo, J.-N.; Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1693.
16. (a) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686. (b) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644.
17. (a) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920. (b) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 105. (c) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.
18. Cossy, J.; Willis, C.; Bellosta, V.; Saint-Jalmes, L. *Synthesis* **2002**, 951.
19. Roush, W. R.; Grover, P. T.; Lin, X. *Tetrahedron Lett.* **1990**, *31*, 7563.
20. (a) Hunt, J. A.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 501. (b) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112.
21. Chika, J.-I.; Takei, H. *Tetrahedron Lett.* **1998**, *39*, 605.
22. Boeckman, R. K., Jr.; Hudack, R. A., Jr. *J. Org. Chem.* **1998**, *63*, 3524.
23. (a) Lombardo, M.; Girotti, R.; Morganti, S.; Trombini, C. *Org.*

Lett. **2001**, *3*, 2981. (b) Lombardo, M.; Girotti, R.; Morganti, S.; Trombini, C. *Chem. Commun.* **2001**, 2310. (c) Lombardo, M.; Morganti, S.; Trombini, C. *J. Org. Chem.* **2003**, *68*, 997. (d) Lombardo, M.; D'Ambrosio, F.; Morganti, S.; Trombini, C. *Tetrahedron Lett.* **2003**, *44*, 2823.

24. Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136.
25. Lombardo, M.; Licciulli, S.; Trombini, C. *Tetrahedron Lett.* **2003**, *44*, 9147.
26. Han, B. H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 751.
27. Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910.
28. (a) Paquette, L. A.; Mitzel, T. M. *J. Org. Chem.* **1996**, *61*, 8799. (b) Paquette, L. A.; Mitzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863.
29. (a) Cintas, P. *Synlett* **1995**, 1087. (b) Li, C. J.; Chan, T. H. Organic Reactions in Aqueous Media; Wiley: New York, 1997. (c) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P., Williamson, T., Eds.; Oxford University Press: New York, 1998. (d) Li, C.-J.; Haberman, J. X.; Keh, C. C. K.; Yi, X.-H.; Meng, Y.; Hua, X.-G.; Venkatraman, S.; Zhang, W.-C.; Nguyen, T.; Wang, D.; Huang, T.; Zhang, J. *Clean Solvents: Alternative Media for Chemical Reactions and Processing*; ACS Symposium Series; 2002, 178–190.
30. Lindstroem, U. M. *Chem. Rev.* **2002**, *102*, 2751.
31. (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (c) Eissen, M.; Mazur, R.; Quebbemann, H.-G.; Pennemann, K.-H. *Helv. Chim. Acta* **2004**, *87*, 524.
32. (a) Sheldon, R. A. *Chemtech* **1994**, 38. (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233. (c) Sheldon, R. A. *Comptes Rendue Chim.* **2000**, *3*, 541.
33. (a) Curzons, A. D.; Constable, D. J. C.; Mortimer, D. N.; Cunningham, V. L. *Green Chem.* **2001**, *3*, 1. (b) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521.
34. (a) Tanaka, K.; Kishigami, S.; Toda, F. *J. Org. Chem.* **1991**, *56*, 4333. See also (b) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.
35. (a) Lankey, L. R.; Anastas, P. T. *Ind. Eng. Chem. Res.* **2002**, *41*, 4498. (b) Azapagic, A. In *Handbook of Green Chemistry and Technology*; Clark, D. H. J., Macquarrie, D., Eds.; Blackwell: Oxford, 2002. (c) Herrchen, M.; Klein, W. *Pure Appl. Chem.* **2000**, *72*, 1247. (d) Lepper, P.; Keller, D.; Herrchen, M.; Wahnschaffe, U.; Mangelsdorf, I. *Chemosphere* **1997**, *35*, 2603.
36. (a) McDonough, W.; Braungart, M.; Anastas, P. T.; Zimmerman, J. B. *Env. Sci. Tech.* **2003**, *37*, 434A. (b) Anastas, P. T. *Env. Sci. Tech.* **2003**, *37*, 423A. (c) Anastas, P. T.; Zimmerman, J. B. *Env. Sci. Tech.* **2003**, *37*, 95A. (d) Poliakoff, M.; Fitzpatrick, J. M.; Farren, T. R.; Anastas, P. T. *Science* **2002**, *297*, 807. (e) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686.
37. (a) Eissen, M.; Metzger, J. O. *Chem. Eur. J.* **2002**, *8*, 3581. (b) Constable, D. J. C.; Curzons, A. D.; Freitas dos Santos, L. M.; Geen, G. R.; Hannah, R. E.; Hayler, J. D.; Kitteringham, J.; McGuire, M. A.; Richardson, J. E.; Smith, P.; LeeWebb, R.; Yu, M. *Green Chem.* **2001**, *3*, 7. (c) Koller, G.; Fischer, U.; Hungerbühler, K. *Ind. Eng. Chem. Res.* **2000**, *39*, 960. (d) Koller, G.; Weirich, D.; Brogli, F.; Heinzle, E.; Hoffmann, V. H.; Verduyn, M. A.; Hungerbühler, K. *Ind. Eng. Chem. Res.* **1998**, *37*, 3408. (e) Heinzle, E.; Weirich, D.; Brogli, F.; Hoffmann, V. H.; Koller, G.; Verduyn, M. A.; Hungerbühler, K. *Ind. Eng. Chem. Res.* **1998**, *37*, 3395. (f) Heinzle, E.; Hungerbühler, K. *Chimia* **1997**, *51*, 176.
38. BUA (1994) *N*,*N*-Dimethylformamide. GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance. Stuttgart, German Chemical Society, Wissenschaftliche Verlagsgesellschaft, December 1991 (BUA Report No. 84).
39. Bernazzani, L.; Cabani, S.; Conti, G.; Mollica, V. *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 649.
40. Carlsen, L.; Sørensen, P. B.; Thomsen, M. *Chemosphere* **2001**, *43*, 295.
41. Czub, G.; McLachlan, M. S. *Environ. Sci. Technol.* **2004**, *38*, 2406.
42. Thiemer, B.; Andreesen, J. R.; Schräder, T. *Arch. Microbiol.* **2003**, *179*, 266.
43. Scott, B. *Fate of N,N*-dimethylformamide in the environment *Review Environment Canada*; National Water Research Institute: Burlington, Ont., 1998.
44. http://www.pesticideinfo.org/Search_Products.jsp.
45. MSDS data for *N*,*N*-dimethylformamide available at the Physical and Theoretical Chemistry Laboratory, Oxford University: http://ptcl.chem.ox.ac.uk/MSDS/DI/N,N-dimethylformamide.html.
46. MSDS data for tetrahydrofuran available at the Physical and Theoretical Chemistry Laboratory, Oxford University: http://ptcl.chem.ox.ac.uk/MSDS/TE/tetrahydrofuran.html.
47. Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64.
48. Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707.
49. Barrett, A. G. M.; Malecha, J. W. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1901.

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A tandem highly stereoselective $FeCl_3$-promoted synthesis of a bisindoline: synthetic utility of radical cations in heterocyclic construction

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Abstract—A conceptually distinctive stereoselective construction of the novel dimer, *N*-[*N*′-acetyl-7,7′-bis-(3,4-dimethoxy-phenyl)-7,8,7′,8′-tetrahydro-*N*′*H*-[8,8′]biindolyl-*N*-yl]-ethanone **25** (bisindoline) is described below. These structures, which include 7-(3,4-dimethoxyphenyl)-indoline **24** (veratryl indoline), were obtained by the tactical combination of palladium-catalysed coupling which produced 10-acetamido-3,4-dimethoxystilbene **9**, followed by $FeCl_3$ induced oxidative cyclization/dimerization. All new structures were fully characterized by 1- and 2D NMR spectroscopy, (proton, carbon-13, COSY, HMBC, HMQC) and mass spectrometry. Configurational assignments were further supported by semi-empirical AM1 calculations. Mechanistic interpretations, consistent with our results, are discussed.

1. Introduction

The importance of the indole ring has been demonstrated by the fact that this skeleton, may be found in a variety of biologically active natural products, for example the essential amino acid tryptophan,[1] serotonin[1,2] (a neurotransmitter in the brain), the hallucinogenic indole, psilocin[1] and the alkaloids reserpine[3] and strychnine.[4] Of particular significance is the 'dimeric' indole alkaloid[5] vincristine (leukaemia) and indomethacin[5] (rheumatoid arthritis). With regards to the indolines, quite apart from oxido-reductive connections with the indoles, other synthetic developments have been reported.[5,6]

In 1954 Woodward et al.[4] reported the total synthesis of strychnine from veratryl indole, the latter being constructed by Fischer indole methodology. In contrast, indole construction by means of Heck coupling has recently been the subject of some fascinating reviews.[7,8] The comprehensive text by Li and Gribble is recommended reading.[8] From the vast literature relating to indole construction, a few of these make use of *ortho*-iodoaniline as a starting material. The palladium acetate-catalysed synthesis of 3-spiro-2-oxindoles[9] and tryptamine[10] are good examples. With regard to bi-indole syntheses, by palladium-catalysed coupling, the synthesis of *N*-methylareyriacyanine by Steglich has been reported.[11] Syntheses of bis(indolyl)-maleimides in 55% yield which exploited a phosphine-free palladium catalyst[12] and caesium fluoride,[13] have been described. In Fukuyama's method a C-2 and C-2′ linked bisindole (biindole) was prepared and used in the synthesis of indolocarbazoles.[14] This approach illustrates the synthetic utility of isonitriles. However, Grigg's synthesis of the unsymmetrical 3,3′-biindole (Scheme 1), constructed by the use of $Pd(OAc)_2$, PPh_3, $(Me_3Sn)_2$, is noteworthy.[15]

This type of structural entity is relatively rare. We have highlighted the Grigg dimer because (i) it contains a C-3/C-3′ link; (ii) one stereogenic centre is generated; and (iii) the molecule lacks C-2 substituents.

Keywords: Ferric chloride; Radical cation; Bisindole; Stereospecific; Stilbene.
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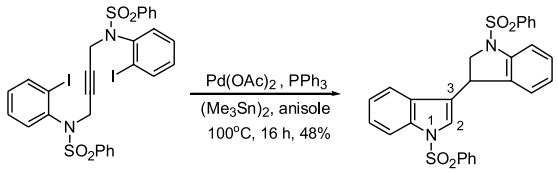


Scheme 1. The Grigg synthesis of the unsymmetrical 3′,3-biindole.

The relevance of the above to our synthetic studies in relation to indoles, indolines and the corresponding dimers possessing C-2 substituents, will become clear during the course of our discussion. We have found that such substituents can exert profound stereo-directing effects.

With regard to C-2 substituted indoles, Larock's[16] elegant one-step synthesis (oxidative addition), starting from protected *ortho*-iodoaniline, is a substantial achievement. Many syntheses along these lines have been described using internal alkynes and dienes as acceptor molecules.[16–18] The 'pyrrole-construction step' in these syntheses is often mediated by palladium reagents, for example, $Pd(OAc)_2$.

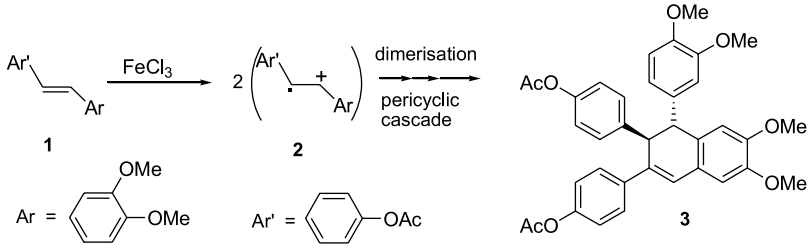
In contrast to the above, we have discovered a conceptually different approach exploiting benzylic radicals (or radical cations) generated from stilbenes. Previously we reported[19] the manganese triacetate-mediated oxidative lactonization for the regio-controlled syntheses of γ-butyrolactones from stilbenes, in which benzylic radicals were invoked. In a subsequent paper,[20] we described the $FeCl_3$-promoted tandem pericyclic synthesis of catechol analogues of restrytisol (Scheme 2). In that paper, we suggested that the crucial reactive intermediate was the radical cation **2**.

We reasoned that, in a departure from previously reported approaches, indole construction could be realized from suitably functionalized stilbenes, in which the benzylic cation was trapped intramolecularly by a nucleophile. Our hypothesis was that cyclization would produce the indole, provided the stilbene possessed an amino group at the *ortho* position (Scheme 3).

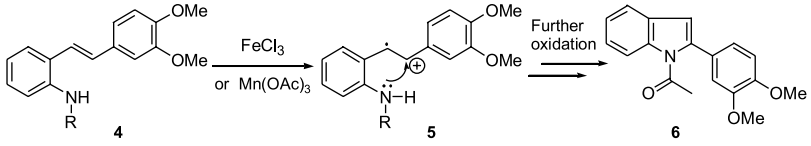
In order to translate the above plan into reality, the reactions described in the next section were performed.

2. Results and discussion

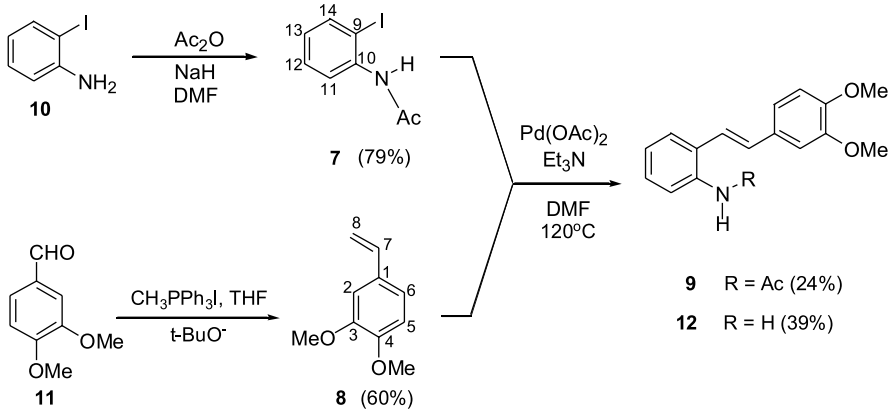
2′-Iodoacetanilide **7** was prepared by reacting iodoaniline **10** in dry DMF with sodium hydride and acetic anhydride to



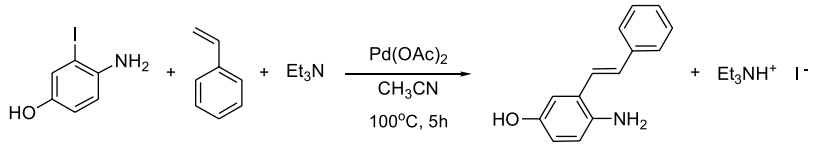
Scheme 2. The $FeCl_3$-promoted tandem pericyclic synthesis of catechol analogues of restrytisol.



Scheme 3. Proposed indole construction by $FeCl_3$ induced oxidative cyclization of the amino stilbene.



Scheme 4. Synthesis of amino- and acetamidostilbenes from iodoaniline and iodoacetamide.

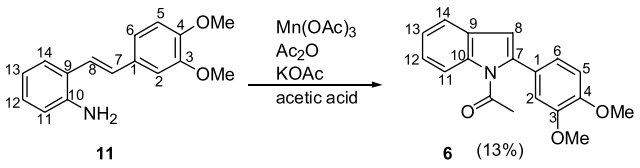


Scheme 5. The synthesis of 2-amino-5-hydroxystilbene via Heck coupling.

produce **7** as brown crystals in 79%. The styrene was prepared by reacting methyltriphenylphosphonium iodide in THF with potassium *tert*-butoxide, to generate the ylide followed by addition of 3,4-dimethoxybenzaldehyde **11**, which produced **8** in 60% yield as a yellowish oil. Stilbene **9** was prepared by treatment of *ortho*-iodoacetanilide **7** with 3,4-dimethoxystyrene **8** in the presence of $Pd(OAc)_2$, Et_3N in DMF. This Heck reaction produced the acetamidostilbene **9** in 24% yield. The aminostilbene **12** was generated in an analogous manner. In accordance with the plan (Scheme 4) we prepared stilbenes **9** and **12** in three and two steps, respectively.

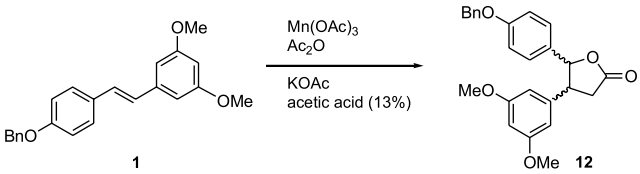
Ziegler and co-workers have reported[21] that highly activated 2-amino-5-hydroxyiodobenzene and styrene react via the Heck coupling reaction to form 2-amino-5-hydroxystilbene in 50% yield (Scheme 5).

Treatment of aminostilbene **12** with manganese triacetate in acetic anhydride/acetic acid produced the indole **6**, which was isolated in 13% yield as the major component from the complex mixture (Scheme 6). The pyrrole NH is acetylated under the reaction conditions. The polar baseline materials, as shown on TLC, were not investigated further at this stage. (All indole structures described in this manuscript, for example, **6**, are numbered according to the stilbene numbering system; see Scheme 6).



Scheme 6. Indole synthesis by manganese triacetate oxidative cyclization.

We have previously reported that under the same reaction conditions (Scheme 7) the stilbene **1** was converted to the γ-butyrolactone **12**.[19]



Scheme 7. Synthesis of the γ-butyrolactone.

We are aware of a report of the construction of a C-2 phenyl substituted indole from an *ortho*-nitrostilbene by Akazome et al.[22]

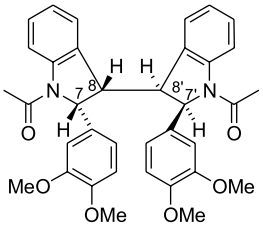
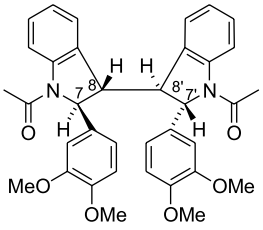
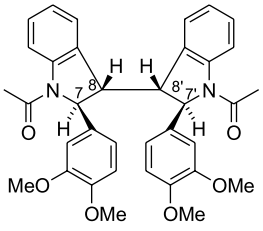
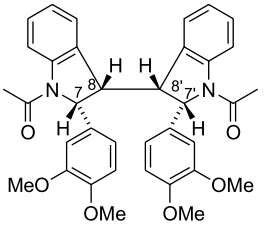
The low yield of the indole **6**, the complexity of the reaction mixture, and our previous experience of stilbene-$Mn(OAc)_3$ reactions[19] (Scheme 7), suggested to us the mechanistic hypothesis described in Scheme 9.

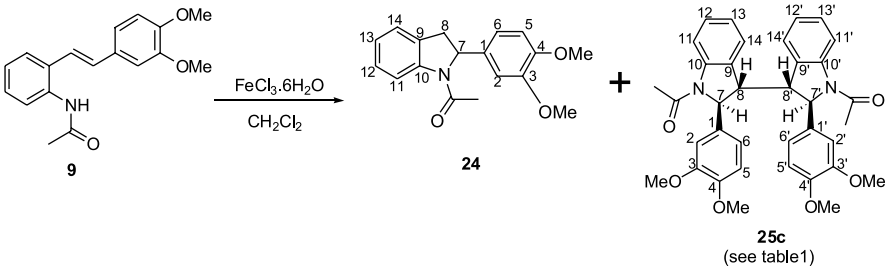
In contrast to Scheme 3, we have found that treatment of the acetamidostilbene **9** with ferric chloride in dichloromethane produced the indoline **24** in 38% yield and the bisindole **25** in 15% yield (Scheme 9). In the case of **25** only one diastereoisomer was obtained. The problem of the relative configuration at the four contiguous stereogenic centres, H-7, H-8, H-8′ and H-7′ and how the assignments were made will be discussed later. In this transformation, the formation of the bisindoline is highly stereoselective. These compounds were isolated by preparative TLC, solvent system hexane:ethyl acetate (7:3, v/v); R_f for the indoline **24** and for bisindoline **25** were 0.4 and 0.27, respectively. With regard to the brownish yellow base line material, all attempts to move it up the plate by addition of methanol to the solvent system were unsuccessful. We think it unlikely that these materials contain any bisindoline diastereoisomers. These baseline products are much more likely to be the result of polymerisation and/or degradation. On this basis we say that this transformation leading to the formation of **25c**, is apparently stereospecific since no other diastereomers are formed. However, we believe highly stereoselective is a better description because the stereochemical outcome (on the product side) cannot be directly related to configurational/stereochemical features in the starting stilbene.[23] The origin of this stereoselectivity lies in radical cation dimerization mechanistic pathways (and the stereo-directing influence of C-2 aryl substituents). This will be more fully explained in Schemes 11(a)–(d) and 12 and Table 1. This reaction may actually be stereospecific in spite of the above (Scheme 8).[23]

2.1. Spectroscopic evidence for synthesised compounds

2.1.1. Indole 6. The UV spectrum of indole **6** showed absorption maxima at 293 and 213 nm (log ε 3.90 and 4.14, respectively) typical of an indole chromophore. High resolution EI mass spectrum gave a molecular ion peak with accurate mass 295.1209 compatible with the molecular formula $C_{18}H_{17}O_3N$ (calculated mass 295.1208, Δ 0.34 ppm). The IR spectrum showed a band at 1702 cm^{-1} representing the C=O stretch. No N–H bands were observed, suggesting that this *N* was tertiary. The ^1H NMR spectrum of **6** integrated for 17 protons. At δ2.07 a singlet corresponding to the methyl protons of the acetyl was observed. The singlets of the methyls at C-3 and C-4 appeared at δ 3.87 and δ 3.90, respectively. H-8 resonated as a singlet at δ6.56. The signals of the seven aromatic ring protons were observed between δ 6.89 and δ 8.32. The chemical shift of each signal in the aromatic region is similar to corresponding protons in the starting aminostilbene, except for H-11, which was deshielded due to its

Table 1. The four possible stereoisomers of bisindoline **25a–25d**

Stereoisomer	Symmetry element	Heat of formation (kcal/mol)	Dihedral angle H-7/H-8
 **25a**	C_2 axis	−70.44	15.8°
 **25b**	C_2 axis	−81.07	10.7° 121° ±1°
 **25c**	Plane (MESO)	−82.85	121° ±1°
 **25d**	Plane (MESO)	−66.65	31.0° 27.2°



Scheme 8. Synthesis of the indoline and bisindoline from acetamido-stilbene **9**.

proximity to the electron-withdrawing amide group. The absence of the *trans* coupling (16 Hz) present in the aminostilbene **11**, coupled with the disappearance of the C-7 proton (originally present in the stilbene **11**) in **6** proved that cyclization had occurred resulting in the formation of the indole ring. In addition, the ^{13}C spectrum showed that the methyne C-7 in **11** had changed to a quaternary C-7 in **6**. The complete assignment of all carbon resonances was obtained from the HMQC and HMBC spectra. Crucial HMBC correlations are shown in Figure 1(a) and (b).

2.1.2. *N*-[7-(3,4-Dimethoxy-phenyl)-7,8-dihydro-indol-*N*-yl]-ethanone 24. The UV spectrum of the dihydroindole

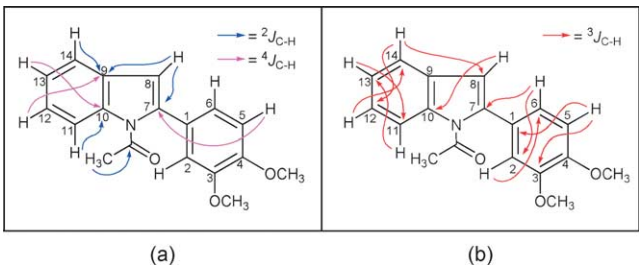


Figure 1. (a) Key ^{2}J and ^{4}J HMBC correlations in **6**. (b) Key ^{3}J HMBC correlations in **6**.

24 showed absorption maxima at 282, 253, 239 and 213 nm (log ε 3.84, 3.10, 3.12 and 3.34) typical of a dihydroindole chromophore. In addition the HREI mass spectrum gave a molecular ion peak with an additional two mass unit compared to **6**; accurate mass measured as 297.1377 is compatible with the molecular formula $C_{18}H_{19}O_3N$ (calculated mass 297.1365, Δ 4.0 ppm). The IR spectrum indicated the presence of a C═O stretch at 1660 cm^{-1} due to the tertiary amide carbonyl. The ^{13}C NMR spectrum showed two methoxyl carbons, one acetyl, one methylene, one methine (stereogenic centre), seven tertiary aromatic carbons and six quaternary carbons. ^{1}H NMR spectrum showed the chemical shift of each signal in the aromatic region to be shifted slightly upfield compared to the indole **6**. This is due to the greater availability of the lone electron pair on the indoline nitrogen (mesomeric delocalization). The COSY spectrum showed correlation signals between H-7 and H-8/8′ thus confirming the existence of the indoline skeleton. In addition the olefinic protons (H-7 and H-8) of the acetamidostilbene (starting material) were replaced by the signals of H-7 at δ 5.29 and H-8/8′ at δ 2.94 and δ 3.78, therefore indicating that a cyclization had occurred resulting in the indoline **24**. Important HMBC correlations are shown in Figure 2(a) and (b).

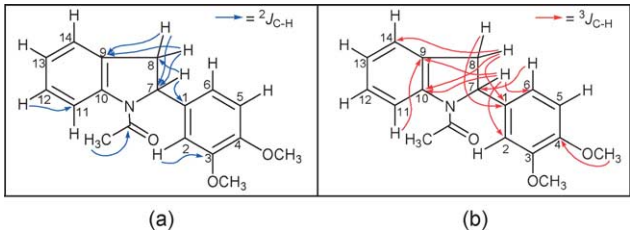


Figure 2. (a) Key ^{2}J HMBC correlations in **24**. (b) Key ^{3}J HMBC correlations in **24**.

2.1.3. *N*-[*N*′-Acetyl-7,7′-bis-(3,4-dimethoxyphenyl)-7,8,7′,8′-tetrahydro-N′*H*-[8,8′]biindolyl-*N*-yl]-ethanone 25.

The UV spectrum showed absorption band at 282 and 214 nm (log ε 3.84 and 4.31) typical of a dihydroindole chromophore. High resolution mass spectrum gave a molecular ion peak at 592.2574 (calculated mass 592.2573, Δ +0.7 ppm) consistent with the molecular formula $C_{36}H_{36}O_6N_2$ corresponding to a dimeric species. The huge (64.7%) peak at *m*/*z* 297 corresponds to the monomeric 24, formed by cleavage of the dimer with the loss of one H. The possibility that dimerization might have occurred within the ionisation chamber was ruled out by the result of a MIKES experiment, which clearly demonstrated

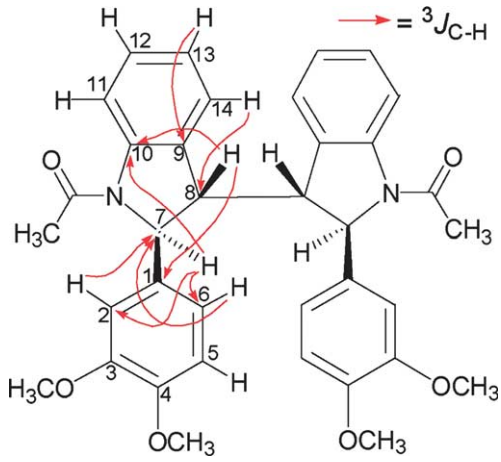
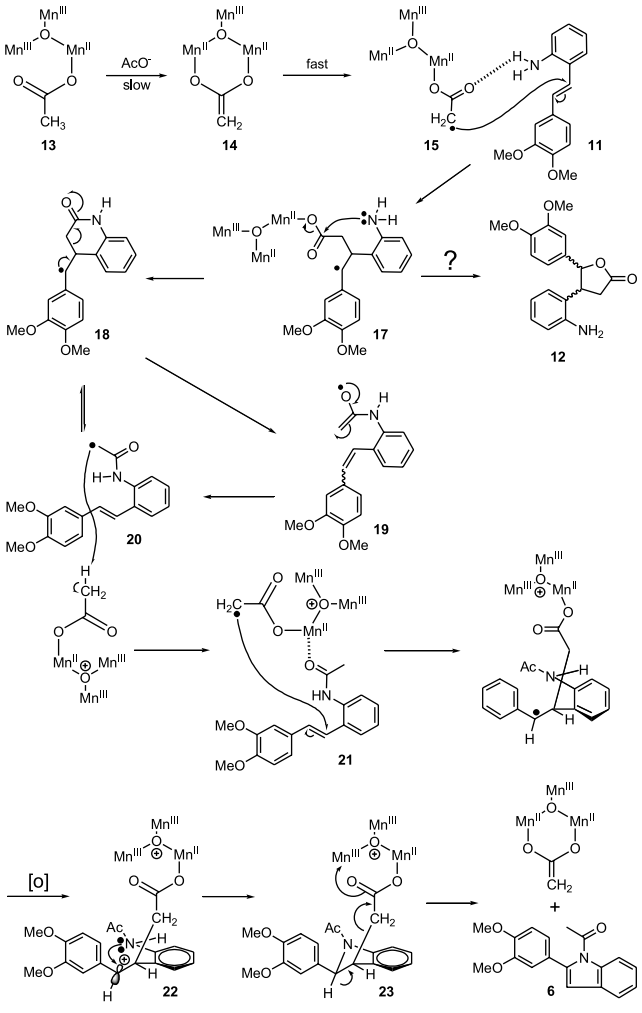
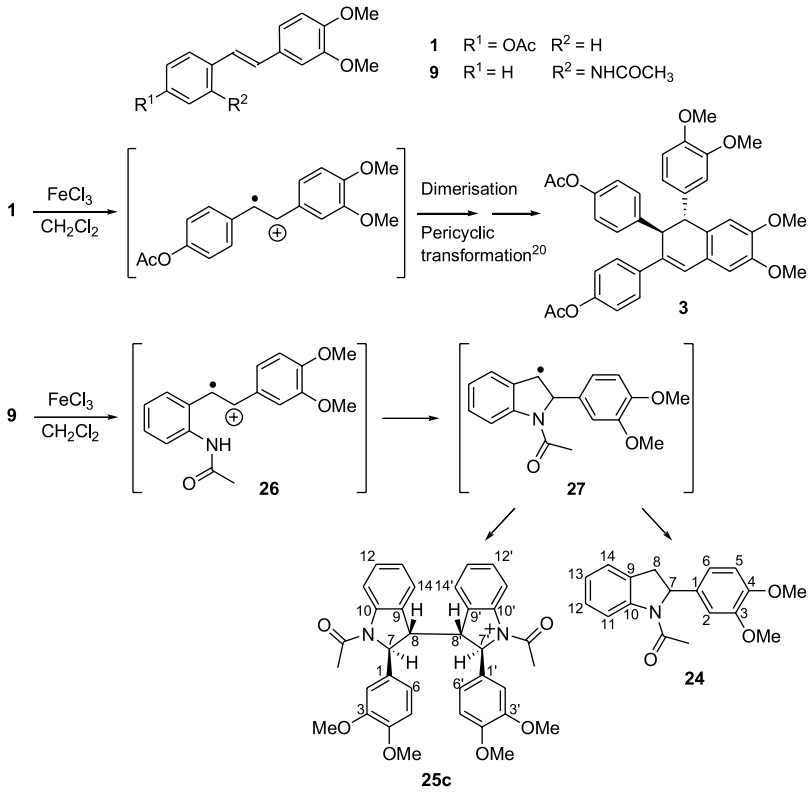


Figure 3. Key ^{3}J HMBC correlations in **25**.

that the *m*/*z* 297 peak originated from the *m*/*z* 592 ion derived from a symmetrical dimer. The IR spectrum showed the presence of C═O stretch at 1666 cm^{-1} due to the C═O of the tertiary amide. The ^{1}H NMR spectrum of the bisdihydroindole **25** was similar to the monomer dihydroindole **24** except for the 5-membered ring system. This revealed two methyne singlets (δ3.51 and δ4.66)



Scheme 9. Proposed mechanism for the formation of 2-phenyl indole via manganese acetate-mediated oxidative cyclization.



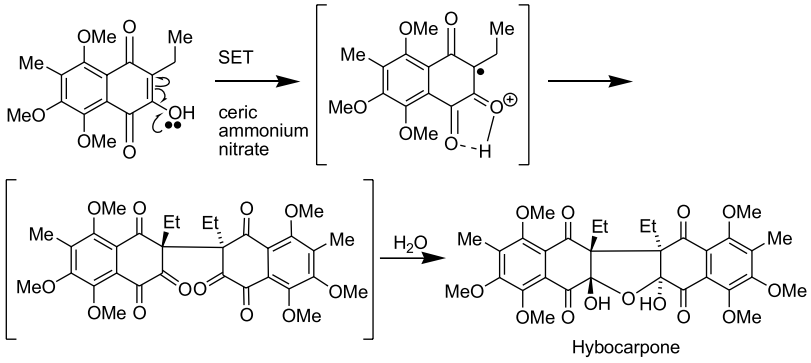
Scheme 10. Proposed mechanism of formation of **24** and **25**.

corresponding to H-7 and H-8, and H-7′ and H-8′. This also proves that **25** is a symmetrical dimer since the methylene signal of H-8 in **24** was replaced by the methyne signal. The ^{13}C spectrum provides additional support for the dimeric structure of by revealing two carbon methyne peaks at δ64.2 and δ56.8 of C-7 and C-8, respectively. The complete assignments of the protons and carbons were confirmed by the COSY, HMQC and HMBC spectra (Fig. 3). The bisdihydroindole **25** possesses 4 stereogenic centres.

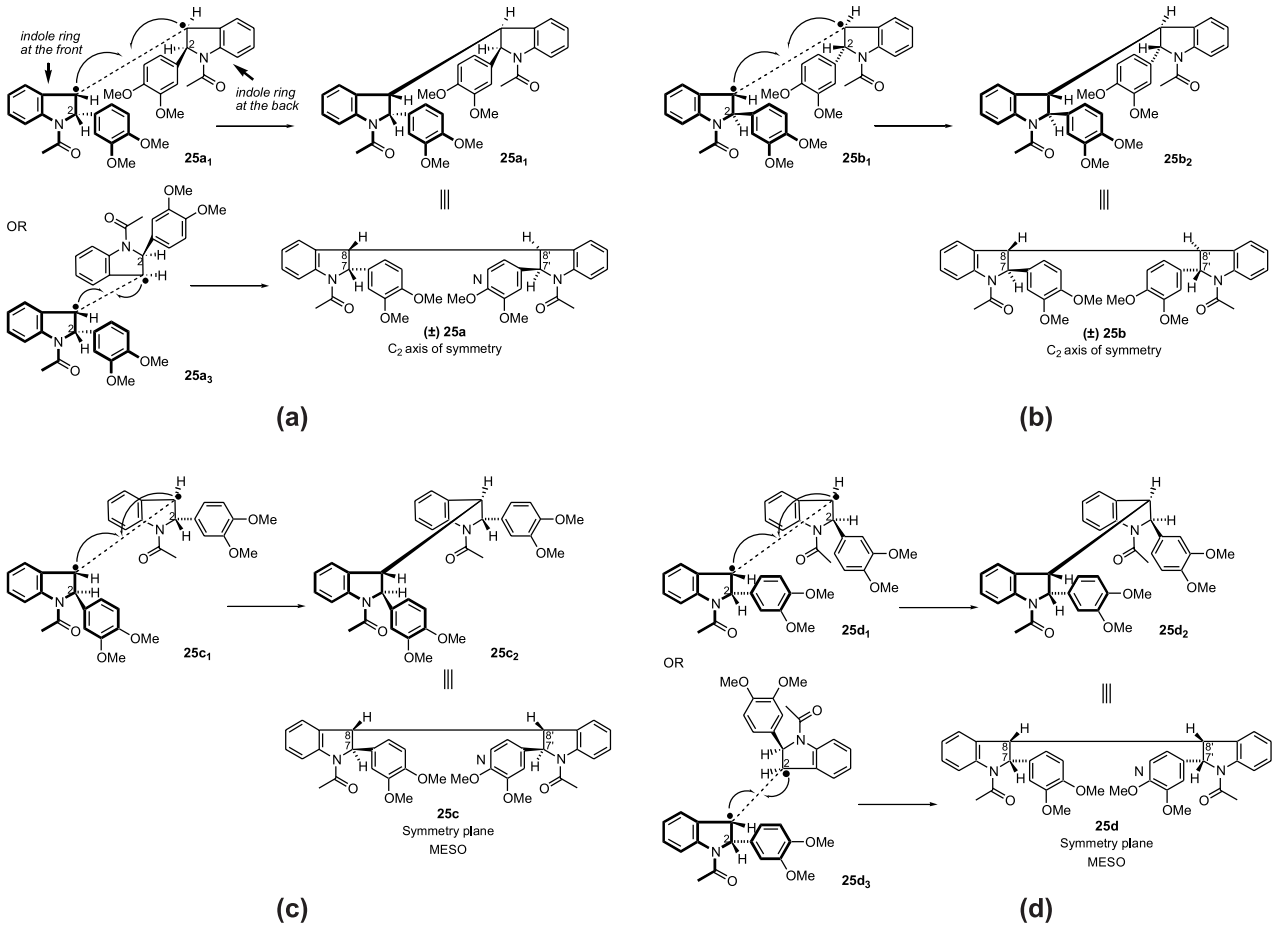
2.2. Mechanistic considerations

Although the indole synthesis has not been fully investigated, a mechanistic interpretation must account for the complex mixture as revealed by TLC (see Schemes 6 and 9). Oxomanganate carbon centred radical complex **15** attacks the double bond in **11** to give benzylic radical **17**. Intramolecular nucleophilic acyl substitution will give rise to the lactam **18**. Ring opening and proton transfer **18**–**20** will generate a second manganese triacetate carbon-centred radical **20**. This will now attack the double bond in the manner depicted (see **21**) resulting in **22** (after further oxidation). Rapid attack by the nucleophilic acetamide NH on the suitably disposed empty *p* orbital leads to **23**. The conformation of **23** allows efficient antiperiplanar elimination of the mangano-acetate complex leading to indole **6**. The complex reaction mixture is better explained by this pathway rather than that originally proposed in Scheme 3.

2.2.1. Mechanism for formation of the indoline 24 in the presence of $FeCl_3$. As we have previously observed[20] (Scheme 2), olefin (stilbene) oxidation by means of Fe^{3+} gives rise to the radical cation **2**. However, the dimerization of the reactive intermediate followed by 6π electrocyclic ring closure that we have observed and previously reported[20] with stilbenes such as **1** (Scheme 10) is not



Scheme 11. The Nicolaou radical cation-mediated synthesis of hybocarpone.



Scheme 12. (a) Dimerisation pathways leading to stereoisomer **25a**. (b) Dimerisation pathways leading to stereoisomer **25b**. (c) Dimerisation pathways leading to stereoisomer **25c**. (d) Dimerisation pathways leading to stereoisomer **25d**.

observed with the acetamidostilbene **9**. Intramolecular nucleophilic attack by the *ortho*-acetamido group would appear to be the favoured pathway leading to **24**. The fact that indole **6** is not obtained under these condition may be attributed to two factors. Firstly, oxidation of the indolyl radical **27** to the corresponding benzylic cation followed by the deprotonation here proceeds more slowly. This may be because chelation of the acetamido group to Fe^{3+} has the effect of withdrawing electrons from the benzene ring, thereby destabilising benzylic carbocations. Secondly, radical promoted dimerisation may be the kinetically more favourable process. We suspect the indolyl radical monomers are held in close proximity to each other by $FeCl_3$ (chelation effect). Mechanistic aspects of radical dimerization pathways leading to **25** will be discussed later. With regard to our synthesis of the dimer **25c** (Scheme 8) for which we have proposed a radical cation pathway, the following observations are worth noting. We have previously reported the first synthesis of restrytisol analogues from stilbenes and proposed a radical cation dimerization/pericyclic pathway. One might propose an alternative pathway involving attack by the indolyl radical **27** on the stilbene **9** (Scheme 10) followed by cyclization which would install the second indole ring. Although this suggestion is worthy of consideration, it lacks the explanatory power of the proposal depicted in Schemes 12(a)–(d) and 13 that effectively addresses the stereochemical issues.

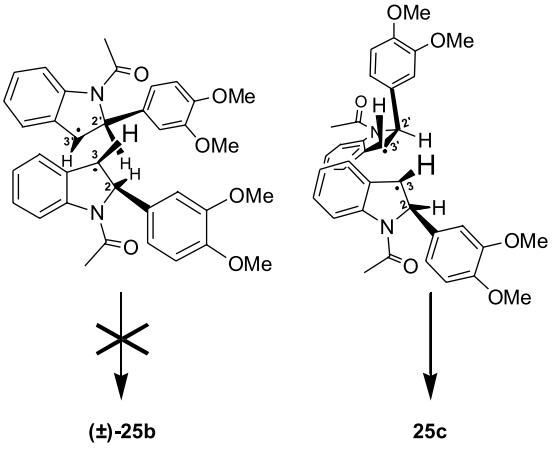
Nicolaou[24] has reported the total synthesis of hybocarpone, which involved a single-electron transfer process that leads to the highly reactive radical cation intermediate (Scheme 11). Kam has reported in the same year the electrochemical one-electron oxidation of the hexacyclic indole alkaloid kopsamine that produced a symmetrical bisindole dimer (via radical cations).[25] Oxidative generation leading to radical cation intermediates has been proposed for the synthesis of bisnaphthol dimers in the presence of copper (II) salt (Smrcina et al.[26]). The construction of aryl–aryl bonds (dibromotetraalkylbiphenyls) by means of ferric chloride reported by Bushby[27] exerted a profound influence on our work. Evidence for the intermediacy of radical cations in the carbon–carbon bond forming step has come from the work of Creasson et al.[28] Oxidative dimerisation involving radical cations is discussed in an interesting review entitled 'Enantioselective radical processes' by Sibi et al.[29] The mechanistic and stereochemical implications of our investigations will now be discussed.

2.2.2. Symmetry and the stereochemistry problem. Although there are fourteen theoretically possible stereoisomers, our conclusion that **25c** represents the correct stereostructure is based on the following considerations We have already described key features of the NMR spectrum of the bisindoline dimer **25** that strongly suggests a symmetrical environment in the vicinity of the H-7 and H-8 (or H-7′ and H-8′protons). The various possibilities are

thus narrowed down to the four structures (**25a**, **25b**, **25c** and **25d**) indicated in Table 1. The precise description of symmetry shown in the table applies strictly to the planar structural representations and not necessarily to the 3-dimensional energy minimized structures (for which other terminology could be applied). For **25a**, **25b**, **25c** and **25d**, energy minimized structures were obtained by means of the annealing method and semi-empirical AM1 calculations.[30,31] Heats of formation and dihedral angles obtained from these calculations are shown in the above-mentioned Table 1. The relative lack of coupling, (H-7 and H-8 are singlets) reflect a dihedral angle close to 90°. That there is a weak coupling between H-7 and H-8 is shown in the COSY spectrum (500 MHz). The proximity of the H-7/H-7′ to the electron-withdrawing acetamide nitrogens would further decrease the coupling constant between the H-7 and H-8 (as well as between H-7′ and H-8′) below the theoretical value obtained from the Karplus equation.[32] Therefore, coupling constants for structures **25a** and **25d** would be inconsistent with the experimental data.[33] The calculated heats of formation of **25a** and **25d** are also much higher than those for **25b** and **25c**. On the basis of these arguments structures **25a** and **25d** must be ruled out.

In both (±)-**25b** and **25c**, semi-empirical calculations indicate that the H-7-H-8 dihedral angle is large enough to account for the extremely weak coupling (for (±)-**25b** and **25c**, 121°). Stereostructure **25c** is, however, 1.8 kcal/mol more stable than (±)-**25b**. Examination of indolyl radical dimerization pathways leading to (±)-**25a** and **25d** provides further convincing reasons for the fact that these stereoisomers are not obtained. It is clear that the approach of the two indolyl radicals (**25a$_1$** or **25a$_3$**). (Scheme 12(a)) or **25d$_1$** or **25d$_3$** (Scheme 12(d)) would result in a destabilizing interaction either between the C-2 substituents (catechol rings) or alternatively between the catechol ring of one component and the indole ring system of the other. Pathways leading to **25a** and **25d** would therefore have higher energy of activation barriers.

With respect to the formation of (±)-**25b** and **25c**, examination of pathways (Scheme 12(b) and (c), respectively) indicates that both indolyl radicals can approach each other without interference from the C-2 phenyl substituents.



Scheme 13. Dimerisation pathways (within bonding distance) leading to **25b** and **25c**.

It is possible to discriminate even more between (±)-**25b** and **25c** by examining physical molecular models. As indolyl radicals approach each other even more closely, formation of (±)-**25b** (Scheme 13) is prohibited by repulsive interactions between C(2)–H, C(3)–H and C(2′)–H. These interactions are reduced to a degree in the case of the formation of **25c** (Scheme 13) **25c** is thus the favoured stereostructure on both kinetic and thermodynamic grounds. The elucidation of the structure of the bisindoline dimer (**25c**) is now complete (Fig. 5).

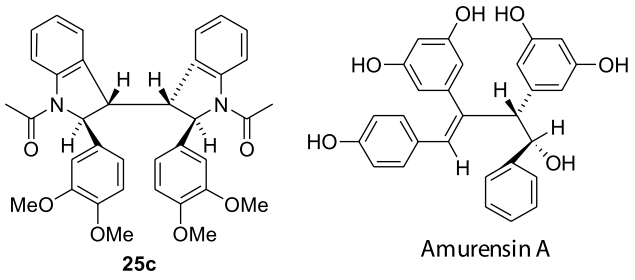


Figure 4. Structural analogy between **25c** and amurensin A.

3. Conclusion

The following inferences may be drawn from this study: (1) the use of the $FeCl_3$ reaction to install two C–N bonds, one C–C bond as well as four new stereogenic centres in one step; (2) the synthetic utility of amino stilbenes prepared by Heck coupling in indole construction. These are to the best of our knowledge very few examples of this strategy; (3) the use of $FeCl_3$ in the oxidative cyclization of the above stilbene to produce indoles and indolines (our catechol indoline is a new compound). Our attention has been drawn to an intriguing 2002 paper by Sayre et al.,[34] in which he revisited the $FeCl_3$ dimerisation of 3-methylindole, first reported in 1957. From a clinical standpoint, Van Vranken's report[35] of the first total synthesis of the antitumour antibiotic AT2433-A1, a bisindolylmaleimide, is noteworthy; (4) the elaboration of the novel bisindoline containing four contiguous stereogenic centres by a mechanistic pathway that involves radical cations. This is certainly a unique feature of this transformation; (5) in the case of bisindole formation, and in contrast to the dimerization of **1** (Scheme 2), the pericyclic pathway is completely suppressed; (6) the solution to the elucidation of the relative configuration of the bisindole by spectroscopic and computational methods.

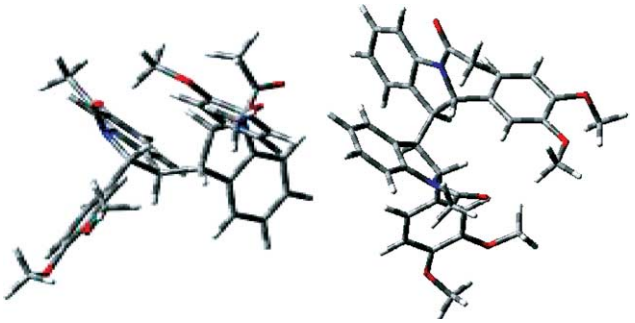


Figure 5. Two views of the computerized model of **25c**.

It has not escaped our attention that the bisindole dimer, with its C8–C8′ bond, bears some relation to the known oligostilbenoid dimer amurensin A[36] (Fig. 4). In the light of our interest in oligostilbenoid dimerization by one-electron oxidants,[19,20] this bisindole can be considered, with respect to the carbon skeleton, as a novel analogue of a natural oligostilbenoid dimer. We are currently investigating the relationship between the substitution pattern of the starting stilbene, the mechanism and the dimerization products from the $FeCl_3$ reaction.

4. Experimental

4.1. General

4.1.1. *N*-[7-(3,4-Dimethoxy-phenyl)-indol-*N*-yl]-ethanone 6. The Heck product, amino stilbene **11** (0.5 g, 1.96 mmol), manganese triacetate (1.052 g, 3.92 mmol), potassium acetate (1.92 g, 0.0196 mol) and 13% acetic acid in acetic anhydride as the solvent (26 ml) were refluxed under nitrogen for 6 h. The mixture was then cooled, diluted with saturated sodium chloride solution and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate. The crude product was purified by column chromatography and preparative thin layer chromatography to yield indole **6** in 13%.

HRMS-EI 295.1209 (calculated mass 295.1208, Δ 0.3 ppm); UV (MeOH) λ_{max} nm (log ε): 282 (5.84), 253 (6.10), 239 (6.12), 213 (6.34); IR ν_{max}: 1605, 1586, 1702; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (d; J=8.32 Hz; 1H) (H-11), 7.5 (d; J=7.32 Hz; 1H) (H-14), 7.31 (t; J=7.08 Hz; 1H) (H-12), 7.24 (t; J=6.84 Hz; 1H) (H-13), 6.99 (dd; J=8.32, 1.96 Hz; 1H) (H-6), 6.92 (d; J=2.44 Hz; 1H) (H-2), 6.89 (d; 1H) (H-5), 6.56 (s; 1H) (H-8), 3.90 (s; 3H) (OMe), 3.87 (s; 3H) (OMe), 2.07 (s; 3H) ($COCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 171.6 ($COCH_3$), 149.5 (C-12), 149.1 (C-11), 139.5 (C-6), 137.5 (C-9), 128.9 (C-5), 126.6 (C-2), 125.1 (C-4), 124.9 (C-3), 123.6 (C-14),121.7 (C-1), 120.1 (C-13), 115.9 (C-10), 112.0 (C-8), 56.2 (OMe), 111.2 (OMe), 110.9 (C-7), 56.0, 55.1 (OMe), 27.6 ($COCH_3$).

4.1.2. 2′-Iodoacetanilide 7. Iodoacetanilide **7** (CAS No 19591-17-4) was prepared by reacting iodoaniline **10** (5 g, 0.023 mol) in dry DMF (40 ml) with sodium hydride (1.096, 0.046 mol) and acetic anhydride (10.87 ml, 0.115 mol) to produce *N*-(2-iodo-phenyl)-acetamide **7** as brown crystals in 79% yield after chromatography (ethyl acetate/hexane 8:2).

4.1.3. 3,4-Dimethoxystyrene 8. Styrene **8** (CAS No 6380-23-0) was prepared by reacting methyltriphenylphosphonium iodide (4.86 g, 0.012 mol) in THF (40 ml), 0 °C with potassium *tert*-butoxide (12 ml, 0.012 mol) and 3,4-dimethoxybenzaldehyde (2 g, 0.012 mol) via Wittig methodology to give yellowish oil **8** in 60% yield after chromatography (ethyl acetate/hexane 8:2).

4.1.4. Acetamido stilbene 9. Replacement of the iodoaniline **10** by **7** (0.3 g, 1.15 mmol) with 3,4-dimethoxystyrene **8** (0.236 g, 1.44 mmol), palladium acetate (4.87 mg, 0.0115 mmol) and triethylamine (0.57 ml, 4.14 mmol) in dry DMF (10 ml) produced the protected acetamidostilbene **9** in 24% yield after chromatography (ethyl acetate/hexane 8:2).

HRMS-EI 297.1353 (calculated mass 297.1365, Δ +4 ppm); UV (MeOH) λ_{max} nm (log ε): 323 (4.48), 209 (4.64); IR ν_{max}: 2837, 1665, 1515; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d; J=8.08 Hz; 1H) (H-11), 7.61 (s; 1H) (N–H), 7.51 (d; J=7.56 Hz; 1H) (H-14), 7.24 (t; J=7.56 Hz; 1H) (H-12), 7.16 (t; J=7.56 Hz; 1H) (H-13), 7.06–6.98 (m; 3H) (H-6, H-2, H-7), 6.89 (d; J=16.12 Hz; 1H) (H-8), 6.85 (d; J=8.08 Hz; 1H) (H-5), 3.90 (s; 3H) (OMe), 3.88 (s; 3H) (OMe), 2.19 (s; 3H) ($COCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 168.9, 149.1, 148.9, 134.4, 131.4, 130.8, 130.2, 127.7, 126.3, 125.5, 124.6, 121.7, 119.8, 111.2, 109.3, 55.8, 23.8.

4.1.5. Amino stilbene 11. The starting material, iodoaniline **10** (8 g, 0.01826 mol) was dissolved in dry DMF (80 ml) in a dry, clean two-necked round bottom flask. The solution was heated to 120 °C and allowed to stir under nitrogen for 5 min. Palladium acetate (0.154 g, 0.3445 mmol) was then added, followed by addition of triethylamine (18.2 ml, 0.0657 mol) and 3,4-dimethoxy styrene **8** (7.5 g, 0.0228 mol). The mixture was refluxed under nitrogen for 48 h. The reaction mixture was then filtered and saturated sodium chloride added. The aqueous mixture was extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous sodium sulphate. The crude was purified by column chromatography (ethyl acetate/hexane 8:2) to give 43% of orange crystals of the aminostilbene **11**.

HRMS-EI 255.1267 (calculated mass 255.1259, Δ +0.8 ppm); UV (MeOH) λ_{max} nm (log ε): 340 (4.18), 294 (4.16), 222 (4.2824); IR ν_{max}: 3373, 1514, 1266; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (d; J=7.8 Hz; 1H) (H-11), 7.12–7.00 (m; 4H) (H-12, H-13, H-2, H-8), 6.91 (d; J=16.12 Hz; 1H) (H-7), 6.84 (d; J=8.04 Hz; 1H) (H-5) 6.79 (d; J=7.56 Hz; 1H) (H-14), 6.71 (d; J=7.8 Hz; 1H) (H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 149.0, 148.7, 143.7, 130.6, 129.9, 128.2, 126.9, 123.9, 122.2, 119.6, 119.6, 119.0, 116.1, 111.1, 108.7, 55.8, 55.7.

4.1.6. *N*-[7-(3,4-Dimethoxy-phenyl)-7,8-dihydro-indol-1-yl]-ethanone 24 and *N*-[*N*′-acetyl-7,7′-bis-(3,4-dimethoxy-phenyl)-7,8,7′,8′-tetrahydro-N′*H*-[8,8′]bi-indolyl-*N*-yl]-ethanone 25. Protected amino stilbene **9** (0.079 g, 0.266 mmol) was dissolved in 6 ml of dichloromethane. $FeCl_3 \cdot 6H_2O$ (0.72 g, 2.66 mmol) was added to the mixture. The mixture was allowed to stir overnight at room temperature and was monitored by TLC. After the consumption of the starting material, the reaction mixture was diluted with saturated sodium chloride and extracted with ethyl acetate. The crude product obtained after evaporation under reduced pressure was subjected to preparative thin layer chromatography. Two pure compounds, **24** (38% yield) and **25** (15% yield) were isolated.

Spectroscopic data for **24**. HRMS-EI 297.1377 (calculated mass 297.1365, Δ +1.2 mmu); UV (MeOH) λ_{max} nm (log ε): 282 (3.84), 253 (4.10), 239 (4.12), 213 (4.34); IR ν_{max}: 1660, 1481, 1462, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d; J=6.8 Hz; 1H) (H-11), 7.23 (t; J=7.8 Hz; 1H) (H-12), 7.09 (d; 1H) (H-14), 7.02 (t; J=7.32 Hz; 1H)

(H-13), 6.75 (d; $J=8.04$ Hz; 1H) (H-5), 6.68 (dd; $J=6.8$, 1.48 Hz; 1H) (H-6), 6.62 (s; 1H) (H-2), 5.29 (d; $J=9.04$ Hz; 1H) (H-7), 3.81 (s; 3H) (OMe), 3.75 (s; 3H) (OMe), 3.78 (d; 1H) (H-8′), 2.94 (d; $J=15.88$ Hz; 1H) (H-8), 2.03 (s; 1H) ($COCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 169.9 ($COCH_3$), 149.8 (C-4), 148.9 (C-3), 143.6 (C-10), 136.0 (C-1), 129.5 (C-9), 127.9 (C-12), 125.1 (C-14), 124.3 (C-13), 117.4 (C-6), 117.2 (C-11), 111.8 (C-5), 108.3 (C-2), 63.6 (C-7), 56.2 (OMe), 56.1 (OMe), 39.4 (C-8), 24.4 ($COCH_3$).

Spectroscopic data for **25**. HRMS-EI 592.2574 (calculated mass 592.2573, Δ +0.1 mmu); UV (MeOH) λ_{max} nm (log ε): 282 (3.84) 214 (4.31); IR ν_{max}: 1666, 1026; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.47 (d; $J=8.08$ Hz; 1H) (H-11), 7.45 (t; $J=7.84$ Hz; 1H) (H-12), 7.31 (d; $J=7.32$ Hz; 1H) (H-14) 7.21 (t; $J=7.08$ Hz; 1H), (H-13), 6.61 d; $J=8.32$ Hz; 1H) (H-5), 6.22 (d; $J=8.04$ Hz; 1H) (H-6), 5.80 (s; 1H) (H-2), 4.66 (s; 1H) (H-7), 3.75 (s; 3H) (OMe), 3.59 (s; 3H) (OMe), 3.51 (s; 1H) (H-8), 1.88 (s; 3H) ($COCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 169.8 ($COCH_3$) 149.4 (C-3), 148.4 (C-4), 143.9 C-10), 134.1 (C-1), 130.1 (C-9), 129.3 C-12), 125.2 (C-14), 124.7 (C-13), 117.7 (C-11), 115.9 (C-6), 111.4 (C-5), 107.5 (C-2), 64.2 (C-7), 56.8 (C-8), 23.6 ($COCH_3$).

Acknowledgements

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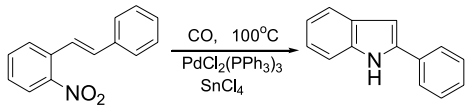
References and notes

1. Mann, J. *Secondary Metabolism*; Oxford University Press: Oxford, 1987.
2. (a) Mann, J. *Chem. Ber.*, 478. (b) Mann, J. *Murder, Magic and Medicine*; Oxford University Press: Oxford, 1992.
3. (a) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2023. (b) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2657. (c) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1.
4. (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. (b) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247.
5. Joule, J. A.; Mills, A. K. In *Heterocyclic Chemistry*, 4th ed.; Blackwell: Oxford, 2000.
6. (a) Solid phase synthesis: Nicolaou, K. C.; Roecker, A. J.; Pfefferkorn, J. A.; Cao, G. Q. *J. Am. Chem. Soc.* **2000**, *122*, 2966. (b) Catalytic (Gribb's): Witulski, B.; Stengel, T.; Fernandez-Hernandez, J. M. *Chem. Commun.* **2000**, 1672. (c) Photolytic: Benali, O.; Miranda, M. A.; Tormas, R.; Gill, S. *J. Org. Chem.* **2002**, *67*, 7915.
7. Frank, W. C.; Kim, Y. C.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2947.
8. Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry: a Guide for the Synthetic Chemist*; Pergamon: Amsterdam, 2000; (indole, indoline and bisindole syntheses are covered in Chapter 3) .
9. Grigg, R.; Rutnikovic, B.; Urch, C. J. *Tetrahedron Lett.* **1996**, *37*, 695.
10. Dong, Y.; Busacca, C. A. *J. Org. Chem.* **1997**, *62*, 6464.
11. Brenner, M.; Mayer, G.; Terpin, A.; Steglich, W. *Chem. Eur. J.* **1997**, *3*, 70.
12. Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.
13. Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.
14. (a) Kobayashi, Y.; Fukuyama, T. *J. Heterocycl. Chem.* **1998**, *35*, 1043. (b) Kobayashi, Y.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519.
15. Grigg, R.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 3859.
16. Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.
17. Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.
18. Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111.
19. Thomas, N. F.; Lee, K. C.; Paraidathathu, T.; Weber, J. F. F.; Awang, K. *Tetrahedron Lett.* **2002**, *43*, 3151.
20. Thomas, N. F.; Lee, K. C.; Paraidathathu, T.; Weber, J. F. F.; Awang, K.; Rondeau, D.; Richomme, P. *Tetrahedron* **2002**, *58*, 7201.
21. Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941.
22. Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375.



23. We thank the referee for his suggestion.
24. Nicolaou, K. C.; Gray, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 761.
25. Kam, T. S.; Lim, T. M.; Tan, G. H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1594.
26. Smrcina, M.; Polakova, J.; Vyskocil, S.; Kocovsky, P. J. *Org. Chem.* **1993**, *58*, 4534.
27. Boden, N.; Bushby, R. J.; Lu, Z.; Headdock, G. *Tetrahedron Lett.* **2000**, *41*, 10117.
28. Creason, S. C.; Wheeler, J.; Nelson, R. *J. Org. Chem.* **1972**, *37*, 4440.
29. Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, 103.
30. Dewar, M. J. S.; Zocbish, E. G.; Healy, E. F.; Stuart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
31. AMPAC version 6.0, 7204 Mullen, SemiChem, Shawne, KS, USA, 1997.
32. Friebolin, H. *Basic One- and Two-dimensional NMR Spectroscopy*; Wiley: Weinheim, 1998; p 93.
33. In the light of the dihedral angles for (±)-**25a** and **25d**, there is some doubt about the 'symmetry' of these compounds. The results of further computational chemistry will be reported in due course.
34. Ling, K. Q.; Ren, T.; Protasiewicz, J. D.; Sayre, L. M. *Tetrahedron Lett.* **2002**, *43*, 6903.
35. Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **2000**, *65*, 7541.
36. Huang, K. S.; Lin, M. *J. Asian Nat. Prod. Res.* **1999**, *2*, 21.

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Stereoselective electrocatalytic transformation of arylidenemalononitriles and malononitrile into (1*R*,5*S*,6*R*)*-6-aryl-2-amino-4,4-dialkoxy-1,5-dicyano-3-azabicyclo[3.1.0]hex-2-enes

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Abstract—Electrolysis of arylidenemalononitriles and malononitrile in alcohols in an undivided cell in the presence of sodium bromide as mediator results in the stereoselective formation of (1*R*,2*S*,6*R*)*-6-aryl-2-amino-4,4-dialkoxy-1,5-dicyano-3-azabicyclo[3.1.0]hex-2-enes in 60–80% yields.

1. Introduction

Malononitrile is a commonly known and widely used reagent in the synthesis of heterocyclic compounds, pharmaceuticals, pesticides, fungicides, solvatochromic dyes, and charge-transfer salts. The unique reactivity of this compound has led to its widespread application in organic chemistry, as well as or even more than other CH acids such as malonate and cyanoacetic esters.[1]

Nevertheless, little is known about the electrochemical transformations of malononitrile. Although the first electrochemical oxidation of the malonate anion was performed in the XIX century,[2] electrooxidation, electroreduction, or any other electrochemical transformations of malononitrile are not mentioned in books or reviews of the electroorganic chemistry[3–6] or in reviews dealing with the application of malononitrile in organic synthesis.[7,8] To our knowledge, apart from the work of our research group, there is only one publication which is concerned with this problem and describes the electrochemical anodic arylation of malononitrile.[9]

The use of alkylidenemalononitriles, which contain an activated double bond together with reactive CN groups, is also quite common in organic synthesis.[10,11] These reagents are usually prepared from malononitrile and carbonyl compounds by the Knoevenagel reaction.[12] Known electrochemical transformations of alkylidenemalononitriles include cathodic hydrogenation,[13] cyclodimerisation of arylidenemalononitriles[14] and cathodic addition of alkylidenemalononitriles to acrylonitrile and methyl acrylate.[15]

In recent decades, mediators and mediator systems have been successfully used for the electrooxidation and electroreduction of organic compounds.[6] Among a variety of mediators, the redox system halide anion/halogen is one of the most useful from the viewpoint of organic synthesis and large-scale processes.[16]

In the course of our study on the electrochemical oxidation of organic compounds, in the presence of alkali metal halides, we have carried out the electrochemical transformation of cyanoacetic ester and aldehydes into 3-substituted-1,2-dicyanocyclopropane-1,2-dicarboxylates,[17] as well as malononitrile and ketones into substituted 1,1,2,2-tetracyanocyclopropanes.[18] The latter process is the electrocatalytic variant of the Wideqvist reaction, that is, the reaction of bromomalononitrile with ketones in the presence of stoichiometric amounts of sodium iodide.[19] In the electrochemical version, bromomalononitrile is replaced by malononitrile and catalytic

Keywords: Electrolysis; Stereoselectivity; Electrocatalytic transformation; Mediators; Malononitrile; Arylidenemalononitriles; Bicyclic pyrrolines.
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amounts of sodium bromide, which is fully regenerated during the electrocatalytic process.

It has also been found that tetracyanocyclopropanes, being electrolysed in alcohols in an undivided cell, are very easily attacked by alkoxide anions generated at cathode and affords the transformation into substituted 2-amino-4, 4-dialkoxy-1,5-dicyano-3-azabicyclo[3.1.0]hex-2-enes[19] (Scheme 1).

Several years ago, we proposed a new approach to the synthesis of functionally substituted cyclopropanes, namely, co-electrolysis of CH-acids with activated olefins[20,21] (Scheme 2).

The co-electrolysis of alkylidenecyanoacetic and malonic esters carried out within the framework of this approach resulted in stereoselective synthesis of (*E*)-isomers of trialkyl-3-substituted-2-cyanocyclopropane-1,1,2-tricarboxylates[22] (Scheme 3).

Recently, we have accomplished electrocatalytic transformation of cycloalkylidenemalononitriles and malononitriles into spirotricyclic compounds containing cyclopropane and pyrroline fragments[23] (Scheme 4).

In the present study we report our results on the stereoselective electrocatalytic transformations of arylidenemalononitriles **1a–i** and malononirile into bicyclic pyrrolines **2a–k** in alcohols in the presence of sodium halide as a mediator (Table 1, Scheme 5):

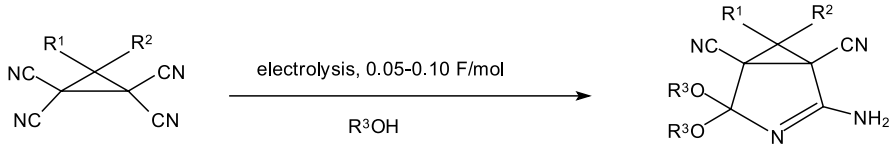
Table 1. Stereoselective electrocatalytic transformation of arylidenemalononitriles **1a–i** and malononirile into bicyclic pyrrolines **2a–k**[a]

Arylidene-malononitrile	R^1	R^2	Mediator	*t* (°C)	Bicyclic pyrroline	Yield (%)[b]
1a	H	Me	NaBr	20	**2a**	38
1a	H	Me	NaBr	10	**2a**	56
1a	H	Me	NaBr	0	**2a**	82
1a	H	Me	NaBr	−10	**2a**	64
1a	H	Me	NaI	0	**2a**	69
1a	H	Et	NaBr	0	**2b**	73
1a	H	Et	NaI	0	**2b**	57
1b	4-Me	Me	NaBr	0	**2c**	69
1c	4-*t*-Bu	Me	NaBr	0	**2d**	59
1d	4-OMe	Me	NaBr	0	**2e**	65
1d	4-OMe	Me	NaI	0	**2e**	54
1e	2-Cl	Me	NaBr	0	**2f**	78
1e	2-Cl	Me	NaI	0	**2f**	62
1e	2-Cl	Et	NaBr	0	**2g**	64
1f	4-Cl	Me	NaBr	0	**2h**	67
1g	3-Br	Me	NaBr	0	**2i**	61
1h	4-I	Me	NaBr	0	**2j**	68
1i	4-NO_2	Me	NaBr	0	**2k**	63

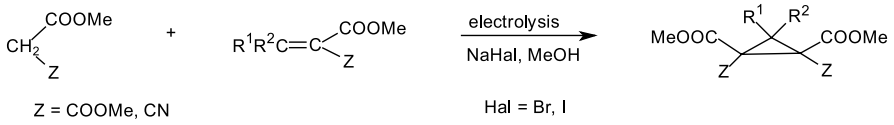
[a] 10 mmol of arylidenemalononitrile, 10 mmol of malononitrile, 5 mmol of mediator, 20 ml of alcohol, Fe-cathode, C-anode, current density 100 mA/cm^2, 2.5 F/mol electricity passed.
[b] Isolated yields.

2. Results and discussion

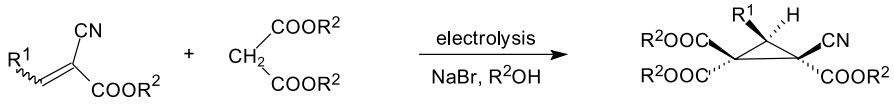
It follows from the data of Table 1, that a decrease in the temperature of electrolysis from 20 to 0 °C ensures the formation of **2a–k** in higher yields. Further decrease in the temperature down to −10 °C led to the formation of



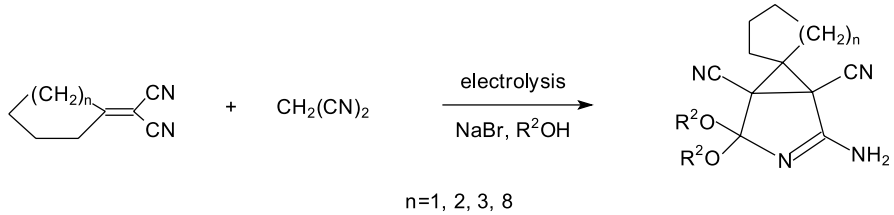
Scheme 1.



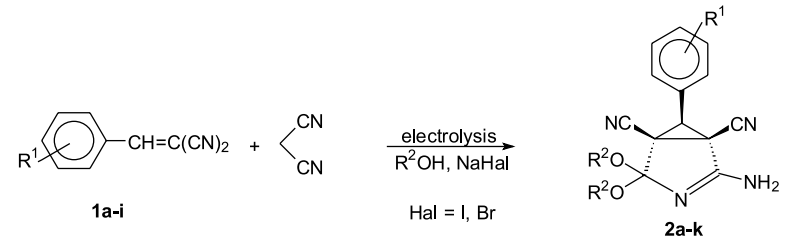
Scheme 2.



Scheme 3.



Scheme 4.



1a-i

a) R^1 = H, b) R^1 = 4-Me, c) R^1 = 4-*t*-Bu, d) R^1 = 4-OMe, e) R^1 = 2-Cl, f) R^1 = 4-Cl, g) R^1 = 3-Br, h) R^1 = 4-I, i) R^1 = 4-NO_2

2a-k

a) R^1 = H, R^2 = Me; b) R^1 = H, R^2 = Et; c) R^1 = 4-Me, R^2 = Me; d) R^1 = 4-*t*-Bu, R^2 = Me; e) R^1 = 4-OMe, R^2 = Me; f) R^1 = 2-Cl, R^2 = Me; g) R^1 = 2-Cl, R^2 = Et; h) R^1 = 4-Cl, R^2 = Me; i) R^1 = 3-Br, R^2 = Me; j) R^1 = 4-I, R^2 = Me; k) R^1 = 4-NO_2, R^2 = Me

Scheme 5.

bicyclic pyrrolines **2a–k** in lower yields. As it was determined by NMR and GLC analysis of the reaction mixtures, in the latter case the conversion of **1a–i** was 80–90%.

Sodium bromide is more efficient as mediator than NaI for the process studied. Thus with the use of NaBr as a mediator the bicyclic pyrrolines **2** were obtained in higher yields.

This new electrochemical reaction takes place with high stereoselectivity. In all experiments, only one of two possible isomers of bicyclic pyrrolines **2a–k** was found by NMR spectroscopy. The structure of **2a** was established by single-crystal X-ray diffraction study (Fig. 1).

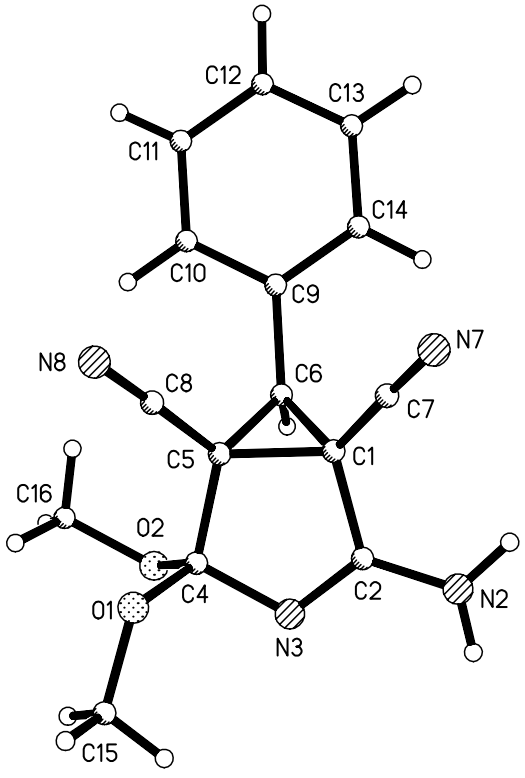
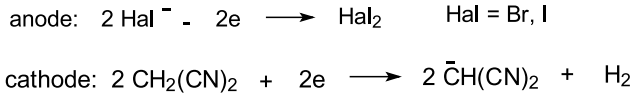


Figure 1. Molecule structure of **2a**.

In bicyclic pyrroline **2a**, the phenyl group and pyrroline ring are in *trans* positions relative to the cyclopropane ring. From the point of view of the less steric hindrance, all other bicyclic pyrrolines **2b–k** should have the similar structures.

Taking into consideration the above results and the data on the mechanism of the electrocatalytic variant of Wideqvist reaction,[19] the following general mechanism of the stereoselective electrochemical transformation of arylidenemalononitriles **1a–i** and malononitrile into bicyclic pyrrolines **2a–k** is suggested.

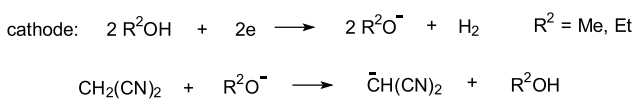
The reactions at the electrodes, which take place during the process, are shown below (Scheme 6):



Scheme 6.

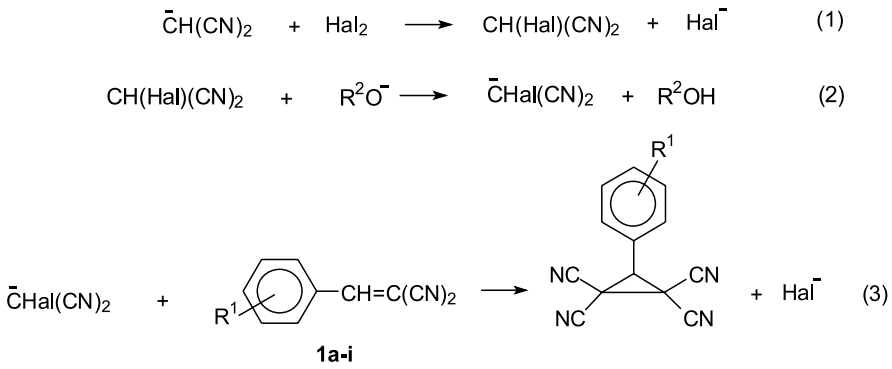
The formation of iodine or bromine at the anode is the well-known process and the corresponding colour was observed when the electrolysis was conducted without stirring the reaction mixture.

The reaction on the cathode could be the formation of alkoxide ion. In this case, the following reaction in solution between alkoxide ion and malononitrile should also lead to the formation of the malononitrile ion as the general result of the cathodic process (Scheme 7).



Scheme 7.

The halogenation of the malononitrile anion by halogen generated at the anode, the formation of the halogenomalononitrile anion, followed by the addition of the latter to arylidenemalonitrile gives rise to 3-aryl-substituted 1,1,2,2-tetracyanocyclopropane (Scheme 8):



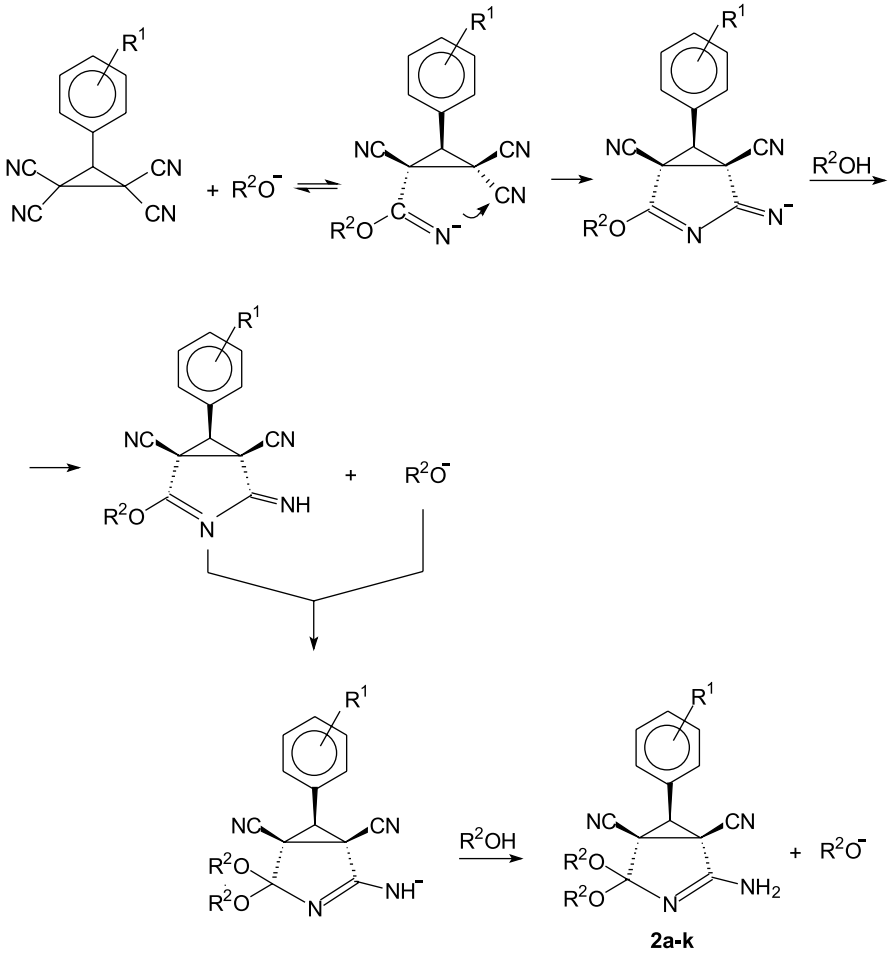
Scheme 8.

The stereoselective formation of **2a–k** is a result of the chain electrocatalytic mechanism shown in Scheme 9 which takes place as the successive addition of two R^2OH molecules to the intermediate tetracyanocyclopropane initiated by R^2O^- ion and includes the regeneration of R^2O^- anion at the last stage, which continues the catalytic chain reaction process by the interaction with the next molecule of tetracyanocyclopropane (Scheme 9).

Sodium bromide is more efficient as a mediator for the above process than sodium iodide. This result is directly related to the fact that intermediate bromomalononitrile is a stronger CH acid than iodomalononitrile and thus the stage of proton abstraction with the formation of the halogenomalononitrile anion (Scheme 8, stage 2) is faster in the case of bromomalononitrile. The stereoselectivity of the process studied could be the result of the stereoselectivity of the alkoxide anion attack on CN-group. This attack takes place on one of two sterically less hindered CN groups, which are in *trans* position to the aryl substituent.

3. Conclusion

Thus, the simple electrocatalytic system can produce under mild conditions direct 'one-pot' stereoselective



Scheme 9.

transformation of arylidenemalononitriles and malononitrile into bicyclic pyrrolines **2a–k** in high yields. Using techniques of classical organic chemistry, this transformation could be accomplished only as a three step process comprising (i) halogenation of malononitrile,[24] (ii) addition of halomalononitrile to the double bond of arylidenemalononitrile followed by cyclization,[25] (iii) reaction of 3-aryl substituted tetracynocyclopropane obtained in step (ii) with alkoxide ions in alcohols.[19] The electrochemical process is efficient and convenient stereoselective method for the synthesis of bicyclic pyrrolines. The procedure utilises inexpensive reagents, simple equipment and undivided cell, it is easily carried out, and the work up is not complicated.

4. Experimental

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. GLC analyses were carried out on a LKhM-80 chromatograph with a flame-ionisation detector, 3 m×3 mm glass columns packed with 5% OV-17 on Inerton (0.16–0.20 mm) or 10% FFAP on Chromaton N-Super (0.13–0.16 mm), respectively. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer.

Arylidenemalononitriles were synthesized by condensation of malononitrile with the corresponding substituted benzaldehydes by a known method.[26]

4.1. General electrolysis procedure

A solution of arylidenemalononitrile (10 mmol), malononitrile (10 mmol), and a mediator (5 mmol) in alcohol (20 ml) was electrolysed in an undivided cell equipped with C-anode and Fe-cathode, thermometer, external cooling and magnetic stirring under constant current density 100 mA/cm^2 at temperature indicated in Table 1. At the end of the electrolysis, when 2.5 F/mol electricity was passed, bicyclic pyrrolines were usually crystallised directly from the reaction mixture and were then filtered off. Additional portion of bicyclic pyrrolines was isolated from the residue of the reaction mixture according to the following procedure. The solvent was removed, and the residue was extracted with ethyl acetate, washed with water, and dried over Na_2SO_4. Ethyl acetate was removed, and the residue was crystallised from acetone–hexane in usual manner.

4.1.1. 2-Amino-1,5-dicyano-4,4-dimethoxy-6-phenyl-3-azabicyclo[3.1.0]hex-2-en (2a). Yield 2.30 g (82%), white solid, mp>350 °C; ^{1}H NMR (DMSO-d$_6$): δ 3.35 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 3.45 (s, 1H, CH), 7.40–7.65 (m, 7H, C_6H_5 and NH_2); ^{13}C NMR (DMSO-d$_6$): δ 35.50 (C), 37.61 (C), 41.62 (CH), 49.63 (OCH_3), 51.26 (OCH_3), 112.30 (CN), 113.61 (CN), 118.75 [$C(OMe)_2$], 128.71, 128.93, 129.17, 129.73 (C_6H_5), 159.36 (C=N); IR (KBr): ν_{max} 3440, 3064, 2248, 1680, 1428, 1172, 1136, 1076, 1104, 700. Anal. calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.51; H, 4.92; N, 19.59.

Crystal data for **2a**: $C_{15}H_{14}N_4O_2$, M=282.30, space group $P2_1/c$, a=14.599 (1) Å, b=7.2553 (5) Å, c=13.318 (1) Å, β=92.306 (2)°, V=1409.6 (2) Å^3, Z=4, D_C=1.330 g cm^{-3}. X-ray diffraction experiments were carried out on SMART Bruker difractometer (T 115 (2)° K, graphite monochromated Mo Kα (λ=0.71073 Å), $2\theta_{max}$=60.02°). The structure **2a** was solved by direct methods and refined by the full-matrix least-squares technique on F^2_{hkl} in the anisotropic approximation. H atoms were located from the difference Fourier synthesis and then refined isotropically. The final disperancy factors were R_1=0.0471 (2279 observed reflections), wR_2=0.0982 (for all 4052 reflections used in refinement). All calculations were carried out with the complex of programs SHELXTL PLUS 5 [Sheldrick G.M. SHELXTL Ver.5, Software Reference Manual, Siemens Industrial Automation, Inc., Madison, 1994].

Crystallographic data for **2a** (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 236712. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.1.2. 2-Amino-1,5-dicyano-4,4-diethoxy-6-phenyl-3-azabicyclo[3.1.0]hex-2-en (2b). Yield 2.26 g, (73%), white solid, mp 246–248 °C; ^{1}H NMR ($CDCl_3$): δ 1.15 (t, 3H, J=7 Hz, CH_3), 1.17 (t, 3H, J=7 Hz, CH_3), 3.47 (s, 1H, CH), 3.71 (q, 2H, J=7 Hz, CH_2O), 3.83 (q, 2H, J=7 Hz, CH_2O), 7.35–7.65 (m, 7H, C_6H_5 and NH_2); ^{13}C NMR (DMSO-d$_6$): δ 15.01 (CH_3), 15.23 (CH_3), 35.41 (C), 38.22 (C), 41.43 (CH), 57.71 (CH_2O), 59.32 (CH_2O), 112.33 (CN), 113.51 (CN), 118.12 [$C(OEt)_2$], 128.80, 128.83, 129.06, 129.73 (C_6H_5), 159.01 (C=N); IR (KBr): ν_{max} 3396, 2980, 2248, 1664, 1444, 1140, 1076, 1048, 700. Anal. calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.64; H, 5.73; N, 18.27.

4.1.3. 2-Amino-1,5-dicyano-4,4-dimethoxy-6-(4-methylphenyl)-3-azabicyclo[3.1.0]hex-2-en (2c). Yield 2.04 g, (69%), white solid, mp>350 °C; ^{1}H NMR (DMSO-d$_6$): δ 2.32 (s, 3H, CH_3), 3.33 (s, 1H, CH), 3.35 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 7.30 (d, 2H, J=8 Hz, Ar), 7.45 (d, 2H, J=8 Hz, Ar), 7.51 (s, 2H, NH_2); ^{13}C NMR (DMSO-d$_6$): δ 20.71 (CH_3), 35.44 (C), 37.60 (C), 40.05 (CH), 49.54 (OCH_3), 51.17 (OCH_3), 112.27 (CN), 113.57 (CN), 118.62 [$C(OMe)_2$], 126.61, 128.69, 129.36, 138.67 (Ar), 159.25 (C=N); IR (KBr): ν_{max} 3404, 3045, 2252, 1688, 1436, 1136, 1116, 1076, 808. Anal. calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.61; H, 5.32; N, 18.69.

4.1.4. 2-Amino-6-(4-*t*-buthylphenyl)-1,5-dicyano-4,4-dimethoxy-3-azabicyclo[3.1.0]hex-2-en (2d). Yield 1.99 g (59%), white solid, mp>350 °C; ^{1}H NMR (DMSO-d$_6$): δ 1.32 (s, 9H, CH_3), 3.33 (s, 1H, CH), 3.35 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 7.50 (d, 2H, J=8 Hz, Ar), 7.52 (d, 2H, J=8 Hz, Ar), 7.59 (s, 2H, NH_2); ^{13}C NMR (DMSO-d$_6$): δ 31.40 (CH_3), 34.86 (C), 35.91 (C), 37.97 (C), 41.84 (CH), 50.01 (OCH_3), 51.62 (OCH_3), 112.76 (CN), 114.09 (CN), 119.18 [$C(OMe)_2$], 126.14, 127.11, 129.00, 152.21 (Ar), 159.80 (C=N); IR (KBr): ν_{max} 3424, 3092, 2248, 1664, 1444, 1104, 1080, 1048, 848. Anal. calcd for $C_{19}H_{22}N_4O_2$: C, 67.44; H, 6.55; N, 16.56. Found: C, 67.21; H, 6.42; N, 16.39.

4.1.5. 2-Amino-1,5-dicyano-4,4-dimethoxy-6-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hex-2-en (2e). Yield 2.03 g (65%), slightly yellow solid, mp > 350 °C; ^{1}H NMR (DMSO-d_6): δ 3.31 (s, 1H, CH), 3.35 (s, 3H, CH_3O), 3.38 (s, 3H, CH_3O), 3.81 (s, 3H, CH_3O), 7.05 (d, 2H, J=8 Hz, Ar), 7.47 (d, 2H, J=8 Hz, Ar),), 7.49 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 35.61 (C), 37.71 (C), 41.27 (CH), 49.57 (CH_3O), 51.23 (CH_3O), 55.29 (CH_3O), 112.37 (CN), 113.71 (CN), 118.66 [$C(OMe)_2$], 114.32, 121.38, 130.19, 159.30 (Ar), 159.72 (C=N); IR (KBr): ν_{max} 3424, 3016, 2248, 1684, 1520, 1256, 1180, 1136, 1008, 828. Anal. calcd for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.46; H, 5.08; N, 17.79.

4.1.6. 2-Amino-6-(2-chlorophenyl)-1,5-dicyano-4,4-dimethoxy-3-azabicyclo[3.1.0]hex-2-en (2f). Yield 2.47 g (78%), white solid, mp > 350 °C; ^{1}H NMR (DMSO-d_6): δ 3.33 (s, 1H, CH), 3.37 (s, 3H, CH_3O), 3.45 (s, 3H, CH_3O), 7.45–7.75 (m, 6H, Ar and NH_2); ^{13}C NMR (DMSO-d_6): δ 35.74 (C), 37.55 (C), 40.04 (CH), 49.72 (CH_3O), 51.63 (CH_3O), 112.14 (CN), 113.63 (CN), 118.74 [$C(OMe)_2$], 127.51, 127.74, 130.06, 130.13, 131.06, 134.77 (Ar), 159.09 (C=N); IR (KBr): ν_{max} 3388, 3082, 2256, 1688, 1432, 1176, 1114, 1056, 736. Anal. calcd for $C_{15}H_{13}ClN_4O_2$: C, 56.88; H, 4.14; Cl, 11.19; N, 17.69. Found: C, 56.57; H, 4.09; Cl, 11.27; N, 17.48.

4.1.7. 2-Amino-6-(2-chlorophenyl)-1,5-dicyano-4,4-diethoxy-3-azabicyclo[3.1.0]hex-2-en (2g). Yield 2.20 g, (64%), white solid, mp > 350 °C; ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H, J=7 Hz, CH_3), 1.31 (t, 3H, J=7 Hz, CH_3), 3.22 (s, 1H, CH), 3.72 (q, 2H, J=7 Hz, OCH_2), 3.88 (q, 2H, J=7 Hz, OCH_2), 7.39–7.74 (m, 6H, Ar and NH_2); ^{13}C NMR (DMSO-d_6): δ 15.39 (CH_3), 15.63 (CH_3), 36.07 (C), 38.55 (C), 40.14 (CH), 58.30 (OCH_2), 60.09 (OCH_2), 112.59 (CN), 114.04 (CN), 118.47 [$C(OMe)_2$], 127.99, 130.37, 130.52, 131.58, 135.13 (Ar), 159.14 (C=N); IR (KBr): ν_{max} 3400, 3076, 2984, 2248, 1660, 1440, 1144, 1080, 760. Anal. calcd for $C_{17}H_{17}ClN_4O_2$: C, 59.22; H, 4.97; Cl, 10.28; N, 16.25. Found: C, 59.47; H, 5.09; Cl, 10.43; N, 16.08.

4.1.8. 2-Amino-6-(4-chlorophenyl)-1,5-dicyano-4,4-dimethoxy-3-azabicyclo[3.1.0]hex-2-en (2h). Yield 2.12 g, (67%), slightly yellow solid, mp > 350 °C; ^{1}H NMR (DMSO-d_6): δ 3.35 (s, 3H, OCH_3), 3.38 (s, 3H, CH_3O), 3.49 (s, 1H, CH), 7.50 (s, 2H, NH_2) 7.60 (m, 4H, Ar); ^{13}C NMR (DMSO-d_6): δ 35.43 (C), 37.52 (C), 40.63 (CH), 49.59. (CH_3O), 51.24 (CH_3O), 112.12 (CN), 113.43 (CN), 118.63 [$C(OMe)_2$], 128.71, 128.94, 130.75, 134.00 (Ar), 159.01 (C=N); IR (KBr): ν_{max} 3440, 3084, 2248, 1680, 1496, 1172, 1140, 1100, 804. Anal. calcd for $C_{15}H_{13}ClN_4O_2$: C, 56.88; H, 4.14; Cl, 11.19; N, 17.69. Found: C, 56.65; H, 4.08; Cl, 11.07; N, 17.47.

4.1.9. 2-Amino-6-(3-bromophenyl)-1,5-dicyano-4,4-dimethoxy-3-azabicyclo[3.1.0]hex-2-en (2i). Yield 2.21 g (61%), white solid, mp 261–263 °C; ^{1}H NMR (DMSO-d_6): δ 3.33 (s, 3H, CH_3O), 3.38 (s, 3H, CH_3O), 3.51 (s, 1H, CH), 7.45–7.70 (m, 5H, Ar ? NH_2), 7.78 (s, 1H, Ar); ^{13}C NMR (DMSO-d_6): δ 35.86 (C), 37.81 (C), 40.82 (CH), 50.07. (CH_3O), 51.75 (CH_3O), 112.57 (CN), 113.88 (CN), 119.12 [$C(OMe)_2$], 122.36, 128.35, 131.51, 132.31, 132.55, 132.71 (Ar), 159.45 (C=N); IR (KBr): ν_{max} 3444, 3072, 2244, 1676, 1428, 1416, 1172, 1140, 1076, 776. Anal. calcd for $C_{15}H_{13}BrN_4O_2$: C, 49.88; H, 3.63; Br, 22.12; N, 15.51. Found: C, 49.67; H, 3.51; Br, 21.93; N, 15.37.

4.1.10. 2-Amino-6-(4-iodophenyl)-1,5-dicyano-4,4-dimethoxy-3-azabicyclo[3.1.0]hex-2-en (2j). Yield 2.77 g (68%), white solid, mp > 350 °C; ^{1}H NMR (DMSO-d_6): δ 3.40 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.54 (s, 1H, CH), 7.41 (d, 2H, J=8 Hz, Ar), 7.65 (s, 2H, NH_2), 7.96 (d, 2H, J=8 Hz, Ar); ^{13}C NMR (DMSO-d_6): δ 35.29 (C), 37.45 (C), 40.91 (CH), 49.60 (OCH_3), 51.22 (OCH_3), 95.86, (Ar), 112.10 (CN), 113.41 (CN), 118.63 [$C(OMe)_2$], 129.49, 130.96, 137.68 (Ar), 159.04 (C=N); IR (KBr): ν_{max} 3436, 3064, 2248, 1684, 1428, 1172, 1140, 1104, 1008. Anal. calcd for $C_{15}H_{13}IN_4O_2$: C, 44.14; H, 3.21; N, 13.73. Found: C, 44.37; H, 3.09; N, 13.47.

4.1.11. 2-Amino-1,5-dicyano-4,4-dimethoxy-6-(4-nitrophenyl)-3-azabicyclo[3.1.0]hex-2-en (2k). Yield 1.66 g (63%), yellow solid, mp > 350 °C; ^{1}H NMR (DMSO-d_6): δ 3.47 (s, 3H, CH_3O), 3.50 (s, 3H, CH_3O), 3.69 (c, 1H, CH), 7.55 (s, 2H, NH_2), 7.85 (d, 2H, Ar), 8.39 (d, 2H, Ar); ^{13}C NMR (DMSO-d_6): δ 35.54 (C), 37.62 (C), 40.61 (CH), 49.79. (CH_3O), 51.44 (CH_3O), 112.12 (CN), 113.41 (CN), 118.78 [$C(OMe)_2$], 124.11, 130.64, 137.02, 147.90 (Ar), 158.93 (C=N); IR (KBr): ν_{max} 3460, 3016, 2252, 1696, 1520, 1352, 1144, 1108, 1056. Anal. calcd for $C_{15}H_{13}N_5O_4$: C 55.05; H, 4.00; N, 21.40. Found: C, 54.87; H, 3.93; N, 21.23.

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References and notes

1. Fatiadi, A. J. *Synthesis* **1978**, 165–204.
2. Mulliken, S. P. *Am. Chem. J.* **1893**, *15*, 523–527.
3. Weinberg, N. L.; Weinberg, H. R. *Chem. Rev.* **1968**, *68*, 449–523.
4. Shäfer, H. J. *Angew. Chem. Int., Ed. Engl.* **1981**, *20*, 911–934.
5. Shono, T. Electroorganic Chemistry as a New Tool in Organic Synthesis In *Reactivity and Structure: Concepts in Organic Chemistry*, *Vol. 20*; Springer: Berlin, 1984.
6. *Novel Trends in Electroorganic Synthesis*; Torii, S., Ed.; Springer: Berlin, 1998.
7. Freeman, F. *Chem. Rev.* **1969**, *69*, 591–624.
8. Fatiadi, A. J. *Synthesis* **1978**, 241–282.
9. Ismail, M. T. *J. Appl. Electrochem.* **1987**, *17*, 881–883.
10. Campaigne, F.; Sohneller, S. W. *Synthesis* **1976**, 705–716.
11. Freeman, F. *Chem. Rev.* **1980**, *80*, 329–350.
12. Jones, G. In *The Knoevenagel Condensation in Organic Reactions*, *Vol. 15*; Wiley: New York, 1967; pp 204–327.
13. Avaca, L. A.; Utley, J. H. P. *J. Chem. Soc., Perkin Trans. 1* **1975**, 971–974.
14. Nadjo, L.; Saveant, J.; Tessier, D. *J. Electroanal. Chem., Interfacial Electrochem.* **1975**, *64*, 143–154.

15. Smirnov, I. D.; Smirnov, S. K.; Tomilov, A. P. *Zh. Org. Khim.* **1974**, *10*, 1597–1603.
16. Shono, T. *Tetrahedron* **1984**, *40*, 811–850.
17. Elinson, M. N.; Lizunova, T. L.; Ugrak, B. I.; Dekaprilevich, M. O.; Nikishin, G. I.; Struchkov, Yu. T. *Tetrahedron Lett.* **1993**, *34*, 5795–5798.
18. Nikishin, G. I.; Elinson, M. N.; Lizunova, T. L.; Ugrak, B. I. *Tetrahedron Lett.* **1991**, *32*, 2655–2656.
19. Elinson, M. N.; Feducovich, S. K.; Lizunova, T. L.; Nikishin, G. I. *Tetrahedron* **2000**, *56*, 3063–3069.
20. Elinson, M. N.; Feducovich, S. K.; Zakharenkov, A. A.; Bushuev, S. G.; Pashchenko, D. V.; Nikishin, G. I. *Mendeleev Commun.* **1998**, 15–17.
21. Elinson, M. N.; Feducovich, S. K.; Bushuev, S. G.; Pashchenko, D. V.; Nikishin, G. I. *Izv. Acad. Nauk Ser. Khim.* **1998**, 1165–1168.
22. Elinson, M. N.; Feducovich, S. K.; Starikova, Z. A.; Olessova, O. S.; Vereshchagin, A. N.; Nikishin, G. I. *Tetrahedron Lett.* **2000**, *41*, 4937–4941.
23. Elinson, M. N.; Feducovich, S. K.; Zaimovskaya, T. A.; Vereshchagin, A. N.; Nikishin, G. I. *Russ. Chem. Bull.* **2003**, *52*, 2241–2246.
24. Ferreira, A. B. B.; Salisbury, K. *J. Chem. Soc., Perkin Trans. 2* **1978**, 995–1001.
25. Hart, H.; Kim, Y. C. *J. Org. Chem.* **1966**, *31*, 2784–2789.
26. Knoevenagel, E. *Chem. Ber.* **1904**, *37*, 4461–4463.

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Novel heterocyclic systems. Synthesis of 2,7-dimethyl-10-oxa-1,8-diaza-anthracen-9-one and derivatives

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Abstract—Synthesis of novel heterocycles, which contain the unique 10-oxa-1,8-diazaanthracen-9-one tricyclic core, is reported. The core structure was assembled via a dehydrative-cyclization strategy.

1. Introduction

During a recent effort in our laboratories directed at the development of chiral ketones for use as asymmetric epoxidation catalysts,[1] we synthesized a series of heterocycles containing the novel 10-oxa-1,8-diazaanthracen-9-one backbone, i.e. compounds **1** and **2** (Fig. 1).

Compounds with related frameworks include 1,8-diaza-10-oxa-9-thia-9,10-dihydroanthracene (**3**)[2], 2,7-bis[2-(*N*,*N*-diethylamino)ethoxy]-1,8-diazafluorenone dihydrochloride (**4**) and tilorone (**5**) (Fig. 2).[3] Compounds such as **3** are of interest for their potential biological activity as central nervous system agents and can be synthetically obtained by the condensation of the disodium salt of 2-mercapto-3-hydroxypyridine and 2-chloro-3-nitropyridine.[2] The 1,8-diazafluorenone **4** is a weakly active interferon inducer in mice and shows interaction with calf thymus DNA similar to that of tilorone (**5**), which in turn exhibits antitumor, anti-inflamatory, immunostimulating, interferogenic and virucidal biological activities.[3] The first synthesis of dimethyl-10-oxa-1,8-diaza-anthracen-9-one (**1**) and the novel derivative **2** are reported herein.

2. Results and discussion

Our approach to ketone **1** involves the preparation and coupling of pyridines **6** and **7**. Formylation of the known iodide **6**[4] provided aldehyde **7** in 75% yield (Scheme 1).[5]

Nucleophilic addition to **7** by the organolithium species derived from iodide **6** via lithium–halogen exchange afforded alcohol **8**. Benzylic oxidation,[6] followed by methyl ether cleavage using aqueous hydrobromic acid yielded ketone **10**.[7]

Exposure of diol **10** to a solution of hydrobromic acid in refluxing acetic acid provided the desired ketone **1**. Alternatively, ketone **9** could be converted to tricycle **1** by direct exposure to refluxing hydrobromic acid in acetic acid, presumably via compound **10**. Mechanistically, diol **10** undergoes a dehydrative-cyclization to provide ketone **1** via intermediate **12** (Scheme 2).[8]

We also developed a mild, two-step protocol for the preparation of ketone **1** from **10** that avoided the use of the harsh HBr/acetic acid medium needed for the dehydrative-cyclization (Scheme 1). Triflation of both hydroxyls in **10** afforded the cyclization precursor **11**. The use of Pd(0) or Ni(0) catalysts did not result in carbon–carbon bond formation at the C-3 positions of the pyridine rings. Instead, the oxo-bridged compound **1** was formed as the sole product. This conversion is presumed to be the result of oxidative addition of the transition metal complex to one of the carbon-trifluoromethanesulfonate bonds. Aqueous hydrolysis of the other trifluoromethanesulfonate moiety promoted by the transition metal complex present, followed by a dehydrating cyclization similar to that operating in Scheme 2, gave the unanticipated product **1**.

Recrystallization from $CHCl_3$/hexanes (1:1) yielded X-ray quality crystals of ketone **1**, which on X-ray analysis unambiguously confirmed the novel 10-oxa-1,8-diaza-anthracen-9-one atom connectivity present in ketone **1** (Fig. 3).[9]

Keywords: Heterocycle; 10-Oxa-1,8-diaza-anthracen-9-one; Dehydrative cyclization.
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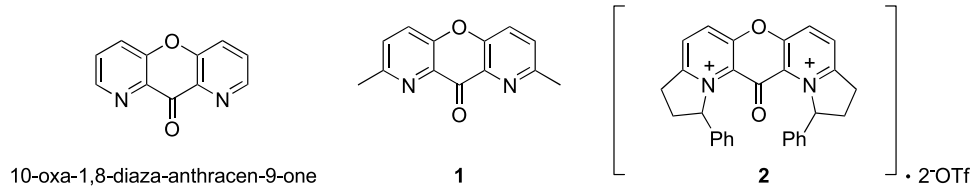


Figure 1. Novel heterocyclic compounds containing the 10-oxa-1,8-diazaanthracen-9-one backbone.

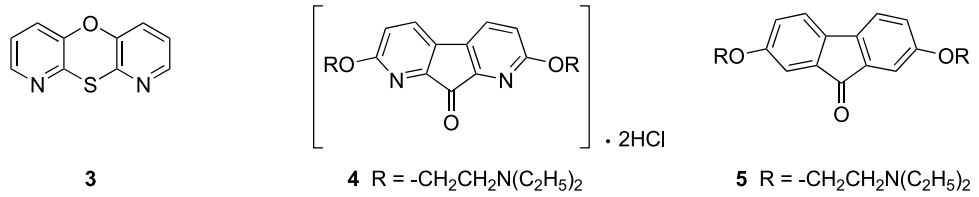
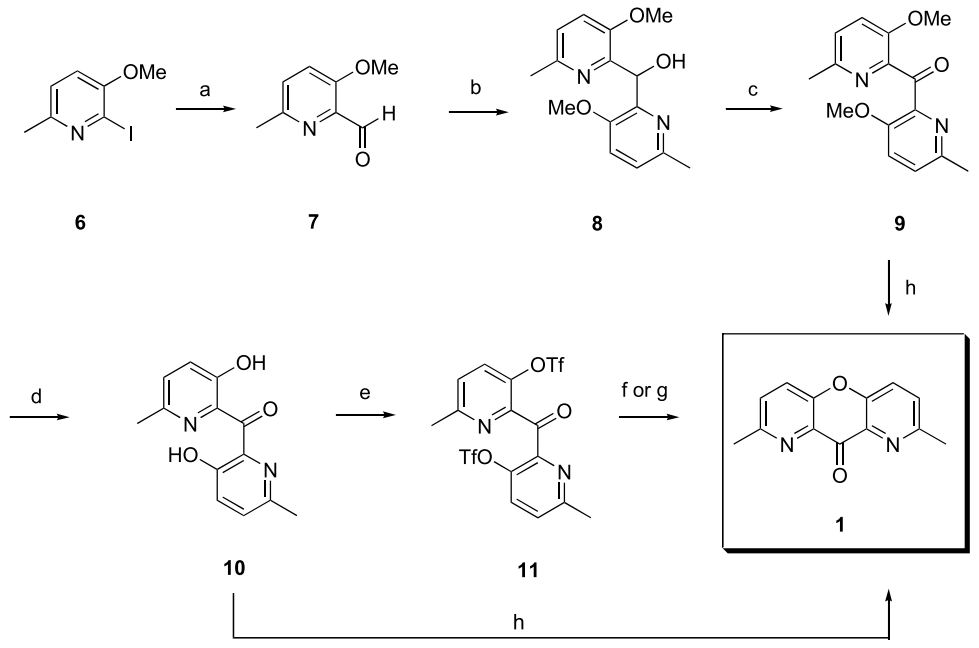
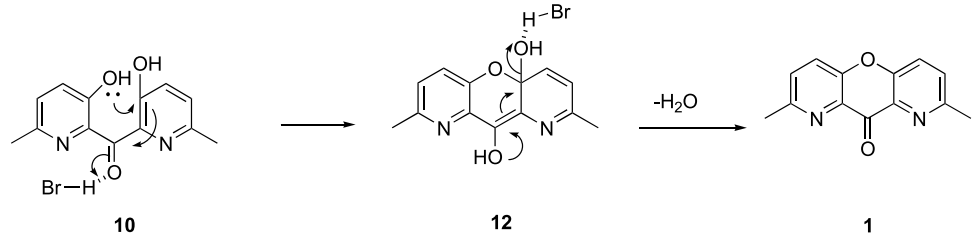


Figure 2. Biologically active heterocycles with related frameworks to that of 10-oxa-1,8-diaza-anthracene-9-one.



Scheme 1. (a) *n*-BuLi, DMF (75%); (b) *n*-BuLi/**6**, then **7** (59%); (c) MnO_2, CH_2Cl_2 (100%); (d) HBr (48% solution in H_2O) (92%); (e) Tf_2O, pyridine, CH_2Cl_2 (96%); (f) $(Ni(COD)_2)$, DMF, 60 °C (83%); (g) $PdCl_2$, bis(pinacolato)diboron, 80 °C; then $PdCl_2$, Na_2CO_3 (2 M solution in H_2O) (55%); (h) HBr (30% solution in AcOH), reflux (99%).



Scheme 2.

Efforts to produce **2** directly from ketone **1** via lateral metalation/alkylation were unsuccessful. Attempts to deprotonate and subsequently alkylate the lateral methyl groups in anthracenone **1** with styrene oxide failed. The use of LiHMDS or KHMDS in THF or a 1:1 mixture of THF and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) at various reaction temperatures did not result in the formation of the desired dianion. This result prompted us

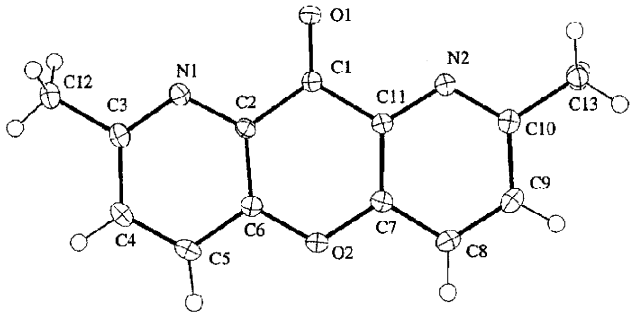
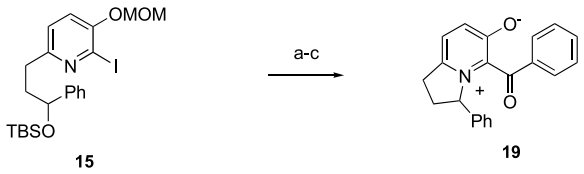


Figure 3. Crystal structure of tricyclic ketone **1**.

to explore alkylation conditions with the 1,3-dioxolane protected ketone. Attempted deprotonation of the lateral methyl groups of the cyclic ketal under a variety of basic conditions quantitatively returned the starting material or resulted in competitive deprotonation of the pyridine rings. We next turned our attention to installing the phenylethyl side chain first. Generation of the dianion from commercially available pyridinol **13** using *sec*-BuLi, and subsequent nucleophilic addition to styrene oxide followed by regiospecific iodination at C-2, generated diol **14** (Scheme 3).[10] Disilylation with TBSCl, followed by selective hydrolysis of the aromatic TBS ether[11] and protection of the resulting pyridinol as the methoxymethyl ether, yielded iodide **15** in good yield.[12] Formylation of the lithiated species resulting from lithium-halogen exchange on **15** was achieved by trapping with ethyl formate rather than dimethylformamide, as the latter gave lower yields of the desired aldehyde **16**. Nucleophilic addition to compound **16** by the aryllithium generated from iodide **15** and *n*-BuLi afforded alcohol **17**. Benzylic oxidation with MnO_2 was followed by selective deprotection of the MOM group with dimethylboron bromide in the presence of the TBS ether.[13] Subsequent triflation of the resulting diol yielded bis-trifluoromethane sulfonate **18**. Similar to the synthesis of **1**, exposure of **18** to bis(1,5-cyclooctadiene)nickel(0) ($Ni(COD)_2$) resulted in the formation of the 10-oxa-1,8,-diaza-anthracene-9-one backbone. Removal of the TBS ether, triflation and in situ cyclization yielded the targeted polyheterocyclic ketone **2** as a mixture of diastereomers.

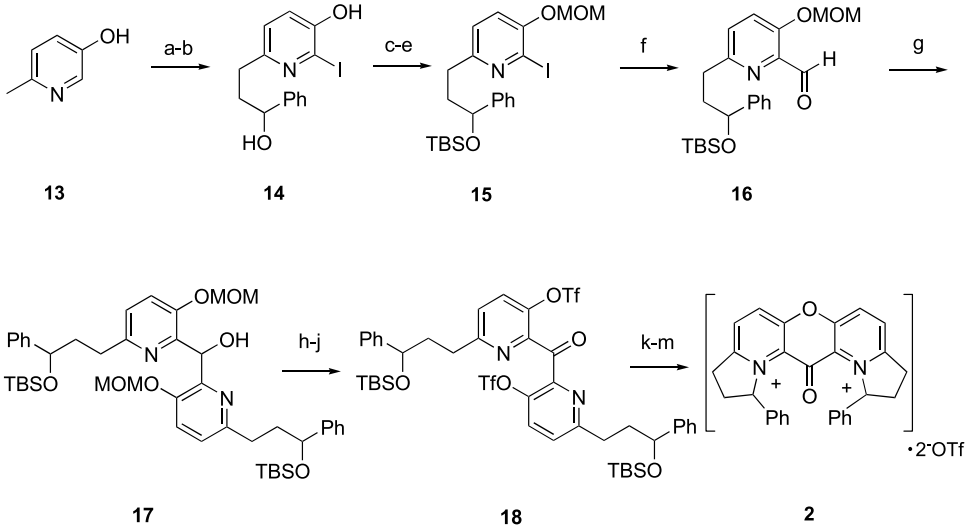
The cylcization of tethered benzylic triflates to provide highly substituted indolizidinium compounds has been extended to the formation of compound **19**. Using similar methodology for the synthesis of ketone **2**, acylation of the methoxymethyl-protected pyridinol **15** using *n*-BuLi and benzoyl chloride, followed by TBS-deprotection, triflation and in situ cyclization yielded the novel racemic zwitterion **19**. Interestingly, the methoxy methyl group proved to be labile upon formation of the indolizidinium ring, and compound **19** was isolated rather than its MOM-protected analog (Scheme 4).



Scheme 4. (a) *n*-BuLi, PhCOCl (69%); (b) TBAF, THF (80%); (c) Tf_2O, DIEA, CH_2Cl_2 (67%).

3. Conclusions

In summary, the synthesis of the novel heterocycles **1** and **2** was accomplished from commercially available materials in 6 and 13 steps, respectively. A novel transition metal-catalyzed dehydrating cyclization was discovered which circumvented the use of a strongly acidic reaction medium to afford the tricyclic core. The unprecedented 10-oxa-1,8-diazaanthracen-9-one backbone of **1** and **2** was unambiguously determined by X-ray crystallographic analysis. Similar to the synthesis of compound **2**, the cyclization of tethered benzylic triflates can be expected to generate other highly substituted indolizidinium compounds. Although this study used racemic styrene oxide, the methodology could



Scheme 3. (a) *sec*-BuLi, then styrene oxide (64%); (b) Na_2CO_3, I_2, THF/H_2O 1:1 (63%); (c) TBSCl, imidazole, DMF (91%); (d) AcOH/THF/H_2O 4:2:1 (77%); (e) MOMCl, DIEA, THF (92%); (f) *n*-BuLi, ethyl formate (75%); (g) *n*-BuLi/**15**, then **16** (68%); (h) MnO_2, CH_2Cl_2 (100%); (i) Me_2BBr, CH_2Cl_2 (88%); (j) Tf_2O, pyridine (97%); (k) $Ni(COD)_2$, DMF (66%); (l) TBAF, THF (83%); (m) Tf_2O, DIEA, CH_2Cl_2 (99%).

lead to enantiopure ketones by alkylating the dianion of 5-hydroxy-2-methylpyridine with the corresponding optically active epoxide, either antipode of which being commercially available.

4. Experimental

4.1. General procedures

All reactions were performed in oven or flame dried glassware under argon atmosphere and stirred magnetically. Tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone ketyl prior to use. Trifluoromethanesulfonic anhydride (triflic anhydride) was distilled and stored under argon. Other reagents and solvents from commercial sources were stored under argon and used directly. Melting points were obtained from a Thomas-Hoover capillary melting point apparatus and are uncorrected. Radial preparative layer chromatography (radial PLC) was performed on a Chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1, 2 or 4 mm layers of Kieselgel 60 PF254 containing gypsum. High-resolution mass spectral analysis (HRMS) was performed at North Carolina State University. Elemental analyses were performed by Atlantic Microlab Inc. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz), Varian Mercury 300 (300 MHz), or Varian Mercury 400 (400 MHz) spectrometer. Chemical shifts are in δ units (ppm) with TMS (0.0 ppm) used as the internal standard for ^{1}H NMR spectra and the $CDCl_3$ absorption (77.2 ppm) or C_6D_6 absorption (128.4 ppm) for ^{13}C NMR spectra. IR spectra were recorded on a Perkin–Elmer 1430 spectrometer. HPLC was performed using Waters and Associates (Milifrod, MA) 600 E multi solvent delivery system with a 486 tunable detector equipped with an YMC-pack sil (150×4.6 mm I.D.) analytical column or an YMC-pack sil (150×10 mm I.D.) preparative column.

4.1.1. Bis-(3-methoxy-6-methylpyridin-2-yl)methanol (8). To a stirred solution of compound **6** (138 mg, 0.550 mmol) in THF (3 mL) at −78 °C was added *n*-BuLi (2.40 M in hexanes, 250 μl, 0.605 mmol) dropwise over 5 min. The resulting solution was stirred for additional 15 min and then compound **7** (91.0 mg, 0.605 mmol) in THF (2.0 mL) was added over 10 min. The mixture was strirred at −78 °C for 2 h and then warmed gradually to 0 °C over 1 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (30 mL), and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and the solvent was removed in vacuo. Purification by silica gel chromatography (20 to 30% EtOAc in hexanes) gave 89.0 mg (59%) of the desired product **8** as a white solid: mp 116.0–117.5 °C; IR (neat) 3425, 1639, 1464, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.03 (m, 4H), 6.23 (bs, 1H), 6.00 (bs, 1H), 3.65 (s, 6H), 2.45 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.4, 149.3, 148.5, 122.5, 118.9, 67.4, 56.0, 23.5. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.79; H, 6.60; N, 10.29.

4.1.2. Bis-(3-methoxy-6-methylpyridin-2-yl)methanone (9). To a solution of **8** (2.94 g, 10.7 mmol) in anhydrous CH_2Cl_2 (100 mL) was added activated MnO_2 (13.96 g, 160.7 mmol), and the resulting mixture was stirred at rt for 48 h under an argon atmosphere. The manganese residues were removed by filtration through Celite, and then washed with CH_2Cl_2 (500 mL). The filtrate was evaporated in vacuo. Purification by silica gel chromatography (80 to 100% EtOAc in hexanes) gave 2.92 g (100%) of the desired product **9** as a white solid: mp 147–148 °C; IR (neat) 2928, 1676, 1464, 1263 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (d, J=8.6 Hz, 2H), 7.17 (d, J=8.6 Hz, 2H), 3.68 (s, 6H), 2.45 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.2, 153.2, 149.5, 145.2, 126.0, 120.3, 56.1, 23.4. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.02; H, 6.02; N, 10.22.

4.1.3. Bis-(3-hydroxy-6-methylpyridin-2-yl)methanone (10). Compound **9** (530 mg, 1.95 mmol) was dissolved in aqueous HBr (48% in H_2O, 30 mL, 0.265 mol). The reaction mixture was refluxed for 24 h, cooled to rt, and the mixture was concentrated in vacuo. To the residue was added aqueous saturated $NaHCO_3$ (50 mL), and the mixture was extracted with EtOAc (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (30 to 50% EtOAc in hexanes) gave 438 mg (92%) of the desired product **10** as a yellow solid: mp 157–158 °C; IR (neat) 3000, 1618, 1582, 1468, 1311 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 14.15 (s, 2H), 7.47 (d, J=8.6 Hz, 2H), 7.38 (d, J=8.6 Hz, 2H), 2.61 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.1, 157.0, 149.0, 136.3, 130.7, 130.4, 23.2. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.90; H, 5.02; N, 11.50.

4.1.4. Trifluoromethanesulfonic acid 6-methyl-2-(6-methyl-3-trifluoromethanesulfonyloxy-pyridine-2-carbonyl)pyridin-3-yl ester (11). A solution of **10** (121 mg, 0.495 mmol) and pyridine (400 μl, 4.96 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to 0 °C under argon. A solution of freshly distilled triflic anhydride (330 μl, 1.98 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise over a period of 5 min. The contents of the flask were allowed to warm to rt over 30 min and then stirred for 3 h. The reaction mixture was filtered through Celite with CH_2Cl_2, and the solvent was removed in vacuo. Purification by silica gel chromatography (10 to 20% EtOAc in hexanes) gave 243 mg (96%) of the desired product **11** as a white solid: mp 82.5–83.5 °C; IR (neat) 2921, 1702, 1584, 1430, 1307, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (d, J=8.6 Hz, 2H), 7.42 (d, J=8.6 Hz, 2H), 2.54 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.8, 158.8, 145.9, 143.8, 130.4, 127.8, 118.6 (1C, q, J=317.5 Hz), 23.9; ^{19}F NMR ($CDCl_3$, 300 MHz) δ 74.0. Anal. Calcd for $C_{15}H_{10}F_6N_2O_7S_2$: C, 35.44; H, 1.98; N, 5.51. Found: C, 35.43; H, 1.98; N, 5.50.

4.1.5. 2,7-Dimethyl-10-oxa-1,8-diazaanthracen-9-one (1). *Method A*. To a solution of **11** (1.038 g, 2.040 mmol) in anhydrous DMF (30 mL) at rt was added $Ni(COD)_2$ (618 mg, 2.25 mmol). The resulting mixture was heated at 60 °C for 72 h. Saturated aqueous $NaHCO_3$ (150 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (3×150 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (20 to 30%

EtOAc in hexanes) gave 357 mg (83%) of the desired product **1** as a yellow solid: mp 255–257 °C; IR (neat) 3037, 1672, 1467, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, $J=8.4$ Hz, 2H), 7.53 (d, $J=8.4$ Hz, 2H), 2.76 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3, 157.0, 151.8, 137.8, 129.5, 127.3, 24.6; HRMS $(M+H)^+$ calcd for $C_{13}H_{10}N_2O_2$ 227.0821, found 227.0817.

Method B. A flask charged with **11** (400 mg, 0.787 mmol), bis(pinacolato)diboron (100 mg, 0.393 mmol) and $PdCl_2$ (58 mg, 0.079 mmol) was flushed with argon. DMF (12 mL) was added, the reaction mixture degassed, and the contents of the flask heated at 80 °C for 2 h. The solution was cooled to rt and $PdCl_2$ (58 mg, 0.079 mmol) and Na_2CO_3 (2.0 M in H_2O, 1.0 mL, 2.0 mmol) were added. The reaction mixture was heated at 80 °C for 24 h. The mixture was cooled to rt and filtered through Celite with MeOH (30 mL). The filtrate was washed with H_2O (30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography (20 to 30% EtOAc in hexanes) gave 91.0 mg (55%) of the desired product **1** as a yellow solid.

Method C. Compound **10** (421 mg, 1.55 mmol) was dissolved in HBr (30% in AcOH, 20 mL, 0.10 mol). The reaction mixture was refluxed for 48 h, cooled to rt, and concentrated in vacuo. To the residue was added aqueous saturated $NaHCO_3$ (50 mL), and the mixture was extracted with EtOAc (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (20 to 30% EtOAc in hexanes) gave 346 mg (99%) of the desired product **1** as a yellow solid.

4.1.6. 6-(3-Hydroxy-3-phenylpropyl)-2-iodopyridin-3-ol (14). A solution of 5-hydroxy-2-methylpyridine (**13**) (1.25 g, 11.5 mmol) in THF (80 mL) was cooled to −20 °C. A solution of *sec*-BuLi (0.97 M in cyclohexane, 24.1 mL, 24.1 mmol) was added dropwise over a period of 5 min. The resulting dark red mixture was stirred at −20 °C for an additional 45 min. The mixture was cooled to −78 °C and neat styrene oxide (6.5 mL, 57 mmol) was added over a period of 10 min. After 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL) and warmed up to rt, during which time it became colorless. The mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (50 to 100% EtOAc in hexanes) gave 1.68 g (64%) of the desired diol product as a colorless oil; IR (neat) 3027, 2360, 1574, 1494, 1452, 1275, 1124, 1060, 911 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.14 (s, 1H), 7.93 (bs, 1H), 7.33 (bs, 1H), 7.22 (m, 5H), 7.11 (d, $J=2.3$ Hz, 1H), 7.00 (d, $J=8.5$ Hz, 1H), 4.80 (t, $J=5.8$ Hz, 1H), 2.87 (t, $J=6.7$ Hz, 2H), 2.12 (q, $J=6.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.0, 151.5, 144.6, 135.6, 128.5, 127.4, 126.0, 125.8, 124.6, 74.1, 38.4, 33.1; HRMS $(M+H)^+$ calcd for $C_{14}H_{15}NO_2$ 230.1181, found 230.1193.

To a solution of the above diol (1.68 g, 7.33 mmol) and Na_2CO_3 (1.63 g, 15.4 mmol) in 1:1 H_2O/THF (220 mL) was added I_2 (1.86 g, 7.33 mmol). After stirring at rt for 1 h, the iodine color disappeared and the reaction was quenched with 10% HCl dropwise until the solution pH was 3. The mixture was filtered through Celite, and the solvent removed in vacuo. Purification by silica gel chromatography (50 to 100% EtOAc in hexanes) gave 1.63 g (63%) of the desired product **14** as a white foam; IR (neat) 3060, 2342, 1557, 1454, 1288, 1064, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 7.09 (d, $J=8.1$ Hz, 1H), 6.96 (d, $J=8.1$ Hz, 1H), 6.10 (bs, 1H), 4.78 (t, $J=6.3$ Hz, 1H), 3.75 (bs, 1H), 2.84 (m, 2H), 2.13 (q, $J=6.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6, 151.0, 144.7, 128.6, 127.6, 126.1, 123.8, 122.5, 110.0, 74.1, 38.5, 33.3; HRMS $(M+H)^+$ calcd for $C_{14}H_{14}INO_2$ 356.0148, found 356.0140.

4.1.7. 6-[3-(*tert*-Butyldimethylsilanyloxy)-3-phenylpropyl]-2-iodo-3-methoxymethoxypyridine (15). To a solution of **14** (1.07 g, 3.01 mmol) in DMF (30 mL) at 20 °C was added imidazole (1.64 g, 24.1 mmol) and *tert*-butyldimethylsilyl chloride (1.81 g, 12.0 mmol). The resulting mixture was stirred at rt for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 1.60 g (91%) of the desired bissilyl ether product as a colorless oil; IR (neat) 2953, 2855, 1541, 1441, 1361, 1295, 1255, 1091, 1059, 896, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.63 (m, 7H), 5.10 (t, $J=5.6$ Hz, 1H), 3.12 (m, 2H), 2.41 (m, 2H), 1.43 (s, 9H), 1.26 (s, 9H), 0.64 (s, 6H), 0.39 (s, 3H), 0.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.4, 150.6, 145.5, 128.3, 127.2, 126.3, 126.2, 124.8, 122.3, 115.3, 74.8, 40.9, 33.4, 26.1, 26.0, 18.5, −3.8, −3.8, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{26}H_{42}INO_2Si_2$ 584.1877, found 584.1879.

The above bissilyl ether (1.60 g, 2.74 mmol) was dissolved in a 4:2:1 mixture of CH_3COOH/H_2O/THF (250 mL) at 20 °C and stirred for 4 h. The reaction mixture was carefully quenched with saturated aqueous $NaHCO_3$ (300 mL) and extracted with CH_2Cl_2 (3×300 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (10 to 30% EtOAc in hexanes) gave 995 mg (77%) of the desired product as a white foam; IR (neat) 3418, 2956, 2856, 1545, 1488, 1359, 1286, 1248, 1085, 981 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29 (m, 5H), 7.09 (d, $J=8.0$ Hz, 1H), 6.94 (d, $J=8.1$ Hz, 1H), 5.30 (bs, 1H), 4.72 (t, $J=5.4$ Hz, 1H), 2.74 (m, 2H), 2.04 (m, 2H), 0.89 (s, 9H), 0.02 (s, 3H), −0.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 151.1, 145.3, 128.3, 127.2, 126.0, 126.4, 122.4, 110.2, 74.7, 41.1, 33.1, 26.1, 18.4, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{20}H_{28}INO_2Si$ 470.1012, found 470.1027.

A solution of the above phenol (1.29 g, 2.75 mmol) in THF (65 mL) was cooled to 0 °C and *N*,*N*-diisopropylethylamine (1.0 mL, 5.43 mmol) was added dropwise over a period of 5 min. After stirring at 0 °C for 15 min, chloromethyl methyl ether (1.50 mL, 19.0 mmol) was added dropwise over 5 min. The mixture was stirred for 30 min, then gradually warmed to rt. After stirring at 20 °C for 40 h, the reaction mixture was quenched with a buffered solution (pH 8) of NH_4OH and NH_4Cl (275 mL) and then extracted

with ethyl acetate (3×250 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite with ethyl acetate, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 1.30 g (92%) of **15** as a colorless oil; IR (neat) 2958, 1551, 1488, 1291, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29 (m, 5H), 7.15 (d, J=8.4 Hz, 1H), 6.96 (d, J=8.4 Hz, 1H), 5.21 (s, 2H), 4.74 (t, J=5.4 Hz, 1H), 3.50 (s, 3H), 2.77 (m, 2H), 2.06 (m, 2H), 0.89 (s, 9H), −0.03 (s, 3 H), −0.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.5, 151.4, 145.4, 128.3, 127.2, 126.2, 122.5, 122.0, 112.0, 95.4, 74.8, 56.8, 40.9, 33.3, 26.1, 18.5, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{22}H_{32}INO_3Si$ 514.1274, found 514.1301.

4.1.8. 6-[3-(*tert*-Butyldimethylsilanyloxy)-3-phenylpropyl]-3-methoxymethoxypyridine- 2-carbaldehyde (16). To a solution of **15** (727 mg, 1.42 mmol) in THF (15 mL) at −78 °C was added *n*-BuLi (2.17 M in hexanes, 720 µl, 1.56 mmol) dropwise over 5 min. The resulting solution was stirred for additional 30 min and then ethyl formate (1.1 mL, 14 mmol) was added over 10 min. The reaction mixture was gradually warmed to 0 °C over 3 h and quenched with saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with ethyl acetate (3× 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 441 mg (75%) of **16** as a colorless oil; IR (neat) 2954, 2927, 2855, 1713, 1561, 1469, 1389, 1250, 1155, 1082, 973, 775, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.30 (s, 1 H), 7.54 (d, J=8.8 Hz, 1H), 7.31 (m, 5H), 7.26 (d, J=8.6 Hz, 1H), 5.29 (s, 2H), 4.76 (t, J= 5.4 Hz, 1H), 3.51 (s, 3H), 2.87 (m, 2H), 2.11 (m, 2H), 0.89 (s, 9H), 0.03 (s, 3H), −0.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.1, 156.1, 154.0, 145.4, 140.9, 128.3, 128.2, 127.2, 126.1, 124.9, 95.1, 74.8, 56.8, 40.8, 33.6, 26.1, 18.5, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{23}H_{33}NO_4Si$ 416.2257, found 416.2253.

4.1.9. Bis-[6-[3-(*tert*-butyldimethylsilanyloxy)-3-phenylpropyl]-3-methoxymethoxypyridin-2-yl]-methanol (17). To a solution of **15** (349 mg, 0.680 mmol) in THF (7 mL) at −78 °C was added *n*-BuLi (2.17 M in hexanes, 310 µl, 0.680 mmol) dropwise over 5 min. The resulting solution was stirred for 15 min, then compound **16** (311 mg, 0.748 mmol) in THF (5 mL) was added dropwise over 10 min. After the addition was complete, the reaction mixture was stirred at −78 °C for 2 h and then warmed gradually to 0 °C over 1 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ (50 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 371 mg (68%) of **17** as a colorless oil; IR (neat) 3375, 2954, 2928, 2856, 1580, 1469, 1403, 1361, 1255, 1155, 1081, 1056, 993, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (m, 12H), 6.94 (d, J=6.2 Hz, 2H), 6.24 (d, J=4.3 Hz, 1H), 6.05 (bs, 1H), 4.98 (m, 4H), 4.74 (m, 2H), 3.19 (s, 3H), 3.18 (s, 3H), 2.75 (m, 4H), 2.03 (m, 4H), 0.91 (s, 18H), −0.02 (s, 6H), −0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.3, 149.7, 148.9, 145.6, 128.1, 127.0, 126.0, 122.3, 121.9, 94.5, 74.7, 68.6, 58.8, 40.9, 33.2, 26.1, 18.4, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{45}H_{66}N_2O_7Si_2$ 803.4487, found 803.4510.

4.1.10. Trifluoromethanesulfonic acid-6-[3-(*tert*-butyldimethylsilanyloxy)-3-phenylpropyl]-3-[6-[3-*tert*-butyldimethylsilanyloxy)-3-phenylpropyl]-3-trifluoromethanesulfonyloxypyridine-2-carbonyl]-pyridin-3-yl ester (18). To a solution of **17** (348 mg, 0.434 mmol) in anhydrous CH_2Cl_2 (20 mL) was added activated MnO_2 (566 mg, 6.50 mmol), and the resulting mixture was stirred at rt for 30 h under an argon atmosphere. The residual manganese was removed by filtration (Celite). The filtrate was concentrated in vacuo. Purification by silica gel chromatography (10 to 20% EtOAc in hexanes) gave 347 mg (100%) of the desired ketone as a white foam; IR (neat) 2956, 2952, 2856, 1698, 1568, 1463, 1404, 1361, 1306, 1255, 1203, 1158, 1083, 981, 836, 777, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, J=8.6 Hz, 2H), 7.24 (m, 10H), 7.12 (d, J=7.7 Hz, 2H), 5.05 (s, 4H), 4.68 (t, J= 5.8 Hz, 2H), 3.34 (s, 6H), 2.74 (m, 4H), 1.97 (m, 4H), 0.88 (s, 18H), −0.03 (s, 6H), −0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.4, 154.7, 150.8, 146.4, 145.5, 128.1, 127.0, 126.0, 125.2, 124.3, 95.3, 74.6, 56.3, 40.6, 33.3, 26.0, 18.4, −4.5, −4.8; HRMS $(M+H)^+$ calcd for $C_{45}H_{64}N_2O_7Si_2$ 801.4330, found 801.4311.

The above ketone (184 mg, 0.229 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) and cooled to −78 °C. Me_2BBr (2.01 M in CH_2Cl_2, 680 µl, 1.37 mmol) was added dropowise and the mixture was stirred at −78 °C for 4 h. Additional Me_2BBr (2.01 M in CH_2Cl_2, 680 µl, 1.37 mmol) was then added. After stirring for 4 h, the mixture was cannulated into a vigorously stirred mixture of THF (10 mL) and saturated aqueous $NaHCO_3$ (15 mL) at 20 °C. After 5 min, the mixture was diluted with ethyl acetate (50 mL). The organic layer was separated and washed successively with H_2O (50 mL), 10% aqueous sodium bisulfate (50 mL), and brine (50 mL). The combined aqueous layers were extracted with ethyl acetate (2× 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by flash chromatography (10 to 20% EtOAc in hexanes) gave 144 mg (88%) of the desired bisphenol as a colorless oil; IR (neat) 3362, 2968, 2857, 1623, 1594, 1464, 1257, 1173, 1084, 972 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, J=8.6 Hz, 2H), 7.29 (m, 14H), 4.78 (t, J=5.8 Hz, 2H), 2.88 (m, 4H), 2.13 (m, 4H), 0.90 (s, 18H), 0.03 (s, 6H), −0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.4, 156.8, 152.9, 145.1, 136.5, 130.1, 129.9, 128.3, 127.2, 126.1, 74.6, 40.7, 33.3, 26.1, 18.4, −4.4, −4.8; HRMS $(M+H)^+$ calcd for $C_{41}H_{56}N_2O_5Si_2$ 713.3806, found 713.3800.

A solution of the above bisphenol (107 mg, 0.150 mmol) and pyridine (120 µl, 1.50 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to 0 °C under argon. A solution of freshly distilled triflic anhydride (130 µl, 0.750 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise over a period of 5 min. The mixture was warmed to rt over 30 min and stirred for 16 h. The reaction mixture was filtered through Celite with CH_2Cl_2 and the solvent was removed in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 142 mg (97%) of **18** as a white foam; IR (neat) 2956, 2858, 1710, 1587, 1462, 1434, 1362, 1253, 1217, 1140,

1086 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, J= 8.6 Hz, 2H), 7.33 (d, J=8.6 Hz, 2H), 7.25 (m, 10H), 4.68 (t, J=5.6 Hz, 2H), 2.81 (m, 4 H), 1.99 (m, 4H), 0.86 (s, 18H), −0.05 (s, 6H), −0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.4, 162.0, 146.1, 145.0, 143.7, 130.3, 127.9, 127.2, 126.9, 126.0, 118.7 (q, J=1275 Hz), 74.2, 39.8, 33.2, 26.0, 18.4, −4.5, −4.9; ^{19}F NMR ($CDCl_3$, 300 MHz) δ −73.9; HRMS $(M+H)^+$ calcd for $C_{43}H_{54}F_6N_2O_9S_2Si_2$ 977.2792, found 977.2810.

4.1.11. 2,7-Bis-3-phenyl-10-oxa-1,8-diazoniacyclopentaneanthracene-9-one bistrifluromethanesulfonate salt (2). To a solution of **18** (416 mg, 0.426 mmol) in anhydrous DMF (10 mL) at rt was added $Ni(COD)_2$ (123 mg, 0.447 mmol). The resulting mixture was heated to 60 °C for 48 h, and then saturated aqueous $NaHCO_3$ (50 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 196 mg (66%) of the desired cyclic ketone product as a yellow solid: mp 170–173 °C; IR (neat) 2928, 2856, 1685, 1466, 1258, 1092, 836, 776, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, J=8.7 Hz, 2H), 7.59 (d, J=8.6 Hz, 2H), 7.28 (m, 10H), 4.81 (t, J=5.8 Hz, 2H), 3.08 (m, 4H), 2.14 (m, 4H), 0.89 (s, 18H), −0.03 (s, 6H), −0.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3, 160.7, 151.9, 145.3, 137.9, 128.7, 128.3, 127.2, 126.1, 74.9, 41.0, 34.7, 26.1, 18.4, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{41}H_{54}N_2O_4Si_2$ 695.3700, found 695.3736.

A solution of the above ketone (45 mg, 0.064 mmol) in THF (1.0 mL) was cooled to 0 °C. Tetrabutylammonium fluoride (1.0 M in THF, 380 µl, 0.384 mmol) was added dropwise over a period of 10 min. The reaction was warmed to rt over a period of 30 min and stirred for an additional 1 h. The mixture was poured into saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (30 to 50% EtOAc in hexanes) gave 25.0 mg (83%) of the desired diol as a colorless oil; IR (neat) 3384, 3067, 2926, 1676, 1604, 1469, 1266, 1124, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.82 (d, J= 8.7 Hz, 2H), 7.58 (d, J=8.6 Hz, 2H), 7.30 (m, 10H), 4.85 (t, J=5.8 Hz, 2H), 3.41 (bs, 2H), 3.15 (m, 4H), 2.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.0, 160.3, 151.9, 145.0, 137.6, 129.2, 128.5, 127.6, 127.4, 126.1, 73.7, 38.7, 34.5; HRMS $(M+H)^+$ calcd for $C_{29}H_{26}N_2O_4$ 467.1971, found 467.1989.

A solution of the above diol (25.0 mg, 0.0536 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was cooled to 0 °C under argon. *N*,*N*-Diisopropylethylamine (20 µl, 0.12 mmol) was added and the reaction mixture was stirred for 15 min at 0 °C. A solution of freshly distilled triflic anhydride (15 µl, 0.085 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise over a period of 5 min. The reaction mixture was warmed to rt over 30 min and stirred for 16 h. The mixture was filtered through Celite with CH_2Cl_2 and the solvent was removed in vacuo. Purification by HPLC (Whatman Partisil 10 C-8 column, 50% H_2O/CH_3CN, 2.0 mL/min) gave 50.0 mg (128%) of the desired crude product **2** as a purple solid; ^1H NMR (CD_3CN, 300 MHz) δ 8.99 (t, J=7.1 Hz, 1H), 8.50 (t, J=6.7 Hz, 1H), 8.23 (m, 1H), 7.25 (m, 2H), 7.15 (m, 1H), 6.98 (m, 1H), 6.69 (bs, 1H), 4.80 (t, J=5.1 Hz, 1H), 3.54 (t, J=5.2 Hz, 1H).[14]

4.1.12. 5-Benzoyl-6-oxy-3-phenyl-2,3-dihydro-1*H*-indolizinylium Zwitter ion (19). To a solution of **15** (64 mg, 0.13 mmol) in THF (2.0 mL) at −78 °C was added *n*-BuLi (2.28 M in hexanes, 60 µl, 0.14 mmol) dropwise over 5 min. The resulting solution was stirred for 15 min, and benzoyl chloride (150 µl, 1.25 mmol) was added over 10 min. The reaction was stirred at −78 °C for 2 h and then warmed to 0 °C over 1 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ (20 mL), and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 42.0 mg (69%) of the desired ketone as a colorless oil; IR (neat) 2954, 2928, 2855, 1681, 1459, 1255, 1155, 1082, 979, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, J= 7.9 Hz, 2H), 7.46 (m, 5H), 7.27 (m, 3H), 7.17 (d, J=8.4 Hz, 2H), 5.10 (s, 2H), 4.75 (t, J=5.9 Hz, 1H), 3.36 (s, 3H), 2.82 (m, 2H), 2.08 (m, 2H), 0.88 (m, 9H), 0.00 (s, 3H), −0.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.2, 155.1, 149.7, 146.9, 145.5, 136.6, 133.6, 130.5, 128.5, 128.2, 127.1, 126.1, 124.5, 124.0, 95.2, 74.8, 56.5, 40.8, 35.5, 26.1, 18.5, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{29}H_{37}NO_4Si$ 492.2570, found 492.2563.

A solution of the above ketone (308 mg, 0.626 mmol) in THF (10 mL) was cooled to 0 °C. Tetrabutylammonium fluoride (1.0 M in THF, 3.8 mL, 3.8 mmol) was added dropwise over a period of 10 min. After the addition was complete, the reaction mixture was warmed to rt over a period of 30 min and stirred for an additional 1 h. The reaction mixture was poured into saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (50 to 100% EtOAc in hexanes) gave 186 mg (80%) of the desired alcohol product as a colorless oil; IR (neat) 3406, 2923, 1675, 1596, 1461, 1255, 1154, 1081, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, J=7.7 Hz, 2H), 7.50 (m, 5H), 7.26 (m, 3H), 7.19 (d, J= 7.7 Hz, 2H), 5.08 (s, 2H), 4.65 (t, J=5.9 Hz, 1H), 3.80 (bs, 1H), 3.33 (s, 3H), 2.87 (m, 2H), 2.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.8, 154.4, 149.7, 146.5, 144.9, 136.3, 133.6, 130.2, 128.5, 128.3, 128.3, 127.2, 124.9, 124.2, 95.0, 73.4, 56.4, 38.6, 33.3; HRMS $(M+H)^+$ calcd for $C_{23}H_{23}NO_4$ 378.1705, found 378.1702.

A solution of the above alcohol (78.0 mg, 0.207 mmol) in anhydrous CH_2Cl_2 (4 mL) was cooled to 0 °C under argon. *N*,*N*-Diisopropylethylamine (40 µl, 0.23 mmol) was added and the reaction mixture was stirred for 15 min at 0 °C. A solution of freshly distilled triflic anhydride (40 µl, 0.227 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise over a period of 5 min. The reaction mixture warmed to rt over 30 min and stirred for 1 h. The reaction mixture was filtered through Celite with CH_2Cl_2 and the solvent removed in vacuo. Purification by flash chromatography (silica gel) with 0–30% MeOH/EtOAc gave 43.3 mg (67%) of **19** as a

colorless oil; IR (neat) 3383, 1646, 1595, 1542, 1480, 1412, 1369, 1221, 1143, 1005 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 7.65 (d, $J=9.1$ Hz, 1H), 7.53 (d, $J=9.1$ Hz, 1H), 7.44 (d, $J=7.5$ Hz, 2H), 7.37 (d, $J=7.3$ Hz, 1H), 7.20 (t, $J=7.7$ Hz, 2H), 7.03 (t, $J=7.9$ Hz, 2H), 6.95 (m, 3H), 6.24 (dd, $J=4.4$, 4.9 Hz, 1H), 3.55 (m, 1H), 3.38 (m, 1H), 2.91 (m, 1H), 2.30 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 193.0, 168.0, 142.9, 140.7, 139.6, 137.1, 136.4, 134.6, 130.5, 130.0, 129.9, 129.1, 128.5, 125.5, 74.1, 32.0, 31.2; HRMS $(M+H)^+$ calcd for $C_{21}H_{17}NO_2$ 316.1338, found 316.1346.

Acknowledgements

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References and notes

1. For leading references on asymmetric epoxidation mediated in situ by chiral ketones see: (a) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155. (b) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391. (c) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (d) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. (e) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. (f) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622. (g) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (h) Adam, W.; Saha-Moller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749. (i) Shu, L.; Shi, Y. *J. Org. Chem.* **2000**, *65*, 8807. (j) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 521. (k) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479. (l) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293.
2. Davies, J. S.; Smith, K.; Turner, J. R.; Gymer, G. *Tetrahedron Lett.* **1979**, *52*, 5035.
3. Szulc, Z.; Mlochowski, J. *Heterocycles* **1984**, *22*, 73.
4. Massa, M. A.; Patt, W. C.; Ahn, K.; Sisneros, A. M.; Herman, S. B.; Doherty, A. *Bioorg. Med. Chem. Lett.* **1988**, *16*, 2117.
5. Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257.
6. Fatiadi, A. J. *Synthesis* **1976**, 133.
7. May, E. L.; Jacobsen, A. E.; Mattson, M. V.; Coop, A.; Aceto, M. D.; Bowman, E. R.; Traynor, J. R.; Wood, J. H.; Harris, L. S. *Med. Chem. Res.* **1988**, *8*, 311.
8. (a) Trecourt, F.; Queguiner, G. *J. Chem. Res. (S)* **1982**, 76. (b) Trecourt, F.; Marsais, F.; Gungor, T.; Queguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2409.
9. Crystallographic data (excluding structure factors) for the structure **1** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 247660. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
10. Saksena, A. K.; Lovey, R. G.; Girijavallabhan, V. M.; Guzik, H.; Ganguly, A. K. *Tetrahedron Lett.* **1993**, *34*, 3267.
11. Klebe, J. *Advances in Organic Chemistry, Methods and Advances*; Wiley-Interscience: New York, 1992; pp 97–178.
12. Interchange of the TBS ether for the labile MOM protecting group in **15** was necessary to obtain aldehyde **16**, as the bulky silyl ether prevented lithium–halogen exchange.
13. Guindon, Y.; Yoahim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912.
14. Purification of crude **2** by HPLC yielded compound **2** contaminated with about 20% *N*,*N*-diisopropylethylamine trifluoromethanesulfonate salt. Hence, the compound was not analyzed by ^{13}C NMR. Note: the validity of the cyclization was confirmed by obtaining the zwitterionic compound **19** from **15**, which undergoes the same type cyclization.

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Synthesis of helical [2.2]paracyclophanes containing carbocyclic and heterocyclic five-membered rings

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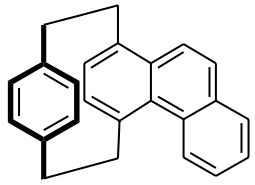
Abstract—The preparation of a [2.2]indenoparacyclophane-based diene is described. Diels–Alder cycloadditions of this diene with *N*-methylmaleimide, *N*-phenylmaleimide and maleic anhydride occurred in good yields and *anti*-diastereoselectively only under high pressure conditions. Heterohelicenophanes were prepared by dehydrogenation of the Diels–Alder products with 10% Pd/C catalyst. A new helicenophanequinone was obtained by the reaction between the diene and 1,4-naphthoquinone.

1. Introduction

Some years ago we began a broad study on the synthesis of angularly annelated [2.2]paracyclophanes. A typical example[1] of these compounds is [2.2](1,4)phenanthrenoparacyclophane (**1**) (Fig. 1). These are inherently chiral molecules that are very interesting because of their helical structure. As a consequence of their helicity and electronic structure, these molecules have extraordinary chirooptical properties.



1

Figure 1.

For several years the main method used to synthesize the helical molecules, helicenes and helicenophanes, was the photocyclodehydrogenation of 1,2-diarylethenes[2] followed by in situ oxidation (O_2, I_2). We have developed a method based on Diels–Alder methodology to rapidly and efficiently construct the carbon framework of future helicenophanes.[3] Diels–Alder reaction has also been used by Katz and co-workers[4] as well as by us to synthesize helicenes.[5] Since there is an increasing interest in small helical molecules in view of their potential applications in the field of materials, we have prepared many racemic and optically active [2.2]paracyclophanes that are angularly annelated in various ways. Attention has also been devoted to modifying the condensed aromatic subunits by replacing one or two benzene units with carbocyclic and/or heterocyclic five-membered rings.[6] The replacement of a benzene unit with a cyclopentadiene ring opens the route for the synthesis of metallocenophanes.

In the present work, we describe the preparation and structure analysis of a new type of angularly annelated [2.2]paracyclophane containing one carbocyclic and one heterocyclic five-membered ring in the condensed subunit. Our two-step approach is based on the Diels–Alder cycloaddition of diene **2**. We also present a systematic ^{1}H and ^{13}C NMR spectroscopic investigation of the Diels–Alder products and of the heterohelicenophanes from the point of view of structural and stereochemical assignments.

2. Results and discussion

2.1. Synthesis of diene 2

Diene **2** was prepared by nucleophilic addition of

Keywords: High pressure; Diels–Alder; Helical cyclophanes.
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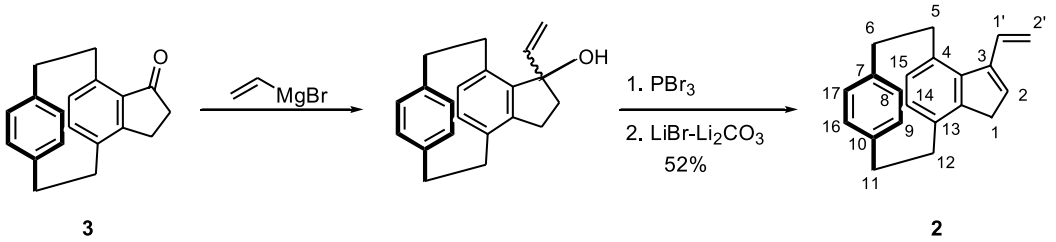


Scheme 1.

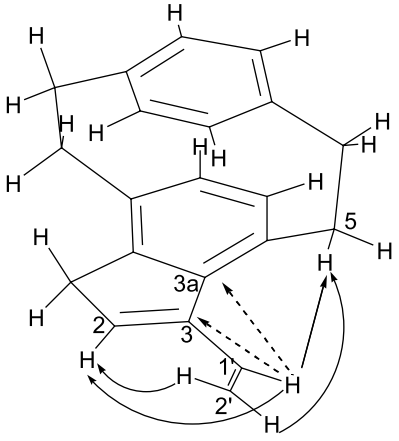


Figure 2. Minimized energy conformations of **2**; the arrows indicate observed NOEs; dotted arrows indicate long-range hetero-correlations.

vinylmagnesiumbromide to the indenophanone **3**;[7] the dehydration of the carbinol was carried out by treating it with PBr_3 in dichloromethane and then with LiBr and Li_2CO_3 (Scheme 1). The overall yield was 52%.

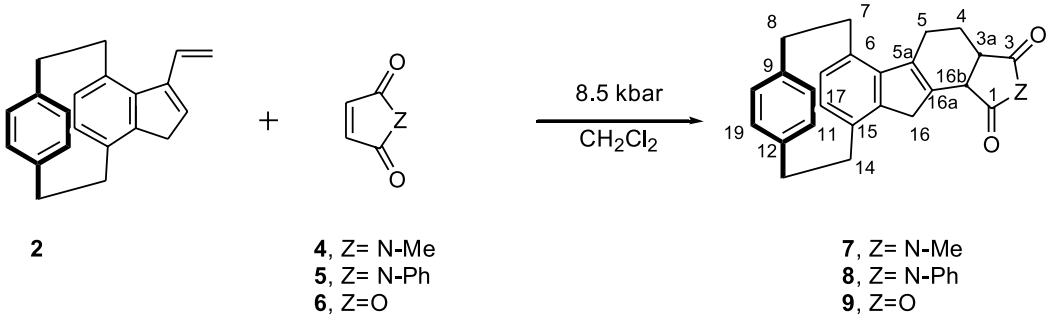
The structure of diene **2** was assigned by NMR spectroscopy. Long-range hetero-correlations with C(2), C(3) and C(3a) were observed upon irradiation of proton H(1′). Furthermore NOEs were observed on H(2) and H_s(5) upon selective irradiation of olefinic protons H(1′) and H_s(2′) indicating that the vinyl group is not planar with the endocyclic double bond as confirmed by the minimized energy conformation depicted in Figure 2.

The deviation from planarity can probably be attributed to the repulsive non-bonded steric interactions between proton H(1′) and the ethane bridge C(5) methylene protons; these interactions destabilize both the *cisoid* conformation of the diene and the transition state, thus causing a decrease in reactivity.

2.2. Diels–Alder reactions between diene 2 and dienophiles 4–6

In order to prepare angularly annelated heterohelicenophanes, the Diels–Alder reactions of diene **2** with the heterocyclic dienophiles *N*-methylmaleimide (**4**), *N*-phenylmaleimide (**5**) and maleic anhydride (**6**) were conducted under thermal conditions and under high pressure.[8] When a toluene solution of diene **2** and the dienophiles **4–6** was heated at reflux temperature and at atmospheric pressure, no reaction occurred and the reactants were always recovered. The Diels–Alder cycloadditions only occurred under high pressure (8.5 kbar) and gave products **7–9** in 52–75% yield (Scheme 2). The experimental conditions are reported in Table 1 (see Section 4).

The structures of compounds **7–9** were assigned by measurements of NOEs and long-range hetero-correlations (see Fig. 3). The assignment of C(5a)–C(16a)



Scheme 2.

Table 1. High pressure Diels–Alder reactions of diene **2** with dienophiles **4–6**

Reactants (ratio)	Conditions	Product	Yield (%)
2–**4** (1:1.5)	8.5 kbar, CH_2Cl_2, 30 °C, 18 h	**7**	72
2–**5** (1:1.5)	8.5 kbar, CH_2Cl_2, 30 °C, 18 h	**8**	75
2–**6** (1:2)	8.5 kbar, CH_2Cl_2, 60 °C, 20 h	**9**	52

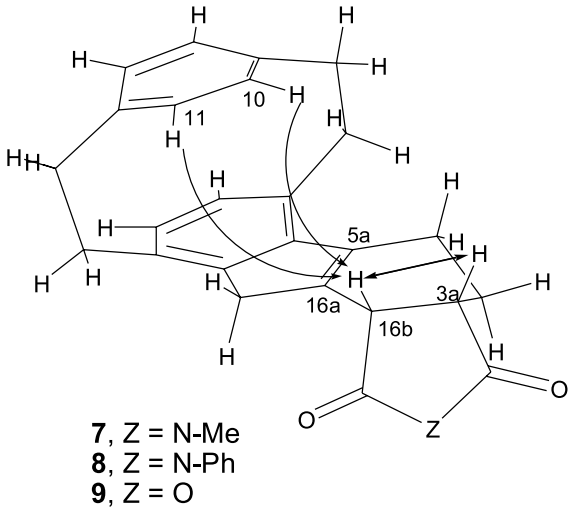


Figure 3. Minimized energy conformations of products **7–9**; the arrows indicate observed NOEs.

carbon–carbon double bond is supported by the long-range hetero-correlations observed on C(5a) and C(16a) upon selective irradiation of H(16) and H(16b). The *cis* stereochemical relationship between bridgehead hydrogens H(3a) and H(16b) follows from the coupling constant $^{3}J_{3a,16b}$= 7.7 Hz for compound **7**, 7.9 Hz for **8** and 8.2 Hz for **9**, together with the NOEs observed between H(3a) and H(16b).

The configurations at C(3a) and C(16b) depicted in the formulas (see Fig. 3) were also assigned on the basis of the NOEs observed on H(16b) upon irradiation of H(10) and H(11); this is in accordance with the *anti*-diastereoselectivity always observed in the Diels–Alder reactions of [2.2]paracyclophane-based dienes. The strong preference for the *anti* (with respect to the unsubstituted arene ring of the [2.2]paracyclophane unit)-diastereoselectivity is justified in view of the steric hindrance of the unsubstituted arene ring. The severe non-bonded interactions between the arene ring and the dienophile strongly destabilize the transition state for *syn*-addition, thus favouring that of *anti*-addition.[9]

Treating the toluene solutions of compounds **7–9** with 10% Pd/C at reflux temperature for 48 h led to the fully aromatized heterohelicenophanes **10–12** in 45–58% yield (Fig. 4).

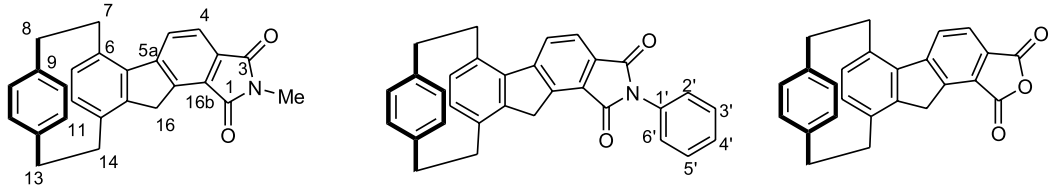
The structures of these compounds were assigned on the basis of the well-known outcome of the dehydrogenation reactions with Pd/C catalysts[10] and on the analysis of their ^{1}H and ^{13}C NMR spectra. ^{1}H- and ^{13}C-chemical shift values, as well as the multiplicities of the carbons, supported the assigned structures.

Finally we decided to also include the synthesis of a helicenophanequinone in this study. Helicenophanequinones, as reported in previous papers, are very interesting for their optical properties.[11] When diene **2** interacted with 1,4-naphthoquinone **13** under CCl_3CO_2H-catalysis in toluene at reflux temperature, helicenophanequinone **14** was obtained in good yield (65%) (Scheme 3).

The primary cycloadduct could not be isolated because it is oxidized[11] under the reaction conditions to the fully aromatized product **14**. The assignment of the structure of quinone **14** was based on the analysis of ^{1}H and ^{13}C NMR spectra which clearly showed the presence of condensed antraquinone, cyclopentadiene and [2.2]paracyclophane units. Quaternary carbons were assigned by long-range hetero-correlated experiments (INEPT). The position of the methylene of the cyclopentadiene moiety was supported by NOE enhancements observed between Hs(18) and H(13) and between H(7) and Hs(9).

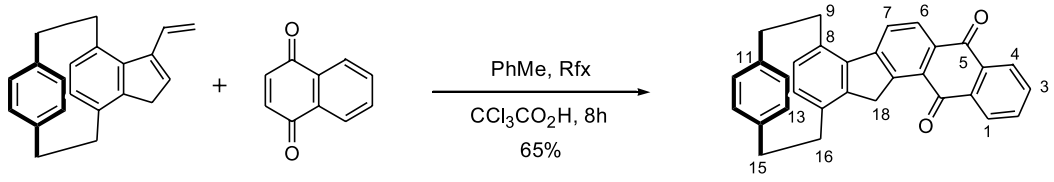
3. Conclusions

A novel type of [2.2]paracyclophanes containing angularly



10 **11** **12**

Figure 4.



2 **13** **14**

Scheme 3.

condensed heterocyclic helical subunits were prepared by a short, two-step method which uses the Diels–Alder reaction to construct the carbon framework. The new [2.2]indenoparacyclophane-based diene **2** is poorly reactive and the cycloadditions with heterodienophiles **4–6** only occurred under high pressure conditions. A new helicenophane quinone was prepared.

4. Experimental

4.1. General

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ solution on a Perkin Elmer Paragon 500 FT-IR. Mass spectra were observed on a Hewlett Packard 5970 GC–MS instrument calibrated with perfluorotributylamine for 70 eV. Absorption chromatography was carried out on Riedel de Haen silica gel (230–400 mesh ASTM). NMR spectra were run in $CDCl_3$ at room temperature on a Varian Associates VXR-400 multinuclear instrument. ^1H and ^{13}C chemical shifts are expressed in ppm downfield from internal TMS. The structures of the reaction products were assigned by analysis of ^1H and ^{13}C NMR spectra. Proton and carbon shift assignments were based on COSY, ^1H-{^1H}NOE and HETCOR experiments; quaternary carbons were assigned by 2D long-range hetero-correlated experiments. The signals with the same superscripts 'a', 'b' or 'c' in the ^1H- and ^{13}C-spectra may be interchanged. Benzene was distilled from $LiAlH_4$.

4.1.1. Preparation of diene 2. A 1 M THF solution of vinylbromide (5 mL) was added dropwise and under stirring to a suspension of magnesium (0.55 g, 22.9 mmol) in dry benzene (20 mL). A few crystals of I_2 were added and the mixture was heated until the reaction started. Vinyl bromide (20 mL) was again added dropwise and the reaction was kept under stirring (until the magnesium reacted completely).

Indenophanone **3**[7] (3 g, 11.4 mmol) was then added portionwise and the reaction mixture was heated at reflux temperature for 1.5 h. It was then cooled and a 10% aqueous ammonium chloride solution was added carefully. Organic layer was separated and aqueous fraction was additionally extracted with EtOAc (50 mL×3). Combined extract was washed with brine (30 mL×2) and dried (Na_2SO_4). After solvent removal the oily residue (3.3 g) was used in the next step without purification.

A solution of PBr_3 (1 mL) in CH_2Cl_2 (48 mL) was added dropwise to a solution of the residue (3.3 g) in anhydrous DMF (75 mL) cooled at −5 °C under nitrogen and under stirring. The reaction mixture was stirred at 0 °C for 1 h. Then LiBr (6.6 g) and Li_2CO_3 (8.4 g) were added and the reaction mixture was stirred for 45 min. It was then cooled, poured into ice-water (50 mL) and extracted with ether (50 mL×3). The combined extracts were washed with brine (50 mL×2), dried (Na_2SO_4) and evaporated in vacuo to give a residue which was purified by column chromatography. Elution with *n*-hexane gave 1.6 g of the pure diene **2** in 52% overall yield; white crystals, mp 87–88 °C (ethyl acetate); ^1H NMR δ 2.68 (ddd, 1H, J=12.9, 9.6, 7.2 Hz, H-6), 2.80 (d, 1H, J=23.7 Hz, H-1), 2.81 (m, 1H, H-5), 3.04 (d, 1H, J=23.7 Hz, H-1), 2.85–3.15 (m, 5H, H-6, H_s-11, H_s-12), 3.58 (ddd, 1H, J=13.5, 9.7, 1.7 Hz, H-5), 5.30 (dd, 1H, J=10.5, 2.1 Hz, H-2′), 5.70 (dd, 1H, J=16.9, 2.1 Hz, H-2′), 6.19 (dd, 1H, J=7.8, 1.8 Hz, H-8), 6.31 (dd, 1H, J=7.8, 1.9 Hz, H-9), 6.42 (d, 1H, J=7.7 Hz, H-14), 6.43 (dd, 1H, J=2.0, 1.6 Hz, H-2), 6.49 (dd, 1H, J=7.8, 1.9 Hz, H-16), 6.52 (d, 1H, J=7.7 Hz, H-15), 6.53 (dd, 1H, J=7.8, 1.8 Hz, H-17), 6.84 (dd, 1H, J=16.9, 10.5 Hz, H-1′); ^{13}C NMR δ 32.3 (C-12), 33.8 (C-5), 34.3 (C-11), 35.1 (C-6), 37.7 (C-1), 116.1 (C-2′), 125.5 (C-9), 128.3 (C-8), 129.7 (C-2), 130.5 (C-14), 132.7 (C-17), 132.9 (C-16), 133.1 (C-1′), 133.8 (C-3a), 133.9 (C-15), 135.1 (C-13), 138.6, 139.4 (C-7, C-10), 145.0 (C-4), 145.5 (C-13a), 146.3 (C-3); MS *m/e* (rel. int.) 104 (11), 152 (44), 153 (100, base), 165 (33), 167 (96), 168 (80), 262 (62, M^+); Anal. calcd for $C_{21}H_{20}$: C, 92.60; H, 7.40. Found: C, 92.57; H, 7.43%.

4.1.2. General procedure for the high pressure Diels–Alder reaction between diene 2 and dienophiles 4–6. The following discussion of the **2–4** reaction also reflects the procedure used for the cycloadditions of diene **2** with dienophiles **5** and **6**. Further details are listed in Table 1.

A solution of *N*-methylmaleimide (**4**) (0.306 g, 2.76 mmol) and diene **2** (0.50 g, 1.84 mmol) in CH_2Cl_2 (15 mL) was placed into a Teflon ampoule and CH_2Cl_2 was then added until the ampoule was completely filled. The ampoule was closed and kept at 8.5 kbar for 18 h at 30 °C. After depressurizing the solvent was removed in vacuo and the crude residue was purified by column chromatography. Elution with 50:50 hexane:ethyl acetate afforded **7** as white crystals (0.46 g, 72%); mp 209–210 °C (ethyl ether); IR: 1702 (s, C=O) cm^{-1}; ^1H NMR δ 2.15 (m, 1H, H-4), 2.27 (m, 1H, H-4), 2.47 (m, 1H, H-5), 2.65 (m, 1H, H-8), 2.77 (m, 1H, H-5), 2.85 (m, 1H, H-7), 2.91 (s, 3H, Me), 2.92 (d, 1H, J=22.1 Hz, H-16), 2.93 (m, 1H, H-14), 3.00–3.08 (m, 2H, H_s-13), 3.18 (m, 1H, H-8), 3.19 (m, 1H, H-14), 3.29 (ddd, 1H, J=7.7, 6.0, 6.0 Hz, H-3a), 3.49 (m, 1H, H-7), 3.50 (d, 1H, J=22.1 Hz, H-16), 3.94 (d, 1H, J=7.7 Hz, H-16b), 6.11 (dd, 1H, J=7.9, 1.9 Hz, H-10), 6.31 (dd, 1H, J=7.9, 2.0 Hz, H-11), 6.40 (d, 1H, J=7.8 Hz, H-17), 6.47 (d, 1H, J=7.8 Hz, H-18), 6.50 (dd, 1H, J=7.8, 2.0 Hz, H-19), 6.54 (dd, 1H, J=7.8, 1.9 Hz, H-20); ^{13}C NMR δ 21.7 (C-5), 23.0 (C-4), 25.0 (Me), 32.4 (C-14), 33.4 (C-7), 34.2 (C-13), 35.7 (C-8), 39.4 (C-16), 40.2 (C-3a), 43.0 (C-16b), 125.5 (C-11), 128.3 (C-10), 130.5 (C-17), 132.7 (C-16a), 132.8 (C-20), 133.1, 135.3 (C-5b, C-6), 133.4 (C-19), 134.1 (C-18), 138.9 (C-9), 139.1 (C-12), 141.2 (C-5a), 144.1, 145.0 (C-15, C-15a), 176.5 (C-3), 179.3 (C-1); Anal. calcd for: $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.40; H, 6.53; N, 3.68%.

Compound **8**. Purified by column chromatography eluting with 70:30 hexane:ethylacetate; white crystals (75%); mp 247 °C (ethyl acetate); IR: 1713 (s, C=O) cm^{-1}; ^1H NMR δ 2.24 (m, 1H, H-4), 2.38 (m, 1H, H-4), 2.59 (m, 1H, H-5), 2.69 (m, 1H, H-8), 2.90 (m, 1H, H-16), 2.80–2.95 (m, 4H, H-5, H-7, H_s-14), 2.97–3.10 (m, 2H, H_s-13), 3.18 (m, 1H, H-8), 3.49 (ddd, 1H, J=7.9, 6.2, 5.4 Hz, H-3a), 3.55 (m, 1H, H-16), 3.58 (m, 1H, H-7), 4.13 (d, 1H, J=7.9 Hz, H-16b), 6.09 (dd, 1H, J=7.8, 1.9 Hz, H-10), 6.37 (dd, 1H,

J=7.8, 1.9 Hz, H-11), 6.42 (d, 1H, J=7.8 Hz, H-17), 6.49 (d, 1H, J=7.8 Hz, H-18), 6.51 (dd, 1H, J=8.0, 1.9 Hz, H-19), 6.56 (dd, 1H, J=8.0. 1.9 Hz, H-20), 7.20 (m, 2H, H-2′, H-6′), 7.36 (m, 1H, H-4′), 7.44 (m, 2H, H-3′, H-5′); ^{13}C NMR δ 21.6 (C-5), 23.0 (C-4), 32.3 (C-14), 33.3 (C-7), 34.1 (C-13), 35.5 (C-8), 39.2 (C-16), 40.2 (C-3a), 43.1 (C-16b), 125.4 (C-11), 126.4 (C-2′, C-6′), 128.1 (C-10), 128.5 (C-4′), 129.1 (C-3′, C-5′), 130.4 (C-17), 131.9 (C-1′) 132.3 (C-5b), 132.8 (C-20), 133.0 (C-16a), 133.3 (C-19), 134.0 (C-18), 135.2 (C-15), 138.8, 139.0 (C-9, C-12), 141.4 (C-5a), 144.1, 144.8 (C-6, C-15a), 175.2 (C-3), 178.0 (C-1); Anal. calcd for: $C_{31}H_{27}NO_2$: C, 83.57; H, 6.11; N, 3.14. Found: C, 83.52; H, 6.13; N, 3.12%.

Compound **9**. Purified by column chromatography eluting with ethyl acetate; white crystals (52%); mp 221–222 °C (ethyl acetate). IR: 1777 (s, C=O) cm^{-1}; ^{1}H NMR δ 2.21 (m, 1H, H-4), 2.30 (m, 1H, H-4), 2.63 (m, 1H, H-8), 2.64 (m, 1H, H-5), 2.84 (m, 2H, H-5, H-7), 2.90–3.07 (m, 3H H$_s$-13, H-14), 3.12 (m, 1H, H-14), 3.16 (m, 1H, H-8), 3.45 (m, 1H, H-7), 3.46 (d, 1H, J=21.0 Hz, H-16), 3.49 (d, 1H, J=21.0 Hz, H-16), 3.57 (ddd, 1H, J=8.2, 6.0, 5.8 Hz, H-3a), 4.21 (d, 1H, J=8.2 Hz, H-16b), 6.07 (dd, 1H, J=7.8, 1.8 Hz, H-10), 6.29 (dd, 1H, J=7.8, 1.8 Hz, H-11), 6.44 (d, 1H, J=7.8 Hz, H-18), 6.49 (d, 1H, J=7.8 Hz, H-17), 6.51 (dd, 1H, J=7.9, 1.8 Hz, H-19), 6.56 (dd, 1H, J=7.9, 1.8 Hz, H-20); ^{13}C NMR δ 21.5 (C-5), 22.3 (C-4), 32.4[a] (C-14), 33.4 (C-7), 34.2[a] (C-13), 35.7 (C-8), 38.8 (C-16), 40.6 (C-3a), 43.4 (C-16b), 125.5 (C-11), 128.3 (C-10), 129.4 (C-16a), 131.1 (C-17), 132.9[b] (C-20), 133.4 (C-5b), 133.6[b] (C-19), 134.4 (C-18), 135.4 (C-15), 138.9 (C-12), 139.2 (C-9), 142.3 (C-5a), 143.9[c] (C-6), 144.5[c] (C-15a), 170.1 (C-3), 172.8 (C-1); Anal. calcd for: $C_{25}H_{22}O_3$: C, 81.06; H, 5.99. Found: C, 81.03, H, 5.95%.

4.1.3. Preparation of compound 10. 10% Pd/C catalyst (0.5 g) was added to a solution of **7** (0.5 g) in toluene (10 mL) and the reaction mixture refluxed for 48 h. It was then cooled, the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography. Elution with 90:10 hexane-ethyl acetate afforded pure helicenophane **10** (0.285 g, 57% yield); orange crystals, mp 266–267 °C (dec, Et$_2$O); IR: 1703 (s, C=O) cm^{-1}; ^{1}H NMR δ 2.86–3.12 (m, 6H, H-7, H-8, H$_s$-13, H$_s$-14), 3.22 (s, 3H, Me), 3.27 (m, 1H, H-8), 3.71 (d, 1H, J=23.3 Hz, H-16), 3.92 (d, 1H, J=23.3 Hz H-16), 3.93 (m, 1H, H-7), 5.67 (d, 1H, J=7.8 Hz, H-10), 6.25 (d, 1H, J=7.8 Hz, H-11), 6.51 (d, 1H, J=7.8 Hz, H-20), 6.59 (d, 1H, J=7.8 Hz, H-19), 6.61 (d, 1H, J=7.7 Hz, H-17), 6.67 (d, 1H, J=7.7 Hz, H-18), 7.87 (d, 1H, J=7.7 Hz, H-4), 8.07 (d, 1H, J=7.7 Hz, H-5); ^{13}C NMR δ 24.0 (Me), 32.3, 33.3, 34.0, 34.2 (C-7, C-8, C-13, C-14), 35.0 (C-16), 122.7, 125.8, 126.7, 128.3, 133.1, 133.7, 133.8, 135.0 (C-4, C-5, C-10, C-11, C-17, C-18, C-19, C-20), 128.0, 128.9, 136.1, 136.6, 138.7, 139.0, 140.4, 141.0, 145.7, 150.7 (C-3a, C-5a, C-5b, C-6, C-9, C-12, C-15, C-15a, C-16a, C-15b), 169.0, 169.2 (C-1, C-3); Anal. calcd for $C_{26}H_{21}NO_2$: C, 82.30; H, 15.58; N, 3.69. Found: C, 82.27; H, 15.54; N, 3.71%.

4.1.4. Preparation of compound 11. Treatment of compound **8** over a 10% Pd/C catalyst according to the above-described procedure led to compound **11** (58% yield) which was purified by column chromatography. Elution with 80:20 hexane-ethyl acetate gave pure **11** as orange crystals; mp 296–297 °C (dec, ethyl ether); IR: 1716 (s, C=O) cm^{-1}; ^{1}H NMR δ 2.88–3.39 (m, 7H, H-7, H$_s$-8, H$_s$-13, H$_s$-14), 3.79 (d, 1H, J=23.3 Hz, H-16), 3.98 (m, 1H, H-7), 4.01 (d, 1H, J=23.3 Hz, H-16), 5.74 (d, 1H, J=7.9 Hz, H-10), 6.31 (d, 1H, J=7.9 Hz, H-11), 6.53 (d, 1H, J=8.0 Hz, H-20), 6.62 (d, 1H, J=8.0 Hz, H-19), 6.64 (d, 1H, J=7.9 Hz, H-17), 6.71 (d, 1H, J=7.7 Hz, H-18), 7.42–7.57 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 8.01 (d, 1H, J=7.8 Hz, H-4), 8.19 (d, 1H, J=7.8 Hz, H-5); ^{13}C NMR δ 32.3, 33.4, 34.1, 34.3 (C-7, C-8, C-13, C-14), 35.1 (C-16), 123.3, 125.9, 126.8, 127.2, 128.1, 128.4, 129.2, 133.1, 133.8, 133.9, 135.1 (C-4, C-5, C-10, C-11, C-17, C-18, C-19, C-20, C-2′, C-3′, C-4′, C-5′, C-6′), 127.5, 132.1, 136.2, 136.7, 138.8, 139.0, 140.9, 141.0, 145.9, 151.2 (C-3a, C-5a, C-5b, C-6, C-9, C-12, C-15, C-15a, C-16a, C-16b, C-1′), 167.8, 168.0 (C-1, C-3); Anal. calcd for $C_{31}H_{23}NO_2$: C, 84.33; H, 5.25; N, 3.17. Found: C, 84.35; H, 5.27, N, 3.20%.

4.1.5. Preparation of compound 12. Treatment of compound **9** over a 10% Pd/C catalyst according to the above-described procedure led to compound **12** (45% yield) which was purified by column chromatography. Elution with dichloromethane afforded pure **12** as yellow crystals; mp 298–299 °C (dec, Et$_2$O); IR: 1774 (s, C=O) cm^{-1}; ^{1}H NMR δ 2.84–3.29 (m, 7H, H-7, H$_s$-8, H$_s$-13, H$_s$-14), 3.80 (d, 1H, J=23.8 Hz, H-16), 3.76 (d, 1H, J=23.8 Hz, H-16), 3.94 (m, 1H, H-7), 5.65 (d, 1H, J=7.7 Hz, H-10), 6.26 (d, 1H, J=7.7 Hz, H-11), 6.53 (d, 1H, J=7.8 Hz, H-20), 6.61 (d, 1H, J=7.8 Hz, H-19), 6.67 (d, 1H, J=7.7 Hz, H-17), 6.73 (d, 1H, J=7.7 Hz, H-18), 8.06 (d, 1H, J=7.9 Hz, H-4), 8.28 (d, 1H, J=7.9 Hz, H-5); ^{13}C NMR δ 32.1, 33.2, 33.8, 34.0 (C-7, C-8, C-13, C-14), 34.9 (C-16), 125.1, 125.6, 128.2, 128.6, 133.0, 133.6, 134.5, 135.2 (C-4, C-5, C-10, C-11, C-17, C-18, C-19, C-20), 127.2, 127.3, 136.5, 136.7, 138.4, 138.8, 140.1, 142.4, 145.6, 152.4 (C-3a, C-5a, C-5b, C-6, C-9, C-12, C-15, C-15a, C-16a, C-16b), 163.2, 163.4 (C-1, C-3); Anal. calcd for: $C_{25}H_{18}O_3$: C, 81.95; H, 4.95. Found: 81.91, H, 4.94%.

4.1.6. Diels–Alder reaction of diene 2 with 1,4-naphthoquinone (13). A solution of diene **2** (0.5 g, 1.83 mmol) and 1,4-naphthoquinone (**13**) (0.7 g, 4.5 mmol) in toluene (10 mL) containing trichloroacetic acid (0.29 g, 1.83 mmol) was heated at reflux temperature for 8 h. The cooled solution was poured into an aqueous saturated sodium bicarbonate solution (50 mL) and extracted with ethyl acetate (30 mL×3). The extract was dried (Na_2SO_4) and evaporated in vacuo to give a residue which was chromatographed. Elution with 80:20 hexane/ethyl acetate afforded 0.51 g (65% yield) of pure **14** as yellow crystals; mp 197–198 °C (ethyl acetate); IR: 1664 (s, C=O) cm^{-1}; ^{1}H NMR δ 2.92 (m, 1H, H-10), 3.04 (m, 2H, H-15, H-16), 3.08 (m, 1H, H-9), 3.18 (m, 1H, H-15), 3.20 (m, 1H, H-10), 3.42 (m, 1H, H-16), 3.98 (m, 1H, H-9), 4.01 (d, 1H, J=23.7 Hz, H-18), 4.24 (d, 1H, J=23.7 Hz, H-18), 5.68 (dd, 1H, J=7.9, 1.9 Hz, H-12), 6.27 (dd, 1H, J=7.9, 2.0 Hz, H-13), 6.52 (dd, 1H, J=7.9, 2.0 Hz, H-22), 6.60 (dd, 1H, J=7.9, 1.9 Hz, H-23), 6.62 (d, 1H, J=7.7 Hz, H-20), 6.68 (d, 1H, J=7.7 Hz, H-2), 7.82 (m, 2H, H-2, H-3), 8.23 (d, 1H, J=8.1 Hz, H-7), 8.36 (m, 2H, H-1, H-4), 8.46 (d, 1H,

$J=8.1$ Hz, H-6); ^{13}C NMR δ 32.4 (C-16), 33.5 (C-10), 34.2 (C-15), 34.3 (C-9), 39.0 (C-18), 126.0 (C-13), 127.2, 127.4 (C-1, C-4), 127.5 (C-7), 128.0 (C-6), 128.5 (C-12), 129.6 (C-18b), 131.5 (C-5a), 133.1 (C-23), 133.7 (C-22), 133.9 (C-20), 133.9[a] (C-19), 134.2 (C-2,C-3), 134.5[a] (C-4a), 134.9 (C-21), 136.3[a] (C-7b), 136.5[a] (C-8), 138.8 (C-11), 139.1 (C-14), 140.6 (C-17), 145.3 (C-18a), 147.31 (C-17a), 150.9 (C-7a), 183.3 (C-5), 185.3 (C-19); Anal. calcd for: $C_{31}H_{22}O_2$: C, 87.30; H, 5.20. Found: C, 87.27; H, 5.23%.

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References and notes

1. Ashraf, A. A.; Hopf, H.; Ernst, L. *Eur. J. Org. Chem.* **2000**, 3021–3029.
2. (a) Mallory, F. B.; Mallory, C. W. In *Organic Reaction*; Wiley: New York, 1984; Vol. 30, pp 1–456. (b) Vögtle, F. In *Fascinating Molecules in Organic Chemistry*; Wiley: New York, 1992; Vol. 156. (c) Meurer, K. P.; Vögtle, F. *Top. Curr. Chem.* **1985**, *127*, 1–76. (d) Laarhoven, W. H.; Prinsen, W. J. *Top. Curr. Chem.* **1984**, *125*, 63–120.
3. (a) Marrocchi, A.; Minuti, L.; Taticchi, A.; Dix, I.; Hopf, H.; Gacs-Baitz, E.; Jones, P. T. *Eur. J. Org. Chem.* **2001**, 4259–4268. (b) Minuti, L.; Taticchi, A.; Marrocchi, A.; Costantini, L.; Gacs-Baitz, E. *Tetrahedron: Asymmetry* **2001**, *12*, 1179–1183.
4. Inter alia: (a) Liu, L.; Katz, T. J. *Tetrahedron Lett.* **1990**, *31*, 3983–3986. (b) Willmore, N. D.; Liu, L.; Katz, T. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1093–1094. (c) Willmore, N. D.; Hoic, D. A.; Katz, T. J. *J. Org. Chem.* **1994**, *59*, 1889–1891. (d) Nuckolls, C.; Katz, T. J.; Castellanos, L. *J. Am. Chem. Soc.* **1996**, *118*, 3767–3768. (e) Day, Y.; Katz, T. J. *J. Org. Chem.* **1997**, *62*, 1274–1285. (f) Verbiest, T.; Van Elshocht, S.; Kauranen, M.; Hellemans, L.; Snauwaert, J.; Nuckolls, C.; Katz, T. J.; Persoons, A. *Science* **1998**, *282*, 913–915. (g) Lovinger, A. J.; Nuckolls, C.; Katz, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 264–268.
5. (a) Minuti, L.; Taticchi, A.; Marrocchi, A.; Gacs-Baitz, E. *Tetrahedron* **1997**, *53*, 6873–6878. (b) Minuti, L.; Taticchi, A.; Marrocchi, A.; Gacs-Baitz, E.; Galeazzi, R. *Eur. J. Org. Chem.* **1999**, 3155–3163.
6. (a) Minuti, L.; Taticchi, A.; Marrocchi, A.; Lanari, D.; Broggi, A.; Gacs-Baitz, E. *Tetrahedron: Asymmetry* **2003**, *14*, 481–487. (b) Minuti, L.; Taticchi, A.; Lanari, D.; Marrocchi, A.; Gacs-Baitz, E. *Tetrahedron: Asymmetry* **2003**, *14*, 2775–2779. (c) Minuti, L.; Taticchi, A.; Marrocchi, A.; Gacs-Baitz, E. *Polycyclic Aromat. Compd.* **2004**, in press.
7. (a) Hopf, H.; Raulfs, F.-W. *Isr. J. Chem.* **1985**, *25*, 210–216. (b) Dannheim, J. PhD Dissertation, Technische Universität Braunschweig, Braunschweig, Germany, 1987.
8. (a) Fringuelli, F.; Taticchi, A. *Diels–Alder reaction. Selected Pratical Methods*; Wiley: New York, 2002. (b) Matsumoto, K.; Morrin, A. *Organic Synthesis at High Pressures*; Wiley: New York, 1990. (c) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741–761. (d) Jenner, G. *Tetrahedron* **2002**, *58*, 5185–5202.
9. (a) Fringuelli, F.; Taticchi, A. Diels–Alder Reaction; Wiley: New York, 1990. (b) Vogel, P. *Stereochemistry and reactivity of system containing π electrons*; Watson, W. H., Ed.; Methods in Stereochemical Analysis; Verlag Chemie: Weinheim, Germany, 1983.
10. Fu, P. P.; Harcey, R. G. *Chem. Rev.* **1978**, *78*, 317–361.
11. (a) Minuti, L.; Taticchi, A.; Marrocchi, A.; Lanari, D.; Gacs-Baitz, E. *Tetrahedron: Asymmetry* **2002**, *13*, 1331–1335. (b) Minuti, L.; Taticchi, A.; Lanari, D.; Marrocchi, A.; Gacs-Baitz, E. *Tetrahedron: Asymmetry* **2003**, *14*, 2387–2392.

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A facile synthesis of bifunctional phospholipids for biomimetic membrane engineering

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Abstract—We report a facile synthesis of bifunctional phospholipid conjugates by acylation of *N*-protected *lyso*-phosphatidylethanolamine with 12-acryloxy-1-dodecanoic acid and followed with deprotection and conjugation with biotin, FITC, Texas Red, or EMC groups. The lipid conjugates can be used to generate a multifunctional substrate-supported phospholipid membrane via bioconjugation reaction to biotin or covalent attachment to EMC at their hydrophilic terminus. In addition, conjugation to fluorophores, FITC or Texas Red, provides a convenient mechanism to monitor lipid membrane formation and stability. Significantly, in situ photopolymerization of the acrylate group at the end of one of two hydrophobic alkyl chains stabilizes the phospholipid membrane.

1. Introduction

Supported lipid membranes that mimic cell and tissue surfaces have attracted considerable attention due to their potential applications as tools to probe cell and molecular interactions and as bioactive coatings for biosensor or medical implant applications.[1] In most studies, lipids differing in chemical composition, saturation and size have been utilized as the primary building blocks of film structures.[2–5] However, an obstacle in the real world application of artificial lipid membranes is their limited long term stability, since the major driving forces for the formation of self-assembled lipid membrane are relatively weak hydrophobic van der Waal's interactions. Polymerization of a lipid assembly provides at least one mechanism to increase the stability of artificial lipid membranes. In the past two decades, a variety of polymerizable lipids have been synthesized, which contain polymerizable groups at the polar head,[6,7] mid-chain[8] and chain terminus.[5,9–13] In this regard, we have previously reported a method to prepare stable, substrate-supported phospholipid films via in situ photopolymerization of an acrylate functionalized phosphatidylcholine (*mono*-AcrylPC, **1**) assembly.[14–16] We have also designed an acrylate functionalized phosphatidylethanolamine (*mono*-AcrylPE, **2**) in which the amino function can serve as a handle for further modifications.[17,18]

We have recognized that a significant limitation in the active application of artificial lipid membranes is the multistep and low-yield preparative methods of the lipid components. Herein, we report a simplified approach for the synthesis of polymerizable phospholipids, including *mono*-AcrylPC (**1**) and bifunctional *mono*-AcrylPE (**2**) derivatives for generating stable, heterofunctional biomimetic membrane assemblies (Fig. 1). Examples of bifunctional *mono*-AcrylPE (**2**) derivatives include acrylate-functionalized phospholipids in which biotin, fluorophores, or maleimide group have been incorporated into the lipid head group. Terminal biotin facilitates the incorporation of proteins or other target molecules via specific high affinity biotin-streptavidin interaction.[19–21] Biotin-based surface

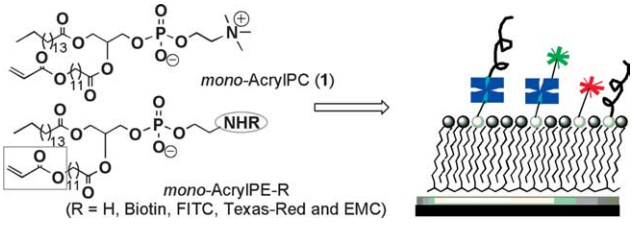

Figure 1. Schematic representation of a chemically heterogeneous, multifunctional polymeric lipid membrane.

Keywords: Polymerizable phospholipid; Biotin; Fluorescent; Membrane-mimetic.
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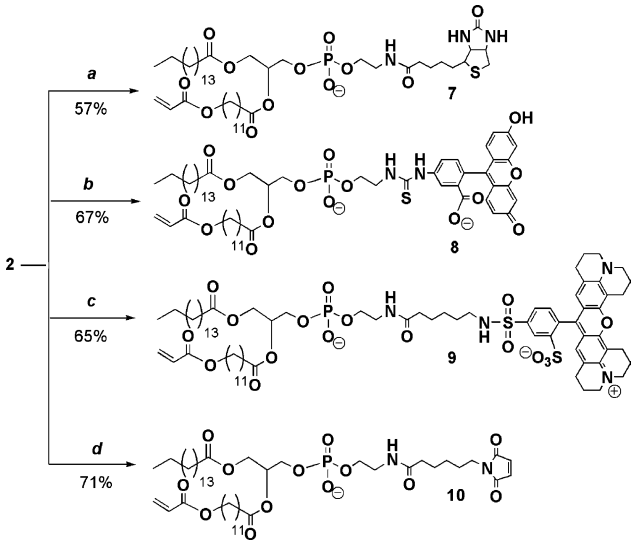
engineering has the advantage of being rapidly completed in a mild aqueous environment with simple washing and purification steps. Thus, potential damage to candidate surface ligand groups due to the conjugation process is limited and any moiety that can be biotinylated can be immobilized onto a streptavidin derivatized surface.[22,23] A fluorescent dye provides a mechanism for direct visualization and monitoring of the lipid membrane.[19,24–26] The ε-maleimidocaproyl (EMC) group facilitates covalent attachment of thiol containing peptides, proteins or other target molecules under mild conditions.[27,28] On the other hand, the terminal acryl group facilitates either polymerization[13–15] or crosslinking for stabilizing the lipid membrane assembly.[29]

2. Results and discussion

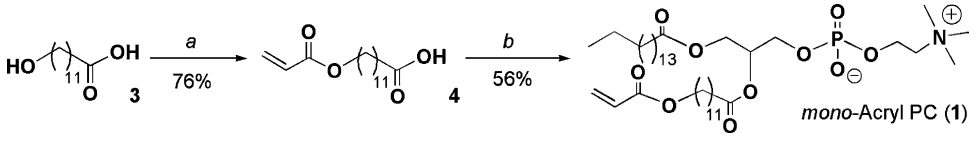
To date, the syntheses of a relatively large number of polymerizable phospholipids have been reported.[30] Nonethless, impractical, inefficient, multi-step preparative methods have typically impeded widespread use of these reagents. In our current research program, we have developed a simplified two-step synthetic approach, in which commercially available ω-hydrooxylalkanoic acid (**3**) is first converted to 12-acryloxy-1-dodecanoic acid (**4**) and then coupled with *lyso*-phosphatidylcholine to afford *mono*-AcrylPC (**1**) in good yield (Scheme 1).

We had previously reported a multi-step approach combining sequential acylation and deprotection, phosphorylation and deprotection for the synthesis of mixed diacyl phosphatidyl-ethanolamine.[17] Likewise, we investigated a simplified approach similar to that used for the synthesis of mixed diacyl phosphatidylcholine (**1**) to prepare mixed diacyl phosphatidyl-ethanolamine **2** directly from commercially available *lyso*-phospholipid via protection/deprotection of the ethanolamine.[13,31] The amine group of the *lyso*-phosphatidylethanolamine was first protected with *tert*-butyloxycarbonyl (BOC), followed by acylation with 12-acryloxy-1-dodecanoic acid (**4**). This provided a BOC-protected *mono*-AcrylPE (**6**), which was treated with trifluoracetic acid to give the desired polymerizable *mono*-AcrylPE (**2**) as a white solid in 95% yield (Scheme 2). Anticipated compound structure was confirmed by NMR spectroscopy. For example, the distinctive multiplet peaks at 5.20 ppm are characteristic of the proton at the C-2 position on the glycerol backbone of 1,2-diacyl glycerol,[32] the NH_3^+ group was noted as a broad peak at 8.51 ppm (3H),[33] and the vinyl group of acrylate was confirmed at 6.39 (dd, 1H), 6.14 (dd, 1H), 5.81 (dd, 1H) ppm as an AMX spin system for *mono*-AcrylPE (**2**).

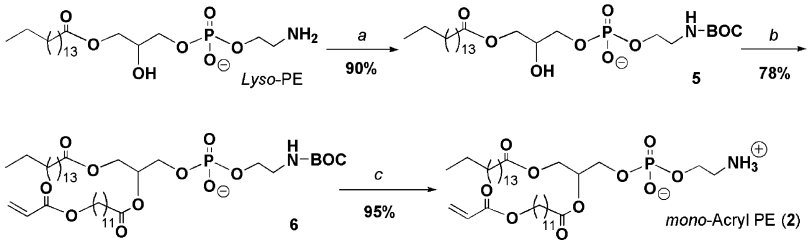
Treatment of *mono*-AcrylPE (**2**) with commercially available *N*-hydroxysuccinimidobiotin (Biotin-NHS), fluorescein isothiocyanate (FITC), Texsa Red-X-Succinimidyl Ester (Texas Red-NHS) and *N*-(ε-maleimidocaproyl)succinimide (EMC-NHS) in the presence of triethylamine provided the desired conjugated lipid *mono*-AcrylPE-Biotin (**7**), *mono*-AcrylPE-FITC (**8**), *mono*-AcrylPE-Texas-Red (**9**), and *mono*-AcrylPE-EMC (**10**)—all in good yield, respectively (Scheme 3). ^{1}H NMR spectroscopy confirmed the anticipated structure of these conjugates. Excluding lipid backbone protons, two amide protons were noted at 7.79 (br, 1H) and 7.00 (br, 1H) ppm for *mono*-AcrylPE-Biotin (**7**); nine aromatic protons were observed at 8.26



Scheme 3. Synthesis of *mono*-AcrylPE conjugates: *a*, Biotin-NHS, Et_3N/DMF; *b*, FITC, Et_3N, DMF, 67%; *c*, Texas Red-NHS, Et_3N/DMF; *d* EMC-NHS, Et_3N/DMF.



Scheme 1. Synthesis of *mono*-AcrylPC (**1**): *a*, Acryl Chloride, DTBC/Pyr.-THF; *b*, Lyso-PC, DTBC, DCC, DMAP/$CHCl_3$.



Scheme 2. Synthesis of *mono*-AcrylPE (**2**): *a*, $(BOC)_2O$, Et_3N, DMAP/MeOH; *b*, **4**, DTBC, DCC, DMAP/$CHCl_3$; *c*, CF_3COOH/CH_2Cl_2.

(m, 1H), 7.40–7.30 (m, 1H), 7.16–7.04 (m, 3H) and 6.68–6.59 (m, 4H) ppm for *mono*-AcrylPE-FITC (**8**); five aromatic protons were observed at 6.73 (s, 2H), 7.17 (d, 1H), 7.41 (m, 1H), 7.69 (m, 1H), 7.99 (d, 1H) ppm for *mono*-AcrylPE-Texas-Red (**9**); and two olefin protons were observed at 6.67 (s, 2H) ppm for AcrylPE-EMC (**10**).

We have previously reported the formation of a robust, substrate-supported, lipid membrane by self-assembly of a polymerizable lipid *mono*-AcrylPC (**1**) on the alkylated surface of a polyelectolyte multilayer with recent extention of this biomimetic membrane system to the coating of cell encapsulating alginate beads.[18] We investigated the capacity of Texas Red-labeled lipid **9** to act as a constituent of a membrane-mimetic film formed on empty alginate bead surfaces. Briefly, *mono*-AcrylPE-Texas Red (**9**)/*mono*-AcrylPC (**1**) lipid mixtures (5:95 mole fraction) were prepared as unilamellar vesicles, fused onto the outer surface of alginate beads that were precoated with polyelectrolyte multilayer comprised of poly-lysine and alginate and an alkylated terpolymer at the outlayer,[18] and photopolymerized (Fig. 2A). Confocal fluorescence images demonstrated a uniform membrane-mimetic film on bead surfaces (Fig. 2B). The stability of the polymeric lipid membrane was evaluated by incubation of labeled beads in Hank's Buffer solution for 8 weeks at 4 °C (Fig. 2C) and after implantation for 8 weeks into the peritoneal cavity of NOD/SCID mice (Fig. 2D). These results indicate that fluorescent conjugated lipids provide a convenient tool to visually monitor lipid membrane formation and membrane stability, both in vitro and in vivo.

In conclusion, we have simplified the scheme for generating bifunctional phospholipid conjugates containing both an acrylate moiety and a terminal functionality, such as a biotin, fluorescent or EMC group. This approach can be easily expanded to other structural bifuctional phospholipids variants such as functionalization with peptide or carbohydrate at the hydrophilic terminus. These conjugates will enhance the capacity to generate stable, self-assembled, biologically functional and chemically heterogeneous biomimetic membranes. Moreover, both biotin and fluorescent dye modified phospholipids yield probes for assessing the assembly and stability of lipid structures in vitro and in vivo.

3. Experimental

3.1. General methods

TLC was performed on Whatman silica gel aluminum baked plates (F254, 250 μm thickness) and detected by fluorescence quenching, sulfuric acid (10 mL% in methanol), or phosphomolybdic acid (20 wt% in ethanol). Column chromatography was performed on silica gel (Fisher Chemical, 200–425 mesh). ^{1}H NMR spectra were recorded at 300 MHz (Varian INOVA) in $CDCl_3$ (internal Me_4Si, $\delta=0$). Mass spectra (EI, FAB) were measured with JEOL JMS-SX 102/SX102A/E mass spectrometer. Confocal microscopy studies were performed on a Zeiss LSM510 Laser Confocal Microscope (Carl Zeiss, Inc., Germany) equipped with external argon (for excitation at 458, 488 and 514 nm), HeNe1 (for excitation at 543 nm), and HeNe2 (for excitation at 633 nm) lasers.

3.1.1. 12-Acryloxyloxy-1-dodecanoic acid (4). Freshly distilled acryl chloride (0.64 mL, 7.5 mmol, 1.5 equiv) in THF (30 mL) was added dropwise to a mixture of 12-hydroxydodecanoic acid (1.08 g, 5 mmol) and pyridine (2.44 mL, 30 mmol, 6 equiv) in THF (50 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for another 12 h. The pyridine chloride was removed by vacuum filtration and the mixture was concentrated by rotary evaporation to give a residue, which was purified by column chromatography (SiO_2) using *n*-hexane/EtOAc (3:1) as eluent, to afford **4** (1.12 g, 76%). ^{1}H NMR ($CDCl_3$) δ (ppm): 6.36 (dd, 1H, $J=15.6$, 1.5 Hz, CH=CH_2), 6.07 (dd, 1H, $J=15.6$, 10.5 Hz, CH=CH_2), 5.79 (dd, 1H, $J=1.5$, 10.5 Hz, CH=CH_2), 4.12 (t, 2H, $J=6.6$ Hz, CH_2–O), 2.32 (t, 2H, $J=7.2$ Hz, CH_2–CO), 1.66–1.62 (m, 4H, C$H_2\times2$), 1.24 (br. s, 14H, C$H_2\times7$). ^{13}C NMR ($CDCl_3$) δ: 180.18, 166.62, 130.68, 128.84, 64.95, 43.25, 29.5, 29.57, 29.41, 29.23, 28.79, 26.11, 24.86. HRMS calculated (FAB) 277.1991, observed 277.1997 $[M+Li]^+$.

3.1.2. 1-*O*-Palmitoyl-2-*O*-(12-acryloyloxy)dodecanoyl-*sn*-glycero-3-phosphocholine (1). The title compound was prepared as previously reported.[13]

3.1.3. 1-Palmitoyl-2-hydroxy-*sn*-glycero-3-phosphoethanolamine-BOC (5). *Lyso*-PE (0.5 g, 1.11 mmol) was dissolved in 20 mL of a 1:1 chloroform and methanol mixture. $(BOC)_2O$ (1.09 g, 5.5 mmol), 0.036 g (0.29 mmol) of dimethylaminopyridine, and 0.54 mL of triethylamine were added to the reaction mixture, which was stirred overnight. The solvent was removed and the colorless liquid was washed once each with 0.1 *N* HCl and saturated sodium bicarbonate solution, and then washed with brine. The organic layer was dried overnight by sodium sulfate. Removal of the solvent and drying in a vacuum for 24 h yielded **5** as a light yellow semisolid (0.551 g 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.07 (dd, 1H, $J=4.5$ Hz, 11.7 Hz), 3.99 (dd, 1H, $J=5.7$ Hz, 11.7 Hz), 3.85 (m, 1H), 3.80 (m, 2H), 3.21 (t, 2H, $J=5.4$ Hz), 2.24 (t, 2H, $J=7.5$ Hz), 60 (m, 2H), 1.32 (s, 9H, BOC), 1.18 (s, broad, 22H), 0.79 (t, 3H, 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 174.42, 160.50, 68.73, 68.61, 34.23, 32.06, 29.82, 29.70, 29.62, 29.48, 29.43, 29.29, 28.42, 24.98, 22.81, 14.20. HRMS calculated (FAB) 552.3301, observed 552.3303 $[M-H]^-$.

3.1.4. *mono*-AcrylPE-BOC (6). To a mixture of **5** (218 mg, 0.39 mmol), 12-(acryloyloxyl)-1-dodecanoic acid (121 mg, 0.47 mmol), DMAP (5 mg, 0.04 mmol), and one crystal of 2,6-di-*tert*-butyl-*p*-cresol, was added 6.0 mL of dry $CHCl_3$. DCC (121 mg, 0.59 mmol) was added and the reaction was stirred in the dark under argon. After 64 h, dicyclohexylurea was filtered off and washed with $CHCl_3$. The filtrate was evaporated and the residue was dissolved in 20.0 mL of MeOH. Bio-Rad AG 501-8· (5.0 g) was added and the reaction stirred at room temperature for 1 h. The resin was filtered and washed with MeOH. The filtrate was dried over Na_2SO_4. The solvent was removed in vacuo to give a residue that was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 5:10 to yield **6** (246 mg, 78%). ^{1}H NMR ($CDCl_3$) δ (ppm): 6.30 (dd, 1H, $J=17.4$, 1.0 Hz,

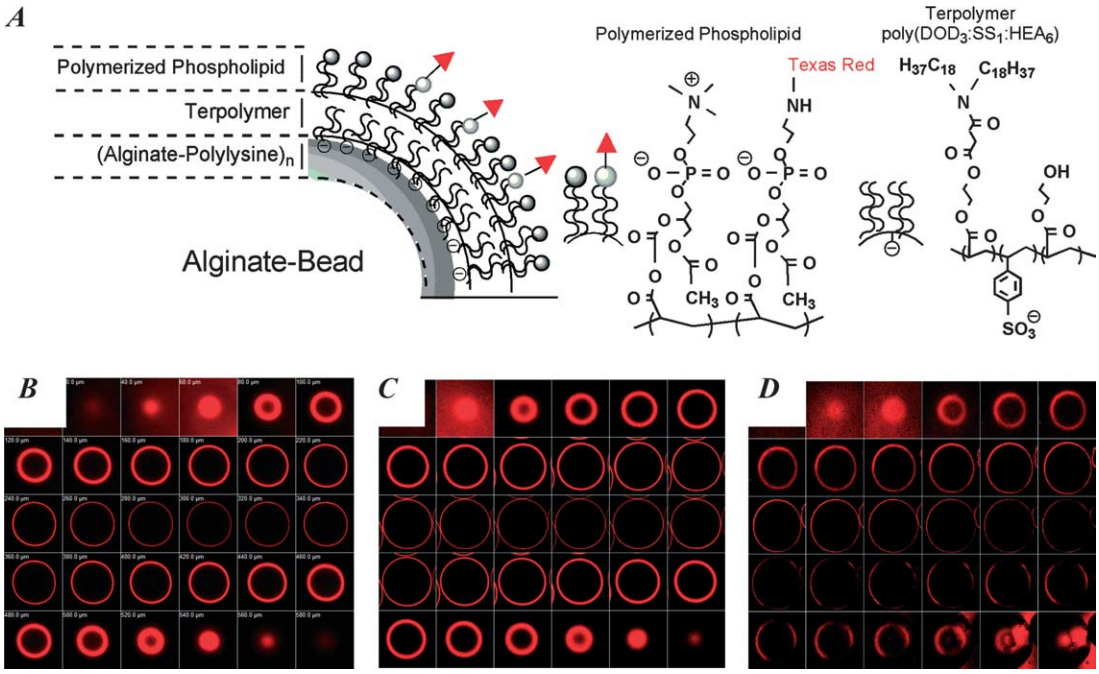


Figure 2. Representative illustration of polymeric lipid-containing membrane coated alginate bead (*A*) and confocal fluorescent image of a lipid assembly comprised of *mono*-AcrylPE-Texas red (**9**) (5 mol%) and *mono*-AcrylPC (**1**) (95 mol%) on alkylated alginate beads after vesicle fusion and polymerization (*B*), after 8 weeks reserved in Hank's Buffer solution. (*C*), after 8 weeks implanted in NOD/scid mouse (*D*). (Z-section images, 10× magnification).

CH=CH_2), 6.12 (dd, 1H, J=17.4, 10.5 Hz, CH=CH$_2$), 5.80 (dd, 1H, J=1.0, 10.5 Hz, CH=CH_2), 5.20 (m, 1H, CH-2), 4.38 (dd, 1H, J=3.0, 12.3 Hz), 4.10 (t, 2H, J=6.6 Hz, CH_2–O), 3.94–3.85 (br, 2H, CH_2–O), 3.16 (br, 1H, CH_2–N), 3.09 (br, 1H, CH_2–N), 2.26 (m, 4H, CH_2CO×2), 1.68–1.57 (m, 6H, CH_2×3), 1.35 (s, 9H, BOC), 1.24 (br. s, 38H, CH_2×19), 0.87 (t, 3H, J=6.6 Hz, CH_3). ^{13}C NMR (CDCl$_3$) δ: 174.62, 169.20, 166.57, 162.60, 163.40, 130.64, 128.85, 97.79, 64.92, 64.61, 34.50, 34.25, 32.12, 29.92, 29.72, 29.65, 29.57, 29.39, 29.36, 28.82, 28.58, 26.14, 25.20, 25.05, 22.89, 14.32. FABMS (*M*/*Z*): 818.9 [M+2Li]$^+$.

3.1.5. 1-*O*-Palmitoyl-2-*O*-(12-acryloyloxy)dodecanoyl-*sn*-glycero-3-phosphoethanolamine (*mono*-AcrylPE, 2). To a solution of **6** (150 mg, 0.186 mmol) in 3 mL of dichloromethane was added 3 mL of trifluoroacetic acid. The solution was stirred at room temperature for 4 h and the solvent and other volatile materials was removed by rotatory evaporation to provide a residue, which was purified by column chromatography (SiO$_2$) using chloroform/methanol/water (65:25:4) as eluent to afford **2** (0.125 g, 95%). ^{1}H NMR (CDCl$_3$) δ (ppm): 8.51 (br, 3H, NH_3^+), 6.39 (dd, 1H, J=17.4, 1.0 Hz, CH=CH_2), 6.11 (dd, 1H, J=17.4, 10.5 Hz, CH=CH$_2$), 5.82 (dd, 1H, J=1.0, 10.5 Hz, CH=CH_2), 5.21 (m, 1H, CH-2), 4.37 (dd, 1H, J=3.0, 12.3 Hz), 4.14 (t, 2H, J=6.6 Hz, CH_2–O), 4.14–4.05 (m, 3H), 3.94 (br, 2H, CH_2–O), 3.16 (br, 2H, CH_2–N), 2.33–2.26 (m, 4H, CH_2CO×2), 1.68–1.57 (m, 6H, CH_2×3), 1.24 (br. s, 38H, CH_2×19), 0.87 (t, 3H, J=6.6 Hz, CH_3). ^{13}C NMR (CDCl$_3$) δ: 173.59, 173.29, 166.48, 130.59, 128.83, 70.50, 64.86, 64.63, 64.09, 62.75, 62.44, 40.61, 34.44, 34.26, 32.11, 29.50, 29.41, 28.81, 27.79, 26.14, 25.13, 25.07, 22.87, 14.30. HRMS calculated (FAB) 728.8894, observed 728.9015 [M+Na]$^+$.

3.1.6. *mono*-AcrylPE-Biotin (7). Triethylamine (0.1 mL, 0.71 mmol) was added to a solution of **2** (50 mg, 0.071 mmol) in DMF (5 mL). After the solution was stirred for 30 min, a solution of *N*-hydroxsuccinimidobiotin (36 mg, 0.11 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, then concentrated in a vacuum to yield a residue, which was purified by Sephadex LH-20 column using methanol as eluent to afford **7** (17 mg, 53%). ^{1}H NMR (CDCl$_3$_CD$_3$OD) δ: 7.79 (br. 1H, NH), 7.00 (br, 1H, NH), 6.38 (dd, 1H, J=17.1, 1.0 Hz, CH=CH_2), 6.10 (dd, 1H, J=17.1, 10.5 Hz, CH=CH$_2$), 5.80 (dd, 1H, J=1.0, 10.5 Hz, CH=CH_2), 5.21 (m, 1H, CH-2), 4.48 (m, 1H), 4.35 (dd, 1H, J=3.0, 12.3 Hz), 4.32 (m, 1H), 4.13 (t, 2H, J=6.6 Hz, CH_2–O), 3.97 (br, 4H), 3.24 (br, 1H), 3.13–3.04 (br, 3H), 2.31–2.20 (m, 5H, CH_2CO), 1.70–1.57 (m, 6H, CH_2×3), 1.24 (br. s, 38H, CH_2×19), 0.85 (t, 3H, J=6.9 Hz, CH_3. ^{13}C NMR (CDCl$_3$) δ: 174.20, 173.65, 173.28, 166.54, 164.62, 130.63, 128.84,.70.43, 64.90, 64.59, 64.11, 62.70, 62.00, 60.58, 55.96, 45.86, 40.72, 34.58, 34.45, 34.28, 32.12, 29.90, 29.85, 29.70, 29.55, 29.51, 29.45, 29.35, 28.85, 28.80, 26.12, 25.20, 25.10, 25.07, 22.88, 14.32, 8.74. HRMS (FAB), calcd for C$_{46}$H$_{82}$N$_3$O$_{12}$PS: 932.1949, observed: 932.1908 [M+H]$^+$.

3.1.7. *mono*-AcrylPE-FITC (8). Triethylamine (0.1 mL, 0.71 mmol) was added to a solution of **2** (50 mg, 0.071 mmol) in DMF (5 mL). After the solution was stirred for 30 min, a solution of fluorescent isothiocyanate (55 mg, 0.142 mmol) was added. The reaction mixture was stirred for 12 h at room temperature in the dark and then concentrated in vacuum to give a residue, which was purified by column chromatography (SiO$_2$) using chloroform/methanol (4:1) as eluent to afford **8** (26 mg, 67%). ^{1}H NMR (CDCl$_3$) δ (ppm): 8.25 (br, 1H, Ph), 7.25 (br, 1H, Ph), 7.16–7.08 (m, 3H, Ph), 6.68 (m, 4H, Ph), 6.59 (dd, 1H,

$J=15.6$, 1.5 Hz, CH=CH_2), 6.09 (dd, 1H, $J=15.6$, 10.5 Hz, CH=CH$_2$), 5.82 (dd, 1H, $J=1.5$, 10.5 Hz, CH=CH_2), 5.17 (m, 1H, CH-2), 4.34 (dd, 1H, J=3.0, 12.3 Hz), 4.11 (t, 2H, $J=6.6$ Hz, CH_2–O), 4.13–4.02 (m, 3H), 3.94 (br, 2H, CH_2–O), 3.36 (br, 2H, CH_2–N), 2.27–2.23 (m, 4H, CH_2CO×2), 1.66–1.54 (m, 6H, CH_2×3), 1.24 (br. s, 38H, CH_2×19), 0.83 (t, 3H, $J=6.6$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 180.58, 174.22, 174.15, 167.08, 160.53, 156.75, 130.82, 129.55, 129.67, 128.56, 103.20, 103.10, 102.20, 101.55, 93.75, 53.28, 70.58, 65.03, 63.95, 63.81, 62.74, 49.14, 48.98, 48.85, 48.71, 48.56, 48.42, 48.27, 34.34, 34.17, 32.00, 29.76, 29.58, 29.41, 29.33, 29.21, 28.64, 26.00, 25.00, 24.95, 22.73, 13.95. HRMS (FAB), calcd for $C_{57}H_{79}N_2O_{15}PS$: 1096.2729, observed 1096.2712 $[M+1]^+$.

3.1.8. *mono*-AcrylPE-Texas-Red (9). To a solution of **2** (13 mg, 0.018 mmol) in DMF (5 mL) was added triethylamine (0.17 mL, 0.122 mmol). After the solution was stirred for 30 min., a solution of Texas-Red-NHS (10 mg, 0.0122 mmol) was added. The reaction mixture was stirred for 12 h at room temperature in the dark and then concentrated in vacuum. The resultant residue was purified by column chromatography (SiO_2) using chloroform/methanol (4:1) as eluent to afford **9** (17 mg, 65%). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.74 (d, 1H, $J=8.4$ Hz), 8.24 (d, 1H, $J=8.4$ Hz), 7.99 (d, 1H, $J=8.1$ Hz), 7.69 (m, 1H), 7.40 (m, 1H), 7.17 (d, 1H, $J=6.3$ Hz), 6.73 (d, 1H), 6.41 (dd, 1H, $J=15.6$, 1.5 Hz, CH=CH_2), 6.149 (dd, 1H, $J=15.6$, 10.5 Hz, CH=CH$_2$), 5.80 (dd, 1H, $J=1.5$, 10.5 Hz, CH=CH_2), 5.19 (m, 1H, OCH-2), 4.36 (dd, 1H, $J=8.7$, 2.2 Hz), 4.13 (t, 2H, $J=6.6$ Hz, CH_2–O), 4.06–3.90 (m, 4H), 3.46 (br, 9H), 3.00 (br, 3H), 2.79 (br, 1H), 2.60 (br, 9H), 2.35–2.23 (m, 6H, CH_2CO×3), 2.16–1.95 (m, 12H,), 1.66–1.54 (m, 6H, CH_2×3), 1.24 (br. s, 44H, CH_2×22), 0.83 (t, 3H, $J=6.6$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 173.71, 172.60, 172.40, 164.90, 150.44, 132. 70, 132.36, 132.29, 132.10, 130.64, 128.85, 128.80, 128.72, 127.25, 125.37, 120.17, 96.32, 70.75, 64.92, 34.43, 34.27, 32.12, 30.19, 29.90, 29.76, 29.57, 29.37, 28.82, 26.16, 25.67, 25.07, 22.90, 14.32. HRMS (FAB), calcd for $C_{73}H10_7N_4NaO_{17}PS_2$: 1430.7403, observed 1430.7357 $[M+Na]^+$.

3.1.9. *mono*-AcrylPE-EMC (10). Triethylamine (0.05 mL, 0.35 mmol) was added to a solution of **2** (25 mg, 0.035 mmol) in DMF (5 mL). After the solution was stirred for 30 min, a solution of *N*-(ε-maleimidocaproyloxy)succinimide (22 mg, 0.11 mmol) was added. The reaction mixture was stirred for 24 h at room temperature and then concentrated in vacuum to give a residue, which was purified by Sephadex LH-20 column using methanol as eluent to afford **10** (23 mg, 71%). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.19 (br, 1H, NH), 6.70 (s, 2H, CH=CH), 6.39 (dd, 1H, $J=17.4$, 1.2 Hz, CH=CH_2), 6.11 (dd, 1H, $J=17.4$, 10.5 Hz, CH=CH$_2$), 5.81 (dd, 1H, $J=1.2$, 10.5 Hz, CH=CH_2), 5.21 (m, 1H, CH-2), 4.37 (dd, 1H, J=3.0, 12.3 Hz), 4.29 (t, 1H, $J=6.9$ Hz), 4.14 (t, 2H, $J=6.9$ Hz, CH_2–O), 4.07–4.01 (m, 3H), 3.95 (br, 4H), 3.15 (br, 5H), 2.33–2.17 (m, 4H, CH_2CO×2), 1.68–1.57 (m, 6H, CH_2×3), 1.24 (br. s, 38H, CH_2×19), 0.87 (t, 3H, $J=6.6$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 174.01, 173.71, 171.20, 169.16, 166.54, 166.11, 134.32, 130.64, 128.84, 70.62, 64.90, 63.10, 45.89, 37.79, 36.18, 34.45, 34.26, 32.13, 29.95, 29.88, 29.82, 29.62, 29.58, 29.51, 29.44, 29.21, 28.83, 28.75, 26.46, 26.15, 25.15, 25.07, 22.89, 14.32. HRMS (FAB), calcd for $C_{46}H_{79}N_2O_{13}P$: 899.9908, observed 899.9915 $[M+1]^+$.

3.2. Generation of alginate beads coated with a polymerized lipid film

At room temperature, alginate beads[17] were incubated with PLL (0.10% w/v) for 30 s and then rinsed twice with PBS. Beads were then incubated in dilute alginate (0.15% w/v) for 30 s followed by two brief saline rinses. This process completed a cycle of forming a single PLL-alginate bilayer and was repeated four times followed by a final 30-second incubation in PLL. The beads were then incubated in a solution containing an alkylated, anionic terpolymer, poly(HEA_6:DOD_3:SSS_1) (0.10 mmol of SSS in 1% DMSO) for 30 s and subsequently rinsed three times with PBS. Poly(HEA_6:DOD_3:SSS_1) is a statistical copolymer of 2-hydroxyethyl acrylate (HEA), *N*,*N*-dioctadecylcarbamoylpropionic acid, and styrene sulfonate (SSS). The formation of a supported lipid film was achieved by incubating beads (0.5 mL) with lipid vesicles comprised of *mono*-AcrylPE-Texas Red (**9**)/*mono*-AcrylPC (**1**) (5:95 mol) for 4 h at 37 °C with gentle mixing. At the end of the incubation period, 10 μL of a photoinitiator mixture (10 mM EY, 225 mM TEA, and 37 mM VP in water) was added. The solution was irradiated with visible light (50 mW/cm^2) for 30 min at room temperature. Beads were then rinsed three times in PBS and were used without further modification for assessment of lipid-coating uniformity and biostability.

3.3. Assessment of biostability of alginate beads coated with a polymerized lipid film

Approximately 0.5 mL of alginate beads coated with a polymerized lipid of *mono*-AcrylPE-Texas Red (**9**)/*mono*-AcrylPC (**1**) prepared above in 4 mL of Hank's Buffer solution was implanted into the peritoneal cavity of Balb/c mouse. These Texas Red labeled microcapsules were recovered at 1, 2, 4 and 8 weeks after implantation and capsules were examined by confocal fluorescence and differential interference contrast (DIC) microscopy. For the In vitro stability, the capsules were stored in the Hank's Buffer solution for a similar time period for confocal microscopy study.

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References and notes

1. Fuhrhop J.-H., Koning, J. *Membranes and Molecular Assemblies: The Synkinetic Approach*; Royal Society of Chemistry, 1994.

2. Sackmann, E.; Tanaka, M. *Trans. Biotechnol.* **2000**, *18*, 58–64.
3. Lamparski, H.; Liman, U.; Frankel, D. A.; Ramaswami, V.; Brown, M. F.; O'Brien, D. F. *Biochemistry* **1992**, *31*, 685–694.
4. Plant, A. L. *Langmuir* **1993**, *9*, 2764–2767.
5. Plant, A. L.; Brigham-Burke, M.; Petrella, E. C.; O'Shannessy, D. J. *Anal. Biochem.* **1995**, *226*, 342–348.
6. O'Brien, D. F.; Armitage, A. B.; Bennett, D. E.; Lamparski, H. G.; Lee, Y.-S.; Srisiri, W.; Sisson, T. M. *Acc. Chem. Res.* **1998**, *31*, 861–868.
7. Kusumi, A.; Singh, M.; Tirrell, D. A.; Oehme, G.; Singh, A.; Samuel, N. K. P.; Hyde, J. S.; Regen, S. L. *J. Am. Chem. Soc.* **1983**, *105*, 2975–2980.
8. Rhodes, D. G.; Xu, Z.; Bittman, R. *Biochim. Biophys. Acta* **1992**, *1128*, 93–104.
9. O'Brien, D. F.; Klingbiel, R. T.; Whitesides, T. H. *J. Polym. Sci., Polym. Lett. Ed.* **1981**, *19*, 95–101.
10. Lamparski, H.; Lee, Y. S.; Sells, T. D.; O'Brien, D. F. *J. Am. Chem. Soc.* **1993**, *115*, 8096–8102.
11. Sells, T. D.; O'Brien, D. F. *Macromolecules* **1994**, *27*, 226–233.
12. Sisson, T. M.; Lamparski, H. G.; Koelchens, S.; Elayadi, A.; O'Brien, D. F. *Macromolecules* **1996**, *29*, 8321–8329.
13. Lamparski, H. G.; Oblinger, E.; O'Brien, D. F. *Macromolecules* **1999**, *32*, 5450–5452.
14. Marra, K. G.; Winger, T. M.; Hanson, S. R.; Chaikof, E. L. *Macromolecules* **1997**, *30*, 6483–6488.
15. Marra, K. G.; Kidani, D. D. A.; Chaikof, E. L. *Langmuir* **1997**, *13*, 5697–5701.
16. Orban, J. M.; Faucher, K. M.; Dluhy, R. A.; Chaikof, E. L. *Macromolecules* **2000**, *33*, 4205–4212.
17. Sun, X.-L.; Liu, H.; Orban, J. M.; Sun, L.; Chaikof, E. L. *Bioconjugate Chem.* **2001**, *12*, 673–677.
18. Liu, H.; Faucher, K. M.; Sun, X.-L.; Feng, J.; Johnson, T. L.; Orban, J. M.; Apkarian, R. D.; Dluhy, R. A.; Chaikof, E. L. *Langmuir* **2002**, *18*, 1332–1339.
19. Plant, A. L.; Brizyge, M. V.; Lacasio-Brown, L.; Durst, R. A. *Anal. Biochem.* **1989**, *176*, 420–426.
20. Kim, D. H.; Klibanov, A. L.; Needham, D. *Langmuir* **2000**, *16*, 2808–2817.
21. Hergenrother, P. J.; Depew, K. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 7849–7850.
22. Wilbur, D. S.; Chyan, M.-K.; Pathare, P. M.; Hamlin, D. K.; Frownfelter, M. B.; Kegley, B. B. *Bioconjugate Chem.* **2000**, *11*, 569–583.
23. Hanink, J. M.; Cornelissen, J. J. L. M.; Farrera, J. A.; Foubert, P.; De Schryver, F. C.; Sommerdijk, N. A. J. M.; Nolte, R. J. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4732–4735.
24. Roy, B. C.; Peerson, R.; Mallik, S.; Campilia, A. D. *J. Org. Chem.* **2000**, *65*, 3644–3651.
25. Einaga, Y.; Sato, O.; Iyoda, T.; Fujishima, A.; Hashimoto, K. *J. Am. Chem. Soc.* **1999**, *121*, 3745–3750.
26. Daugherty, D. L.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 4325–4333.
27. Viitala, T.; Vikholm, I.; Peltonen, J. *Langmuir* **2000**, *16*, 4953–4961.
28. Elliott, J. T.; Prestwich, G. D. *Bioconjugate Chem.* **2000**, *11*, 832–841.
29. Halter, M.; Nogata, T.; Dannenberger, O.; Sasaki, T.; Vogel, V. *Lagmuir* **2004**, *20*, 2416–2423.
30. Muller, A.; O'Brien, D. F. *Chem. Rev.* **2002**, 727–757 and references therein.
31. Martin, S. F.; Josey, J. A.; Wong, Y.-L.; Dean, D. W. *J. Org. Chem.* **1994**, *59*, 4805–4820.
32. Ponpipom, M. M.; Bugianesi, R. L. *Lipid Res.* **1980**, *21*, 336–339.
33. Srisiri, W.; Lee, Y.-S.; O'Brien, D. F. *Tetrahedron Lett.* **1995**, *36*, 8945–8948.

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Synthesis and characterization of anthracene-clustering dendrimers: observation of fluorescence resonance energy transfer in the multichromophoric system

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Abstract—A series of anthracene-clustering dendrimers bearing various aliphatic substituents at the terminal positions were synthesized using a direct coupling strategy. A remarkable effect of the side chains was imparted to chemical properties of the dendrimers such as drastically increased solubility. Although the multibranched anthracene arrays in the dendritic architectures exhibited no cooperativity in terms of the absorption feature and behaved as single chromophoric systems, investigations focusing on fluorescence properties revealed that a type of cooperativity was present as expressed in the reduced quantum yields of fluorescence. An alternative approach utilizing time-resolved fluorescence decay measurements clearly demonstrated that the most reasonable mechanism of the cooperative action should involve two discernible channels of intramolecular fluorescence resonance energy transfer (FRET) occurring from one chromophore to the others within and across junctions of the branching units.

1. Introduction

Nature has developed the most sophisticated solar energy storage systems in photosynthetic organisms, which contain large numbers of porphyrins held in particular three-dimensional arrays.[1,2] These complex assemblies capture photons at the light-harvesting antenna pigments and transport them into reaction centers for initiation of the photosynthetic reaction cascades. Based on this fact, a considerable effort has been devoted to mimic the natural light-harvesting system in order to create artificial photosynthetic models.[3–8] Since it has been shown that aromatic dendrimers exhibited the collective phenomena from light-harvesting peripheral units into molecular centers of their globular structures, there is much current interest in the study directed towards designing and synthesizing effective light-harvesting dendrimers capable of converting solar energy into useable photonic power.[9–12] Accordingly, ensuing search for effective light-collecting antennae may offer versatile solutions to produce more potential photonic system since the light-harvesting step is the first critical event in the natural photosynthetic processes.[13] In this regard, anthracene is envisaged as a potentially functionalized candidate for use in the light-harvesting dendrimers due to its high absorption coefficient as well as its high fluorescence quantum yield. Recently, we have reported that a primitive type of anthracene-clustering dendrimer **1** (R = H in Fig. 1), which represents an aggregated form of anthracene chromophores immobilized in a dendritic framework, exhibited an energy transport property within the supramolecular framework.[14] Although this property has been shown to be of direct relevance to practical fabrication of fluorescence resonance dendritic antennae, the resulting dendrimer exhibited poor solubility in common organic solvents and certain structural modification should therefore be given to establish more practical molecular systems. As part of our continuing efforts in synthesis and investigation of the designed molecules, we report here a convenient and general protocol for the preparation of anthracene-clustering dendrimers bearing various aliphatic side chains at their peripheral positions. During the course of studying effects of the substituents on physical and chemical properties of the dendrimers, we found that the presence of aliphatic auxiliaries markedly affected the solubility in a wide range of organic solvents without

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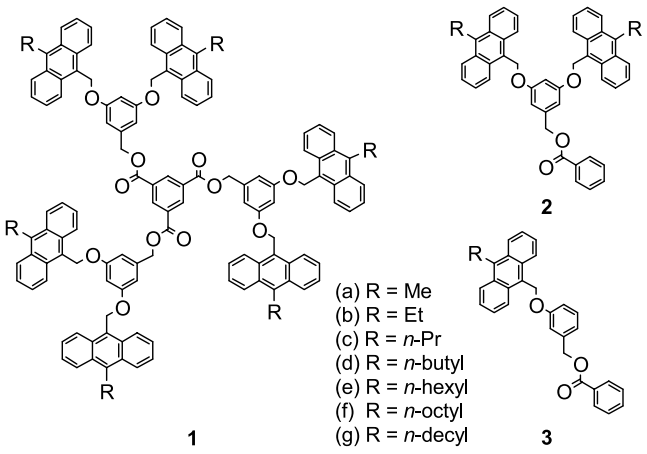
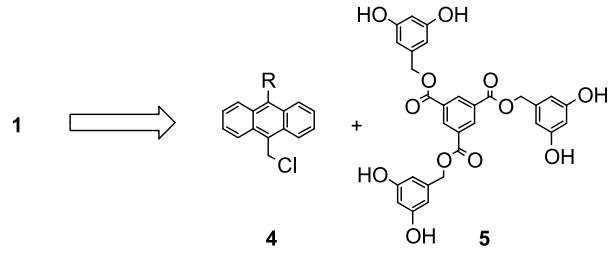


Figure 1. Structures of dendrimer **1** and its structurally simplified analogues **2** and **3**.

altering their own photophysical properties. One of the most remarkable findings in this context is that the aggregated chromophoric groups exhibited pronounced cooperative actions of energy transfer from one dendritic branch to the others as expressed in reduced quantum yields as well as faster transient decay profiles of their fluorescence signals relative to monomeric anthracene analogues.

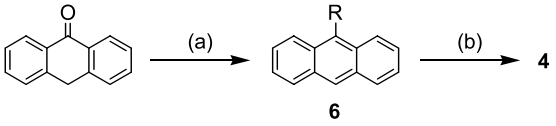
2. Results and discussion

Our previous report has shown that a successive convergent strategy can be used to construct a multichromophoric array of anthracenes in the dendritic framework. In this manner, synthetic route was established in several steps involving ether bond formation and subsequent esterification to connect all structural components of the dendritic architecture.[14] Despite the noteworthy synthetic achievement with high yields (75–98%) in all steps, the proposed synthetic strategy employed a multistep sequence of bond-forming events resulting in low yield recovery of the final product. To gain convenient access to the functionalized dendrimers, we decided to pursue an alternative approach of in situ coupling between anthracene units **4** and a dendritic backbone **5** as a useful and practical protocol (Scheme 1).

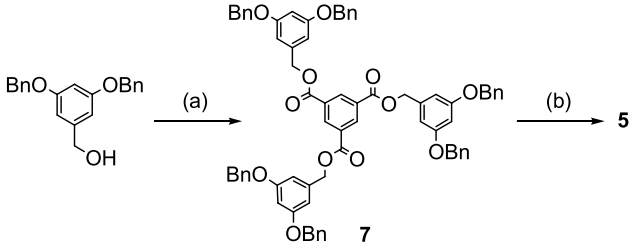


Scheme 1. Retrosynthetic analysis of **1**.

All 10-alkyl-substituted 9-anthryl chlorides **4** were prepared from anthrone according to an established literature procedure used for preparation of 9-chloromethyl-10-methylanthracene **4a**, which involved nucleophilic addition of the corresponding Grignard reagents to the carbonyl group of anthrone, aromatization after acidic dehydration of the resulting benzhydrol intermediate giving rise to a series of 9-alkylanthracenes **6**, and subsequent chloromethylation to form the corresponding **4** (Scheme 2).[15,16] Alternatively, one could synthesize the dendritic backbone **5** via catalytic hydrogenolysis of the Fréchet type dendrimer **7** in methanolic solvent, which could be prepared by esterification of commercially available 3,5-bis(benzyloxy)benzyl alcohol with trimesoyl chloride under the basic condition (Scheme 3).[17] All these structural components of the dendritic architectures were purified by recrystallization of the crude materials prior to their reactions.

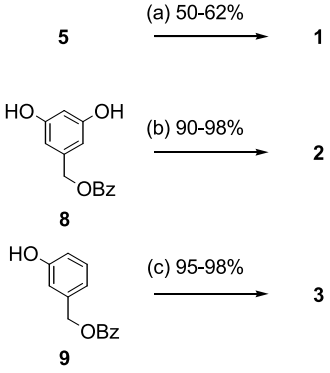


Scheme 2. Synthesis of **4**. Conditions: (a) RMgX (X=Br or I)/ether, benzene (1:1), reflux; (b) $(CH_2O)_n$/HClaq, AcOH, rt.



Scheme 3. Synthesis of **5**. Conditions: (a) Trimesoyl chloride, Et_3N/benzene, rt; (b) cat. Pd–C, $H_2/CHCl_3$, CH_3OH (1:1).

With two components in hand, a series of dendrimers **1a–g** were synthesized by a straightforward way carrying out the reaction of **5** with an excess of the corresponding anthryl chlorides **4**. As a result, nucleophilic attacks of phenolate ions onto **4** preferentially occurred at the multiple reaction sites of **5**, giving rise to the variously substituted dendrimers **1a–g** in predominant yields (50–62%) for all cases (Scheme 4). These dendrimers were purified by recrystallization from chloroform–methanol solutions and were fully characterized by elemental analyses and a range of



Scheme 4. Syntheses of **1**, **2**, and **3**. Conditions: (a) **4** (8.0 equiv), K_2CO_3 (8.0 equiv), 18-Crown-6 (3.0 equiv)/DMF, 55 °C; (b) **4** (2.5 equiv), K_2CO_3 (2.5 equiv), 18-Crown-6 (1.0 equiv)/DMF, 55 °C; (c) **4** (1.5 equiv), K_2CO_3 (1.5 equiv), 18-Crown-6 (0.15 equiv)/DMF, 55 °C.

Table 1. Size exclusion chromatography (SEC) results and side chain effects on solubilities of dendrimers **1**

Entry	Formula	M_w/M_n[a]	Nominal M_w	M_w[a]	[**1**] (mmol/mL)[b]
1a	$C_{126}H_{96}O_{12}$	1.006	1801	1385	0.6
1b	$C_{132}H_{108}O_{12}$	1.003	1885	1497	3.7
1c	$C_{138}H_{120}O_{12}$	1.003	1969	1666	5.9
1d	$C_{144}H_{132}O_{12}$	1.002	2053	1799	6.6
1e	$C_{156}H_{156}O_{12}$	1.004	2221	2074	10.0
1f	$C_{168}H_{180}O_{12}$	1.003	2389	2307	37.7
1g	$C_{180}H_{204}O_{12}$	1.003	2558	2567	44.5

[a] Calibrated with narrow-dispersity polystyrene standards.
[b] Maximum concentrations dissolved in chloroform at 20 °C.

spectroscopies. In terms of structural details, structural homogeneity of the products was well confirmed by observation of simplicity in the ^1H and ^{13}C NMR spectra due to their highly symmetric nature, wherein all the building components should be equivalent as previously demonstrated.[14] Consequently, this direct synthetic protocol provides an important strategic advantage over the previous methodology in accessing higher generation dendritic systems since this method has simplicity of synthesis allowing us to form highly ordered symmetric arrays of the molecular units rapidly. On the other hand, this synthetic strategy can be applied in the construction of structurally simpler analogous systems **2** and **3** that possess a small number of anthracenes, employing the corresponding phenolic backbones **8** and **9**, respectively, instead of **5**. These reactions worked well with less molar equivalents of **4** and gave rise to the mono- and bichromophoric products in excellent yields (90–98%) as confirmed by complete characterization data (Scheme 4).

Size effects of the external functional groups on the dendritic shell can be inferred from comparison of retention volumes on the size exclusion chromatography (SEC). This demonstrated each dendrimer gave a sharp and symmetrical peak in chloroform with a polydispersity index (PDI) $M_w/M_n < 1.01$ that should be in the range typically found for unified dendrimers (Table 1).[17] Figure 2 shows correlation diagrams for a series of polystyrene standards, indicating that retention volumes of the polystyrenes exhibited a linear dependence on logarithmic number of their averaged molecular weights following reverse order paralleling the molecular sizes. Such a trend was observed for the dendritic system (**1a**–**g**), giving the monomodal distribution, albeit

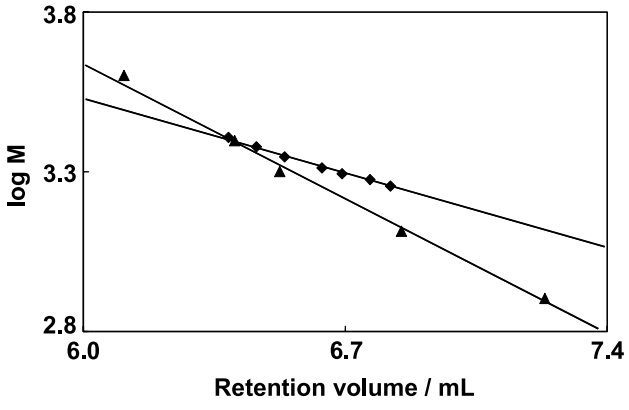


Figure 2. Semilogarithmic plot of average molecular weight versus SEC retention volumes for polystyrene standards (▲) and dendrimers (♦).

with a less steep downward slope as seen in Figure 2. It has been well recognized in this context that dendritic structures should be denser and more compact than linear polymers, giving underestimated values when determining the molecular weights by calibration with the linear polymers.[18] Thus, this rule also seems to be applicable to our macromolecular system functionalized with a range of alkyl groups at the surfaces of the commonly used dendritic motif. Table 1 summarizes the molecular weights of the dendrimers (M_w) determined by SEC calibrated with the polystyrene standards. As can be surveyed in Table 1, the estimated data for the longer chained homologues **1f**–**g** are close to the nominal molecular weights, whereas those for the smaller-sized dendrimers should be extremely deviated from the theoretical values with up to 23% weight loss. These observations indicate that the longer chained molecules were behaving as flexible spheres like linear polymers, which could change substantially in size or shape through the efficient interaction with solvent molecules. This correlation may exist only if relative contribution of the longer alkyl moieties to the macromolecular properties should be much larger than that of the rigid dendritic shell.

In this regard, degree of solvation is suggested to be more important in interpreting concomitant influence of the external alkyl groups on the lipophilic nature of dendrimers. It can be obviously seen that increasing chain length of the alkyl groups markedly enhanced the relative solubility of dendrimers in common organic solvents such as chloroform, THF, and toluene. Table 1 also includes maximum solubilities of the dendrimers, which were determined by dissolving the samples in chloroform and measuring their UV absorption maxima around 380 nm. From these data, significant difference was observed in the solubility among the dendrimer derivatives, where the critical concentrations ranged from 0.6 to 44.5 mmol/L. As a consequence, the structural modification significantly improved these values showing the maximum difference to be as large as nearly 74-fold. These results can be explained on the basis of a change in hydrodynamic radius of the dendrimers in the organic solvents.[18] In general, flexible dendrimers have mobile structures displaying large changes in hydrodynamic radii in various solvent systems, whereas rigid dendrimers are intuitively much more shape persistent and thus show little change in hydrodynamic radii as a function of solvent.[19] The experimental results of our preliminary studies are in good agreement with this theoretical proposal, which clearly demonstrates the local structural alteration at the external surfaces of dendrimers gives the larger

hydrodynamic radii and thus renders the resulting molecules soluble in a wide range of solvents.

As part of our continuing interest in the fundamental aspects of the multichromophoric dendrimer system, we focused attention on some of their photophysical properties in order to gain insight into the electronic details of polyaromatic aggregates. Figure 3 shows representative absorption and fluorescence spectra for constituent members of ethyl side chain analogues **1b–3b** composed of one to six anthracene groups, where all signals were normalized with respect to the corresponding absorption maxima and optical densities of the chromophoric units, respectively. As shown in Figure 3, three discrete spectra of **1b–3b** exhibited a closely overlapping feature around three typical absorption maxima at 359, 378, and 399 nm attributed to π,π^* transitions of the anthracene excitation, while the corresponding molar absorption coefficients were found to be approximately proportional to the number of the anthracene units. These results suggest that the anthracene groups of **1b** and **2b** behave like monomeric species and thus the contribution of each chromophoric unit to the absorption character is virtually the same in the ground-state, providing little or no intramolecular electronic interaction. However, pronounced differences were noticed in the fluorescence emission spectra of these systems. Figure 3 also illustrates the steady-state fluorescence spectra of **1b–3b** exhibiting the emission maxima at 407, 430, and 455 nm attributed to emission from the anthracene groups. It should be noted that three individual molecules showed markedly different intensity levels, whose quantum efficiencies (Φ_F) decreased with an increase in the number of chromophores. This can be rationalized by assuming that the relative contribution of each fluorescent unit in the multichromophoric systems such as **1** and **2** to the emission behavior clearly changed as expressed in the reduced quantum yields of fluorescence. Table 2 summarizes estimated values of fluorescence quantum yields for all dendrimers and their related analogues. In agreement with the above result, the other members also showed similar trends of their fluorescence quantum efficiencies following the order **3**>**2**>**1** throughout the whole given series of molecules. Additionally, the bi- and multichromophoric systems **1–2** did not produce photoproducts in any significant quantities during all measurements, and neither showed any sign of aggregate and excimer formation when all these solutions were dilute enough that intermolecular interactions should be negligible. While these processes causing a serious decrease in fluorescence quantum yields can be discounted, intramolecular energy transfer mechanism from one branch to the others provides a plausible rationale for the systematic decrease of quantum yields. Besides, it was found that a specific geometrical bias of the methyl group at the C10-position on the anthracene rings was also attributed to significant decrease in the quantum yields, where the methyl-substituted series **1a–3a** exhibited the markedly lowered quantum efficiencies of fluorescence in comparison to the other series. The interpretation of this effect was that rotational motion of the methyl group should lead to effective free rotor radiationless deactivation over the others as a result of less steric constraints.

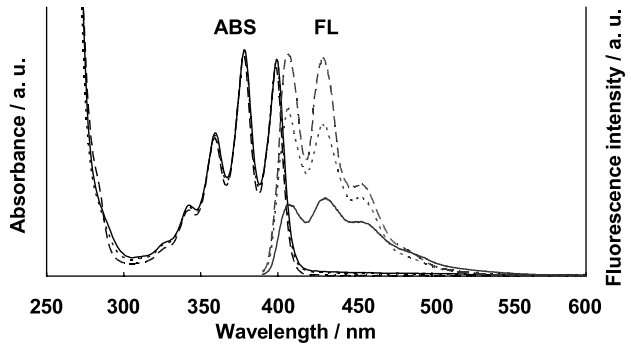


Figure 3. Absorption (ABS) and steady-state fluorescence spectra (FL) of a series of **1b** (solid line), **2b** (dotted line), and **3b** (dashed line) in chloroform solutions. The absorption spectra are normalized at the anthracene maxima (378 nm). The fluorescence spectra were obtained by excitation at 387 nm and are normalized to the same optical density at the excitation wavelength. All measurements were conducted in sufficiently low concentrations (10^{-8}–10^{-6} mol/mL) of the analytes to exclude the possibilities of intermolecular interactions.

Table 2. Fluorescence quantum yields (Φ_F) of **1–3**[a]

Entry	1	2	3
a	0.09	0.26	0.36
b	0.17	0.32	0.41
c	0.20	0.33	0.42
d	0.20	0.34	0.43
e	0.20	0.36	0.44
f	0.20	0.38	0.44
g	0.19	0.38	0.44

[a] Determined by referring to the value of anthracene as a standard.[20]

In our efforts to address a question as to how the multichromophoric molecular frameworks affect the fluorescence efficiencies, we explored an alternative approach utilizing time-resolved fluorescence decay measurements, which allow us to gain some further insights into photodynamic characters during the fluorescence emission processes. The measurements were performed on the ethyl-substituted anthracene series **1b–3b**, where the samples were dissolved in THF solutions and the fluorescence decay traces were recorded at excitation wavelengths of 355 nm as depicted in Figure 4. The decay traces for the monochromophoric system **3b** followed a simple

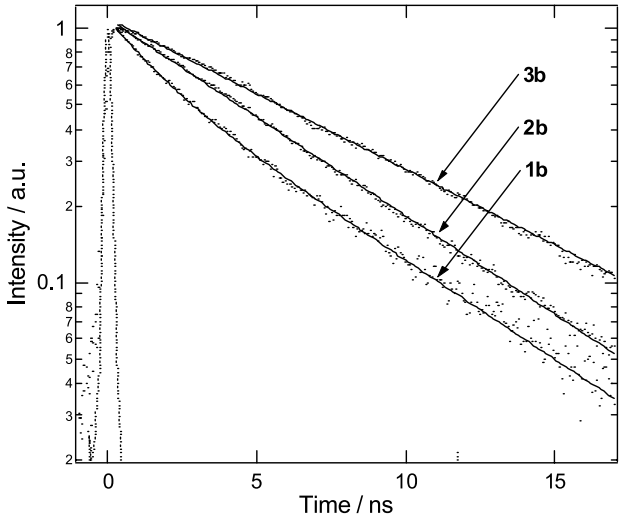


Figure 4. Fluorescence decay profiles of **1b–3b** in THF solutions at the excitation wavelength of 355 nm.

monoexponential decrease with a lifetime of 7.3 ns, which is close to the values reported for 9,10-disubstituted anthracenes.[21] Under identical conditions, the bichromophoric system **2b** behaved similarly attending a monoexponential mode of action but with a significantly short lifetime decay of 5.6 ns. The observation of reduced lifetime for **2b** suggests strongly that a type of cooperativity, which may be interpreted in terms of intramolecular energy migration from one chromophore to another, is present in this molecular system. As a matter of fact, the feasibility of intramolecular energy transfer step depends to a large extent upon accessible orientation of neighboring nonbonded chromophores in the multichromophoric systems. The structural description of **2b** guarantees that two anthracenes are immobilized in close proximity to interact as confirmed previously by X-ray structural analysis and molecular modeling study.[14] Therefore, it appears that the origin of energy delocalization responsible for the fast fluorescence decay can be a result of structurally unique disposal of the chromophoric groups. In contrast to the relative behavior of these two examples, the dendritic system **1b** showed a remarkable difference in the decay profile, which follows a double exponential curve with a much faster decay rate. The decay curve was well fitted with a double exponential function, which provides two product distributions classified into a longer-lived component (5.6 ns, 66%) and a short-lived component (1.6 ns, 34%). The decay time of the longer-lived component is in good agreement with that of **2b** and is therefore assigned to originate from the bichromophoric character of interactions between closely disposed chromophores within the branching units. From this, it can be deduced that the presence of the faster decay component should be explained on the basis of another radiationless deactivation channel emerging from chromophore-clustering domains in the three-dimensional molecular framework. As a consequence of these considerations, we can draw a speculative conclusion that the short-lived component is attributed to a fluorescence emission involving interactions from one bichromophoric unit to the other chromophores. On the other hand, strength of the Förster-type energy transfer interactions may depend largely on the amount of spectral overlap between absorption spectra of chromophoric acceptors and emission profiles of chromophoric donors.[22–25] In this context, all three series of compounds **1**–**3** showed a considerable degree of spectral overlap between the absorption and fluorescence spectra attributed to the anthracene groups, where the absorption tails extend over the region of the emission bands beyond 400 nm (Fig. 3). This spectroscopic feature may offer an opportunity for the fluorescence resonance energy transfer (FRET), which ultimately provides the energy transport character of the multichromophoric systems. We therefore conclude that the multichromophoric dendrimer systems offer a number of opportunities for the intramolecular FRET pathways available to the efficient energy transport of captured photons within the nanoscopic dimension of molecular architectures.

3. Conclusion

In conclusion, we have developed a new synthetic approach to the anthracene-clustering dendrimers employing a general and simple methodology. This synthetic procedure is beneficial and gives many practical and potential applications for the construction of a variety of higher generation dendrimer systems composed of anthracene residues as a functional repeat unit. Investigations of the physical and chemical properties of the dendrimer derivatives revealed that functionalization of the surface groups of the dendritic architectures should play critical roles in the solubility in common organic solvents. Furthermore, we have demonstrated that these dendrimers exhibited intriguing photophysical properties in terms of the intramolecular FRET between the peripheral chromophoric units. This photophysical outcome was noticed in the reduced quantum yields of fluorescence, the emission spectra, and the more complex time-dependent behavior due to the chromophore-clustering nature of the dendritic system. A detailed investigation of this property based on the time-resolved transient emission measurements revealed unambiguously that the dendrimer system offered two discrete channels for the FRET processes occurring from one chromophore to the others within and across the junctions of branching units. The results of our preliminary studies of the dendrimers indicate that this supramolecular system may act as a potential mediator for energy transport of absorbed photons and thus offer many advantages for applications in design and synthesis of artificial light-harvesting nanostructured materials.

4. Experimental

4.1. General

All solvents and reagents were of reagent grade quality from Wako Pure Chemicals used without further purification. A series of polystyrene standards (molecular weights = 800, 1300, 2000, 2500, and 4000) were purchased from Pressure Chemical Co. and used without further purification. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra operating at the frequencies of 300 and 75 MHz, respectively, were recorded on a JEOL JNM-AL300 spectrometer in chloroform-*d* ($CDCl_3$) or acetone-d_6 ($(CD_3)_2CO$). Chemical shifts are reported in parts per million (ppm) relative to TMS and the solvent used as internal standards, and the coupling constants are reported in Hertz (Hz). Fourier transform infrared (FT-IR) spectra were recorded on a JASCO FT/IR-410 spectrometer as KBr disks. Absorption spectra were recorded on a JASCO model V-570 UV-VIS-NIR spectrophotometer. Fluorescence spectra were measured on a Hitachi F-4500 spectrofluorometer. Melting points were determined on a Yanaco MP-S3 melting point apparatus. Fast atom bombardment (FAB) mass spectra were determined by a JASCO JMS-HX110A using a 3-nitrobenzyl alcohol matrix. Elemental analyses were obtained from Perkin-Elmer-240 instrument. Size exclusion chromatography (SEC) was performed on a system consisting of a JASCO model 880-PU pump at a flow rate of 0.5 mL/min and JASCO 875-UV absorbance detector (254 nm) equipped with a Shodex K-802 column, where chloroform was used as mobile phase. Time-resolved fluorescence decay measurements were performed on a system consisting of a Hamamatsu C5094 imaging spectrograph and a B. M. Industries 5022 D. PS. DP.10

passively/actively mode-locked Nd:YAG laser employing the third harmonic at 355 nm. The decays were fitted with the least-squares (LS) method to evaluate the fluorescence lifetimes. The quality of the fits has been judged from the estimated values and residuals. Samples of 9-chloromethyl-10-methylanthracene **4a**,[16] 9-chloromethyl-10-ethylanthracene **4b**,[26] 9-chloromethyl-10-butylanthracene **4d**,[27] and a series of 9-alkylanthracenes **6a–g**[15,28–31] were prepared by the sequence of procedures reported in the literature. Their physical properties and spectroscopic data were in full agreement with those reported earlier. The fluorescence quantum yields of **1–3** were measured in comparison to anthracene in ethanol solution ($\Phi_F=0.27$) as a standard.[20]

4.2. General procedure for the synthesis of 1

All dendrimers **1** were prepared as described in the following typical procedure. For example, synthesis of **1a** was exemplified as follows.

4.2.1. Tris[3,5-bis((10-methyl-9-anthracenediyl)-methoxy)benzyl] benzene-1,3,5-tricarboxylate 1a. A solution containing **4a** (0.33 g, 1.39 mmol), **5** (0.10 g, 0.17 mmol), potassium carbonate (0.19 g, 1.39 mmol), and 18-crown-6 (0.14 g, 0.52 mmol) in DMF (5 mL) was heated at 55 °C with stirring under argon atmosphere. After 4 h, the reaction mixture was then precipitated in ice-cold diluted HCl solution (50 mL). The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum to afford a pale yellow solid. After complete vacuum drying, the solid sample was purified by recrystallization from chloroform–methanol, affording **1a** (0.16 g, 50%) as a pale yellow powdery material; mp 192–193 °C; UV ($CHCl_3$) 359 nm (ε 40,200), 378 nm (ε 64,500), 399 nm (ε 60,900); IR (KBr) 1593 cm^{-1} (C=C), 1732 cm^{-1} (C=O); MS (FAB+) *m/z* 1801 (s*M*+), 1802 (*MH*+); ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 18H, C*H*$_3$), 5.42 (s, 6H, C*H*$_2$), 5.83 (s, 12H, C*H*$_2$), 6.8–6.9 (m, 9H, Ar*H*), 7.4–7.5 (m, 24H, Ar*H*), 8.2–8.3 (m, 24H, Ar*H*), 9.02 (s, 3H, Bz*H*); ^{13}C NMR ($CDCl_3$) δ 14.4 (*C*H$_3$), 63.0 (*C*H$_2$), 67.4 (*C*H$_2$), 102.2 (*C*H), 107.6 (*C*H), 124.5 (*C*H), 124.9 (*C*H), 125.3 (*C*H), 126.0 (*C*H), 129.9 (*C*), 130.7 (*C*), 132.7 (*C*), 135.1 (*C*H), 138.0 (*C*), 160.7 (*C*), 164.8 (*C*). Anal. Calcd for $C_{126}H_{96}O_{12}$: C, 83.98; H, 5.37; N, 0.00. Found: C, 83.89; H, 5.60; N, 0.00.

4.2.2. Tris[3,5-bis((10-ethyl-9-anthracenediyl)methoxy)-benzyl] benzene-1,3,5-tricarboxylate 1b. This compound was obtained (0.19 g, 60%) as a pale yellow powdery material from chloroform–methanol solution; mp 191–192 °C; UV ($CHCl_3$) 359 nm (ε 42,100), 378 nm (ε 66,600), 399 nm (ε 63,800); IR (KBr) 1593 cm^{-1} (C=C), 1729 cm^{-1} (C=O); MS (FAB+) *m/z* 1885 (*M*+), 1886 (*MH*+); ^{1}H NMR ($CDCl_3$) δ 1.41 (t, *J*=7.3 Hz, 18H, CH_2CH_3), 3.59 (q, *J*=7.3 Hz, 12H, CH_2CH_3), 5.41 (s, 6H, C*H*$_2$), 5.84 (s, 12H, C*H*$_2$), 6.8–6.9 (m, 9H, Ar*H*), 7.4–7.5 (m, 24H, Ar*H*), 8.2–8.3 (m, 24H, Ar*H*), 9.00 (s, 3H, Bz*H*); ^{13}C NMR ($CDCl_3$) δ 15.5 (*C*H$_3$), 21.4 (*C*H$_2$), 63.0 (*C*H$_2$), 67.3 (*C*H$_2$), 102.0 (*C*H), 107.5 (*C*H), 124.7 (*C*H), 124.9 (*C*H), 125.1 (*C*H), 126.0 (*C*H), 128.9 (*C*), 130.9 (*C*), 131.3 (*C*), 135.1 (*C*H), 138.1 (*C*), 139.1 (*C*), 160.7 (*C*), 164.8 (*C*). Anal. Calcd for $C_{132}H_{108}O_{12}$: C, 84.05; H, 5.77; N, 0.00. Found: C, 84.11; H, 5.52; N, 0.05.

4.2.3. Tris[3,5-bis((10-propyl-9-anthracenediyl)methoxy)-benzyl] benzene-1,3,5-tricarboxylate 1c. This compound was obtained (0.20 g, 59%) as a pale yellow powdery material from chloroform–methanol solution; mp 189–190 °C; UV ($CHCl_3$) 360 nm (ε 40,900), 379 nm (ε 66,000), 400 nm (ε 63,300); IR (KBr) 1594 cm^{-1} (C=C), 1728 cm^{-1} (C=O); MS (FAB+) *m/z* 1969 (*M*+), 1970 (*MH*+); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, *J*=7.3 Hz, 18H, $CH_2CH_2CH_3$), 1.82 (sext, *J*=7.9 Hz, 12H, $CH_2CH_2CH_3$), 3.55 (t, *J*=8.0 Hz, 12H, $CH_2CH_2CH_3$), 5.41 (s, 6H, C*H*$_2$), 5.86 (s, 12H, C*H*$_2$), 6.8–6.9 (m, 9H, Ar*H*), 7.4–7.5 (m, 24H, Ar*H*), 8.2–8.3 (m, 24H, Ar*H*), 9.01 (s, 3H, Bz*H*); ^{13}C NMR ($CDCl_3$) δ 14.7 (*C*H$_3$), 24.6 (*C*H$_2$), 30.4 (*C*H$_2$), 63.0 (*C*H$_2$), 67.3 (*C*H$_2$), 102.0 (*C*H), 107.5 (*C*H), 124.6 (*C*H), 124.98 (*C*H), 125.04 (C), 125.1 (*C*), 125.2 (*C*H), 126.0 (*C*H), 129.4 (*C*), 130.9 (*C*), 133.3 (*C*), 135.1 (*C*H), 137.8 (*C*), 138.1 (*C*), 160.7 (*C*), 164.8 (*C*). Anal. Calcd for $C_{138}H_{120}O_{12}$: C, 84.12; H, 6.14; N, 0.00. Found: C, 84.01; H, 6.13; N, 0.02.

4.2.4. Tris[3,5-bis((10-butyl-9-anthracenediyl)methoxy)-benzyl] benzene-1,3,5-tricarboxylate 1d. This compound was obtained (0.20 g, 56%) as a pale yellow powdery material from chloroform–methanol solution; mp 187–188 °C; UV ($CHCl_3$) 360 nm (ε 39,600), 379 nm (ε 64,300), 400 nm (ε 61,700); IR (KBr) 1594 cm^{-1} (C=C), 1728 cm^{-1} (C=O); MS (FAB+) *m/z* 2053 (*M*+), 2054 (*MH*+); ^{1}H NMR ($CDCl_3$) δ 1.00 (t, *J*=7.3 Hz, 18H, $(CH_2)_3CH_3$), 1.57 (sext, *J*=7.3 Hz, 12H, $(CH_2)_2CH_2CH_3$), 1.7–1.8 (m, 12H, $CH_2CH_2CH_2CH_3$), 3.55 (t, *J*=7.9 Hz, 12H, $CH_2(CH_2)_2CH_3$), 5.40 (s, 6H, C*H*$_2$), 5.83 (s, 12H, C*H*$_2$), 6.8–6.9 (s, 9H, Ar*H*), 7.4–7.5 (m, 24H, Ar*H*), 8.2–8.3 (m, 24H, Ar*H*), 9.00 (s, 3H, Bz*H*); ^{13}C NMR ($CDCl_3$) δ 14.0 (*C*H$_3$), 23.4 (*C*H$_2$), 28.1 (*C*H$_2$), 33.5 (*C*H$_2$), 63.0 (*C*H$_2$), 67.3 (*C*H$_2$), 102.0 (*C*H), 107.5 (*C*H), 124.6 (*C*H), 125.0 (*C*H), 125.1 (*C*H), 126.0 (*C*H), 129.3 (*C*), 130.9 (*C*), 131.3 (*C*), 135.1 (*C*H), 138.0 (*C*), 138.1 (*C*), 160.7 (*C*), 164.8 (*C*). Anal. Calcd for $C_{144}H_{132}O_{12}$: C, 84.18; H, 6.48; N, 0.00. Found: C, 84.27; H, 6.33; N, 0.09.

4.2.5. Tris[3,5-bis((10-hexyl-9-anthracenediyl)methoxy)-benzyl] benzene-1,3,5-tricarboxylate 1e. This compound was obtained (0.20 g, 54%) as a pale yellow powdery material from chloroform–methanol solution; mp 184–185 °C; UV ($CHCl_3$) 360 nm (ε 40,600), 379 nm (ε 65,900), 400 nm (ε 63,300); IR (KBr) 1594 cm^{-1} (C=C), 1730 cm^{-1} (C=O); MS (FAB+) *m/z* 2221 (*M*+), 2222 (*MH*+); ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J*=7.3 Hz, 18H, $(CH_2)_5CH_3$), 1.3–1.4 (m, 24H, $(CH_2)_3(CH_2)_2CH_3$), 1.5–1.6 (m, 12H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.7–1.8 (m, 12H, $CH_2CH_2(CH_2)_3CH_3$), 3.55 (t, *J*=7.9 Hz, 12H, $CH_2(CH_2)_4CH_3$), 5.42 (s, 6H, C*H*$_2$), 5.85 (s, 12H, C*H*$_2$), 6.8–6.9 (s, 9H, Ar*H*), 7.4–7.5 (m, 24H, Ar*H*), 8.2–8.3 (m, 24H, Ar*H*), 9.02 (s, 3H, Bz*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (*C*H$_3$), 22.7 (*C*H$_2$), 28.5 (*C*H$_2$), 30.1 (*C*H$_2$), 31.4 (*C*H$_2$), 31.8 (*C*H$_2$), 63.1 (*C*H$_2$), 67.4 (*C*H$_2$), 102.1 (*C*H), 107.5 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.1 (*C*H), 126.0 (*C*H), 129.3 (*C*), 130.9 (*C*), 131.4 (*C*), 135.4 (*C*H), 135.1 (C), 138.1 (*C*), 160.7 (*C*), 164.8 (*C*). Anal. Calcd for $C_{156}H_{156}O_{12}$: C, 84.29; H, 7.07; N, 0.00. Found: C, 84.29; H, 7.00; N, 0.06.

4.2.6. Tris[3,5-bis((10-octyl-9-anthracenediyl)methoxy)-benzyl] benzene-1,3,5-tricarboxylate 1f. This compound was obtained (0.25 g, 61%) as a pale yellow powdery

material from chloroform–methanol solution; mp 181–182 °C; UV ($CHCl_3$) 360 nm (ε 40,800), 379 nm (ε 66,200), 400 nm (ε 63,600); IR (KBr) 1595 cm^{-1} (C=C), 1731 cm^{-1} (C=O); MS (FAB+) *m/z* 2390 (*M*+), 2391 (*MH*+); ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=6.8$ Hz, 18H, $(CH_2)_7CH_3$), 1.2–1.4 (m, 48H, $(CH_2)_3(CH_2)_4CH_3$), 1.5–1.6 (m, 12H, $(CH_2)_2CH_2(CH_2)_4CH_3$), 1.7–1.8 (m, 12H, $CH_2CH_2(CH_2)_5CH_3$), 3.54 (t, $J=8.0$ Hz, 12H, $CH_2(CH_2)_6CH_3$), 5.41 (s, 6H, CH_2), 5.84 (s, 12H, CH_2), 6.8–6.9 (m, 9H, Ar*H*), 7.4–7.5 (m, 24H, Ar*H*), 8.2–8.3 (m, 24H, Ar*H*), 9.01 (s, 3H, Bz*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.4 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 30.4 (CH_2), 31.4 (CH_2), 31.9 (CH_2), 63.0 (CH_2), 67.3 (CH_2), 102.1 (*C*H), 107.5 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.1 (*C*H), 126.0 (*C*H), 129.3 (*C*), 130.9 (*C*), 131.3 (*C*), 135.1 (*C*H), 138.0 (*C*), 138.1 (*C*), 160.7 (*C*), 164.8 (*C*). Anal. Calcd for $C_{168}H_{180}O_{12}$: C, 84.38; H, 7.59; N, 0.00. Found: C, 84.09; H, 7.56; N, 0.03.

4.2.7. Tris[3,5-bis((10-decyl-9-anthracenediyl)methoxy)-benzyl] benzene-1,3,5-tricarboxylate 1g. This compound was obtained (0.27 g, 62%) as a pale yellow powdery material from chloroform–methanol solution; mp 174–175 °C; UV ($CHCl_3$) 360 nm (ε 41,300), 379 nm (ε 66,400), 400 nm (ε 64,000); IR (KBr) 1594 cm^{-1} (C=C), 1730 cm^{-1} (C=O); MS (FAB+) *m/z* 2558 (*M*+), 2559 (*MH*+); ^1H NMR ($CDCl_3$) δ 0.87 (t, $J=6.8$ Hz, 18H, $(CH_2)_9CH_3$), 1.2–1.4 (m, 72H, $(CH_2)_3(CH_2)_6CH_3$), 1.5–1.6 (m, 12H, $(CH_2)_2CH_2(CH_2)_6CH_3$), 1.7–1.8 (m, 12H, $CH_2CH_2(CH_2)_7CH_3$), 3.54 (t, $J=7.9$ Hz, 12H, $CH_2(CH_2)_8CH_3$), 5.41 (s, 6H, CH_2), 5.85 (s, 12H, CH_2), 6.8–6.9 (m, 9H, Ar*H*), 7.4–7.5 (m, 24H, Ar*H*), 8.2–8.3 (m, 24H, Ar*H*), 9.01 (s, 3H, Bz*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.4 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.65 (CH_2), 29.70 (CH_2), 30.4 (CH_2), 31.4 (CH_2), 31.9 (CH_2), 63.0 (CH_2), 67.4 (CH_2), 102.0 (*C*H), 107.5 (*C*H), 124.6 (*C*H), 124.9 (*C*), 125.0 (*C*H), 125.1 (*C*H), 126.0 (*C*H), 129.3 (*C*), 130.9 (*C*), 131.3 (*C*), 135.1 (*C*H), 138.1 (*C*), 160.7 (*C*), 164.8 (*C*). Anal. Calcd for $C_{180}H_{204}O_{12}$: C, 84.47; H, 8.03; N, 0.00. Found: C, 84.45; H, 7.97; N, 0.04.

4.3. General procedure for the synthesis of 2

All bichromophoric compounds **2** were prepared as described in the following typical procedure. For example, synthesis of **2a** was exemplified as follows.

4.3.1. 3,5-Bis[(10-methyl-9-anthracenediyl)methoxy]-benzyl benzoate 2a. A solution containing **4a** (0.25 g, 1.02 mmol), **8** (0.10 g, 0.41 mmol), potassium carbonate (0.14 g, 1.02 mmol), and 18-crown-6 (0.11 g, 0.41 mmol) in DMF (5 mL) was heated at 55 °C with stirring under argon atmosphere. After 3 h, the reaction mixture was then precipitated in ice-cold diluted HCl solution (50 mL). The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum to afford a pale yellow solid. After complete vacuum drying, the solid sample was purified by recrystallization from chloroform–hexane solution, affording **2a** (0.24 g, 90%) as a pale yellow powdery material; mp 243–244 °C; UV ($CHCl_3$) 359 nm (ε 13,600), 378 nm (ε 21,700), 399 nm (ε 20,900); IR (KBr) 1595 cm^{-1} (C=C), 1719 cm^{-1} (C=O); MS (FAB+) *m/z* 653 (*M*+), 654 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{46}H_{36}O_4$: 652.2614, found 652.2594; ^1H NMR ($CDCl_3$) δ 3.13 (s, 6H, CH_3), 5.40 (s, 2H, CH_2), 5.93 (s, 4H, CH_2), 6.92 (s, 3H, Ar*H*), 7.4–7.6 (m, 11H, Ar*H*), 8.0–8.2 (m, 2H, Bz*H*), 8.2–8.4 (m, 8H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3), 63.1 (CH_2), 66.5 (CH_2), 101.4 (*C*H), 107.1 (*C*H), 124.6 (*C*H), 125.0 (*C*H), 125.4 (*C*H), 126.1 (*C*H), 128.4 (*C*H), 129.8 (*C*H), 130.0 (*C*), 130.1 (*C*), 130.8 (*C*), 132.5 (*C*), 133.1 (*C*H), 138.7 (*C*), 160.7 (*C*), 166.4 (*C*).

4.3.2. 3,5-Bis[(10-ethyl-9-anthracenediyl)methoxy]-benzyl benzoate 2b. This compound was obtained (0.27 g, 95%) as a pale yellow powdery material from chloroform–hexane solution; mp 146–147 °C; UV ($CHCl_3$) 359 nm (ε 13,600), 378 nm (ε 21,800), 399 nm (ε 21,100); IR (KBr) 1594 cm^{-1} (C=C), 1719 cm^{-1} (C=O); MS (FAB+) *m/z* 681 (*M*+), 682 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{48}H_{40}O_4$: 680.2927, found 680.2955; ^1H NMR ($CDCl_3$) δ 1.45 (t, $J=7.5$ Hz, 6H, CH_2CH_3), 3.66 (q, $J=7.5$ Hz, 4H, CH_2CH_3), 5.41 (s, 2H, CH_2), 5.91 (s, 4H, CH_2), 6.92 (s, 3H, Ar*H*), 7.4–7.6 (m, 11H, Ar*H*), 8.09 (d, $J=8.4$ Hz, 2H, Bz*H*), 8.1–8.4 (m, 8H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 15.5 (CH_3), 21.5 (CH_2), 63.0 (CH_2), 66.5 (CH_2), 101.3 (*C*H), 107.0 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.1 (*C*H), 126.1 (*C*H), 128.4 (*C*H), 129.0 (*C*), 129.8 (*C*H), 130.0 (*C*), 130.9 (*C*), 133.1 (*C*H), 138.7 (*C*), 139.2 (C), 160.7 (*C*), 166.4 (*C*).

4.3.3. 3,5-Bis[(10-propyl-9-anthracenediyl)methoxy]-benzyl benzoate 2c. This compound was obtained (0.29 g, 91%) as a pale yellow powdery material from chloroform–hexane solution; mp 202–203 °C; UV ($CHCl_3$) 360 nm (ε 13,700), 379 nm (ε 22,200), 400 nm (ε 21,500); IR (KBr) 1593 cm^{-1} (C=C), 1726 cm^{-1} (C=O); MS (FAB+) *m/z* 709 (*M*+), 710 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{50}H_{44}O_4$: 708.3240, found 708.3250; ^1H NMR ($CDCl_3$) δ 1.16 (t, $J=7.3$ Hz, 6H, $(CH_2)_2CH_3$), 1.86 (sext, $J=7.7$ Hz, 4H, $CH_2CH_2CH_3$), 3.5–3.7 (m, $J=8.1$ Hz, 4H, $CH_2CH_2CH_3$), 5.41 (s, 2H, CH_2), 5.91 (s, 4H, CH_2), 6.92 (s, 3H, Ar*H*), 7.3–7.6 (m, 11H, Ar*H*), 8.0–8.2 (m, 2H, Bz*H*), 8.2–8.4 (m, 8H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3), 24.7 (CH_2), 30.4 (CH_2), 63.1 (CH_2), 66.5 (CH_2), 101.4 (*C*H), 107.1 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.1 (*C*), 125.2 (*C*H), 126.1 (*C*H), 128.4 (*C*H), 129.4 (*C*), 129.8 (*C*H), 130.1 (*C*), 130.9 (*C*), 133.0 (*C*H), 137.9 (*C*), 138.7 (*C*), 160.7 (*C*), 166.4 (*C*).

4.3.4. 3,5-Bis[(10-butyl-9-anthracenediyl)methoxy]-benzyl benzoate 2d. This compound was obtained (0.30 g, 93%) as a pale yellow powdery material from chloroform–hexane solution; mp 189–190 °C; UV ($CHCl_3$) 360 nm (ε 13,400), 379 nm (ε 21,900), 400 nm (ε 21,200); IR (KBr) 1593 cm^{-1} (C=C), 1716 cm^{-1} (C=O); MS (FAB+) *m/z* 736 (*M*+), 737 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{52}H_{48}O_4$: 736.3553, found 736.3517; ^1H NMR ($CDCl_3$) δ 1.02 (t, $J=7.3$ Hz, 6H, $(CH_2)_3CH_3$), 1.60 (sext, $J=7.3$ Hz, 4H, $(CH_2)_2CH_2CH_3$), 1.7–1.9 (m, 4H, $CH_2CH_2CH_2CH_3$), 3.61 (t, $J=7.9$ Hz, 4H, $CH_2(CH_2)_2CH_3$), 5.41 (s, 2H, CH_2), 5.90 (s, 4H, CH_2), 6.92 (s, 3H, Ar*H*), 7.3–7.6 (m, 11H, Ar*H*), 8.0–8.2 (m, 2H, Bz*H*), 8.2–8.4 (m, 8H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 23.4 (CH_2), 28.1 (CH_2), 33.5 (CH_2), 63.1 (CH_2), 66.5 (CH_2), 101.4 (*C*H), 107.1 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.2 (*C*H), 126.1 (*C*H), 128.4 (*C*H), 129.4 (*C*), 129.8 (*C*H), 130.1 (*C*), 130.9

(*C*), 131.0 (C), 133.0 (*C*H), 138.1 (*C*), 138.7 (*C*), 160.8 (*C*), 166.4 (*C*).

4.3.5. 3,5-Bis[(10-hexyl-9-anthracenediyl)methoxy]-benzyl benzoate 2e. This compound was obtained (0.31 g, 94%) as a pale yellow powdery material from chloroform–hexane solution; mp 136–137 °C; UV ($CHCl_3$) 360 nm (ε 13,500), 379 nm (ε 22,000), 400 nm (ε 21,300); IR (KBr) 1595 cm^{-1} (C=C), 1715 cm^{-1} (C=O); MS (FAB+) *m/z* 792 (*M*+), 793 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{56}H_{56}O_4$: 792.4179, found 792.4208; ^1H NMR ($CDCl_3$) δ 0.92 (t, J=7.0 Hz, 6H, $(CH_2)_5CH_3$), 1.3–1.5 (m, 8H, $(CH_2)_3(CH_2)_2CH_3$), 1.5–1.7 (m, 4H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.7–1.9 (m, 4H, $CH_2CH_2(CH_2)_3CH_3$), 3.61 (t, J=8.2 Hz, 4H, $CH_2(CH_2)_4CH_3$), 5.41 (s, 2H, CH_2), 5.91 (s, 4H, CH_2), 6.92 (s, 3H, Ar*H*), 7.3–7.6 (m, 11H, Ar*H*), 8.0–8.2 (m, 2H, Bz*H*), 8.2–8.4 (m, 8H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (*C*H_3), 22.7 (*C*H_2), 28.5 (*C*H_2), 30.0 (*C*H_2), 31.4 (*C*H_2), 31.8 (*C*H_2), 63.1 (*C*H_2), 66.5 (*C*H_2), 101.4 (*C*H), 107.1 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.2 (*C*H), 126.1 (*C*H), 128.4 (*C*H), 129.3 (*C*), 129.8 (*C*H), 130.1 (*C*), 130.9 (*C*), 133.0 (*C*H), 138.1 (*C*), 138.7 (*C*), 160.7 (*C*), 166.4 (*C*).

4.3.6. 3,5-Bis[(10-octyl-9-anthracenediyl)methoxy]-benzyl benzoate 2f. This compound was obtained (0.35 g, 98%) as a pale yellow powdery material from chloroform–hexane solution; mp 166–167 °C; UV ($CHCl_3$) 360 nm (ε 13,500), 379 nm (ε 22,100), 400 nm (ε 21,300); IR (KBr) 1594 cm^{-1} (C=C), 1724 cm^{-1} (C=O); MS (FAB+) *m/z* 848 (*M*+), 849 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{60}H_{64}O_4$: 848.4805, found 848.4846; ^1H NMR ($CDCl_3$) δ 0.89 (t, J=6.8 Hz, 6H, $(CH_2)_7CH_3$), 1.2–1.5 (m, 16H, $(CH_2)_3(CH_2)_4CH_3$), 1.5–1.7 (m, 4H, $(CH_2)_2CH_2(CH_2)_4CH_3$), 1.7–1.9 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 3.62 (t, J=8.2 Hz, 4H, $CH_2(CH_2)_6CH_3$), 5.41 (s, 2H, CH_2), 5.94 (s, 4H, CH_2), 6.93 (s, 3H, Ar*H*), 7.3–7.6 (m, 11H, Ar*H*), 8.0–8.2 (m, 2H, Bz*H*), 8.2–8.4 (m, 8H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (*C*H_3), 22.7 (*C*H_2), 28.5 (*C*H_2), 29.3 (*C*H_2), 29.5 (*C*H_2), 30.4 (*C*H_2), 31.4 (*C*H_2), 31.9 (*C*H_2), 63.1 (*C*H_2), 66.5 (*C*H_2), 101.4 (*C*H), 107.1 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.2 (*C*H), 126.1 (*C*H), 128.4 (*C*H), 129.4 (*C*), 129.8 (*C*H), 130.1 (*C*), 131.0 (*C*), 133.0 (*C*H), 138.2 (*C*), 138.7 (*C*), 160.8 (*C*), 166.4 (*C*).

4.3.7. 3,5-Bis[(10-decyl-9-anthracenediyl)methoxy]-benzyl benzoate 2g. This compound was obtained (0.36 g, 96%) as a pale yellow powdery material from chloroform–hexane solution; mp 130–131 °C; UV ($CHCl_3$) 360 nm (ε 13,500), 379 nm (ε 22,100), 400 nm (ε 21,400); IR (KBr) 1596 cm^{-1} (C=C), 1714 cm^{-1} (C=O); MS (FAB+) *m/z* 904 (*M*+), 905 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{64}H_{72}O_4$: 904.5431, found 904.5424; ^1H NMR ($CDCl_3$) δ 0.90 (t, J=7.0 Hz, 6H, $(CH_2)_9CH_3$), 1.2–1.5 (m, 24H, $(CH_2)_3(CH_2)_6CH_3$), 1.5–1.7 (m, 4H, $(CH_2)_2CH_2(CH_2)_6CH_3$), 1.7–1.9 (m, 4H, $CH_2CH_2(CH_2)_7CH_3$), 3.64 (t, J=7.9 Hz, 4H, $CH_2(CH_2)_8CH_3$), 5.44 (s, 2H, CH_2), 5.95 (s, 4H, CH_2), 6.95 (s, 3H, Ar*H*), 7.44 (t, J=7.2 Hz, 9H), 7.5–7.6 (m, 9H, Ar*H*), 8.13 (d, J=7.2 Hz, 2H, Bz*H*), 8.3–8.4 (m, 8H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (*C*H_3), 22.7 (*C*H_2), 28.5 (*C*H_2), 29.3 (*C*H_2), 29.57 (*C*H_2), 29.63 (*C*H_2), 29.7 (*C*H_2), 30.4 (*C*H_2), 31.4 (*C*H_2), 31.9 (*C*H_2), 63.0 (*C*H_2), 66.5 (*C*H_2), 101.3 (*C*H), 107.0 (*C*H), 124.6 (*C*H), 124.96 (*C*H), 125.04 (*C*H), 125.2 (*C*H), 126.1 (*C*H), 128.4 (*C*H), 129.3 (*C*H), 129.8 (*C*), 130.0 (*C*), 130.9 (*C*), 133.1 (*C*), 138.2 (*C*), 138.7 (*C*), 160.7 (*C*), 166.4 (*C*).

4.4. General procedure for the synthesis of 3

All monochromophoric compounds **3** were prepared as described in the following typical procedure. For example, synthesis of **3a** was exemplified as follows.

4.4.1. 3-[(10-Methyl-9-anthracenediyl)methoxy]benzyl benzoate 3a. A solution containing **4a** (0.32 g, 1.32 mmol), **9** (0.20 g, 0.88 mmol), potassium carbonate (0.18 g, 1.32 mmol), and 18-crown-6 (0.04 g, 0.13 mmol) in DMF (5 mL) was heated at 55 °C with stirring under argon atmosphere. After 3 h, the reaction mixture was then quenched by slow addition of 1.0 mol/L HCl. The resulting mixture was extracted with ethyl acetate, and the combined organic extracts were intensively washed with water, saturated $NaHCO_3$ solution, and brine. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give pale yellow oily residue. Purification of the residue by silica-gel column chromatography (50% chloroform, 50% hexane) gave **3a** as a pale yellow crystalline mass (0.36 g, 95%). Further purification was achieved by recrystallization from chloroform–methanol solution affording purely pale yellow needles; mp 148–149 °C; UV ($CHCl_3$) 359 nm (ε 7200), 378 nm (ε 11,100), 399 nm (ε 10,400); IR (KBr) 1584 cm^{-1} (C=C), 1714 cm^{-1} (C=O); MS (FAB+) *m/z* 432 (*M*+), 433 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{30}H_{24}O_3$: 432.1725, found 432.1710; ^1H NMR ($CDCl_3$) δ 3.12 (s, 3H, CH_3), 5.38 (s, 2H, CH_2), 5.93 (s, 2H, CH_2), 7.1–7.2 (m, 2H, Ar*H*), 7.22 (br s, 1H, Ar*H*), 7.3–7.6 (m, 8H, Ar*H*), 8.0–8.1 (m, 2H, Bz*H*), 8.2–8.4 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.5 (*C*H_3), 62.9 (*C*H_2), 66.5 (*C*H_2), 114.5 (*C*H), 114.6 (*C*H), 120.7 (*C*H), 124.6 (*C*H), 124.9 (*C*H), 125.1 (*C*), 125.4 (*C*H), 126.0 (*C*H), 128.4 (*C*H), 129.7 (*C*H), 129.8 (*C*H), 129.9 (*C*), 130.1 (*C*), 130.7 (*C*), 132.8 (*C*), 133.0 (*C*H), 137.8 (*C*), 159.5 (*C*), 166.4 (*C*).

4.4.2. 3-[(10-Ethyl-9-anthracenediyl)methoxy]benzyl benzoate 3b. This compound was obtained (0.38 g, 96%) as a pale yellow powdery material from chloroform–methanol solution; mp 140–141 °C; UV ($CHCl_3$) 359 nm (ε 7000), 378 nm (ε 11,100), 399 nm (ε 10,500); IR (KBr) 1583 cm^{-1} (C=C), 1720 cm^{-1} (C=O); MS (FAB+) *m/z* 446 (*M*+), 447 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{31}H_{26}O_3$: 446.1882, found 446.1875; ^1H NMR ($CDCl_3$) δ 1.46 (t, J=7.6 Hz, 3H, CH_3), 3.67 (q, J=7.6 Hz, 2H, CH_2), 5.39 (s, 2H, CH_2), 5.93 (s, 2H, CH_2), 7.1–7.2 (m, 2H, Ar*H*), 7.23 (br s, 1H, Ar*H*), 7.3–7.6 (m, 8H, Ar*H*), 8.0–8.1 (m, 2H, Bz*H*), 8.2–8.4 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 15.5 (*C*H_3), 21.5 (*C*H_2), 62.9 (*C*H_2), 66.5 (*C*H_2), 114.4 (*C*H), 114.5 (*C*H), 120.7 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.1 (*C*H), 125.2 (*C*), 126.0 (*C*H), 128.4 (*C*H), 129.0 (*C*), 129.7 (*C*H), 129.8 (*C*H), 130.1 (*C*), 131.0 (*C*), 133.0 (*C*H), 137.8 (*C*), 139.2 (*C*), 159.5 (*C*), 166.4 (*C*).

4.4.3. 3-[(10-Propyl-9-anthracenediyl)methoxy]benzyl benzoate 3c. This compound was obtained (0.38 g, 95%) as a pale yellow powdery material from chloroform–methanol solution; mp 130–131 °C; UV ($CHCl_3$) 360 nm (ε 7100), 379 nm (ε 11,400), 400 nm (ε 10,800); IR (KBr)

1585 cm^{-1} (C=C), 1715 cm^{-1} (C=O); MS (FAB+) *m/z* 460 (*M*+), 461 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{32}H_{28}O_3$: 460.2038, found 460.2053; ^1H NMR ($CDCl_3$) δ 1.17 (t, $J=7.4$ Hz, 3H, $(CH_2)_2CH_3$), 1.87 (sext, $J=7.7$ Hz, 2H, $CH_2CH_2CH_3$), 3.5–3.7 (m, 2H, $CH_2CH_2CH_3$), 5.39 (s, 2H, CH_2), 5.92 (s, 2H, CH_2), 7.1–7.2 (m, 2H, Ar*H*), 7.23 (br s, 1H, Ar*H*), 7.3–7.6 (m, 8H, Ar*H*), 8.0–8.1 (m, 2H, Bz*H*), 8.2–8.4 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.7 (*C*H_3), 24.7 (*C*H_2), 30.4 (*C*H_2), 63.0 (*C*H_2), 66.5 (*C*H_2), 114.4 (*C*H), 114.5 (*C*H), 120.7 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.2 (*C*H), 126.0 (*C*H), 128.4 (*C*H), 129.4 (*C*), 129.7 (*C*H), 129.8 (*C*H), 130.1 (*C*), 131.0 (*C*), 133.0 (*C*H), 137.8 (*C*), 137.9 (*C*), 159.5 (*C*), 166.4 (*C*).

4.4.4. 3-[(10-Butyl-9-anthracenediyl)methoxy)benzyl benzoate 3d. This compound was obtained (0.40 g, 96%) as a pale yellow powdery material from chloroform–methanol solution; mp 134–135 °C; UV ($CHCl_3$) 360 nm (ε 6900), 379 nm (ε 11,200), 400 nm (ε 10,600); IR (KBr) 1584 cm^{-1} (C=C), 1715 cm^{-1} (C=O); MS (FAB+) *m/z* 474 (*M*+), 475 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{33}H_{30}O_3$: 474.2195, found 474.2210; ^1H NMR ($CDCl_3$) δ 1.04 (t, $J=7.3$ Hz, 3H, $(CH_2)_3CH_3$), 1.61 (sext, $J=7.5$ Hz, 2H, $(CH_2)_2CH_2CH_3$), 1.7–1.9 (m, 2H, $CH_2CH_2CH_2CH_3$), 3.63 (t, $J=8.2$ Hz, 2H, $CH_2(CH_2)_2CH_3$), 5.39 (s, 2H, CH_2), 5.93 (s, 2H, CH_2), 7.1–7.2 (m, 2H, Ar*H*), 7.23 (br s, 1H, Ar*H*), 7.3–7.6 (m, 8H, Ar*H*), 8.0–8.1 (m, 2H, Bz*H*), 8.2–8.4 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.0 (*C*H_3), 23.4 (*C*H_2), 28.1 (*C*H_2), 33.5 (*C*H_2), 63.0 (*C*H_2), 66.5 (*C*H_2), 114.5 (*C*H), 114.6 (*C*H), 120.7 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.2 (*C*H), 126.0 (*C*H), 128.4 (*C*H), 129.4 (*C*), 129.7 (*C*H), 129.8 (*C*H), 130.1 (*C*), 131.0 (*C*), 133.0 (*C*H), 137.8 (*C*), 138.0 (*C*), 159.5 (*C*), 166.4 (*C*).

4.4.5. 3-[(10-Hexyl-9-anthracenediyl)methoxy)benzyl benzoate 3e. This compound was obtained (0.42 g, 95%) as a pale yellow powdery material from chloroform–methanol solution; mp 93–94 °C; UV ($CHCl_3$) 360 nm (ε 7000), 379 nm (ε 11,300), 400 nm (ε 10,700); IR (KBr) 1585 cm^{-1} (C=C), 1718 cm^{-1} (C=O); MS (FAB+) *m/z* 502 (*M*+), 503 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{35}H_{34}O_3$: 502.2508, found 502.2529; ^1H NMR ($CDCl_3$) δ 0.93 (t, $J=7.1$ Hz, 3H, $(CH_2)_5CH_3$), 1.3–1.5 (m, 4H, $(CH_2)_3(CH_2)_2CH_3$), 1.5–1.7 (m, 2H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.7–1.9 (m, 2H, $CH_2CH_2(CH_2)_3CH_3$), 3.61 (t, $J=8.3$ Hz, 2H, CH_2 $(CH_2)_4CH_3$), 5.39 (s, 2H, CH_2), 5.93 (s, 2H, CH_2), 7.1–7.2 (m, 2H, Ar*H*), 7.23 (br s, 1H, Ar*H*), 7.3–7.6 (m, 8H, Ar*H*), 8.0–8.1 (m, 2H, Bz*H*), 8.2–8.4 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (*C*H_3), 22.7 (*C*H_2), 28.5 (*C*H_2), 30.1 (*C*H_2), 31.4 (*C*H_2), 31.8 (*C*H_2), 63.0 (*C*H_2), 66.5 (*C*H_2), 114.4 (*C*H), 114.5 (*C*H), 120.7 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.2 (*C*), 126.0 (*C*H), 128.4 (*C*H), 129.3 (*C*), 129.7 (*C*H), 129.8 (*C*H), 130.1 (*C*), 130.9 (*C*), 133.0 (*C*H), 137.8 (*C*), 138.1 (*C*), 159.5 (*C*), 166.4 (*C*).

4.4.6. 3-[(10-Octyl-9-anthracenediyl)methoxy]benzyl benzoate 3f. This compound was obtained (0.46 g, 98%) as a pale yellow powdery material from chloroform–methanol solution; mp 98–99 °C; UV ($CHCl_3$) 360 nm (ε 6800), 379 nm (ε 11,000), 400 nm (ε 10,000); IR (KBr) 1584 cm^{-1} (C=C), 1714 cm^{-1} (C=O); MS (FAB+) *m/z* 530 (*M*+), 531 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{37}H_{38}O_3$: 530.2821, found 530.2795; ^1H NMR ($CDCl_3$) δ 0.90 (t, $J=6.8$ Hz, 3H, $(CH_2)_9CH_3$), 1.2–1.5 (m, 8H, $(CH_2)_3(CH_2)_4CH_3$), 1.59 (quint, $J=7.7$ Hz, 2H, $(CH_2)_2CH_2(CH_2)_4CH_3$), 1.82 (quint, $J=7.8$ Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.61 (t, $J=8.2$ Hz, 2H, $CH_2(CH_2)_6CH_3$), 5.38 (s, 2H, CH_2), 5.92 (s, 2H, CH_2), 7.1–7.2 (m, 2H, Ar*H*), 7.22 (br s, 1H, Ar*H*), 7.3–7.6 (m, 8H, Ar*H*), 8.0–8.1 (m, 2H, Bz*H*), 8.2–8.4 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (*C*H_3), 22.7 (*C*H_2), 28.5 (*C*H_2), 29.3 (*C*H_2), 29.5 (*C*H_2), 30.4 (*C*H_2), 31.4 (*C*H_2), 31.9 (*C*H_2), 62.9 (*C*H_2), 66.5 (*C*H_2), 114.4 (*C*H), 114.5 (*C*H), 120.7 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.1 (*C*), 125.2 (*C*H), 126.0 (*C*H), 128.4 (*C*H), 129.3 (*C*), 129.7 (*C*H), 129.8 (*C*H), 130.1 (*C*), 130.9 (*C*), 133.0 (*C*H), 137.8 (*C*), 138.1 (*C*), 159.5 (*C*), 166.4 (*C*).

4.4.7. 3-[(10-Decyl-9-anthracenediyl)methoxy)benzyl benzoate 3g. This compound was obtained (0.48 g, 97%) as a pale yellow powdery material from chloroform–methanol solution; mp 93–94 °C; UV ($CHCl_3$) 360 nm (ε 6900), 379 nm (ε 11,200), 400 nm (ε 10,600); IR (KBr) 1583 cm^{-1} (C=C), 1714 cm^{-1} (C=O); MS (FAB+) *m/z* 558 (*M*+), 559 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{39}H_{42}O_3$: 558.3134, found 558.3121; ^1H NMR ($CDCl_3$) δ 0.89 (t, $J=6.5$ Hz, 3H, $(CH_2)_9CH_3$), 1.2–1.5 (m, 12H, $(CH_2)_3(CH_2)_6CH_3$), 1.5–1.7 (m, 2H, $(CH_2)_2CH_2(CH_2)_6CH_3$), 1.7–1.9 (m, 2H, $CH_2CH_2(CH_2)_7CH_3$), 3.61 (t, $J=8.2$ Hz, 2H, $CH_2(CH_2)_8CH_3$), 5.39 (s, 2H, CH_2), 5.92 (s, 2H, CH_2), 7.1–7.2 (m, 2H, Ar*H*), 7.23 (br s, 1H, Ar*H*), 7.3–7.6 (m, 8H, Ar*H*), 8.0–8.1 (m, 2H, Bz*H*), 8.2–8.4 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (*C*H_3), 22.7 (*C*H_2), 28.5 (*C*H_2), 29.3 (*C*H_2), 29.56 (*C*H_2), 29.63 (*C*H_2), 29.7 (*C*H_2), 30.4 (*C*H_2), 31.4 (*C*H_2), 31.9 (*C*H_2), 63.0 (*C*H_2), 66.5 (*C*H_2), 114.4 (*C*H), 114.5 (*C*H), 120.7 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.2 (*C*H), 126.0 (*C*H), 128.4 (*C*H), 129.3 (*C*), 129.7 (*C*H), 129.8 (*C*H), 130.1 (*C*), 130.9 (*C*), 133.0 (*C*H), 137.8 (*C*), 138.1 (*C*), 159.5 (*C*), 166.4 (*C*).

4.5. General procedure for the synthesis of 4

All 10-alkyl-9-chloromethylanthracenes **4** were synthesized according to the established literature procedure used for preparation of **4a**. For example, synthesis of **4c** was exemplified as follows.

4.5.1. 9-Chloromethyl-10-propylanthracene 4c. A solution containing **6c** (1.0 g, 4.54 mmol), paraformaldehyde (1.0 g), and concd HCl (10 mL) in acetic acid (20 mL) was heated at room temperature with vigorous stirring. After 14 h, the reaction mixture was then precipitated in ice-cold (50 mL). The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum to afford a pale yellow solid. After complete vacuum drying, the solid sample was purified by recrystallization from chloroform–hexane solution, affording **4c** (1.1 g, 92%) as a pale yellow powdery material; mp 123–124 °C; IR (KBr) 759, 1249, 1444, 1478 cm^{-1}; MS (FAB+) *m/z* 268 (*M*+), 269 (*MH*+); ^1H NMR ($CDCl_3$) δ 1.14 (t, $J=7.5$ Hz, 3H, $CH_2CH_2CH_3$), 1.82 (sext, $J=7.5$ Hz, 2H, $CH_2CH_2CH_3$), 3.5–3.6 (m, 2H, CH_2), 5.57 (s, 2H, CH_2), 7.4–7.6 (m, 4H, Ar*H*), 8.2–8.4 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.7 (*C*H_3), 24.7 (*C*H_2), 30.4 (*C*H_2), 39.5 (*C*H_2), 124.1 (*C*H), 125.1 (*C*H), 125.4 (*C*H), 126.2 (*C*), 126.3 (*C*H), 129.5 (*C*), 129.9 (*C*), 138.2 (*C*). Anal. Calcd for $C_{18}H_{17}Cl$: C, 80.43; H, 6.38; N, 0.00. Found: C, 80.51; H, 6.49; N, 0.05.

4.5.2. 9-Chloromethyl-10-hexylanthracene 4e. This compound was obtained (1.1 g, 89%) from **6e** (1.0 g, 3.82 mmol) as a pale yellow powdery material from chloroform–hexane solution; mp 114–115 °C; IR (KBr) 756, 1246, 1446, 1459, 1479 cm^{-1}; MS (FAB+) *m/z* 310 (*M*+), 311 (*MH*+); ^1H NMR ($CDCl_3$) δ 0.91 (t, *J*=7.0 Hz, 3H, $(CH_2)_5CH_3$), 1.3–1.5 (m, 4H, $(CH_2)_3(CH_2)_2CH_3$), 1.56 (quint, *J*=7.3 Hz, 2H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.77 (quint, *J*=7.5 Hz, 2H, $CH_2CH_2(CH_2)_3CH_3$), 3.56 (t, *J*=8.2 Hz, 2H, $CH_2(CH_2)_4CH_3$), 5.56 (s, 2H, CH_2), 7.4–7.6 (m, 4H, Ar*H*), 8.2–8.4 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.5 (CH_2), 30.0 (CH_2), 31.4 (CH_2), 31.7 (CH_2), 39.5 (CH_2), 124.1 (*C*H), 125.2 (*C*H), 125.3 (*C*H), 126.1 (*C*), 126.30 (*C*H), 129.33 (*C*), 129.9 (*C*), 138.4 (*C*). Anal. Calcd for $C_{21}H_{23}Cl$: C, 81.14; H, 7.46; N, 0.00. Found: C, 81.25; H, 7.50; N, 0.00.

4.5.3. 9-Chloromethyl-10-octylanthracene 4f. This compound was obtained (0.99 g, 85%) from **6f** (1.0 g, 3.45 mmol) as a pale yellow powdery material from chloroform–hexane solution; mp 96–97 °C; IR (KBr) 760, 1248, 1445, 1459, 1479 cm^{-1}; MS (FAB+) *m/z* 338 (*M*+), 339 (*MH*+); ^1H NMR ($CDCl_3$) δ 0.88 (t, *J*=7.0 Hz, 3H, $(CH_2)_7CH_3$), 1.2–1.4 (m, 8H, $(CH_2)_3(CH_2)_4CH_3$), 1.56 (quint, *J*=7.6 Hz, 2H, $(CH_2)_2CH_2(CH_2)_4CH_3$), 1.79 (quint, *J*=7.7 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.58 (t, *J*=8.2 Hz, 2H, $CH_2(CH_2)_6CH_3$), 5.59 (s, 2H, CH_2), 7.4–7.6 (m, 4H, Ar*H*), 8.2–8.4 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.5 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 30.4 (CH_2), 31.5 (CH_2), 31.9 (CH_2), 39.6 (CH_2), 124.1 (*C*H), 125.2 (*C*H), 125.4 (*C*H), 126.1 (*C*), 126.3 (*C*H), 129.4 (*C*), 129.9 (*C*), 138.5 (*C*). Anal. Calcd for $C_{23}H_{27}Cl$: C, 81.51; H, 8.03; N, 0.00. Found: C, 81.52; H, 8.21; N, 0.00.

4.5.4. 9-Chloromethyl-10-decylanthracene 4g. This compound was obtained (0.96 g, 83%) from **6g** (1.0 g, 3.14 mmol) as a pale yellow powdery material from chloroform–hexane solution; mp 95–96 °C; IR (KBr) 760, 1249, 1445, 1459, 1477 cm^{-1}; MS (FAB+) *m/z* 366 (*M*+), 367 (*MH*+); ^1H NMR ($CDCl_3$) δ 0.88 (t, *J*=7.0 Hz, 3H, $(CH_2)_9CH_3$), 1.2–1.4 (m, 12H, $(CH_2)_3(CH_2)_6CH_3$), 1.57 (quint, *J*=7.3 Hz, 2H, $(CH_2)_2CH_2(CH_2)_6CH_3$), 1.79 (quint, *J*=7.7 Hz, 2H, $CH_2CH_2(CH_2)_7CH_3$), 3.57 (t, *J*=8.2 Hz, 2H, $CH_2(CH_2)_8CH_3$), 5.57 (s, 2H, CH_2), 7.4–7.6 (m, 4H, Ar*H*), 8.2–8.4 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.5 (CH_2), 29.3 (CH_2), 29.55 (CH_2), 29.62 (CH_2), 29.7 (CH_2), 30.4 (CH_2), 31.5 (CH_2), 31.9 (CH_2), 39.5 (CH_2), 124.1 (*C*H), 125.2 (*C*H), 125.4 (*C*H), 126.1 (*C*), 126.3 (*C*H), 129.4 (*C*), 129.9 (*C*), 138.5 (*C*). Anal. Calcd for $C_{25}H_{31}Cl$: C, 81.82; H, 8.51; N, 0.00. Found: C, 82.04; H, 8.57; N, 0.02.

4.5.5. Preparation of tris(3,5-dihydroxybenzyl) benzene-1,3,5-tricarboxylate 5. The following synthetic procedure was also used for the sample preparations of benzoyl 3,5-dihydroxybenzylate **8** and benzoyl 3-hydroxybenzylate **9**. To a solution of **7** (1.26 g, 1.13 mmol) in a mixture of HPLC grade methanol (20 mL) and chloroform (20 mL) was added a catalytic amount of 10% Pd–C (0.1 g) in some portions at room temperature. The mixture was stirred under a hydrogen gas atmosphere at ambient temperature for 20 h. The catalyst was removed by filtration and the filtrate was then evaporated to dryness to obtain a colorless oily residue. Purification of the residue by column chromatography (67% ethyl acetate, 33% hexane) and recrystallization from hexane–ethyl acetate gave **5** (0.51 g, 78%) as a white powdery material; mp 219–220 °C; IR (KBr) 1608 cm^{-1} (C=C), 1714 cm^{-1} (C=O), 3391 cm^{-1} (OH); MS (FAB+) *m/z* 576 (*M*+), 578 (*MH*+); HRMS (FAB+) *m/z* calcd for $C_{30}H_{24}O_{12}$: 576.1268, found 576.1245; ^1H NMR (acetone-d_6) δ 5.31 (s, 6H, CH_2), 6.34 (t, *J*=2.1 Hz, 3H, Ph*H*), 6.49 (d, *J*=2.1 Hz, 6H, Ph*H*), 8.32 (s, 6H, O*H*), 8.85 (s, 3H, Bz*H*); ^{13}C NMR (acetone-d_6) δ 68.3 (CH_2), 103.5 (*C*H), 107.4 (*C*), 132.7 (*C*), 135.3 (*C*H), 139.3 (*C*), 159.8 (*C*), 166.0 (*C*).

4.5.6. Preparation of tris(3,5-bis(benzyloxy)benzyl) benzene-1,3,5-tricarboxylate 7. To a solution containing 3,5-bis(benzyloxy)benzyl alcohol (0.56 g, 1.75 mmol) and triethylamine (0.34 mL, 2.44 mmol) in anhydrous benzene (20 mL) was added dropwise to a solution trimesoyl chloride (0.15 g, 0.55 mmol) in anhydrous benzene (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h, quenched by slow addition of 1.0 mol/L HCl, and then extracted with an additional benzene (150 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Silica-gel column chromatography (50% chloroform, 50% hexane) of the crude sample furnished **7** (0.60 g, 98%) as a colorless crystalline mass. Further purification was achieved by recrystallization from chloroform–hexane giving a purely powdery material; mp 123–124 °C; IR (KBr) 1597 cm^{-1} (C=C), 1724 cm^{-1} (C=O); MS (FAB+) *m/z* 1117 (*M*+), 1118 (*MH*+); ^1H NMR ($CDCl_3$) δ 5.00 (s, 12H, CH_2), 5.33 (s, 6H, CH_2), 6.58 (t, *J*=2.2 Hz, 3H, Ph*H*), 6.67 (d, *J*=2.2 Hz, 6H, Ph*H*), 7.2–7.4 (m, 30H, Ar*H*), 8.90 (s, 3H, Bz*H*); ^{13}C NMR ($CDCl_3$) δ 67.2 (CH_2), 70.1 (CH_2), 102.0 (*C*H), 107.3 (*C*H), 127.5 (*C*H), 128.0 (*C*H), 128.6 (*C*H), 131.2 (*C*), 135.0 (*C*H), 136.7 (*C*), 137.7 (*C*), 160.2 (*C*), 164.7 (*C*). Anal. Calcd for $C_{72}H_{60}O_{12}$: C, 77.40; H, 5.41; N, 0.00. Found: C, 77.41; H, 5.27; N, 0.07.

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References and notes

1. McDermott, G.; Prince, S. M.; Freer, A. A.; Hawthornthwaite-Lawless, A. M.; Papiz, M. Z.; Cogdell, R. J.; Isaacs, N. W. *Nature* **1995**, *374*, 517–521.
2. Vasil'ev, S.; Orth, P.; Zouni, A.; Owens, T. G.; Bruce, D. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 8602–8607.
3. Gust, D.; Moore, T. A. *Science* **1989**, *244*, 35–41.

4. Gust, D.; Moore, T. A.; Moore, A. L. *Acc. Chem. Res.* **2001**, *34*, 40–48.
5. Byrd, H.; Suponeva, E. P.; Bocarsly, A. B.; Thompson, M. E. *Nature* **1996**, *380*, 610–612.
6. Imahori, H.; Norieda, H.; Yamada, H.; Nishimura, Y.; Yamazaki, I.; Sakata, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **2001**, *123*, 100–110.
7. Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74–91.
8. Wolf-Klein, H.; Kohl, C.; Mullen, K.; Paulsen, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3378–3380.
9. Jiang, D.-L.; Aida, T. *Nature* **1997**, *388*, 454–456.
10. Adronov, A.; Fréchet, J. M. J. *Chem. Commun.* **2000**, 1701–1710.
11. Hahn, U.; Gorka, M.; Vögtle, F.; Vicinelli, V.; Ceroni, P.; Maestri, M.; Balzani, V. *Angew. Chem., Int. Ed.* **2002**, *41*, 3595–3598.
12. Choi, M.-S.; Yamazaki, T.; Yamazaki, I.; Aida, T. *Angew. Chem., Int. Ed.* **2003**, *43*, 150–158.
13. Fetisova, Z. G.; Freiberg, A. M.; Timpmann, K. E. *Nature* **1988**, *334*, 633–634.
14. Takahashi, M.; Odagi, T.; Tomita, H.; Oshikawa, T.; Yamashita, M. *Tetrahedron Lett.* **2003**, *44*, 2455–2458.
15. Norman, R. O. C.; Waters, W. A. *J. Chem. Soc.* **1958**, 167–170.
16. Adelfang, J. L.; Daub, G. H. *J. Am. Chem. Soc.* **1958**, *80*, 1405–1409.
17. Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.
18. Aharoni, S. M.; Crosby, C. R.; Walsh, E. K. *Macromolecules* **1982**, *15*, 1093–1098.
19. Mansfield, M. L.; Klushin, L. I. *J. Phys. Chem.* **1992**, *96*, 3994–3998.
20. Dawson, W. R.; Windsor, M. W. *J. Phys. Soc.* **1968**, *72*, 3251–3260.
21. Hirayama, S.; Lampert, R. A.; Phillips, D. *J. Chem. Soc., Faraday Trans. 2* **1985**, *81*, 371–382.
22. Stewart, G. M.; Fox, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 4354–4360.
23. Yeow, E. K. L.; Ghiggino, K. P.; Reek, J. N. H.; Crossley, M. J.; Bosman, A. W.; Schenning, A. P. H. J.; Meijer, E. W. *J. Phys. Chem. B* **2000**, *104*, 2596–2606.
24. Brousmiche, D. W.; Serin, J. M.; Fréchet, J. M. J.; He, G. S.; Lin, T.-C.; Chung, S. J.; Prasad, P. N. *J. Am. Chem. Soc.* **2003**, *125*, 1448–1449.
25. Hofkens, J.; Cotlet, M.; Vosch, T.; Tinnefeld, P.; Weston, K. D.; Ego, C.; Grimsdale, A.; Mullen, K.; Beljonne, D.; Bredas, J. L.; Jordens, S.; Schweitzer, G.; Markus, S.; De Schryver, F. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 13146–13151.
26. Gibson, S.; Mosnaim, D.; Nonhebel, D. C.; Russell, J. A. *Tetrahedron* **1969**, *25*, 5047–5057.
27. Stewart, F. H. C. *Aust. J. Chem.* **1960**, *13*, 478–487.
28. Sieglitz, A.; Marx, R. *Chem. Ber.* **1923**, *56*, 1619–1621.
29. Winkler, H. J. S.; Bollinger, R.; Winkler, H. *J. Org. Chem.* **1967**, *32*, 1700–1706.
30. Armillotta, N.; Bartoli, G.; Bosco, M.; Dalpozzo, R. *Synthesis* **1982**, 836–839.
31. Effenberger, F.; Heid, S.; Merkle, R.; Zimmermann, P. *Synthesis* **1995**, 1115–1120.

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Palladium-catalyzed intramolecular α-arylation of aliphatic ketone, formyl, and nitro groups

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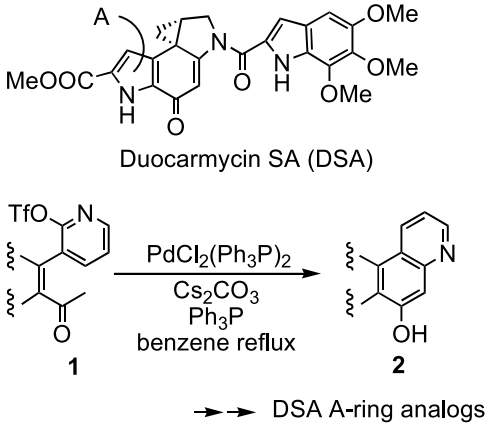
Abstract—Intramolecular arylation of properly designed substrates bearing a ketone, formyl, or nitro terminating group was achieved by use of a $PdCl_2(Ph_3P)_2$–Cs_2CO_3 reaction system to form a variety of carbocyclic compounds. Arylation in ketone compounds afforded benzene-annulated bridged or spirocycloalkanone derivatives, depending on the structure of the cyclization precursors. Arylation in formyl compounds occurred at the α-position (α-arylation) or at the carbonyl carbon (carbonyl-arylation) depending on the structure of the cyclization precursors and on the reaction solvent. An α-arylated secondary nitro group was partially transformed to ketone in the manner of the Nef reaction, whereas a tertiary nitro group was partially eliminated to afford a styrene-type olefin.

1. Introduction

Pd-catalyzed carbon–carbon bond formation reactions have been important and versatile synthetic tools in modern organic chemistry for several decades.[1] The Heck, Stille, and Suzuki reactions have often been employed in synthetic organic chemistry. These reactions involve olefins, organotin compounds, and organo-borane compounds as the terminating groups, respectively. Furthermore, recent developments in intermolecular α-arylation of ketones[2] and formation of arylamine[3] or arylether[4] from aryl halides have increased the utility of Pd-catalyzed reactions by allowing exploitation of other functional groups as the terminating group. Various reaction conditions for the α-arylation of ketone[5,6] or 1,3-dicarbonyl compounds[7] have been widely studied.

When we previously synthesized A-ring analogs of the potent antitumor antibiotic duocarmycin SA (DSA), the transformation of acetyl triflates **1** to phenols **2** was required, and we achieved this by devising a novel palladium-catalyzed method with bis(triphenylphosphine)-palladium(II) dichloride [$PdCl_2(Ph_3P)_2$], cesium carbonate (Cs_2CO_3), and triphenylphosphine (Ph_3P) in boiling benzene (Scheme 1).[8] This phenol-forming reaction (**1**→**2**) is intrinsically an intramolecular α-arylation reaction of aliphatic ketones with aryltriflates. Therefore, we set out to investigate the use of other functional groups as well as the ketone group as the terminating group of the Pd-catalyzed cyclization reaction. We found that aliphatic ketone (**3**), formyl (**4**),[9] and nitro (**5**)[10] groups could function as the terminating group for the Pd-catalyzed intramolecular α-arylation reaction (Scheme 2). A number of substances (**6**–**11**) having potential value as intermediates for further elaboration could be synthesized by means of the intramolecular α-arylation reaction. Indeed, we have completed a total synthesis of nominine (**13**), a heptacyclic hetisine-type aconite alkaloid, employing a tricyclic compound **12** prepared by the α-arylation of a formyl group



Scheme 1. DSA and phenol-forming reaction.

Keywords: Palladium-catalyst; α-Arylation; Ketone; Formyl; Nitro; Carbocycle.
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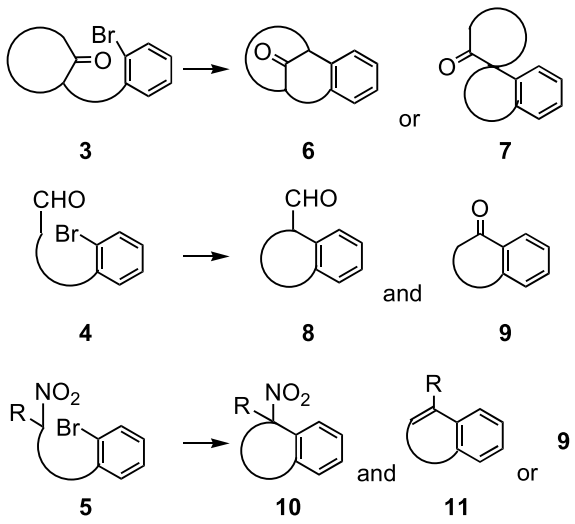
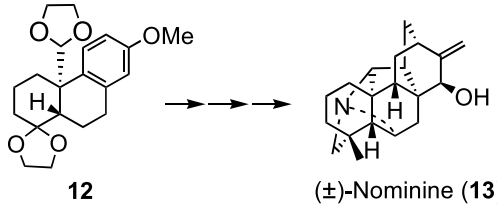


Scheme 2. Pd-catalyzed intramolecular α-arylation.



Scheme 3. Nominine synthesis by way of intermediate **12**.

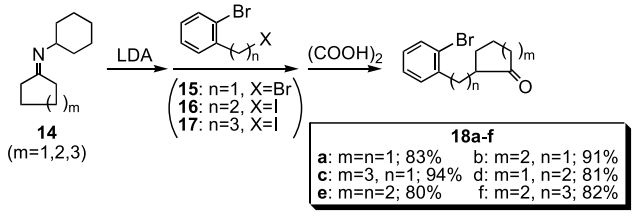
(Scheme 3).[11] Here we present full details of the course of the Pd-catalyzed cyclization reactions.[12]

2. Results and discussion

2.1. Preparation of arylation precursors

Many substances bearing a 2-bromophenyl moiety and a terminating group of aliphatic ketone, formyl, or nitro group were prepared in the following manner.

2.1.1. Ketone terminating group. Readily accessible precursors **18a–f** were prepared in order to examine whether the reaction conditions used for **1**→**2** were generally applicable (Scheme 4). Thus, anions of *N*-cycloalkylidenecyclohexylamines (**14**) were prepared with lithium diisopropylamide (LDA), and alkylated with 2-bromobenzyl bromide (**15**), 1-bromo-2-(2-iodoethyl)benzene[13] (**16**) or 1-bromo-2-(3-iodopropyl)benzene[14] (**17**) to afford **18a**,[15] **18b**,[15c,16] **18c**,[15] **18d**, **18e**, and **18f** in high yields after hydrolysis of the resulting imine with oxalic acid.



Scheme 4. Preparation of **18a–f** with a ketone terminating group.

2.1.2. Formyl terminating group. If functional groups other than ketone can be used as the terminating group, the application range of this intramolecular arylation reaction should expand greatly. Therefore, we synthesized the precursors **19–23** having a formyl terminating group (Scheme 5).

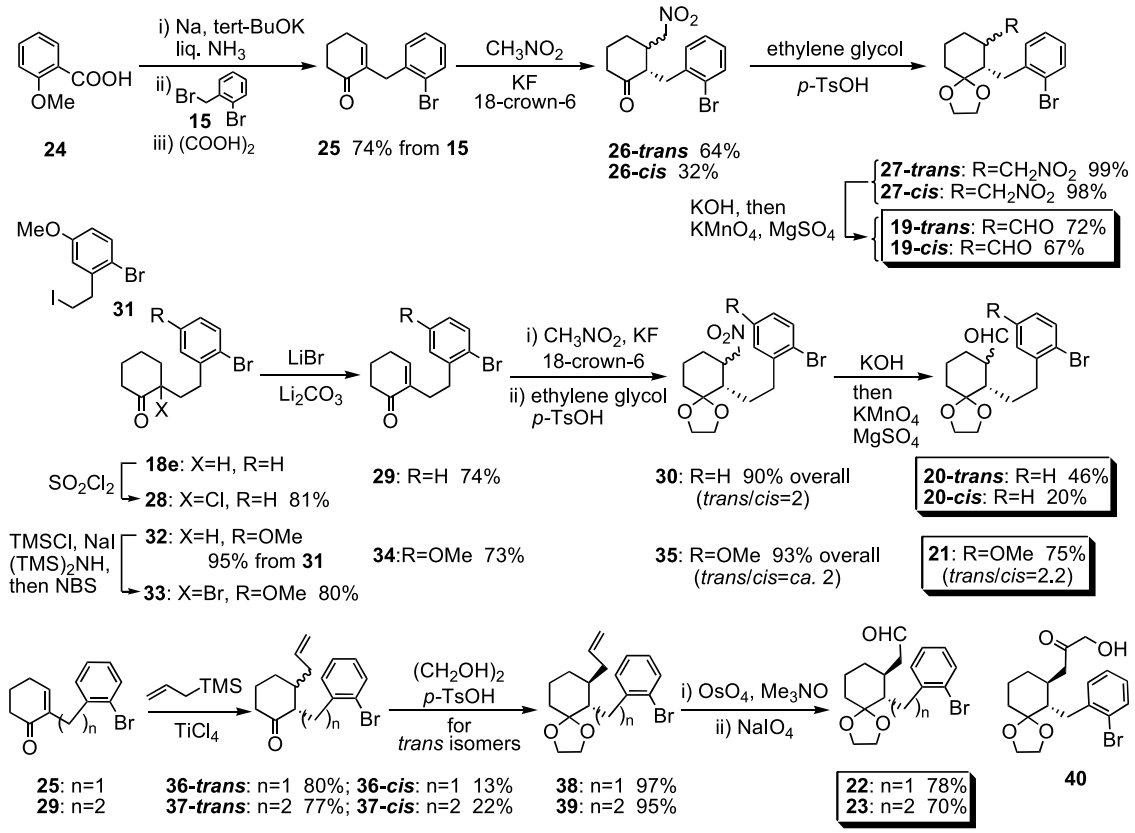
(i) Preparation of **19**-*trans* and **19**-*cis*. According to the literature,[17] 2-methoxybenzoic acid (**24**) was treated with sodium in the presence of potassium *tert*-butoxide (*tert*-BuOK) to give the anion, which was then trapped with **15**. Hydrolysis with oxalic acid, with concomitant decarboxylation, provided the enone **25**. The Michael addition of nitromethane (CH_3NO_2) to **25** catalyzed with potassium fluoride (KF) and 18-crown-6 proceeded readily, giving **26**-*trans* and **26**-*cis* in respective yields of 64 and 32%. The stereochemistry was determined from the ^{1}H NMR spectrum of **26**-*trans*, in which the coupling constant between H-2 and H-3 was 9.5 Hz. The carbonyl group of **26**-*trans* and -*cis* was protected as ethylene acetal to afford **27**-*trans* and -*cis*, whose nitromethyl group was then converted to a formyl group under oxidative conditions[18] [(i) potassium hydroxide (KOH), (ii) potassium permanganate ($KMnO_4$), magnesium sulfate ($MgSO_4$)] to acquire **19**-*trans* and **19**-*cis*.

(ii) Preparation of **20**-*trans* and **20**-*cis*. Compound **18e** was chlorinated with sulfuryl chloride (SO_2Cl_2) to give **28** in a good yield. Dehydrochlorination of **28** followed by addition of nitromethane and acetalization afforded **30** (mixture of two stereoisomers) by way of the enone **29**. The above oxidative conditions employed for the conversion of **27** to **19** led **30** to **20**-*trans* and **20**-*cis*. The stereochemistry of the major isomer was tentatively determined to be *trans* by analogy with that of **19**, as definite spectroscopic evidence was not obtained.

(iii) Preparation of **21**. The same coupling reaction of 2-bromo-5-methoxyphenethyl iodide[19] (**31**) and **14** ($m=2$) as above furnished **32**[20] in 95% yield. Bromination at C-2 of **32** was executed by *N*-bromosuccinimide (NBS) treatment of the silyl enol ether, since chlorination with SO_2Cl_2 gave rise to an intractable mixture, different from the case of **18e**. The bromide **33** was transformed to **21** [mixture of *trans* and *cis* (ca. 2.2:1)] by way of **34** and **35** using the same method as for the preparation of **20** from **28**. Attempted synthesis of **34** by the method employed for the preparation of **25** resulted in the formation of 2-bromo-5-methoxystyrene from **31**.

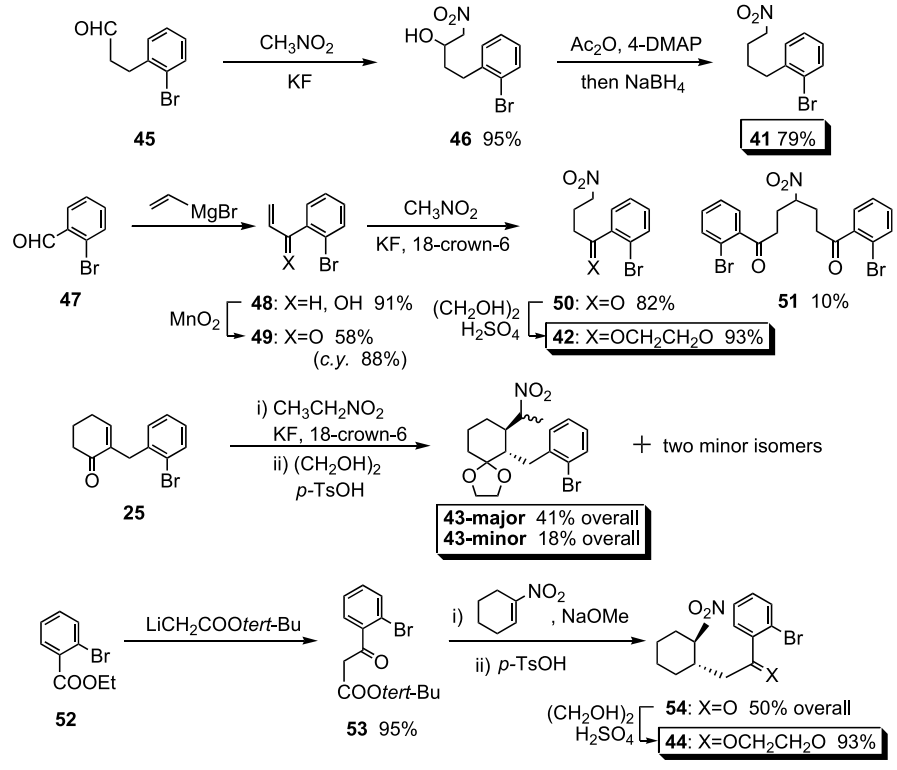
(iv) Preparation of **22** and **23**. The Michael addition of the allyl group to **25** and **29** afforded **36**-*trans*, -*cis* and **37**-*trans*, -*cis*, respectively. In both cases the major isomers were determined to be *trans*, since the coupling constant between H-2 and H-3 in the ^{1}H NMR spectrum of **36**-*trans* was 8.5 Hz. Acetalization of the major *trans* isomers, **36**-*trans* and **37**-*trans*, gave **38**, **39**, and they were converted to **22** and **23** by catalytic dihydroxylation with osmium tetroxide (OsO_4) and trimethylamine *N*-oxide (Me_3NO), followed by oxidative cleavage of the obtained diols with sodium metaperiodate ($NaIO_4$). The Lemieux oxidation of **38** was found to afford a considerable amount (25%) of the ketoalcohol **40** as a by-product along with the desired **22** (50%).

2.1.3. Nitro terminating group. As the α-position of nitroalkane is acidic enough to generate a salt with Cs_2CO_3



Scheme 5. Preparation of precursors **19**–**23** with a formyl terminating group.

even in a non-polar solvent, the resulting cesium salt is expected to cyclize to an intramolecular arylpalladium species. The products with a nitro group should serve as versatile intermediates for the synthesis of various natural compounds, including alkaloids. With this prospect in mind, the precursors **41**–**44** were synthesized (Scheme 6). In addition to these compounds, **27**-*trans*, **27**-*cis*, and **30** were also subjected to the next arylation step.



Scheme 6. Preparation of precursors **41**–**44** with a nitro terminating group.

(i) Preparation of **41**. The aldehyde **45**[21] was allowed to react with CH_3NO_2 in the presence of KF to give the nitroalcohol **46** in a high yield. Then **46** was reduced to **41** by the literature method[22] with acetic anhydride (Ac_2O) and 4-(dimethylamino)pyridine (4-DMAP), followed by sodium borohydride ($NaBH_4$).

(ii) Preparation of **42**. 2-Bromobenzaldehyde (**47**) was converted to **49** via **48** on treatment with vinylmagnesium bromide followed by manganese(IV) oxide (MnO_2). Addition of CH_3NO_2 to **49** as above gave **50** along with **51**. The former was acetalized with ethylene glycol and sulfuric acid (H_2SO_4) to provide desired **42**. The use of *p*-TsOH in place of H_2SO_4 hardly gave **42**.

(iii) Preparation of **43**. Addition of nitroethane to **25** followed by the usual acetalization with *p*-TsOH furnished **43**-major and **43**-minor. They were assigned as stereoisomers around the carbon bearing the nitro group and their side chains at C-2 and C-3 were deduced to be in *trans* relationship in accordance with the precedent of **25** to **26**.

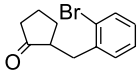
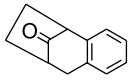
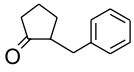
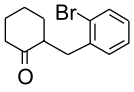
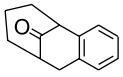
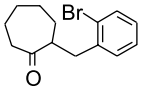
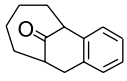
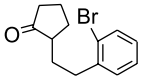
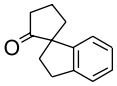
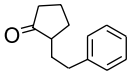
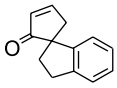
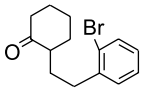
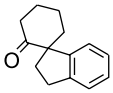
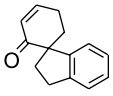
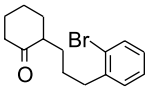
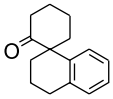
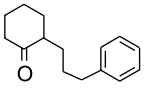
(iv) Preparation of **44**. Ethyl 2-bromobenzoate (**52**) was allowed to react with the lithium salt of *tert*-butyl acetate to produce the β-ketoester **53**. It was then condensed with 1-nitro-1-cyclohexene in the presence of sodium methoxide and the product was converted to **54** on treatment with *p*-TsOH. The stereochemistry of **54** was assigned as *trans* on the basis that the coupling constant between H-1 and H-2 is 11 Hz in the ^1H NMR spectrum. The H_2SO_4-catalyzed acetalization of **54** readily afforded **44**.

2.2. Intramolecular arylation reaction

With the precursors bearing aliphatic ketone, formyl, and nitro terminating groups in hand, we executed the Pd-catalyzed intramolecular arylations, employing the $PdCl_2$-$(Ph_3P)_2$–Cs_2CO_3 reaction system which had been applied to our synthesis of DSA analogs.[8]

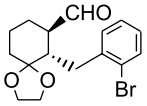
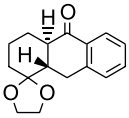
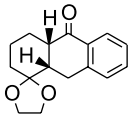
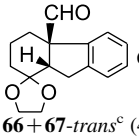
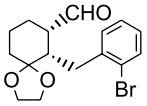
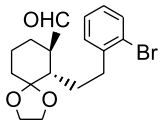
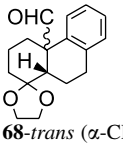
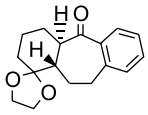
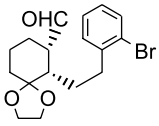
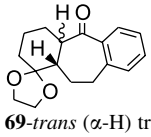
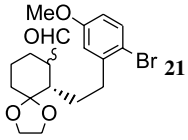
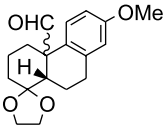
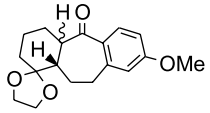
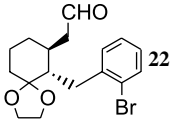
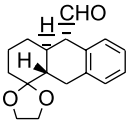
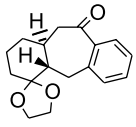
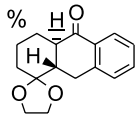
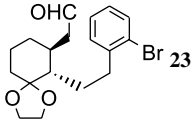
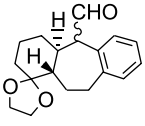
2.2.1. Ketone terminating group. The substrates **18a–f** having a ketone terminating group were subjected to the Pd-catalyzed cyclization (Table 1). The reactions were carried out in the presence of $PdCl_2(Ph_3P)_2$ (10 mol%) and Cs_2CO_3 (3 equiv) in THF (at 100 °C in a sealed tube) or in toluene (at reflux) under an Ar atmosphere. According to the structure of the substrates, a bridged or spiro compound was obtained. Thus, in the case of 2-(2-bromobenzyl)cycloalkanones **18a–c**, the α,γ-bridged β-tetralone derivatives **55**,[23] **57**,[24] and **58** were formed, respectively, in modest to good yields in THF (runs 1, 2 and 5). The debromo derivative **56**[25] was isolated as a by-product in run 1, where the yield of the cyclized product **55** was low. Using toluene as a solvent gave rise to only a trifling difference (run 3). Addition of Ph_3P brought about no improvement, but required a longer reaction time (run 4). On the other hand, 2-bromophenethyl cycloalkanones **18d**, **18e** and 2-[3-(2bromophenyl)propyl]cyclohexanone **18f** were cyclized to afford the spiro derivatives **59**, **62**, and **64**, respectively (runs 6–8), though the yield of **64** was modest due to formation of the debromo compound **65**[26] (run 8). Some other by-products **60**,[27] **61** (run 6), **63** (run 7) were also isolated. The enone derivatives **61**, **63** were

Table 1. Pd-catalyzed intramolecular cyclization of the substrates with a ketone terminating group

Run[a]	Substrate	Solvent	Temperature	Time (h)	Product (isolated yield)	By-products (isolated yield)
1	 **18a**	THF[b]	100 °C	16	 **55**[c] 26%	 **56**[c] 19%
2	 **18b**	THF[b]	100 °C	13	 **57**[d] 83%	
3	**18b**	Toluene	Reflux	6	**57** 63%	
4[e]	**18b**	Toluene	Reflux	14	**57** 64%	
5	 **18c**	THF[b]	100 °C	14	 **58**[d] 61%	
6	 **18d**	THF[b]	100 °C	14	 **59**[c] 71%	 **60** 2%  **61**[c] 2%
7	 **18e**	Toluene	Reflux	12	 **62** 57%	 **63** 4%
8	 **18f**	THF[b]	100 °C	14	 **64** 35%	 **65** 29%

[a] All reactions were carried out in the presence of $PdCl_2(Ph_3P)_2$ (10 mol%) and Cs_2CO_3 (3 equiv).
[b] In a sealed tube.
[c] Obtained as an inseparable mixture, isolated after acetallization followed by separation and acid hydrolysis.
[d] Contained trace amount (less then 2%) of inseparable contaminants.
[e] Ph_3P (0.3 equiv) was added.

Table 2. Pd-catalyzed intramolecular cyclization of the substrates with a formyl terminating group

Run[a]	Substrate	Solvent	Temperature	Time (h)	Products (isolated yield)	
1	 **19**-*trans*	Toluene	Reflux	5	 **67**-*trans* 76%	 **67**-*cis* 11%
2	**19**-*trans*	THF[b]	100 °C	24	 **66** **66**+**67**-*trans*[c] (46%, 1:1.7)	**67**-*cis* 9%
3	 **19**-*cis*	Toluene	Reflux	6	**66**+**67**-*trans*[c] (45%, 1:2.5)	**67**-*cis* 17%
4	**19**-*cis*	THF[b]	100 °C	22	**66**+**67**-*trans*[c] (50%, 1:1.6)	**67**-*cis* 10%
5	 **20**-*trans*	Toluene	Reflux	3	 **68**-*trans* (α-CHO) 4% **68**-*cis* (β-CHO) 49%	 **69**-*trans* 22%
6	**20**-*trans*	THF[b]	100 °C	3	**68**-*trans* 9% **68**-*cis* 52%	
7	 **20**-*cis*	Toluene	Reflux	3	**68**-*trans* 22% **68**-*cis* 52%	 **69**-*trans* (α-H) trace **69**-*cis* (β-H) 6%
8	**20**-*cis*	THF[b]	100 °C	3	**68**-*trans* 7% **68**-*cis* 48%	
9	 **21**	Toluene	Reflux	3.5	 **70**-*trans* (α-CHO) +**70**-*cis*[d] (β-CHO) (1:7.5) 14%	 **71**-*trans* (α-H) 34% **71**-*cis* (α-H) 10%
10	**21**	THF	Reflux	14	**70**-*trans*+**70**-*cis*[d] (1:4.2) 65%	**71**-*trans* 11% **71**-*cis* 6%
11	 **22**	Toluene	Reflux	1.5	 **72**[e] (**77** 32%)	 **73** 23%
12	**22**	THF	Reflux	14	**73** 23%	 **67**-*trans* 30%
13	 **23**	Toluene	Reflux	4	 **74**[e] (**78** 40%)	

[a] All reactions were carried out in the presence of $PdCl_2(Ph_3P)_2$ (10 mol%) and Cs_2CO_3 (3 equiv).
[b] In a sealed tube.
[c] Mixture, separated and characterized after reduction with $NaBH_4$.
[d] The ratios were determined by GC.
[e] Characterized after reduction with $NaBH_4$. The figures denote the yield of the resulting alcohols **77**, **78** (Fig. 1).

probably formed by Pd-catalyzed dehydrogenation of **59**, **62**, respectively. In runs 1 and 6, inseparable mixtures of **55** and **56**, and **59** and **61** were transformed to mixtures of ethylene acetals, followed by isolation and acid hydrolysis to give pure **55** and **59**. To sum up, our reaction conditions with $PdCl_2(Ph_3P)_2$ and Cs_2CO_3 were found to be useful for the intramolecular α-arylation of aliphatic ketones.

2.2.2. Formyl terminating group. Next we looked into the Pd-catalyzed intramolecular α-arylation of the substrates (**19**–**23**) with a formyl terminating group (Table 2). The reactions were executed in the same manner as described in Table 1 with $PdCl_2(Ph_3P)_2$ (10 mol%) and Cs_2CO_3 (3 equiv) in refluxing toluene or in THF at 100 °C (sealed tube) or at reflux. The following results were obtained.

(i) The arylation towards the formyl group took place at the α-position (α-arylation) to form **66**, **68**-*trans*, -*cis*, **70**-*trans*, -*cis*, **72**, and **74** or at the carbonyl carbon (carbonyl-arylation) to form **67**-*trans*, -*cis*, **69**-*trans*, -*cis*, **71**-*trans*, -*cis*, and **73**, depending on the reaction solvent. Thus, the α-arylation tended to increase in more polar THF. On the other hand, the carbonyl-arylation increased in less polar toluene (run 2 vs. 1, 6 vs. 5, 8 vs. 7, 10 vs. 9). The carbonyl-arylation can be evaluated as a weak basic intramolecular acylation method which can take the place of the strongly acidic Friedel–Crafts acylation.

(ii) In THF, there was no significant difference between the products from *trans* or *cis* substrate (run 2 vs. 4, 6 vs. 8), whereas the products in toluene reflected the configuration of the starting material to some extent (run 1 vs. 3, 5 vs. 7).

(iii) A six-membered ring was formed in preference to five- and seven-membered rings. Thus, even in THF as a solvent, six-membered carbonyl-arylation products **67**-*trans*, -*cis* were the major products from the substrates **19**-*trans*, -*cis* (runs 2 and 4). Furthermore, six-membered α-arylation products **68**-*trans*, -*cis* were formed preferentially from **20**-*trans*, -*cis* in toluene (run 5 and 7). On the other hand, in the case of the substrate **21** bearing a methoxy group on the benzene ring, the employed solvent exerted a greater influence upon the products; seven-membered products **71**-*trans*, -*cis* were obtained as major products in toluene (run 9).

(iv) Under the standard Heck reaction conditions with tertiary amine as a base, no reaction other than epimerization of the formyl group occurred. For example, attempted cyclization of **19**-*trans* with $Pd(OAc)_2$ (10 mol%), $P(o\text{-tol})_3$ (25 mol%), and *i*-Pr_2NEt (1.5 equiv) in toluene under reflux for 17 h resulted in formation of the epimer **19**-*cis* (14%) along with recovery of **19**-*trans* (41%).

(v) Use of stronger bases such as NaH, $(TMS)_2NK$, or *tert*-BuONa resulted in considerably lower yields. For example, on treatment of **21** with $PdCl_2(Ph_3P)_2$ (10 mol%), $(TMS)_2NK$ (5 equiv) in THF under reflux for 1.5 h, a mixture of **70**-*trans* and **70**-*cis* (1:20, 41%) was obtained, where the stereoselection of **70**-*cis* over **70**-*trans* was much higher than that with Cs_2CO_3.

The reaction mechanisms will be discussed later (vide infra). The products **66** and **67**-*trans*, obtained as a mixture, were reduced with $NaBH_4$ and the two products **75**, **76** (Fig. 1) were separated and characterized. As the formyl compounds **72** and **74** existed partially as enol-forms, these were characterized after respective conversion to **77** and **78** by $NaBH_4$ reduction. Structures of the obtained products were assigned as follows. The ring juncture of the compound **75** derived from **66** was determined to be *cis*, since in its NMR spectrum NOESY was observed between H-9a and methylene protons at C-4a, as depicted in Figure 1. The coupling constant ($J=9$ Hz) between H-4a and H-10 in the ^1H NMR spectrum of **76** derived from **67**-*trans* revealed both were axial protons. The *trans* ring juncture of **67**-*trans* was disclosed by the fact that the *J*-value between the ring juncture protons was 13 Hz, whereas the corresponding *J*-value of **67**-*cis* was 5 Hz. A mixture of **70**-*trans*, -*cis*, which we subsequently use as a synthetic intermediate of (±)-nominine,[11] partially crystallized on standing and repeated recrystallization provided **70**-*cis* (mp 130–131 °C, CH_2Cl_2–hexane), whose structure was unambiguously determined by single crystal X-ray analysis (Figure 2, see Section 4.5.5 for details). The stereochemistry of **68**-*trans* and -*cis* was determined from the similarity of their ^1H NMR spectra to those of **70**-*trans* and -*cis*. The *J*-value of the ring

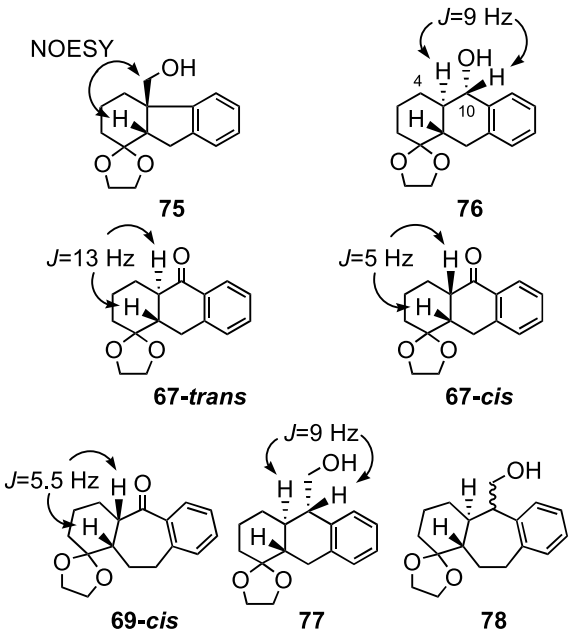


Figure 1. Structure determination of **67**-*trans*, -*cis*, **69**-*cis*, and **75**–**78**.

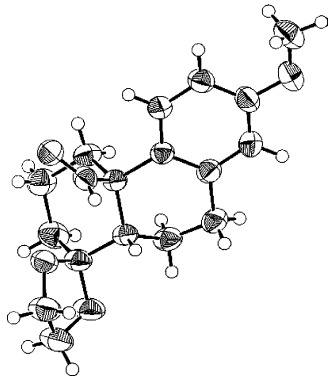
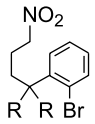
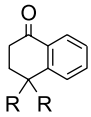
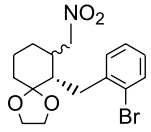
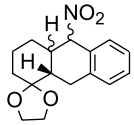
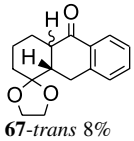
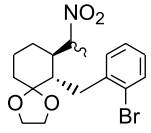
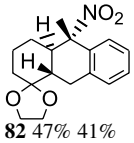
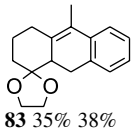
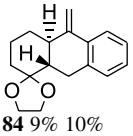
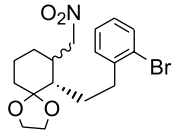
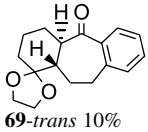
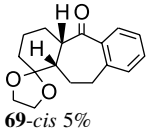
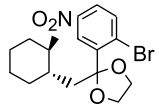
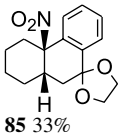
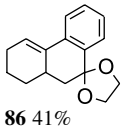
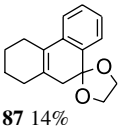


Figure 2. ORTEP drawing of **70**-*cis*.

Table 3. Pd-catalyzed intramolecular cyclization of the substrates with a nitro terminating group

Run[a]	Substrate	Solvent	Time (h)	Products (isolated yield)
1[b,c]	 **41**: R=H	Toluene	3	 **79**: R=H (α-tetralone) 59% **80**: R,R=O(CH$_2$)$_2$O 46%
2[b,c]	**42**: R,R=O(CH$_2$)$_2$O	Toluene	8	
3[b]	 **27**-*trans*	Benzene	6	 
4[b]	**27**-*cis*	Benzene	4	**81a**: α-H, α-NO$_2$ 58% **81b**: α-H, β-NO$_2$ 25% **81c**: βα-H, α-NO$_2$ 32% **67**-*trans* 8% **67**-*cis* 57%
5[d]	 **43**-major	Xylene	6	  
6[d]	**43**-minor	Xylene	6	**82** 47% 41% **83** 35% 38% **84** 9% 10%
7[c,d]	 **30**	Toluene	20	 
				69-*trans* 10% **69**-*cis* 5%
8[d]	 **44**	Toluene	22	  
				85 33% **86** 41% **87** 14%

[a] All reactions other than run 8 were carried out at the solvent reflux temperature, whereas run 8 was carried out at 140 °C in a sealed tube.
[b] In the presence of $PdCl_2(Ph_3P)_2$ (5 mol%) and Cs_2CO_3 (2 equiv).
[c] The products were isolated as ketones with: (1) KOH or Cs_2CO_3, (2) H_2SO_4.
[d] In the presence of $PdCl_2(Ph_3P)_2$ (10 mol%) and Cs_2CO_3 (3 equiv).

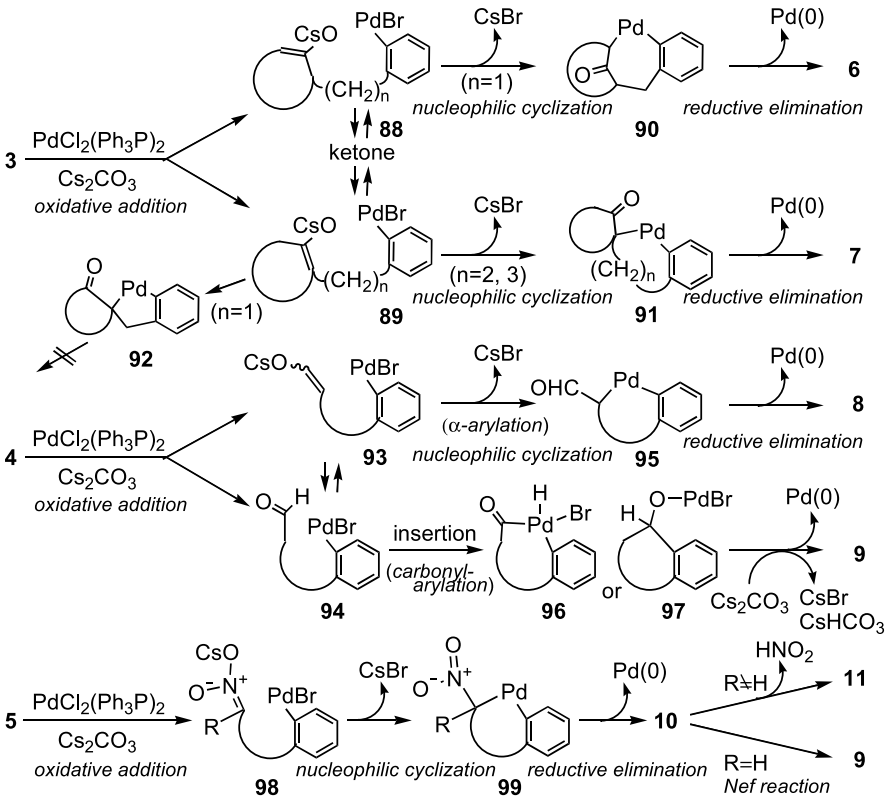
juncture protons of **69**-*cis* was 5.5 Hz, and the structures of **71**-*trans*, -*cis* were deduced as above by comparison of their ^{1}H NMR spectra with those of **69**-*trans*, -*cis*. The compound **77** derived from **72** also has $J=9$ Hz between H-4a and H-10, like **76**, and this proved the structure as depicted, whereas the stereochemistry of the formyl group of **74** was unable to be determined from the ^{1}H NMR of **78**. Thus, the reaction system of $PdCl_2(Ph_3P)_2$, Cs_2CO_3 in toluene or THF was proved to be effective for the intramolecular cyclization of substrates with a formyl terminating group to obtain polycyclic compounds such as **67**–**74**.

2.2.3. Nitro terminating group. We next investigated whether the above reaction system is applicable to the intramolecular α-arylation of the substrates (**27**-*trans*, -*cis*, **30**, **41**–**44**) with a nitro terminating group (Table 3). The reactions were executed with the same reaction system as for Table 1 with $PdCl_2(Ph_3P)_2$ (5 mol% for runs 1–4, 10 mol% for runs 5–8) and Cs_2CO_3 (2 equiv for runs 1–4, 3 equiv for runs 5–8). Benzene, toluene, or xylene was employed as the reaction solvent, since the α-position of nitroalkane is acidic enough to generate a Cs salt with Cs_2CO_3 even in such non-polar solvents. All the reactions other than run 8 were carried out at the refluxing temperature of the solvents used, whereas run 8 was performed at 140 °C in a sealed tube. The following points are apparent from Table 3.

(i) Cyclization of simple substrates with high flexibility, **41**, **42**, afforded the bicyclic α-tetralone (**79**) and **80** only in moderate yields (runs 1 and 2). In contrast, stereochemically more restricted substrates, **27**-*trans*, -*cis*, **43**-major, -minor, and **44**, provided tricyclic products in high combined yields, around 90% (runs 3–6 and 8).

(ii) Primary nitro derivatives cyclized readily at the temperature of benzene reflux (runs 3 and 4), whereas secondary ones required an elevated temperature (runs 5, 6 and 8).

(iii) The secondary nitro group of the products was partially transformed into a ketone group (runs 1–4 and 7) to form **79**, **80**, **67**-*trans*, -*cis*, **69**-*trans*, -*cis*; and the tertiary nitro group was partially eliminated to afford a styrene-type olefin (runs 5, 6 and 8), **83**, **84**, **86**, **87**. The products of runs 1, 2 and 7 were isolated after treatment with base (KOH or Cs_2CO_3) and then with H_2SO_4 (Nef reaction conditions), since the initial nitro products



Scheme 7. Proposed reaction mechanism for the Pd-catalyzed intramolecular α-arylation reactions.

were gradually converted to ketone during purification on SiO_2.

Thus, the nitro group could function as a terminating group in the intramolecular arylation reaction to provide a variety of compounds, such as **79**–**87**.

2.3. Proposed reaction mechanism

The following reaction mechanisms are proposed for the above Pd-catalyzed intramolecular α-arylation reactions (Scheme 7).

2.3.1. Ketone terminating group. On treatment of **3** with $PdCl_2(Ph_3P)_2$ and Cs_2CO_3, palladated cesium enolates **88** and **89** are generated. Nucleophilic cyclization from enolates to palladium of **88** and **89** takes place to form six- or seven-membered palladacycles **90** ($n=1$) and **91** ($n=2$, 3), which are then transformed to products **6** and **7**, respectively, via reductive elimination of Pd(0). The high yield (83%) of **57** (Table 1, run 2) suggests the existence of an equilibrium between **88** and **89** through the intermediary ketone. The five-membered palladacycle **92** may be generated from **89** ($n=1$), but neither **92** itself nor benzocyclobutene derived reductively from **92** has been isolated so far.

2.3.2. Formyl terminating group. The palladated cesium enolate **93** is readily generated in a more polar solvent, THF. This intermediate is led to **8** via **95** in the same manner as above (α-arylation). On the other hand, in a less polar solvent, toluene, the enolization is so slow that the ratio of aldehyde **94** to enolate **93** would increase, and insertion of palladium (II) into the formyl C–H bond (**96**) or of carbonyl group into the Pd–aryl bond (**97**) occurs to produce **9** (carbonyl-arylation). Intermediary seven- and eight-membered palladacycles **96** (or six- and seven-membered alkoxypalladium species **97**) are formed and are led to **67** and **69**, **71**, **73**, respectively (Table 2). In contrast, no nine-membered palladacycle (or eight-membered alkoxypalladium) seemed to be formed from **23**, and only the α-arylation product **74** was obtained even in toluene (Table 2, run 13). The reaction mechanism for the formation of the deformylated product **67**-*trans* from **22** (Table 2, run 12) remains unclear.

2.3.3. Nitro terminating group. The α-position of a nitro alkane is so acidic that the palladated cesium salt **98** is readily formed with $PdCl_2(Ph_3P)_2$ and Cs_2CO_3 even in a non-polar solvent, such as benzene, toluene, or xylene. Then **98** is cyclized to the palladacycle **99** and subsequent reductive elimination affords the nitro product **10**. Partial Nef reaction of **10** takes place with excess Cs_2CO_3 and saturated NH_4Cl–H_2O or citric acid–H_2O used for the quenching to give **9** in the case of R=H, whereas **10** being tertiary nitro compound, β-elimination of HNO_2 occurs to afford the styrene **11**.

3. Conclusion

In summary, ketone, formyl, and nitro groups were proved to function as efficient terminators in the intramolecular Pd-catalyzed arylation reaction with $PdCl_2(Ph_3P)_2$ and Cs_2CO_3 to afford various kinds of carbocyclic compounds. The cyclization products are expected to serve as exploitable

intermediates for synthetic studies of complex natural products, including terpenes, alkaloids and so on.

4. Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus (hot plate), and are not corrected. MS and high-resolution MS (HRMS) were recorded on a Hitachi M-80B spectrometer in gas chromatography (GC) or direct inlet (DI) mode at an ionizing voltage of 70 eV, and figures in parentheses indicate the relative intensities. IR spectra were measured on a Hitachi 215 or Shimadzu IR-460 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian EM390 (90 MHz) or on a Varian Mercury 300 (300 MHz) in $CDCl_3$ unless otherwise specified with tetramethylsilane as an internal reference. ^{13}C NMR spectra were measured on a Varian Mercury 300 (75 MHz) in $CDCl_3$. Column chromatography was conducted on silica gel (SiO_2, Fuji Davison BW 200), and weight of SiO_2, eluting solvent were indicated in parentheses. Preparative TLC (PTLC) was carried out on glass plates (20×20 cm^2) coated with Merck Silica gel $60PF_{254}$ (0.8 mm thick) unless otherwise specified and developing solvent was indicated in parentheses. Usual work-up refers to washing of the organic layers with water or brine, drying over anhydrous Na_2SO_4, and evaporating off the solvents under reduced pressure.

4.1. Preparation of 2-[ω-(2-bromophenyl)alkyl]cycloalkanones (18a–f)

4.1.1. 2-[(2-Bromophenyl)methyl]cyclohexanone (18b). Preparation of **18b** was described as a typical procedure. *n*-BuLi (1.47 M, 1.90 ml, 2.79 mmol) was added to a cooled (0 °C) solution of *i*-Pr_2NH (0.50 ml, 3.57 mmol) in THF (4 ml) under an Ar atmosphere and the mixture was stirred for 10 min. A THF (4 ml) solution of *N*-cyclohexylidenecyclohexylamine (501 mg, 2.80 mmol) was added dropwise to this and the whole was stirred at 0 °C for 30 min. The mixture was cooled to −18 °C and a THF (2 ml) solution of 2-bromobenzyl bromide (**15**, 500 mg, 2.00 mmol) was added. After having been stirred at −18 °C for 40 min, saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up left a residue (790 mg). Oxalic acid in H_2O (1 M, 3.0 ml, 3.0 mmol) was added to a solution of the residue in THF (12 ml) and the mixture was stirred at 27 °C for 6 h. H_2O was added and the whole was extracted with CH_2Cl_2. Washing with saturated $NaHCO_3$-H_2O, usual work-up followed by SiO_2 column chromatography [15 g, hexane–EtOAc (39:1)] afforded **18b** (485 mg, 91%) as a colorless oil. Anal. [2,4-dinitrophenylhydrazone, mp 163–164 °C, orange prisms (MeOH–CH_2Cl_2)] calcd for $C_{19}H_{19}BrN_4O_4$: C, 51.02; H, 4.28; Br, 17.86; N, 12.53. Found: C, 50.91; H, 4.16; Br, 17.70; N, 12.42. GC–MS *m/z*: 187 (M^+-Br, 100), 171, 169 (23, 22), 115 (26), 91 (25), 42 (29). IR (neat) cm^{-1}: 1710. ^{1}H NMR (90 MHz) δ: ca. 1.14–2.23 (6H, m), ca. 2.23–2.92 (4H, m), 3.14–3.54 (1H, m), 6.91–7.36 (3H, m), 7.44–7.63 (1H, m).

4.1.2. 2-[(2-Bromophenyl)methyl]cyclopentanone (18a). Colorless oil. Anal. [2,4-dinitrophenylhydrazone, mp 147–148 °C, yellow needles (MeOH–CH_2Cl_2)] calcd for $C_{18}H_{17}BrN_4O_4$: C, 49.90; H, 3.96; Br, 18.44; N, 12.93. Found: C, 49.77; H, 3.89; Br, 18.25; N, 12.79. GC–MS *m/z*: 173 (M^+-Br, 100), 171, 169 (11, 11), 145 (9), 131 (19), 117 (11), 116 (10), 115 (11). IR ($CHCl_3$) cm^{-1}: 1735. ^{1}H NMR (90 MHz) δ: 1.32–2.81 (8H, m), 3.14–3.55 (1H, m), 6.94–7.33 (3H, m), 7.54 (1H, d, $J=7.5$ Hz).

4.1.3. 2-[(2-Bromophenyl)methyl]cycloheptanone (18c). Colorless oil. GC–MS *m/z*: 239, 237 (M^+-COCH_2-H, 10, 10), 201 (100), 184, 182 (8, 8), 171, 169 (29, 30), 119 (36), 83 (53), 56 (35), 42 (53). IR (neat) cm^{-1}: 1700. ^{1}H NMR (90 MHz) δ: 1.13–2.04 (8H, m), 2.31–2.62 (2H, m), 2.68 (1H, dd, $J=12$, 7 Hz), ca. 2.76–3.16 (1H, m), 3.21 (1H, dd, $J=12$, 5.5 Hz), 6.91–7.31 (3H, m), 7.53 (1H, d, $J=7.5$ Hz).

4.1.4. 2-[2-(2-Bromophenyl)ethyl]cyclopentanone (18d). Colorless oil. GC–MS *m/z*: 187 (M^+-Br, 12), 184, 182 (2, 2), 171, 169 (8, 8), 84 (100), 42 (15). IR (neat) cm^{-1}: 1730. ^{1}H NMR (90 MHz) δ: 1.24–2.52 (9H, m), 2.80 (2H, t, $J=7.5$ Hz), 6.91–7.32 (3H, m), 7.51 (1H, d, $J=7.5$ Hz).

4.1.5. 2-[2-(2-Bromophenyl)ethyl]cyclohexanone (18e). Colorless oil. GC–HRMS calcd for $C_{14}H_{17}BrO$: 282.0443, 280.0462. Found: 282.0427, 280.0484. GC–MS *m/z*: 282, 280 (M^+, 0.5, 0.6), 201 (2), 184, 182 (2, 2), 171, 169 (7, 7), 98 (100), 83 (10), 70 (15), 56 (7), 42 (13). IR ($CHCl_3$) cm^{-1}: 1706. ^{1}H NMR (90 MHz) δ: 1.16–2.57 (11H, m), 2.76 (2H, t, $J=7.5$ Hz), 6.90–7.36 (3H, m), 7.51 (1H, d, $J=7.5$ Hz).

4.1.6. 2-[3-(2-Bromophenyl)propyl]cyclohexanone (18f). Colorless oil. GC–HRMS calcd for $C_{15}H_{19}BrO$: 296.0599, 294.0619. Found: 296.0590, 294.0600. GC–MS *m/z*: 296, 294 (M^+, 6, 6), 215 (2), 184, 182 (5, 4), 171, 169 (16, 11), 111 (27), 98 (100), 56 (23), 42 (23). IR (neat) cm^{-1}: 1705. ^{1}H NMR (90 MHz) δ: 1.04–2.56 (13H, m), 2.70 (2H, t, $J=7.5$ Hz), 6.88–7.30 (3H, m), 7.49 (1H, d, $J=7.5$ Hz).

4.2. Preparation of 19–23

4.2.1. 2-[(2-Bromophenyl)methyl]-2-cyclohexenone (25). *tert*-BuOK (2.240 g, 20 mmol) and *tert*-BuOH (2.00 ml, 20.9 mmol) were added to a solution of **24** (3.040 g, 20 mmol) in THF (20 ml) and the mixture was stirred at 20 °C for 5 min. After the mixture having been cooled (−78 °C), liq. NH_3 (ca. 70 ml) and THF (5 ml) were added and Na (1.150 g, 50 mmol) was slowly added portionwise in small pieces and the whole was stirred at −78 °C for 30 min. A solution of **15** (4.002 g, 16 mmol) in THF (5 ml) was added dropwise and the resulting mixture was stirred at −78 °C for 15 min. After removal of NH_3 with stirring at an ambient temperature, brine and CH_2Cl_2 were added and then the pH of aqueous layer was adjusted to ca. 4 with 10% HCl–H_2O. Separation of the layers followed by usual work-up left a residue (5.93 g). The residue and oxalic acid (2.50 g, 27.8 mmol) were dissolved in 1,2-dichloroethane (60 ml) and H_2O (5 ml) and the solution was refluxed with stirring for 2 h. Saturated $NaHCO_3$-H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and purification by SiO_2 column chromatography [35 g, hexane–EtOAc (9:1)] afforded 2-[(2-bromophenyl)methyl]-3-cyclohexenone (106 mg, 2.5%) and **25** (3.148 g, 74%) in order of increasing polarity.

Compound **25**. Colorless syrup. GC–MS *m/z*: 185 (M^+-Br, 100), 157 (8), 129 (21), 115 (11). IR ($CHCl_3$) cm^{-1}: 1664. ^1H NMR (90 MHz) δ: 1.79–2.16 (2H, m), 2.16–2.62 (4H, m), 3.57–3.79 (2H, m), 6.36–6.57 (1H, m), 6.96–7.35 (3H, m), 7.56 (1H, d, $J=8$ Hz).

2-[(2-Bromophenyl)methyl]-3-cyclohexenone. Colorless syrup. GC–HRMS calcd for $C_{13}H_{13}BrO$: 266.0130, 264.0150. Found: 266.0153, 264.0166. GC–MS *m/z*: 266, 264 (M^+, 0.5, 0.8), 185 (100), 171, 169 (77, 79), 143 (34), 128 (40), 39 (28). IR ($CHCl_3$) cm^{-1}: 1715. ^1H NMR (90 MHz) δ: 2.29–3.00 (4H, m), 2.73 (1H, dd, $J=16$, 11 Hz), 3.13–3.39 (1H, m), 3.35 (1H, dd, $J=16$, 5.5 Hz), 5.57 (1H, br d, $J=10$ Hz), 5.84 (1H, br d, $J=10$ Hz), 6.94–7.33 (3H, m), 7.54 (1H, d, $J=8$ Hz).

4.2.2. (2*S,3*R**)- and (2*S**,3*S**)-2-[(2-Bromophenyl)-methyl]-3-(nitromethyl)cyclohexanones (26-*trans* and 26-*cis*).** A solution of **25** (146 mg, 0.551 mmol), CH_3NO_2 (0.45 ml, 8.31 mmol), KF (13 mg, 0.224 mmol), and 18-crown-6 (29 mg, 0.110 mmol) in CH_3CN (4 ml) was stirred under reflux for 12 h. After having been cooled, saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and separation by PTLC [hexane–EtOAc (24:1)] provided **26**-*trans* (117 mg, 64%) and **26**-*cis* (58 mg, 32%) in order of decreasing polarity.

Compound **26**-*trans*. Colorless prisms, mp 101–102 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{14}H_{16}BrNO_3$: C, 51.55; H, 4.94; Br, 24.50; N, 4.30. Found: C, 51.48; H, 4.94; Br, 24.41; N, 4.39. GC–MS *m/z*: 281, 279 (M^+-NO_2, 7, 7), 246 (68), 211, 209 (25, 27), 185 (100), 171, 169 (50, 49), 128 (27), 115 (23), 90 (29), 41 (45). IR (KBr) cm^{-1}: 1707, 1550. ^1H NMR (300 MHz) δ: 1.60–1.86 (2H, m), 2.00–2.14 (2H, m), 2.34 (1H, dddd, $J=13.5$, 11, 5.5, 1 Hz), 2.50 (1H, dddd, $J=13.5$, 5.5, 5.5, 1 Hz), 2.57 (1H, ddddd, $J=9.5$, 9.5, 9.5, 4.5, 4.5 Hz), 2.72 (1H, dddd, $J=9.5$, 8.5, 4, 1 Hz), 2.85 (1H, dd, $J=14$, 4 Hz), 3.29 (1H, dd, $J=14$, 8.5 Hz), 4.41 (1H, dd, $J=12.5$, 9.5 Hz), 4.73 (1H, dd, $J=12.5$, 4.5 Hz), 7.07 (1H, ddd, $J=8$, 8, 2 Hz), 7.23 (1H, ddd, $J=8$, 8, 1.5 Hz), 7.41 (1H, dd, $J=8$, 2 Hz), 7.51 (1H, dd, $J=8$, 1.5 Hz).

Compound **26**-*cis*. Colorless prisms, mp 75–76 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{14}H_{16}BrNO_3$: C, 51.55; H, 4.94; Br, 24.50; N, 4.30. Found: C, 51.41; H, 4.90; Br, 24.29; N, 4.45. GC–MS *m/z*: 281, 279 (M^+-NO_2, 14, 13), 246 (100), 211, 209 (38, 41), 185 (80), 171, 169 (65, 66), 128 (35), 115 (28), 90 (38), 41 (61). IR (KBr) cm^{-1}: 1716, 1558. ^1H NMR (300 MHz) δ: 1.80–2.10 (4H, m), 2.32–2.52 (2H, m), 2.67 (1H, dd, $J=12.5$, 3.5 Hz), 3.07–3.24 (4H, m), 4.30 (1H, dd, $J=12.5$, 11 Hz), 4.52 (1H, dd, $J=12.5$, 4 Hz), 7.09 (1H, ddd, $J=8$, 7.5, 1.5 Hz), 7.24 (1H, ddd, $J=7.5$, 7.5, 1 Hz), 7.31 (1H, dd, $J=7.5$, 1.5 Hz), 7.54 (1H, dd, $J=8$, 1 Hz).

4.2.3. (6*S,7*R**)-6-[(2-Bromophenyl)methyl]-7-(nitromethyl)-1,4-dioxaspiro[4,5]decane (27-*trans*).** A solution of **26**-*trans* (84 mg, 0.258 mmol), ethylene glycol (0.29 ml, 5.21 mmol), and *p*-TsOH·H_2O (4 mg, 0.021 mmol) in benzene (5 ml) was refluxed with a Dean–Stark water-separator for 2.5 h. After having been cooled, saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–EtOAc (9:1)] gave **27**-*trans* (94 mg, 99%) as a colorless syrup. DI–HRMS calcd for $C_{16}H_{20}BrNO_4$: 371.0555, 369.0575. Found: 371.0562, 369.0558. DI–MS *m/z*: 371, 369 (M^+, 1, 1), 341, 339 (1, 1), 325. 323 (6, 6), 311, 309 (2, 3), 171, 169 (14, 15), 141 (17), 99 (100), 86 (28), 41 (24). IR ($CHCl_3$) cm^{-1}: 1554. ^1H NMR (90 MHz) δ: 1.10–2.19 (7H, m), 2.31–2.68 (1H, m), 2.77 (1H, dd, $J=14.5$, 10 Hz), 3.20 (1H, dd, $J=14.5$, 4 Hz), 3.96 (4H, s), 4.40 (1H, dd, $J=12.5$, 8.5 Hz), 4.56 (1H, dd, $J=12.5$, 6.5 Hz), 6.95–7.35 (3H, m), 7.56 (1H, d, $J=8$ Hz).

4.2.4. (6*S,7*S**)-6-[(2-Bromophenyl)methyl]-7-(nitromethyl)-1,4-dioxaspiro[4,5]decane (27-*cis*).** In the same manner as for the preparation of **27**-*trans*, **27**-*cis* (62 mg, 98%) was obtained from **26**-*cis* (56 mg, 0.200 mmol) after PTLC [hexane–EtOAc (14:1)] as a colorless syrup. DI–HRMS calcd for $C_{16}H_{20}BrNO_4$: 371.0555, 369.0575. Found: 371.0555, 369.0602. DI–MS *m/z*: 371, 369 (M^+, 1, 1), 341, 339 (2, 1), 325. 323 (8, 9), 311, 309 (4, 5), 171, 169 (23, 23), 141 (26), 99 (100), 86 (38), 41 (24). IR ($CHCl_3$) cm^{-1}: 1553. ^1H NMR (90 MHz) δ: 1.19–2.17 (6H, m), 2.28–2.76 (2H, m), 2.65 (1H, dd, $J=14$, 9.5 Hz), 3.15 (1H, dd, $J=14$, 3.5 Hz), 3.97 (4H, s), 4.50 (1H, dd, $J=12.5$, 5 Hz), 4.65 (1H, dd, $J=12.5$, 9.5 Hz), 6.96–7.35 (3H, m), 7.56 (1H, d, $J=8$ Hz).

4.2.5. (6*S,7*R**)-6-[(2-Bromophenyl)methyl]-1,4-dioxaspiro[4,5]decane-7-carboxaldehyde (19-*trans*).** KOH (85%, 12 mg, 0.182 mmol) was added to a solution of **27**-*trans* (61 mg, 0.165 mmol) in MeOH (3 ml) and the mixture was stirred at 0 °C for 15 min. To this mixture was added a solution of $KMnO_4$ (17.5 mg, 0.111 mmol) and $MgSO_4$ (15 mg, 0.125 mmol) in MeOH–H_2O (1:1, 1 ml) and the whole was stirred at 0 °C for 30 min and at 17 °C for 30 min. Citric acid–H_2O (0.1 N) was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$-H_2O and then treated as usual. Separation by PTLC [hexane–CH_2Cl_2 (3:2)] afforded **19**-*trans* (40 mg, 72%) as a colorless syrup along with recovered **27**-*trans* (7.5 mg, 12%). DI–MS *m/z*: 312, 310 (M^+-CO, 15, 12), 269, 267 (4, 5), 171, 169 (12, 21), 141 (34), 99 (100), 86 (20), 55 (20). IR ($CHCl_3$) cm^{-1}: 1720. ^1H NMR (90 MHz) δ: 1.32–2.03 (6H, m), 2.13–2.36 (1H, m), 2.49–2.95 (2H, m), 3.04–3.36 (1H, m), 3.76–4.18 (4H, m), 6.93–7.31 (3H, m), 7.54 (1H, d, $J=7.5$ Hz), 9.37 (1H, s).

4.2.6. (6*S,7*S**)-6-[(2-Bromophenyl)methyl]-1,4-dioxaspiro[4,5]decane-7-carboxaldehyde (19-*cis*).** In the same manner as above, **27**-*cis* (70 mg, 0.189 mmol) was led to **19**-*cis* (43 mg, 67%), colorless syrup, along with recovered **27**-*cis* (13 mg, 19%). DI–MS *m/z*: 312, 310 (M^+-CO, 17, 14), 269, 267 (6, 6), 171, 169 (15, 23), 141 (44), 99 (100), 86 (20), 55 (18). IR ($CHCl_3$) cm^{-1}: 1713. ^1H NMR (90 MHz) δ: 1.27–2.16 (6H, m), 2.40–2.68 (1H, m), 2.68–3.14 (2H, m), 3.30 (1H, dd, $J=12$, 3 Hz), 4.03 (4H, s), 6.96–7.42 (3H, m), 7.58 (1H, d, $J=7.5$ Hz), 9.77 (1H, s).

4.2.7. 2-[2-(2-Bromophenyl)ethyl]-2-chlorocyclohexanone (28). A solution of SO_2Cl_2 (0.32 ml, 3.98 mmol) in CCl_4 (3 ml) was added dropwise during 2 min to a cooled (0 °C) solution of **18e** (939 mg, 3.34 mmol) in CCl_4 (7 ml). The stirring was continued at 0 °C for 30 min and at 22 °C for 2.5 h. Saturated $NaHCO_3$-H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up followed by SiO_2

column chromatography [40 g, hexane–benzene (3:2)] furnished **28** (855 mg, 81%) as a colorless syrup. DI–HRMS calcd for $C_{14}H_{16}^{81}Br^{37}ClO$, $C_{14}H_{16}^{81}Br^{35}ClO$, $C_{14}H_{16}^{79}Br^{37}ClO$, $C_{14}H_{16}^{79}Br^{35}ClO$: 318.0024, 316.0053, 316.0043, 314.0073. Found: 318.0012, 316.0071, 316.0021, 314.0073. DI–MS *m/z*: 318, 316, 314 (M^+, 0.1, 0.6, 0.4), 280, 278 (0.7, 0.7), 237, 235 (0.5, 0.6), 171, 169 (17, 18), 134, 132 (34, 100), 97 (14), 90 (14). IR ($CHCl_3$) cm^{-1}: 1721. ^1H NMR (90 MHz) δ: 1.13–2.54 (10H, m), 2.76 (2H, t, $J=7.5$ Hz), 6.91–7.38 (3H, m), 7.52 (1H, d, $J=7.5$ Hz).

4.2.8. 2-[2-(2-Bromophenyl)ethyl]-2-cyclohexenone (29). LiBr (56 mg, 0.644 mmol) and Li_2CO_3 (48 mg, 0.649 mmol) were added to a solution of **28** (170 mg, 0.539 mmol) in DMF (3 ml) and the mixture was heated in an oil bath at 120 °C under an Ar atmosphere for 1 h. After having been cooled, H_2O was added and the whole was extracted with EtOAc. Usual work-up and PTLC [hexane–benzene (1:1)] provided **29** (111 mg, 74%) as a colorless syrup. GC–HRMS calcd for $C_{14}H_{15}BrO$: 280.0286, 278.0306. Found: 280.0293, 278.0289. GC–MS *m/z*: 280, 278 (M^+, 1, 1), 199 (100), 181 (13), 171, 169 (43, 44), 90 (25), 81 (23), 53 (38), 41 (19), 39 (19). IR ($CHCl_3$) cm^{-1}: 1662. ^1H NMR (90 MHz) δ: 1.74–2.14 (2H, m), 2.14–2.68 (6H, m), 2.68–3.05 (2H, m), 6.59 (1H, dd, $J=4$, 4 Hz), 6.91–7.34 (3H, m), 7.51 (1H, d, $J=7.5$ Hz).

4.2.9. 6-[2-(2-Bromophenyl)ethyl]-7-(nitromethyl)-1,4-dioxaspiro[4,5]decane (30). In a similar manner as for the preparation of **26** from **25**, **29** (106 mg, 0.380 mmol) was treated with CH_3NO_2 (0.41 ml, 7.57 mmol), KF (18 mg, 0.310 mmol), and 18-crown-6 (40 mg, 0.152 mmol) to give a residue (150 mg). The residue was subjected to acetalization with ethylene glycol (0.42 ml, 7.54 mmol) and *p*-TsOH·H_2O (5 mg, 26.3 μmol) to yield **30** (131 mg, 90% overall) as a colorless syrup after PTLC [hexane–EtOAc (6:1)], which consisted of two diastereomers (*trans*/*cis*=ca. 2) by gas chromatography (GC) analysis [OV-1; 180 °C; carrier gas: N_2 (115 kPa); *trans*: 47.4 min, *cis*: 50.6 min)]. GC–HRMS calcd for $C_{17}H_{22}BrNO_4$: 385.0712, 383.0731. Found: 385.0736, 383.0718. GC–MS *m/z*: 385, 383 (M^+, 1.6, 1.4), 355, 353 (1, 1), 339, 337 (5, 5), 325, 323 (1, 2), 214 (33), 171, 169 (9, 11), 141 (9), 99 (100), 86 (17), 55 (21), 41 (14). IR ($CHCl_3$) cm^{-1}: 1553. ^1H NMR (90 MHz) δ: 1.09–2.17 (9H, m), 2.42–2.85 (1H, m), 2.79 (1H, t, $J=7.5$ Hz), 3.73–4.09 (4H, m), 4.46 (1H, dd, $J=12$, 7 Hz), 4.69 (1H, dd, $J=12$, 5.5 Hz), 6.92–7.37 (3H, m), 7.53 (1H, d, $J=7.5$ Hz).

4.2.10. (6*S,7*R**)- and (6*S**,7*S**)-6-[2-(2-Bromophenyl)-ethyl]-1,4-dioxaspiro[4,5]decane-7-carboxaldehydes (20-*trans* and 20-*cis*).** In the same manner as for the preparation of **19** from **27**, **30** (117 mg, 0.305 mmol) was allowed to react with KOH (85%, 24 mg, 0.364 mmol), and then with $KMnO_4$ (32 mg, 0.203 mmol) and $MgSO_4$ (27 mg, 0.225 mmol) to afford **20**-*trans* (49 mg, 46%), **20**-*cis* (21 mg, 20%) and recovered **30** (16 mg, 14%) in order of decreasing polarity after PTLC (benzene).

Compound **20**-*trans*. Colorless syrup. GC–HRMS calcd for $C_{17}H_{21}BrO_3$: 354.0654, 352.0673. Found: 354.0647, 352.0681. GC–MS *m/z*: 354, 352 (M^+, 0.1, 0.1), 325, 323 (4, 4), 297, 295 (2, 2), 283, 281 (2, 2), 183 (17), 171, 169 (12, 14), 155 (53), 99 (100), 86 (25), 55 (24), 41 (17). IR ($CHCl_3$) cm^{-1}: 1718. ^1H NMR (90 MHz) δ: 1.17–2.33 (9H, m), 2.39–2.68 (1H, m), 2.85 (1H, t, $J=8$ Hz), 3.97 (4H, s), 6.98–7.44 (3H, m), 7.60 (1H, d, $J=7.5$ Hz), 9.75 (1H, s).

Compound **20**-*cis*. Colorless syrup. GC–HRMS calcd for $C_{17}H_{21}BrO_3$: 354.0654, 352.0673. Found: 354.0673, 352.0664. GC–MS *m/z*: 354, 352 (M^+, 0.1, 0.1), 325, 323 (4, 4), 297, 295 (2, 2), 283, 281 (2, 2), 183 (17), 171, 169 (12, 13), 155 (54), 99 (100), 86 (23), 55 (22), 41 (16). IR ($CHCl_3$) cm^{-1}: 1712. ^1H NMR (90 MHz) δ: 1.16–2.36 (9H, m), 2.60–3.04 (1H, m), 2.84 (1H, t, $J=7.5$ Hz), 3.97 (4H, s), 6.86–7.43 (3H, m), 7.57 (1H, d, $J=7.5$ Hz), 9.93 (1H, s).

4.2.11. 2-[2-(2-Bromo-5-methoxyphenyl)ethyl]cyclohexanone (32). *n*-BuLi (1.54 M, 17.5 ml, 27.0 mmol) was added to a cooled (0 °C) solution of *i*-Pr_2NH (4.25 ml, 30.4 mmol) in THF (40 ml) under an Ar atmosphere. After having been stirred for 30 min, *N*-cyclohexylidenecyclohexylamine (4.83 g, 27.0 mmol) in THF (10 ml) was added dropwise at 0 °C. Stirring was continued at the temperature for 30 min and at 27 °C for 1.5 h and then the mixture was cooled in an ice-salt bath (−18 °C). A THF (10 ml) solution of **31**[18] (7.67 g, 22.5 mmol) was added slowly at −18 °C under an Ar atmosphere and the mixture was stirred at −18 °C for 1 h. The resulting mixture was poured into saturated NH_4Cl–H_2O and the whole was extracted with EtOAc. After usual work-up, a residue (10.0 g) was obtained. The residue was dissolved in THF (40 ml) and H_2O (10 ml) and to this was added oxalic acid (2.63 g, 29.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and at 27 °C for 8 h. H_2O was added and the whole was extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$-H_2O and then worked up as usual. Purification was carried out by SiO_2 column chromatography [100 g, hexane–EtOAc (14:1)] to provide **32** (6.66 g, 95%) as a colorless syrup. GC–HRMS calcd for $C_{15}H_{19}BrO_2$: 312.0548, 310.0568. Found: 312.0533, 310.0550. GC–MS *m/z*: 312, 310 (M^+, 15, 14), 214, 212 (93, 100), 201, 199 (16, 16), 98 (63), 91 (28), 77 (26), 55 (24), 41 (53). IR ($CHCl_3$) cm^{-1}: 1711. ^1H NMR (300 MHz) δ: 1.38–1.57 (2H, m), 1.59–1.77 (2H, m), 1.80–1.92 (1H, m), 1.98–2.22 (3H, m), 2.25–2.46 (3H, m), 2.70 (2H, dd, $J=8$, 7.5 Hz), 3.77 (3H, s), 6.61 (1H, dd, $J=8.5$, 3 Hz), 6.79 (1H, d, $J=3$ Hz), 7.38 (1H, d, $J=8.5$ Hz). ^{13}C NMR δ: 24.9, 28.0, 29.8, 33.7, 34.0, 42.0, 50.0, 55.3, 113.1, 114.6, 115.6, 132.9, 142.3, 158.7, 212.6.

4.2.12. 2-Bromo-2-[2-(2-bromo-5-methoxyphenyl)ethyl]-cyclohexanone (33). NaI (10.1 g, 67.3 mmol) and TMSCl (8.53 ml, 67.3 mmol) were successively added to a cooled (0 °C) solution of **32** (16.1 g, 51.8 mmol) and $(TMS)_2NH$ (19.7 ml, 93.3 mmol) in CH_3CN (80 ml) under an Ar atmosphere. After stirring at 0 °C for 4 h, the mixture was poured into saturated $NaHCO_3$–H_2O and the whole was extracted with hexane. The hexane layer was separated from H_2O (lower) and CH_3CN (middle) layers and washed successively with saturated $CuSO_4$-H_2O and saturated $NaHCO_3$-H_2O, then was worked up as usual to leave a residue (19.3 g). The residue was dissolved in THF (100 ml) and to this was added portionwise NBS (9.68 g, 54.4 mmol) at −18 °C under an Ar atmosphere. Stirring was continued at −18 to 23 °C for 14 h. Saturated $NaHCO_3$–H_2O and saturated $Na_2S_2O_3$–H_2O were added to the mixture and the

whole was extracted with EtOAc. Usual work-up followed by SiO_2 column chromatography [150 g, hexane–benzene (1:1)] yielded **33** (16.2 g, 80%) along with recovered **32** (2.08 g, 13%).

Compound **33**. Colorless syrup. GC–HRMS calcd for $C_{15}H_{18}Br_2O_2$: 391.9634, 389.9654, 387.9673. Found: 391.9630, 389.9639, 387.9669. GC–MS *m/z*: 392, 390, 388 (M^+, 7, 14, 7), 311, 309 (5, 5), 310, 308 (6, 5), 229 (23), 214, 212 (100, 100), 201, 199 (36, 36), 178, 176 (21, 21), 77 (28), 41 (34). IR ($CHCl_3$) cm^{-1}: 1712. ^1H NMR (300 MHz) δ: 1.56–1.76 (1H, m), 1.79–1.98 (2H, m), 2.00–2.17 (2H, m), 2.15 (1H, ddd, $J=14.5$, 12, 5 Hz), 2.34–2.50 (2H, m), 2.51 (1H, dddd, $J=14.5$, 3, 3, 3 Hz), 2.84 (1H, ddd, $J=13$, 12, 5 Hz), 2.92 (1H, ddd, $J=13$, 12, 5 Hz), 3.24 (1H, ddd, $J=14.5$, 14, 6 Hz), 3.78 (3H, s), 6.64 (1H, dd, $J=9$, 3 Hz), 6.84 (1H, d, $J=3$ Hz), 7.39 (1H, d, $J=9$ Hz). ^{13}C NMR δ: 22.0, 26.5, 32.2, 37.1, 39.7, 40.4, 55.4, 70.3, 113.5, 114.5, 115.8, 133.0, 141.5, 158.8, 203.8.

4.2.13. 2-[2-(2-Bromo-5-methoxyphenyl)ethyl]-2-cyclohexenone (34). The same procedure as for the preparation of **29** from **28** and subsequent purification by SiO_2 column chromatography [40 g, hexane–1,2-dimethoxyethane (DME) (19:1)] provided **34** (1.632 g, 73%) from **33** (2.828 g, 7.25 mmol) as a colorless syrup. GC–HRMS calcd for $C_{15}H_{17}BrO_2$: 310.0392, 308.0412. Found: 310.0381, 308.0394. GC–MS *m/z*: 310, 308 (M^+, 14, 14), 229 (100), 211 (27), 201, 199 (39, 42), 77 (26), 53 (43), 41 (24). IR ($CHCl_3$) cm^{-1}: 1663. ^1H NMR (300 MHz) δ: 1.97 (2H, ddt, $J=7$, 7, 6 Hz), 2.30 (2H, dt, $J=4$, 6 Hz), 2.40–2.47 (2H, m), 2.44–2.52 (2H, m), 2.70–2.90 (2H, m), 3.76 (3H, s), 6.61 (1H, dd, $J=8.5$, 3 Hz), 6.63 (1H, br t, $J=4$ Hz), 6.74 (1H, d, $J=3$ Hz) 7.38 (1H, d, $J=8.5$ Hz). ^{13}C NMR δ: 23.0, 26.0, 30.0, 35.2, 38.5, 55.3, 113.2, 114.7, 115.8, 132.8, 138.2, 141.8, 145.9, 158.6, 198.9.

4.2.14. 6-[2-(2-Bromo-5-methoxyphenyl)ethyl]-7-(nitromethyl)-1,4-dioxaspiro[4,5]decane (35). In the same manner as for the preparation of **30** from **29**, **34** (1.57 g, 5.09 mmol) was converted to **35** (1.95 g, 93% in two steps) as a mixture of two diastereomers (*trans*/*cis*=ca. 2) after SiO_2 column chromatography [35 g, hexane–EtOAc (6:1)].

Compound **35**. Colorless syrup. DI–HRMS calcd for $C_{18}H_{24}BrNO_5$: 415.0817, 413.0837. Found: 415.0824, 413.0825. DI–MS *m/z*: 415, 413 (M^+, 5, 5), 369, 367 (5, 4), 214, 212 (31, 11), 201, 199 (7, 10), 99 (100), 86 (16), 55 (17), 41 (12). IR ($CHCl_3$) cm^{-1}: 1553. ^1H NMR (300 MHz) of *trans* and *cis* isomers δ: 1.28–1.98 (9H, m), 2.55–2.91 (3H, m), 3.78 (3H, s), 3.84–4.02 (4H, m), 4.49 and 4.50 (1H, dd each, $J=12.5$, 9, 12.5, 4.5 Hz, respectively), 4.69 and 4.60 (1H, dd each, $J=12.5$, 5.5, 12.5, 10.5 Hz, respectively), 6.63 (1H, dd, $J=8.5$, 3 Hz), 6.78 and 6.79 (1H, d each, $J=3$ Hz each), 7.39 and 7.40 (1H, d each, $J=8.5$ Hz each).

4.2.15. 6-[2-(2-Bromo-5-methoxyphenyl)ethyl]-1,4-dioxaspiro[4,5]decane-7-carboxaldehydes (21). In the same manner as for the preparation of **20** from **30**, **21** (1.36 g, 75%) was obtained from **35** (1.95 g, 4.71 mmol) along with recovered **35** (0.180 g, 9%, *trans*/*cis*=1.4) after SiO_2 column chromatography (40 g, benzene). The purified **21** was a mixture of two diastereomers (*trans*/*cis*=ca. 2.2) which was hardly separated.

Compound **21**. Colorless syrup. GC–HRMS calcd for $C_{18}H_{23}BrO_4$: 384.0759, 382.0779. Found: 384.0771, 382.0780. GC–MS *m/z*: 384, 382 (M^+, 4, 3), 355, 353 (3, 3), 275 (9), 214, 212 (7, 7), 201, 199 (10, 10), 183 (18), 155 (37), 142 (31), 99 (100), 55 (22), 41 (15). IR ($CHCl_3$) cm^{-1}: 1721. ^1H NMR (300 MHz) of *trans* and *cis* isomers δ: 1.38–2.24 (9H, m), 2.46–2.86 (3H, m), 3.78 (3H, s), 3.86–7.04 (4H, m), 6.63 (1H, dd, $J=9$, 3 Hz), 6.79 and 6.78 (1H, d each, $J=3$ Hz each), 7.40 (1H, d, $J=9$ Hz), 9.64 and 9.83 (1H, s each).

4.2.16. (2*S,3*S**)- and (2*S**,3*R**)-2-[(2-Bromophenyl)-methyl]-3-(2-propenyl)cyclohexanones (36-*trans* and 36-*cis*).** $TiCl_4$ (0.10 ml, 0.911 mmol) was added to a cooled (−78 °C) solution of **25** (122 mg, 0.460 mmol) and allyltrimethylsilane (0.22 ml, 1.39 mmol) under an Ar atmosphere and the mixture was stirred for 30 min at that temperature. Saturated $NaHCO_3$-H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and separation by PTLC [hexane–EtOAc (69:1)] provided **36**-*trans* (113 mg, 80%) and **36**-*cis* (19 mg, 13%) in order of decreasing polarity.

Compound **36**-*trans*. Colorless syrup. GC–MS *m/z*: 267, 265 (M^+−allyl, 2, 2), 227 (69), 185 (100), 171, 169 (43, 39), 41 (33), 39 (27). IR ($CHCl_3$) cm^{-1}: 1710, 1639. ^1H NMR (300 MHz) δ: 1.45–1.60 (1H, m), 1.65–1.86 (2H, m), 1.94–2.08 (2H, m), 2.11 (1H, br ddd, $J=14$, 8.5, 8.5 Hz), 2.30 (1H, dddd, $J=13$, 10, 5.5, 1 Hz), 2.38–2.50 (2H, m), 2.70 (1H, dddd, $J=8.5$, 8.5, 4.5, 1 Hz), 2.98 (1H, dd, $J=14$, 4.5 Hz), 3.14 (1H, dd, $J=14$, 8.5 Hz), 4.99–5.07 (2H, m), 5.74 (1H, dddd, $J=18$, 9, 8, 6.5 Hz), 7.03 (1H, ddd, $J=7.5$, 7.5, 2 Hz), 7.20 (1H, ddd, $J=7.5$, 7.5, 1 Hz), 7.34 (1H, dd, $J=7.5$, 2 Hz), 7.50 (1H, dd, $J=7.5$, 1 Hz).

Compound **36**-*cis*. Colorless syrup. GC–MS *m/z*: 267, 265 (M^+−allyl, 2, 4), 227 (100), 185 (66), 171, 169 (51, 56), 107 (49), 41 (70), 39 (35). IR ($CHCl_3$) cm^{-1}: 1711, 1640. ^1H NMR (300 MHz) δ: 1.48–2.57 (9H, m), 2.68 (1H, dd, $J=12.5$, 5 Hz), 2.90–3.15 (1H, m), 3.25 (1H, dd, $J=12.5$, 7.5 Hz), 4.89–5.27 (2H, m), 5.47–6.02 (1H, m), 6.93–7.44 (3H, m), 7.53 (1H, dd, $J=7.5$, 1.5 Hz).

4.2.17. (2*S,3*S**)- and (2*S**,3*R**)-2-[2-(2-Bromophenyl)-ethyl]-3-(2-propenyl)cyclohexanones (37-*trans* and 37-*cis*).** In the same manner as for the preparation of **36**-*trans* and -*cis* from **25**, **37**-*trans* (164 mg, 77%) and **37**-*cis* (48 mg, 22%) were obtained from **29** (192 mg, 0.688 mmol) after PTLC [hexane–DME (99:1)].

Compound **37**-*trans*. Colorless syrup. DI–MS *m/z*: 184, 182 (M^+−2-bromostyrene, 0.4, 0.5), 171, 169 (7, 8), 97 (100), 55 (17), 41 (45), 39 (22). IR ($CHCl_3$) cm^{-1}: 1703, 1635. ^1H NMR (90 MHz) δ: 1.22–2.96 (14H, m), 4.88–5.23 (2H, m), 5.76 (1H, dddd, $J=17.5$, 9, 6.5, 6.5 Hz), 6.92–7.39 (3H, m), 7.53 (1H, d, $J=8$ Hz).

Compound **37**-*cis*. Colorless syrup. GC–MS *m/z*: 184, 182 (M^+−2-bromostyrene, 0.5, 0.6), 171, 169 (8, 8), 97 (100), 55 (17), 41 (46), 39 (25). IR ($CHCl_3$) cm^{-1}: 1705, 1636. ^1H

NMR (90 MHz) δ: 1.26–2.87 (14H, m), 4.86–5.20 (2H, m), 5.69 (1H, dddd, $J=18$, 10, 7, 7 Hz), 6.93–7.38 (3H, m), 7.54 (1H, d, $J=7.5$ Hz).

4.2.18. (6*S,7*S**)-6-[(2-Bromophenyl)methyl]-7-(2-propenyl)-1,4-dioxaspiro[4,5]decane (38).** In the same way as for the preparation of **27**-*trans* from **26**-*trans*, **38** (124 mg, 97%) was obtained from **36**-*trans* (112 mg, 0.365 mmol) as a colorless syrup after purification by PTLC [hexane–EtOAc (14:1)]. GC–HRMS calcd for $C_{18}H_{23}BrO_2$: 352.0861, 350.0881. Found: 352.0847, 350.0884. GC–MS *m/z*: 352, 350 (M^+, 4, 4), 311, 309 (6, 7), 181 (10), 171, 169 (11, 11), 99 (100), 86 (30), 55 (14), 41 (16). IR ($CHCl_3$) cm^{-1}: 1635. ^1H NMR (90 MHz) δ: 0.87–2.57 (10H, m), 2.79 (1H, dd, $J=$ 15, 7 Hz), 3.08 (1H, dd, $J=15$, 5 Hz), 3.73–4.18 (4H, m), 4.89 (1H, br d, $J=18$ Hz), 4.93 (1H, br d, $J=11$ Hz), 5.40–5.92 (1H, m), 6.91–7.22 (1H, m), 7.22–7.46 (2H, m), 7.56 (1H, d, $J=7.5$ Hz).

4.2.19. (6*S,7*S**)-6-[2-(2-Bromophenyl)ethyl]-7-(2-propenyl)-1,4-dioxaspiro[4,5]decane (39).** In the same way as for the preparation of **27**-*trans* from **26**-*trans*, **39** (182 mg, 95%) was obtained from **37**-*trans* (169 mg, 0.526 mmol) as a colorless syrup after purification by PTLC [hexane–EtOAc (49:1)]. DI–HRMS calcd for $C_{19}H_{25}BrO_2$: 366.1017, 364.1037. Found: 366.0988, 364.1050. DI–MS *m/z*: 366, 364 (M^+, 0.4, 0.3), 325, 323 (1, 2), 195 (7), 171, 169 (9, 9), 99 (100), 86 (35), 55 (38), 41 (38). IR ($CHCl_3$) cm^{-1}: 1634. ^1H NMR (90 MHz) δ: 0.74–2.23 (11H, m), 2.29–2.66 (1H, m), 2.84 (2H, t, $J=8.5$ Hz), 3.80–4.14 (4H, m), 4.88–5.22 (2H, m), 5.54–6.06 (1H, m), 6.90–7.34 (3H, m), 7.50 (1H, d, $J=8$ Hz).

4.2.20. (6*S,7*S**)-6-[(2-Bromophenyl)methyl]-1,4-dioxaspiro[4,5]decane-7-acetaldehyde (22).** $Me_3NO\cdot 2H_2O$ (34 mg, 0.306 mmol) and OsO_4 (3 mg, 11.8 μmol) were added successively to a solution of **38** (82 mg, 0.234 mmol) in acetone (3.6 ml) and H_2O (0.4 ml) at 21 °C and the mixture was stirred for 2.5 h. Saturated $Na_2S_2O_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up afforded a residue (103 mg). The residue was dissolved in THF (3.6 ml) and H_2O (0.4 ml) and $NaIO_4$ (75 mg, 0.350 mmol) was added to this at 0 °C. Stirring was continued at 0 °C for 15 min and at 21 °C for 2 h. Addition of saturated $Na_2S_2O_3$–H_2O, extraction with CH_2Cl_2, usual work-up, and PTLC [hexane–EtOAc (6:1)] furnished **22** (64 mg, 78% in two steps) as a colorless syrup. DI–HRMS calcd for $C_{17}H_{21}BrO_3$: 354.0654, 352.0673. Found: 354.0674, 352.0663. DI–MS *m/z*: 354, 352 (M^+, 2, 2), 326, 324 (2, 3), 311, 309 (5, 6), 283, 281 (5, 5), 256, 254 (5, 6), 245 (25), 171, 169 (11, 12), 155 (13), 141 (12), 99 (100), 86 (23), 55 (17), 41 (14). IR ($CHCl_3$) cm^{-1}: 1720. ^1H NMR (90 MHz) δ: 1.01–2.68 (10H, m), 2.74 (1H, dd, $J=14.5$, 7.5 Hz), 3.13 (1H, dd, $J=14.5$, 4 Hz), 3.77–4.16 (4H, m), 6.93–7.40 (3H, m), 7.54 (1H, d, $J=8$ Hz), 9.59 (1H, dd, $J=$ 1.5, 1.5 Hz).

4.2.21. (6*S,7*S**)-1-Hydroxy-3-[6-(2-bromophenyl)-methyl-1,4-dioxaspiro[4,5]dec-7-yl]-2-propanone (40) and 22.** OsO_4 (2 mg, 7.87 μmol) and $NaIO_4$ (103 mg, 0.481 mmol) were added successively to a solution of **38** (42 mg, 0.120 mmol) in THF (3 ml) and H_2O (1 ml) at 0 °C and the mixture was stirred at 0 °C for 10 min and at 21 °C for 1.5 h. Saturated $Na_2S_2O_3$-H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–EtOAc (4:1)] afforded **22** (21 mg, 50%) and **40** (11.5 mg, 25%) in order of increasing polarity.

Compound **40**. Colorless syrup. DI–HRMS calcd for $C_{18}H_{23}BrO_4$: 384.0759, 382.0779. Found: 384.0760, 382.0760. DI–MS *m/z*: 384, 382 (M^+, 11, 10), 370, 368 (2, 3), 353, 351 (4, 4), 311, 309 (8, 9), 213 (18), 171, 169 (14, 14), 99 (100), 86 (26), 55 (14), 31 (20). IR ($CHCl_3$) cm^{-1}: 1714. ^1H NMR (90 MHz) δ: 0.90–2.69 (10H, m), 2.73 (1H, dd, $J=15$, 8.5 Hz), 2.87 (1H, br s, OH), 3.11 (1H, dd, $J=15$, 4 Hz), 3.83–4.13 (4H, m), 3.88 (1H, d, $J=18.5$ Hz), 4.13 (1H, d, $J=18.5$ Hz), 6.91–7.39 (3H, m), 7.52 (1H, d, $J=$ 8 Hz).

4.2.22. (6*S,7*S**)-6-[2-(2-Bromophenyl)ethyl]-1,4-dioxaspiro[4,5]decane-7-acetaldehyde (23).** In the same way as for the preparation of **22** from **38**, **23** (128 mg, 70%) was prepared from **39** (182 mg, 0.499 mmol) as a colorless syrup in two steps after PTLC [hexane–EtOAc (6:1)]. DI–HRMS calcd for $C_{18}H_{23}BrO_3$: 368.0810, 366.0830. Found: 368.0800, 366.0804. DI–MS *m/z*: 368, 366 (M^+, 0.2, 0.2), 340, 338 (1, 1), 325, 323 (1, 1), 297, 295 (3, 3), 197 (14), 171, 169 (7, 14), 141 (17), 99 (100), 86 (26), 55 (25), 41 (19). IR ($CHCl_3$) cm^{-1}: 1721. ^1H NMR (90 MHz) δ: 0.74–2.57 (11H, m), 2.57–3.02 (3H, m), 3.80–4.14 (4H, m), 6.92–7.37 (3H, m), 7.53 (1H, d, $J=8$ Hz), 9.73–9.88 (1H, m).

4.3. Preparation of 41–44

4.3.1. 2-Bromo-α-(nitromethyl)benzenepropanol (46). KF (8 mg, 0.138 mmol) was added to a solution of **45** (284 mg, 1.33 mmol) and CH_3NO_2 (0.36 ml, 6.65 mmol) in 2-propanol (3 ml) at 21 °C and the mixture was stirred for 14 h. Citric acid–H_2O (0.1 N) was added and the mixture was extracted with CH_2Cl_2. Usual work-up followed by PTLC [hexane–CH_2Cl_2 (5:2)] gave **46** (348 mg, 95%) as a colorless syrup. GC–MS *m/z*: 257, 255 (M^+-H_2O, 4, 4), 210, 208 (5, 5), 171, 169 (97, 100), 133 (65), 105 (24), 104 (23), 103 (25), 90 (34), 77 (43). IR (neat) cm^{-1}: 1553. ^1H NMR (90 MHz) δ: 1.65–1.98 (2H, m), 2.62–3.18 (2H, m), 3.08 (1H, br s, OH), 4.19–4.56 (3H, m), 6.94–7.38 (3H, m), 7.53 (1H, d, $J=7.5$ Hz).

4.3.2. 1-Bromo-2-(4-nitrobutyl)benzene (41). 4-DMAP (8 mg, 65.8 μmol) was added to a solution of **46** (348 mg, 1.27 mmol) and Ac_2O (180 μl, 1.91 mmol) in Et_2O and the mixture was stirred at 21 °C for 1.5 h. The mixture was diluted with EtOH (7 ml) and $NaBH_4$ (97 mg, 2.55 mmol) was added to this. After having been stirred at 0 °C for 10 min and at 21 °C for 1 h, saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–benzene (7:1)] afforded **41** (258 mg, 79%) as a colorless oil. GC–HRMS calcd for $C_{10}H_{12}BrNO_2$: 259.0032, 257.0051. Found: 259.0037, 257.0068. GC–MS *m/z*: 259, 257 (M^+, 4, 3), 211, 209 (11, 11), 198, 196 (6, 6), 187, 185 (27, 38), 171, 169 (96, 100), 130 (51), 90 (45), 77 (33). IR (neat) cm^{-1}: 1552. ^1H NMR (90 MHz) δ: 1.50–2.30 (4H, m), 2.79 (2H, t, $J=7.5$ Hz), 4.38 (2H, t, $J=6.5$ Hz), 6.92–7.35 (3H, m), 7.52 (1H, d, $J=$ 8 Hz).

4.3.3. 2-Bromo-α-(ethenyl)benzenemethanol (48). Vinylmagnesium bromide was prepared from Mg (1.17 g, 48.8 mg atom) and vinyl bromide (25% v/v in THF, 17.2 ml, 61.0 mmol) in THF (40 ml) at 20 °C under an Ar atmosphere and then it was cooled at −18 °C. A THF (5 ml) solution of **47** (4.50 g, 24.3 mmol) was added dropwise to this and the resulting mixture was stirred at −18 °C for 20 min. Quenching with saturated NH_4Cl–H_2O followed by extraction with EtOAc, usual work-up, and SiO_2 column chromatography [80 g, hexane–benzene (9:1)] provided **48** (4.70 g, 91%) as a colorless oil. GC–HRMS calcd for C_9H_9BrO: 213.9817, 211.9837. Found: 213.9836, 211.9854. GC–MS *m/z*: 214, 212 (M^+, 6, 5), 213, 211 (14, 14), 187, 185 (8, 21), 185, 183 (21, 15), 133 (100), 105 (30), 77 (77), 55 (34), 51 (40). IR (neat) cm^{-1}: 1639. ^1H NMR (90 MHz) δ: 2.61 (1H, br s, OH), 5.20 (1H, ddd, J=10, 1, 1 Hz), 5.34 (1H, ddd, J=17, 1, 1 Hz), 5.57 (1H, d, J=5 Hz), 6.02 (1H, ddd, J=17, 10, 5 Hz), 7.11 (1H, ddd, J=7.5, 7.5, 2.5 Hz), 7.33 (1H, ddd, J=7.5, 7, 1.5 Hz), 7.44–7.67 (2H, m).

4.3.4. 1-(2-Bromophenyl)-2-propen-1-one (49). MnO_2 (1.77 g, 20.3 mmol) was added to a solution of **48** (433 mg, 2.03 mmol) in CH_2Cl_2 (15 ml) and the mixture was refluxed with stirring for 6 h. The whole was filtered through a celite pad and the celite was washed thoroughly with CH_2Cl_2. Evaporation of the solvent and PTLC [hexane–CH_2Cl_2 (3:2)] furnished **49** (249 mg, 58%, c.y.: 88%) along with recovered **48** (147 mg, 34%). GC–HRMS calcd for C_9H_7BrO: 211.9661, 209.9669. Found: 211.9672, 209.9669. GC–MS *m/z*: 212, 210 (M^+, 40, 38), 185, 183 (100, 99), 157, 155 (35, 36), 76 (45), 55 (55), 50 (50), 27 (52). IR (neat) cm^{-1}: 1665, 1607. ^1H NMR (90 MHz) δ: 6.06 (1H, dd, J=10, 1 Hz), 6.09 (1H, dd, J=17.5, 1 Hz), 6.76 (1H, dd, J=17.5, 10 Hz), 7.18–7.48 (3H, m), 7.55–7.75 (1H, m).

4.3.5. 1-(2-Bromophenyl)-4-nitrobutanone (50). KF (18 mg, 0.310 mmol), and 18-crown-6 (42 mg, 0.159 mmol) were added to a solution of **49** (169 mg, 0.797 mmol) and CH_3NO_2 (2.17 ml, 40.1 mmol), in CH_3CN (3 ml) and the mixture was stirred at 22 °C for 3.5 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–EtOAc (5:1)] gave **50** (178 mg, 82%) and 4-nitro-1,7-di(2-bromophenyl)-1,7-heptanedione (**51**, 19 mg, 10%) in order of increasing polarity.

Compound **50**. Colorless syrup. GC–HRMS calcd for $C_{10}H_{10}BrNO_3$: 272.9824, 270.9844. Found: 272.9824, 270.9846. GC–MS *m/z*: 273, 271 (M^+, 3, 2), 227, 225 (1, 1), 185, 183 (96, 100), 157, 155 (22, 22), 76 (21), 50 (17). IR (neat) cm^{-1}: 1709, 1555. ^1H NMR (90 MHz) δ: 2.43 (2H, tt, J=6.5, 6.5 Hz), 3.09 (2H, t, J=6.5 Hz), 4.59 (1H, t, J=6.5 Hz), 7.23–7.55 (3H, m), 7.55–7.78 (1H, m).

Compound **51**. Colorless syrup. GC–MS *m/z*: 439, 437, 435 (M^+-NO_2, 2, 3, 3), 438, 436, 434 (3, 4, 3), 185, 183 (100, 100), 157, 155 (20, 20), 76 (16), 50 (7). IR ($CHCl_3$) cm^{-1}: 1700, 1551. ^1H NMR (90 MHz) δ: 2.36 (4H, dt, J=7, 7 Hz), 3.04 (4H, t, J=7 Hz), 4.77 (1H, quintet, J=7 Hz), 7.16–7.51 (6H, m), 7.51–7.74 (2H, m).

4.3.6. 2-(2-Bromophenyl)-2-(3-nitropropyl)-1,3-dioxolane (42). Ethylene glycol (0.76 ml, 13.6 mmol) and conc. H_2SO_4 (73 μl, 1.37 mmol) were added to a solution of **50** (185 mg, 0.680 mmol) in 1,2-dichloroethane (7 ml) and the mixture was stirred under reflux with a Dean–Stark apparatus for 24 h. After having been cooled in an ice bath, saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–EtOAc (4:1)] afforded **42** (199 mg, 93%) as a colorless syrup. GC–MS *m/z*: 271, 269 (M^+-NO_2, 1, 1), 229, 227 (97, 100), 185, 183 (41, 42), 160 (15), 157, 155 (13, 13), 86 (13), 76 (17), 41 (14). IR ($CHCl_3$) cm^{-1}: 1552. ^1H NMR (90 MHz) δ: 1.92–2.41 (4H, m), 3.65–3.91 (2H, m), 3.91–4.18 (2H, m), 4.45 (2H, t, J=7 Hz), 7.13 (1H, ddd, J=7.5, 7.5, 2 Hz), 7.30 (1H, ddd, J=7.5, 7.5, 2 Hz), 7.50–7.77 (2H, m).

4.3.7. (6*S,7*R**)-6-[(2-Bromophenyl)methyl]-7-[(1ξ)-1-nitroethyl]-1,4-dioxaspiro[4,5]decanes (43-major and 43-minor).** KF (17 mg, 0.293 mmol) and 18-crown-6 (39 mg, 0.148 mmol) were added to a solution of **25** (155 mg, 0.585 mmol) and nitroethane (1.05 ml, 14.6 mmol) in CH_3CN (5 ml) and the mixture was refluxed with stirring for 22 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and rough separation by PTLC [hexane–EtOAc (9:1)] afforded an intermixture of products (139 mg). The intermixture was dissolved in benzene (6 ml) and ethylene glycol (0.46 ml, 8.26 mmol), and *p*-TsOH·H_2O (4 mg, 21.1 μmol) was added and the resulting mixture was refluxed with a Dean–Stark apparatus for 3 h. Quenching with saturated $NaHCO_3$-H_2O, extraction with CH_2Cl_2, usual work-up, and PTLC [hexane–benzene (1:2)] provided **43**-minor (40 mg, 18%) and a crude **43**-major in order of increasing polarity. The crude **43**-major was further purified by PTLC [hexane–DME (39:1)] to give **43**-major (93 mg, 41%).

Compound **43**-major. Colorless syrup. DI–HRMS calcd for $C_{17}H_{22}BrNO_4$: 385.0712, 383.0731. Found: 385.0728, 383.0710. DI–MS *m/z*: 385, 383 (M^+, 0.3, 0.5), 355, 353 (2, 1), 339, 337 (9, 9), 311, 309 (6, 7), 171, 169 (16, 17), 155 (17), 99 (100), 86 (23), 41 (23). IR ($CHCl_3$) cm^{-1}: 1552. ^1H NMR (90 MHz) δ: 1.24 (3H, d, J=7 Hz), 1.24–2.41 (8H, m), 2.79 (1H, dd, J=14.5, 9.5 Hz), 3.14 (1H, dd, J=14.5, 4 Hz), 3.96 (4H, s), 5.18 (1H, dq, J=9, 7 Hz), 6.94–7.40 (3H, m), 7.54 (1H, d, J=8 Hz).

Compound **43**-minor. Colorless syrup. DI–HRMS calcd for $C_{17}H_{22}BrNO_4$: 385.0712, 383.0731. Found: 385.0726, 383.0741. DI–MS *m/z*: 385, 383 (M^+, 2, 1), 355, 353 (1, 2), 339, 337 (8, 7), 311, 309 (7, 7), 171, 169 (14, 16), 155 (12), 99 (100), 86 (22), 41 (11). IR ($CHCl_3$) cm^{-1}: 1551. ^1H NMR (90 MHz) δ: 1.29 (3H, d, J=6.5 Hz), 1.29–2.39 (8H, m), 2.77 (1H, dd, J=13.5, 10 Hz), 3.27 (1H, dd, J=13.5, 4 Hz), 3.95 (4H, s), 5.20 (1H, dq, J=10.5, 6.5 Hz), 6.97–7.41 (3H, m), 7.57 (1H, d, J=7.5 Hz).

4.3.8. *tert*-Butyl 2-bromo-β-oxobenzenepropanoate (53). *n*-BuLi (1.47 M, 15.0 ml, 22.1 mmol) was added to a solution of *i*-Pr_2NH (3.64 ml, 26.0 mmol) in THF (40 ml) at −20 °C and the mixture was stirred for 15 min under an Ar atmosphere, then was allowed to cool to −78 °C. *tert*-Butyl acetate (2.96 ml, 22.0 mmol) was added to this and the mixture was stirred at −78 °C for 20 min. A THF (5 ml) solution of **52** (2.29 g, 10.0 mmol) was further added to this and the resulting mixture was stirred at −78 °C for 30 min.

The mixture was poured into saturated NH_4Cl–H_2O and the whole was extracted with EtOAc. Usual work-up followed by SiO_2 column chromatography [30 g, hexane–EtOAc (24:1)] yielded **53** (2.84 g, 95%) as a colorless oil. IR (neat) cm^{-1}: 1735, 1700, 1629. ^1H NMR (90 MHz) of a mixture of keto and enol forms (ca. 2:1); (keto form) δ: 1.38 (9H, s), 3.93 (2H, s), 7.19–7.75 (4H, m); (enol form) δ: 1.53 (9H, s), 7.19–7.75 (5H, m), 12.62 (1H, s, OH).

4.3.9. 1-(2-Bromophenyl)-2-[(1*S,2*R**)-2-nitrocyclohexyl]ethanone (54).** A MeOH (4 ml) solution of **53** (232 mg, 0.776 mmol) was treated with NaOMe (63 mg, 1.17 mmol) at 0 °C for 15 min. A solution of 1-nitrocyclohexene (148 mg, 1.17 mmol) in MeOH (1 ml) was added to the mixture and the whole was stirred at 0 °C for 30 min and at 21 °C for 6 h. Saturated NH_4Cl–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up gave a residue (385 mg) which was subjected to the next step without purification. A solution of the residue and *p*-TsOH·H_2O (37 mg, 0.195 mmol) in benzene (8 ml) was stirred under reflux for 4 h. After having been cooled, $NaHCO_3$ (16 mg, 0.190 mmol) and H_2O were added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–EtOAc (6:1)] yielded **54** (126 mg, 50% overall) as a colorless syrup. GC–HRMS calcd for $C_{14}H_{16}BrNO_3$: 327.0293, 325.0313. Found: 327.0314, 325.0304. GC–MS *m/z*: 327, 325 (M^+, 1, 1), 281, 279 (2, 3), 280, 278 (3, 3), 200, 198 (15, 15), 185, 183 (98, 100), 157, 155 (17, 19), 81 (16), 76 (18), 41 (16). IR ($CHCl_3$) cm^{-1}: 1701, 1551. ^1H NMR (90 MHz) δ: 0.94–3.03 (9H, m), 2.67–3.12 (2H, m), 4.42 (1H, ddd, J=11, 11, 4 Hz), 7.17–7.51 (3H, m), 7.51–7.74 (1H, m).

4.3.10. 2-(2-Bromophenyl)-2-[[(1*R,2*S**)-2-nitrocyclohexyl]methyl]-1,3-dioxolane (44).** In a similar manner as for the preparation of **42** from **50**, heating of **54** (158 mg, 0.485 mmol) with ethylene glycol (0.54 ml, 9.69 mmol) and conc. H_2SO_4 (52 µl, 0.972 mmol) in 1,2-dichloroethane (8 ml) for 60 h afforded **44** (173 mg, 96%) after PTLC [hexane–EtOAc (14:1)].

Compound **44**. Colorless syrup. DI–MS *m/z*: 229, 227 (M^+, 100, 93), 214 (10), 185, 183 (25, 20). IR ($CHCl_3$) cm^{-1}: 1553. ^1H NMR (90 MHz) δ: 0.93–2.49 (11H, m), 3.58–4.19 (4H, m), 4.29 (1H, ddd, J=10, 10, 4.5 Hz), 7.13 (1H, ddd, J=7.5, 7.5, 2 Hz), 7.29 (1H, ddd, J=7.5, 7.5, 1.5 Hz), 7.50–7.77 (2H, m).

4.4. Pd-catalyzed intramolecular cyclization of the substrates 18a–f (Table 1)

4.4.1. Table 1, run 2. The procedure for run 2 was described as a representative in Table 1. A slurry of **18b** (50 mg, 0.187 mmol), $PdCl_2(Ph_3P)_2$ (13 mg, 18.5 µmol), and Cs_2CO_3 (183 mg, 0.561 mmol) in THF (4 ml) was stirred at 100 °C in a sealed tube under an Ar atmosphere for 13 h. After having been cooled in an ice bath, saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–EtOAc (14:1)] furnished 5,6,7,8,9,10-hexahydro-5,9-methanobenzocycloocten-11-one (**57**) as colorless prisms, mp 50–50.5 °C (hexane) [lit.[22] mp 49.5–52 °C (hexane)]. GC–HRMS calcd for $C_{13}H_{14}O$: 186.1044. Found: 186.1047. GC–MS *m/z*: 186 (M^+, 67), 143 (33), 129 (100), 115 (54), 91 (17), 77 (14), 63 (14), 52 (16). IR (KBr) cm^{-1}: 1747, 1703. ^1H NMR (300 MHz) δ: 1.40–1.51 (1H, m), 1.51–1.67 (1H, m), 1.95–2.12 (3H, m), 2.13 (1H, ddd, J=13, 4.54, 4 Hz), 2.73–2.80 (1H, m), 3.19 (1H, d, J=17.5 Hz), 3.45 (1H, dd, J=17.5, 7.5 Hz), 3.45–3.50 (1H, m) 6.94–7.01 (1H, m), 7.12–7.21 (3H, m). ^{13}C NMR δ: 17.1, 37.3, 37.9, 38.1, 45.7, 52.3, 126.7, 126.8, 127.1, 128.3, 136.1, 138.4, 215.9.

4.4.2. Table 1, run 1. In the same way as above, **18a** (59 mg, 0.233 mmol) was cyclized to give a mixture of **55** and **56** (19 mg) after separation by PTLC [hexane–EtOAc (59:1)]. The mixture was acetalized with ethylene glycol (0.3 ml, 5.39 mmol) and *p*-TsOH·H_2O (2 mg, 10.5 µmol) in benzene (8 ml) with a Dean–Stark water-separator for 2 h. Saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–EtOAc (59:1)] provided ethylene acetal of **55** (13.5 mg, 27%) and ethylene acetal of **56** (10 mg, 20%) in order of decreasing polarity. The former was dissolved in DME (1 ml) and to this was added 10% HCl–H_2O (0.5 ml). After having been stirred at 25 °C for 20 h, saturated $NaHCO_3$–H_2O was added. Extraction with CH_2Cl_2, usual work-up, and PTLC [hexane–EtOAc (19:1)] afforded 6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-10-one (**55**) (10.5 mg, 26% overall) Similarly, the latter was hydrolyzed with HCl to give 2-benzylcyclopentanone (**56**) (7.5 mg, 19% overall).

Compound **55**. Colorless needles, mp 59–60 °C (hexane) [lit.[21] mp 59–60 °C (hexane)]. GC–HRMS calcd for $C_{12}H_{12}O$: 172.0888. Found: 172.0902. GC–MS *m/z*: 172 (M^+, 65), 144 (16), 129 (100), 116 (51), 63 (13). IR (KBr) cm^{-1}: 1745. ^1H NMR (300 MHz) δ: 1.75–1.91 (1H, m), 2.01–2.10 (1H, m), 2.11–2.27 (2H, m), 2.48–2.56 (1H, m), 3.07–3.11 (1H, m), 3.20 (1H, dd, J=16, 2.5 Hz), 3.54 (1H, dd, J=16, 4 Hz), 6.94–6.98 (1H, m), 7.09–7.22 (3H, m). ^{13}C NMR δ: 17.1, 37.3, 37.9, 38.1, 45.7, 52.3, 126.7, 126.8, 127.1, 128.3, 136.1, 138.4, 215.9.

6′,7′,8′,9′-Tetrahydrospiro[1,3-dioxolane-2,10′-[5,8]methano[5H]benzocycloheptene (*ethylene acetal of* **55**). Colorless syrup. DI–HRMS calcd for $C_{14}H_{16}O_2$: 216.1149. Found: 216.1140. DI–MS *m/z*: 216 (M^+, 100), 188 (13), 144 (26), 143 (26), 129 (52), 115 (34), 99 (40), 73 (44), 56 (28). ^1H NMR (90 MHz) δ: 1.31–2.41 (5H, m), 2.70–2.91 (1H, m), 2.74 (1H, d, J=17 Hz), 3.37 (1H, br d, J=17 Hz), 3.82–4.17 (4H, m), 6.87–7.22 (4H, m).

Compound **56**. Colorless syrup. GC–HRMS calcd for $C_{12}H_{14}O$: 174.1044. Found: 174.1061. GC–MS *m/z*: 174 (M^+, 65), 146 (17), 117 (40), 96 (16), 91 (100), 83 (14), 78 (14), 65 (15). IR ($CHCl_3$) cm^{-1}: 1732. ^1H NMR (90 MHz) δ: 1.36–2.73 (8H, m), 2.98–3.33 (1H, m), 7.05–7.44 (4H, m).

6-Benzyl-1,4-dioxaspiro[4,4]nonane (ethylene acetal of **56**). Colorless syrup. GC–HRMS calcd for $C_{14}H_{18}O_2$: 218.1306. Found: 218.1321. GC–MS *m/z*: 218 (M^+, 41), 189 (16), 175 (16), 99 (100), 91 (26), 86 (17), 65 (8), 56 (23). ^1H NMR (90 MHz) δ: 1.22–2.02 (6H, m), 2.02–2.63 (2H, m), 2.71–3.07 (1H, m), 3.89 (4H, s), 7.21 (5H, s).

4.4.3. Table 1, run 5. In the same manner as above,

6,7,8,9,10,11-hexahydro-5,10-methano-5*H*-benzocyclononen-12-one (**58**, 22.5 mg, 61%) was obtained from **18c** (52 mg, 0.185 mmol). About 2% of contaminant was detected by GC analysis.

Compound **58**. Colorless syrup. GC–HRMS calcd for $C_{14}H_{16}O$: 200.1200. Found: 200.1206. GC–MS *m/z*: 200 (M^+, 91), 172 (11), 157 (14), 145 (60), 129 (100), 115 (67), 91 (30), 42 (24), 40 (39). IR ($CHCl_3$) cm^{-1}: 1720, 1701. ^1H NMR (300 MHz) δ: 1.09–1.22 (3H, m), 1.61–1.89 (3H, m), 2.04–2.26 (2H, m), 2.89–2.99 (1H, m), 2.94 (1H, dd, $J=17$, 2.5 Hz), 3.19 (1H, dd, $J=17$, 5 Hz), 3.66 (1H, dd, $J=5$, 4 Hz), 7.14–7.25 (4H, m). ^{13}C NMR δ: 26.0, 26.3, 28.6, 33.6, 36.9, 47.0, 51.6, 126.5, 126.8, 127.4, 129.6, 134.6, 137.4, 215.0.

4.4.4. Table 1, run 6. In the same manner as for the preparation of **55** and **56** from **18a** (run 1), 2′,3′-dihydrospiro[cyclopantane-1,1′-[1*H*]inden]-2-one (**59**, 30 mg, 71% overall by way of acetal), 2′,3′-dihydrospiro[3-cyclopantene-1,1′-[1*H*]inden]-2-one (60, 1 mg, 2%), and 2-(2-phenylethyl)cyclopentanone (**61**, 1 mg, 2% overall by way of acetal) were obtained from **18d** (61 mg, 0.228 mmol).

Compound **59**. Colorless syrup. GC–HRMS calcd for $C_{13}H_{14}O$: 186.1044. Found: 186.1042. GC–MS *m/z*: 186 (M^+, 29), 158 (4), 130 (100), 115 (28). IR (neat) cm^{-1}: 1734. ^1H NMR (300 MHz) δ: 1.92–2.08 (2H, m), 2.09–2.55 (6H, m), 2.95 (1H, br ddd, $J=16$, 8, 6 Hz), 3.07 (1H, br ddd, $J=16$, 8.5, 6.5 Hz), 7.00–7.04 (1H, m), 7.13–7.23 (2H, m), 7.23–7.27 (1H, m).

2″,3″-Dihydrodispiro[1,3-dioxolane-2,1′-cyclopentane-2′, 1″-[1H]-indene] (*ethylene acetal of* **59**). Colorless syrup. GC–HRMS calcd for $C_{15}H_{18}O_2$: 230.1306. Found: 230.1312. GC–MS *m/z*: 230 (M^+, 38), 202 (10), 184 (20), 168 (16), 143 (38), 130 (100), 115 (51), 99 (63), 56 (20). ^1H NMR (90 MHz) δ: 1.51–3.21 (10H, m), 3.21–3.51 (2H, m), 3.51–3.87 (2H, m), 7.04–7.26 (3H, m), 7.26–7.52 (1H, m).

Compound **60**. Colorless syrup. GC–HRMS calcd for $C_{13}H_{12}O$: 184.0888. Found: 184.0894. GC–MS *m/z*: 184 (M^+, 100), 169 (36), 155 (34), 141 (39), 130 (35), 128 (56), 115 (77), 63 (19). IR ($CHCl_3$) cm^{-1}: 1701. ^1H NMR (300 MHz) δ: 2.07 (1H, ddd, $J=13$, 8.5, 7 Hz), 2.51 (1H, ddd, $J=13$, 8.5, 5.5 Hz), 2.92 (1H, ddd, $J=19$, 2.5, 2 Hz), 3.00 (1H, ddd, $J=16$, 8.5, 5.5 Hz), 3.01 (1H, ddd, $J=19$, 2.5, 2 Hz), 3.24 (1H, ddd, $J=16$, 8.5, 7 Hz), 6.26 (1H, ddd, $J=5.5$, 2, 2 Hz), 6.90 (1H, d, $J=7$ Hz), 7.13 (1H, dd, $J=7$, 7 Hz), 7.19 (1H, dd, $J=7$, 7 Hz), 7.27 (1H, d, $J=7$ Hz), 7.84 (1H, ddd, $J=5.5$, 2.5, 2.5 Hz).

Compound **61**. GC–HRMS calcd for $C_{13}H_{16}O$: 188.1200. Found: 188.1203. GC–MS *m/z*: 188 (M^+, 8), 104 (17), 91 (36), 84 (100), 65 (10), 41 (17). IR ($CHCl_3$) cm^{-1}: 1728. ^1H NMR (90 MHz) δ: 1.39–2.38 (9H, m), 2.51–2.84 (2H, m), 6.97–7.41 (5H, m).

6-(2-Phenylethyl)-1,4-dioxaspiro[4,4]nonane (*ethylene acetal of* **61**). Colorless syrup. GC–HRMS calcd for $C_{15}H_{20}O_2$: 232.1462. Found: 232.1479. GC–MS *m/z*: 232 (M^+, 11), 189 (8), 141 (40), 128 (23), 99 (100), 91 (28), 55 (23), 41 (20). ^1H NMR (90 MHz) δ: 1.15–2.12 (9H, m), 2.41–2.79 (2H, m), 3.88 (4H, s), 6.96–7.43 (5H, m).

4.4.5. Table 1, run 7. In the same manner as above, 2′,3′-dihydrospiro[cyclohexane-1,1′-[1*H*]inden]-2-one (**62**, 24 mg, 57%) and 2′,3′-dihydrospiro[cyclohexane-1,1′-[1*H*]inden]-2-one (**63**, 1.5 mg, 4%) were produced from **18e** (59 mg, 0.210 mmol).

Compound **62**. Colorless syrup. GC–HRMS calcd for $C_{14}H_{16}O$: 200.1200. Found: 200.1201. GC–MS *m/z*: 200 (M^+, 37), 172 (3), 156 (12), 143 (63), 130 (100), 115 (37). IR (neat) cm^{-1}: 1702. ^1H NMR (300 MHz) δ: 1.80–2.13 (6H, m), 2.15 (1H, dt, $J=13$, 7.5 Hz), 2.38 (1H, dt, $J=13$, 7 Hz), ca. 2.50–2.62 (2H, m), 2.92 (2H, dd, $J=7.5$, 7 Hz), 7.20–7.28 (4H, m). ^{13}C NMR δ: 22.4, 27.1, 30.3, 36.4, 39.1, 39.6, 62.6, 124.6, 124.8, 126.3, 127.4, 143.7, 145.2, 212.3.

Compound **63**. Colorless syrup. GC–HRMS calcd for $C_{14}H_{14}O$: 198.1044. Found: 198.1041. GC–MS *m/z*: 198 (M^+, 25), 170 (5), 130 (100), 115 (29), 40 (16). IR ($CHCl_3$) cm^{-1}: 1665. ^1H NMR (300 MHz) δ: 2.00 (1H, ddd, $J=13$, 7, 6 Hz), 2.05 (1H, ddd, $J=13$, 5.5, 5.5 Hz), 2.28 (1H, ddd, $J=13$, 6, 6 Hz), 2.44–2.51 (2H, m), 2.61 (1H, ddd, $J=13$, 8.5, 7.5 Hz), 2.89–3.06 (2H, m), 6.16 (1H, ddd, $J=10$, 2, 2 Hz), 7.06 (1H, ddd, $J=10$, 4, 4 Hz), 7.10–7.28 (4H, m).

4.4.6. Table 1, run 8. In the same manner as above, 3′,4′-dihydrospiro[cyclohexane-1,1′(2*H*)naphthalen]-2-one (**64**, 14 mg, 35%) and 2-(3-phenylpropyl)cyclohexanone (**65**, 11.5 mg, 29%) were obtained from **18f** (55 mg, 0.186 mmol).

Compound **64**. Colorless syrup. GC–HRMS calcd for $C_{15}H_{18}O$: 214.1357. Found: 214.1356. GC–MS *m/z*: 214 (M^+, 51), 170 (16), 157 (41), 144 (100), 129 (91), 115 (33), 91 (17), 42 (16). IR (neat) cm^{-1}: 1702. ^1H NMR (300 MHz) δ: 1.64–1.95 (5H, m), 1.98–2.21 (5H, m), 2.40–2.48 (1H, m), 2.60–2.69 (1H, m), 2.69–2.84 (2H, m), 7.03–7.20 (4H, m).

Compound **65**. Colorless syrup. GC–HRMS calcd for $C_{15}H_{20}O$: 216.1513. Found: 216.1519. GC–MS *m/z*: 216 (M^+, 22), 125 (7), 117 (11), 111 (33), 104 (28), 98 (100), 91 (56), 56 (24), 42 (28). IR (neat) cm^{-1}: 1708. ^1H NMR (90 MHz) δ: ca. 1.02–2.59 (13H, m), 2.59 (2H, t, $J=7.5$ Hz), 6.97–7.41 (5H, m).

4.5. Pd-catalyzed intramolecular cyclization of the substrates 19–23 (Table 2)

4.5.1. Table 2, runs 1–4. The procedure for Table 2, run 2 was described as representative of runs 1–4. Following the procedure used for Table 1, run 2, a slurry containing **19**-*trans* (51 mg, 0.150 mmol), $PdCl_2(Ph_3P)_2$ (10 mg, 14.2 μmol), and Cs_2CO_3 (147 mg, 0.451 mmol) in THF (5 ml) was stirred at 100 °C in a sealed tube under an Ar atmosphere for 24 h. The same work up as above followed by PTLC [hexane–EtOAc (12:1)] furnished **66**+**67**-*trans* (1:1.7, 18 mg, 46%), recovered **19**-*trans* (2 mg, 4%), and (4a*S**,9a*S**)-3,4,4a,9,9a,10-hexahydrospiro[anthracene-1(2*H*),2′-[1,3]dioxolan]-10-one (**67**-*cis*, 3.5 mg, 9%) in order of increasing polarity. The obtained **66**+**67**-*trans* was

dissolved in MeOH (3 ml) and to this was added $NaBH_4$ (8 mg, 0.211 mmol). The mixture was stirred at 22 °C for 30 min. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [benzene–EtOAc (5:1)] provided (4′a*R**,9′a*S**−3′,4′,9′, 9′a-tetrahydrospiro[1,3-dioxolane-2,1′[1*H*]fluorene]-4′a-(2′*H*)-methanol (**75**, 6.5 mg, 17% overall) and (4a*R**, 9a*S**,10*S**)-3,4,4a,9,9a,10-hexahydrospiro[anthracene-1(2*H*),2′-[1,3]-dioxolan]-10-ol (**76**, 11.5 mg, 29% overall) in order of decreasing polarity.

Compound **75**. Colorless syrup. DI–HRMS calcd for $C_{16}H_{20}O_3$: 260.1411. Found: 260.1415. DI–MS *m/z*: 260 (M^+, 10), 229 (38), 128 (23), 115 (17), 99 (100), 86 (20), 55 (23). ^{1}H NMR (300 MHz) δ: 1.33 (1H, ddd, J=14, 12.5, 4 Hz), 1.54–1.64 (1H, m), 1.64–1.96 (4H, m), 2.59 (1H, dd, J=11, 9 Hz), ca. 2.63 (1H, br s, OH), 2.92 (1H, dd, J=16, 11 Hz), 3.04 (1H, dd, J=16, 9 Hz), 3.86 (1H, br d, J=11 Hz), 3.91–4.11 (4H, m), 4.10 (1H, br d, J=11 Hz), 7.08–7.28 (4H, m). ^{13}C NMR δ: 20.7, 30.3, 32.4, 33.7, 49.5, 52.4, 64.3 (2C), 68.8, 110.5, 121.4, 124.8, 126.4, 126.8, 141.2, 148.8.

Compound **76**. Colorless syrup. GC–HRMS calcd for $C_{16}H_{20}O_3$: 260.1411. Found: 260.1415. GC–MS *m/z*: 260 (M^+, 22), 242 (11), 217 (17), 198 (15), 159 (100), 141 (22), 99 (51), 91 (22), 86 (27), 55 (19). ^{1}H NMR (90 MHz) δ: 0.87–2.10 (8H, m, including OH), 2.34 (1H, br d, J=12 Hz), 2.78 (2H, d, J=7 Hz), 4.00 (4H, s), 4.20–4.54 (1H, m, changed to 4.36, d, J=9 Hz with D_2O), 6.94–7.40 (3H, m), 7.40–7.71 (1H, m).

Compound **67**-*cis*. Colorless prisms, mp 100–101 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.34; H, 6.93. GC–HRMS calcd for $C_{16}H_{18}O_3$: 258.1255. Found: 258.1261. GC–MS *m/z*: 258 (M^+, 14), 215 (5), 112 (100), 99 (47), 86 (45). IR ($CHCl_3$) cm^{-1}: 1678. ^{1}H NMR (300 MHz) δ: 1.56–1.86 (6H, m), 2.46 (1H, ddd, J=10.5, 5.5, 5 Hz), 2.93 (1H, ddd, J=10, 5, 5 Hz), 3.00 (1H, dd, J=16.5, 5.5 Hz), 3.11 (1H, dd, J=16.5, 10.5 Hz), 3.76–4.01 (4H, m), 7.26 (1H, br d, J=7.5 Hz), 7.30 (1H, br dd, J=7.5, 7.5 Hz), 7.47 (1H, ddd, J=7.5, 7.5, 1.5 Hz), 8.03 (1H, dd, J=7.5, 1.5 Hz).

4.5.2. (4a*R,9a*S**)-3,4,4a,9,9a,10-Hexahydrospiro[anthracene-1(2*H*),2′-[1,3]dioxolan]-10-one (67-*trans*, Table 2, run 1).** Colorless prisms, mp 101–102 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.42; H, 6.96. GC–HRMS calcd for $C_{16}H_{18}O_3$: 258.1255. Found: 258.1258. GC–MS *m/z*: 258 (M^+, 14), 215 (15), 112 (100), 99 (43), 86 (43). IR ($CHCl_3$) cm^{-1}: 1679. ^{1}H NMR (300 MHz) δ: 1.27 (1H, dddd, J=13.5, 13.5, 11.5, 4 Hz), 1.38 (1H, ddd, J=13, 13, 4 Hz), 1.61 (1H, ddddd, J=13.5, 13.5, 13.5, 4, 4 Hz), 1.78–1.90 (2H, m), 2.22 (1H, ddd, J=13, 10.5, 5.5 Hz), 2.43 (1H, br d, J=13.5 Hz), 2.55 (1H, ddd, J=13, 11.5, 3.5 Hz), 2.96 (1H, dd, J=16.5, 10.5 Hz), 3.03 (1H, dd, J=16.5, 5.5 Hz), 4.01–4.10 (4H, m), 7.25 (1H, d, J=7.5, 1.5 Hz), 7.29 (1H, dd, J=7.5, 7.5 Hz), 7.46 (1H, ddd, J=7.5, 7.5, 1.5 Hz), 8.01 (1H, dd, J=7.5, 1.5 Hz).

4.5.3. Table 2, runs 5–8. The procedure of Table 2, run 7 was described as a representative of runs 5–8. In a similar manner as for the procedure of Table 2, run 2, **20**-*cis* (30 mg, 85.0 μmol) was stirred under reflux in toluene (4 ml) with $PdCl_2(Ph_3P)_2$ (6 mg, 8.55 μmol) and Cs_2CO_3 (83 mg, 0.255 mmol) under an Ar atmosphere for 3 h. Saturated NH_4Cl–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–CH_2Cl_2 (1:1)] gave (4′a*S**,10′a*S**)-3′,4′,10′,10′a-tetrahydrospiro[1,3-dioxolane-2,1′(2′*H*)-phenathrene]-4′a(9′*H*)-carboxaldehyde (**68**-*trans*, 5 mg, 22%), (4′a*R**,10′a*S**)-3′,4′,10′,10′a-tetrahydrospiro[1,3-dioxolane-2,1′(2′*H*)-phenathrene]-4′a(9′*H*) carboxaldehyde (**68**-*cis*, 12 mg, 52%), and a mixture of **69**-*trans* and -*cis* (2 mg) in order of increasing polarity. The mixture was further purified by PTLC [benzene–EtOAc (59:1)] to yield (4a*R**,11a*S**)-3,4,4a,10, 11,11a-hexahydrospiro[1*H*-dibenzo[*a*,*d*]cycloheptene-1,2′-[1,3]-dioxolan]-5(2*H*)-one (**69**-*trans*, less than 0.5 mg, trace) and (4a*S**, 11a*S**)-3,4,4a,10,11,11a-hexahydrospiro-[1*H*-dibenzo[*a*,*d*]-cycloheptene-1,2′-[1,3]-dioxolan]-5(2*H*)-one (**69**-*cis*, 1.5 mg, 6%) in order of increasing polarity.

Compound **68**-*trans*. Colorless prisms, mp 114–116 °C (hexane). GC–HRMS calcd for $C_{17}H_{20}O_3$: 272.1411. Found: 272.1429. GC–MS *m/z*: 272 (M^+, 0.6), 244 (11), 182 (30), 129 (17), 128 (18), 115 (11), 99 (100), 55 (32). IR ($CHCl_3$) cm^{-1}: 1712. ^{1}H NMR (300 MHz) δ: 1.42–1.58 (1H, m), 1.27 (1H, dddd, J=13, 13, 4, 2 Hz), 1.69–1.95 (3H, m), 2.05–2.24 (3H, m), 2.91–3.06 (3H, m), 3.90–4.08 (4H, m), 7.10–7.19 (3H, m), 7.20–7.25 (1H, m), 9.85 (1H, d, J=2 Hz).

Compound **68**-*cis*. Colorless prisms, mp 131–133 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.08; H, 7.41. GC–HRMS calcd for $C_{17}H_{20}O_3$: 272.1411. Found: 272.1411. GC–MS *m/z*: 272 (M^+, 3), 244 (13), 182 (14), 129 (21), 115 (11), 99 (100), 86 (13), 55 (23). IR ($CHCl_3$) cm^{-1}: 1721. ^{1}H NMR (300 MHz) δ: 1.44–1.70 (4H, m), 1.71–1.93 (2H, m), 2.14–2.23 (1H, m), 2.25–2.35 (2H, m), 2.83–2.97 (2H, m), 3.88–4.06 (4H, m), 6.91–6.96 (1H, m), 7.09–7.19 (3H, m), 9.27 (1H, d, J=2 Hz).

Compound **69**-*trans*. Colorless syrup. GC–HRMS calcd for $C_{17}H_{20}O_3$: 272.1411. Found: 272.1396. GC–MS *m/z*: 272 (M^+, 29), 227 (33), 112 (31), 99 (100), 86 (26), 55 (30). IR ($CHCl_3$) cm^{-1}: 1680. ^{1}H NMR (300 MHz) δ: 1.36–1.68 (3H, m), 1.74–1.87 (4H, m), 1.89 (1H, ddd, J=12, 7.5, 2 Hz), 2.34 (1H, dddd, J=15, 7, 2, 2 Hz), 2.85 (1H, ddd, J=17, 7, 1.5 Hz), 3.16–3.36 (1H, m), 3.46 (1H, br dd, J=17, 11.5 Hz), 3.95–4.12 (4H, m), 7.20 (1H, br d, J=7.5 Hz), 7.25 (1H, br dd, J=7.5, 7.5 Hz), 7.36 (1H, ddd, J=7.5, 7.5, 1.5 Hz), 7.72 (1H, dd, J=7.5, 1.5 Hz).

Compound **69**-*cis*. Colorless syrup. GC–HRMS calcd for $C_{17}H_{20}O_3$: 272.1411. Found: 272.1416. GC–MS *m/z*: 272 (M^+, 25), 227 (29), 112 (30), 99 (100), 86 (29), 55 (25). IR ($CHCl_3$) cm^{-1}: 1678. ^{1}H NMR (300 MHz) δ: 1.44–1.87 (6H, m), 1.94–2.09 (1H, m), 2.13–2.29 (2H, m), 2.89 (2H, t, J=6 Hz), 3.07 (1H, br dd, J=5.5, 5.5, 5.5 Hz), 3.79–3.96 (4H, m), 7.17 (1H, br d, J=7.5 Hz), 7.27 (1H, br dd, J=7.5, 7.5 Hz), 7.36 (1H, ddd, J=7.5, 7.5, 1.5 Hz), 7.62 (1H, br d, J=7.5 Hz).

4.5.4. Table 2, runs 9 and 10. The procedure of Table 2, run 10 was described as a representative of runs 9 and 10. In the

same way as for the procedure of Table 2, run 2, **21** (93 mg, 0.243 mmol) was stirred under reflux in THF (6 ml) with $PdCl_2(Ph_3P)_2$ (17 mg, 24.2 μmol) and Cs_2CO_3 (236 mg, 0.724 mmol) under an Ar atmosphere for 14 h. The same work-up as above and separation by PTLC (benzene) afforded a mixture of (4′a*S**,10′a*S**)- and (4′a*R**,10′a*S**)-3′,4′,10′,10′a-tetrahydro-7′-methoxyspiro[1,3-dioxolane-2,1′(2′*H*)-phenathrene]-4′a(9′*H*)carboxaldehyde [**70**-*trans*+**70**-*cis* (1:4.2), 48 mg, 65%], and a mixture of **71**-*trans* and -*cis* (13 mg) in order of increasing polarity. The latter was further purified by PTLC [hexane-1,2-dimethoxyethane (DME) (24:1)] to isolate (4a*R**,11a*S**)-3,4,4a,10,11,11a-hexahydro-8-methoxyspiro[1*H*-dibenzo-[*a*,*d*]cycloheptene-1,2′-[1,3]-dioxolan]-5(2*H*)-one (**71**-*trans*, 8 mg, 11%) and (4a*S**,11a*S**)-3,4,4a,10,11,11a-hexahydro-8-methoxyspiro-[1*H*-dibenzo[*a*,*d*]cycloheptene-1,2′-[1,3]-dioxolan]-5(2*H*)-one (**71**-*cis*, 4.5 mg, 6%) in order of increasing polarity.

Compound **70**-*trans*+**70**-*cis*. Colorless syrup, whose ratio (1:4.2) was determined by GC analysis [OV-1; 200 °C; carrier gas: N_2 (115 kPa); **70**-*cis*: 13.6 min, **70**-*trans*: 15.9 min)]. The mixture partially crystallized on standing and repeated recrystallization provided pure **70**-*cis*, whose single crystal X-ray analysis is described at the next paragraph.

Compound **70**-*cis*. Colorless prisms, mp 130–131 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.37; H, 7.27. GC–HRMS calcd for $C_{18}H_{22}O_4$: 302.1517. Found: 302.1515. GC–MS *m*/*z*: 302 (M^+, 2), 273 (15), 115 (5), 99 (100), 86 (4), 55 (11). IR (KBr) cm^{-1}: 1708. ^1H NMR (300 MHz) δ: 1.45 (1H, dddd, *J*=13.5, 13.5, 4, 2 Hz), 1.50–1.90 (5H, m), 2.16 (1H, ddt, *J*=13, 3, 3.5 Hz), 2.16–2.31 (2H, m), 2.87 (2H, dd, *J*=9, 3.5 Hz), 3.76 (3H, s), 3.86–4.07 (4H, m), 6.65–6.71 (2H, m), 6.84 (1H, dd, *J*=7.5, 1.5 Hz), 9.21 (1H, d, *J*=2 Hz). ^{13}C NMR δ: 20.2, 20.3, 29.4, 29.8, 30.3, 44.5, 54.9, 55.1, 64.3, 64.4, 110.1, 112.1, 114.4, 126.0, 129.8, 138.2, 158.2, 200.3. ^1H NMR of **70**-*trans* (300 MHz, only selected from ^1H NMR spectrum of the mixture) δ: 1.20 (1H, dddd, *J*=13, 13, 4, 1.5 Hz), ca. 2.89–2.98 (2H, m), 7.11 (1H, d, *J*=8.5 Hz), 9.78 (1H, d, *J*=1.5 Hz).

Compound **71**-*trans*. Colorless prisms, mp 92.5–93.5 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.26; H, 7.30. GC–HRMS calcd for $C_{18}H_{22}O_4$: 302.1517. Found: 302.1523. GC–MS *m*/*z*: 302 (M^+, 43), 257 (45), 202 (15), 176 (22), 112 (37), 99 (100), 86 (25), 55 (30). IR ($CHCl_3$) cm^{-1}: 1667. ^1H NMR (300 MHz) δ: 1.38 (1H, ddd, *J*=13, 13, 4 Hz), 1.44–1.63 (2H, m), 1.73–1.90 (5H, m), 2.36 (1H, dd, *J*=15, 7 Hz), 2.79 (1H, dd, *J*=16.5, 7 Hz), 3.18 (1H, ddd, *J*=11.5, 10.5, 4 Hz), 3.48 (1H, dd, *J*=16.5, 12 Hz), 3.83 (3H, s), 3.94–4.12 (4H, m), 6.69 (1H, d, *J*=2.5 Hz), 6.77 (1H, dd, *J*=8.5, 2.5 Hz), 7.78 (1H, d, *J*=8.5 Hz). ^{13}C NMR δ: 22.3, 25.7, 26.5, 32.6, 34.9, 44.4, 50.6, 55.2, 64.6, 65.0, 111.2, 111.4, 114.6, 130.8, 131.6, 147.1, 161.5, 203.1.

Compound **71**-*cis*. Colorless needles, mp 102.5–104 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.37; H, 7.19. GC–HRMS calcd for $C_{18}H_{22}O_4$: 302.1517. Found: 302.1519. GC–MS *m*/*z*: 302 (M^+, 41), 257 (46), 202 (14), 176 (24), 112 (36), 99 (100), 77 (17), 55 (27). IR ($CHCl_3$) cm^{-1}: 1666. ^1H NMR (300 MHz) δ: 1.46 (1H, ddd, *J*=13, 9.5, 4 Hz), 1.55–1.96 (5H, m), 2.02–2.34 (3H, m), 2.82–2.97 (2H, m), 3.09 (1H, ddd, *J*=6, 6, 4.5 Hz), 3.76–3.96 (4H, m), 3.83 (3H, s), 6.69 (1H, d, *J*=2.5 Hz), 6.78 (1H, dd, *J*=8.5, 2.5 Hz), 7.77 (1H, d, *J*=8.5 Hz). ^{13}C NMR δ: 21.9, 25.1 (2C), 32.6, 32.8, 44.1, 49.2, 55.2, 64.4, 65.1, 110.0, 111.3, 114.5, 130.9, 131.8, 144.4, 161.7, 203.7.

4.5.5. Single crystal X-ray analysis of 70-*cis*. Crystal data for **70**-*cis*: $C_{18}H_{22}O_4$, *M*=302.37, monoclinic, $P2_1/c$, *a*=17.395(3) Å, *b*=7.419(2) Å, *c*=11.989(2) Å, β=98.80(1)°, *V*=1529.0(5) $Å^3$, *Z*=4, ρ_c=1.313 g/cm^3, *F*(000)=648, λ=1.54178 Å, *T*=296(1) K, μ(Cu Kα)=7.47 cm^{-1}, crystal size 0.25×0.30×0.35 mm^3, 2995 reflections (2897 independent, R_{int}=0.052) were collected on a Rigaku AFC7R diffractometer. The structure was solved by direct methods (SHELXS-97)[28] and 200 variable parameters were refined using the least-squares method on F^2. The maximum electron density residue: 0.27 $e^-/Å^3$, R_1(for $I>2\sigma(I)$)=0.060 and *wR*=0.228 (all data) with $R_1=\Sigma||F_o|-|F_c||/\Sigma|F_o|$ and $wR=[\sum w(F_o^2-F_c^2)/\sum w(F_o^2)^2]^{0.5}$. Crystallographic data for **70**-*cis* reported in this paper have been deposited at the Cambridge Crystallgraphic Data Centre, under publication number CCDC 244251 The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.5.6. Table 2, runs 11 and 12. The procedure of Table 2, run 11 was described as a representative of runs 11 and 12. In the same manner as above, a mixture of **22** (28 mg, 79.3 μmol), $PdCl_2(Ph_3P)_2$ (5.5 mg, 7.83 μmol), and Cs_2CO_3 (78 mg, 0.239 mmol) in toluene (4 ml) was refluxed with stirring under an Ar atmosphere for 1.5 h. The same work-up as above and separation by PTLC [benzene–EtOAc (99.5:0.5)] yielded **72** (8.5 mg) and (4a*S**,11a*S**)-2,3,4a,5,11,11a-hexahydrospiro[4*H*-dibenzo[*a*,*d*]cycloheptene-4,2′-[1,3]-dioxolan]-10(1*H*)-one (**73**, 5 mg, 23%) in order of increasing polarity. The former was converted to **77** as follows, since **72** partially existed as enol-form. The obtained **72** was dissolved in EtOH (2.5 ml) and $NaBH_4$ (4 mg) was added to this. After the mixture having been stirred at 21 °C for 20 min, saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [benzene–EtOAc (9:1)] gave (4a*S**,9a*S**,10*S**)-3,4,4a,9,9a,10-hexahydrospiro[anthracene-1(2*H*),2′-[1,3]-dioxolan]-10-methanol (**77**, 7 mg, 32% overall).

Compound **77**. Colorless syrup. GC–HRMS calcd for $C_{17}H_{22}O_3$: 274.1568. Found: 274.1572. GC–MS *m*/*z*: 274 (M^+, 14), 231 (42), 181 (40), 144 (99), 141 (26), 129 (37), 128 (38), 115 (22), 99 (100), 86 (52), 73 (25), 55 (22), 31 (23). ^1H NMR (300 MHz) δ: 1.11 (1H, dddd, *J*=12.5, 12.5, 12.5, 4 Hz), 1.40 (1H, ddd, *J*=13, 13, 4 Hz), 1.48 (1H, br s, OH), 1.54–1.93 (5H, m), 2.00–2.10 (1H, m), 2.57 (1H, dd, *J*=15.5, 11.5 Hz), 2.67 (1H, ddd, *J*=9, 4, 4 Hz), 2.73 (1H, dd, *J*=15.5, 3.5 Hz), 3.78 (1H, dd, *J*=11, 4 Hz), 3.97–4.06 (4H, m), 3.99 (1H, dd, *J*=11, 4 Hz), 7.10–7.20 (3H, m), 7.23–7.27 (1H, m).

Compound **73**. Colorless syrup. GC–HRMS calcd for $C_{17}H_{20}O_3$: 272.1411. Found: 272.1401. GC–MS *m/z*: 272 (M^+, 10), 229 (55), 112 (100), 99 (84), 86 (48), 55 (22), 41 (18). IR ($CHCl_3$) cm^{-1}: 1673. ^1H NMR (300 MHz) δ: 1.23–1.38 (2H, m), 1.49 (1H, dddd, $J=13$, 13, 3.5, 3.5 Hz), 1.65–1.86 (4H, m), 2.07 (1H, ddddd, $J=12$, 12, 8, 4.5, 3.5 Hz), 2.57 (1H, dd, $J=15.5$, 8 Hz), 2.87 (1H, dd, $J=15.5$, 4.5 Hz), 2.93–3.07 (2H, m), 3.87–3.97 (1H, m), 3.98–4.06 (1H, m), 4.08–4.14 (2H, m), 7.17 (1H, br d, $J=7.5$ Hz), 7.26 (1H, ddd, $J=7.5$, 7.5, 1 Hz), 7.38 (1H, ddd, $J=7.5$, 7.5, 1.5 Hz), 7.64 (1H, dd, $J=7.5$, 1.5 Hz).

4.5.7. Table 2, run 13. In the same manner as above, a mixture of **23** (38 mg, 0.104 mmol), $PdCl_2(Ph_3P)_2$ (7.5 mg, 10.7 μmol), and Cs_2CO_3 (101 mg, 0.310 mmol) in toluene (5 ml) was refluxed with stirring under an Ar atmosphere for 4 h. The same work-up as above afforded a residue (45 mg). $NaBH_4$ (16 mg, 0.421 mmol) was added to a solution of the residue in EtOH (4 ml) and the mixture was stirred at 23 °C for 30 min. The same work-up as above and purification by PTLC [benzene–EtOAc (14:1)] furnished (4a*S**,11a*S**)-2,3,4,4a,5,10,11,11a-octahydrospiro[1*H*-dibenzo[*a*,*d*]cycloheptene-1,2′-[1,3]-dioxolan]-5-methanol (**78**, 12 mg, 40% overall) as a colorless syrup. DI–HRMS calcd for $C_{18}H_{24}O_3$: 288.1724. Found: 288.1716. GC–MS *m/z*: 288 (M^+, 10), 270 (1), 257 (4), 245 (4), 158 (23), 153 (11), 141 (13), 99 (100), 86 (19), 55 (16). ^1H NMR (300 MHz, $CDCl_3$-D_2O, 45 °C) δ: 1.14–1.80 (8H, m), 1.88–2.02 (1H, m), 2.08–2.22 (1H, m), 2.69–3.05 (3H, m), 3.80–3.97 (4H, m), 3.98 (1H, dd, $J=$ 10.5, 5.5 Hz), 4.10 (1H, dd, $J=10.5$, 10 Hz), 7.05–7.15 (4H, m).

4.6. Pd-catalyzed intramolecular cyclization of the substrates 27-*trans*, -*cis*, 30, 41–44 (Table 3)

4.6.1. Table 3, run 1. A slurry of **41** (45 mg, 0.174 mmol), $PdCl_2(Ph_3P)_2$ (6 mg, 8.55 μmol), and Cs_2CO_3 (114 mg, 0.350 mmol) in toluene (4 ml) was refluxed with stirring under an Ar atmosphere for 3 h. After the mixture having been cooled in an ice bath, citric acid monohydrate (73 mg, 0.348 mmol) and H_2O were added and the pH of the whole was adjusted to ca. 6 with saturated $NaHCO_3$-H_2O. Extraction with CH_2Cl_2 and usual work-up left a residue (39 mg). The residue was dissolved in MeOH (2.5 ml) and DME (0.5 ml) and to this was added KOH (85%, 23 mg, 0.349 mmol) at 0 °C. After stirring for 10 min, H_2SO_4 in MeOH (20% v/v, 0.46 ml, 1.73 mmol) was added at −18 °C and the mixture was stirred for 10 min. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by PTLC (benzene) yielded **79** (15 mg, 59%) which was identical with commercially available α-tetralone.

4.6.2. Table 3, run 2. A slurry of **42** (57 mg, 0.180 mmol), $PdCl_2(Ph_3P)_2$ (6.5 mg, 9.26 μmol), and Cs_2CO_3 (118 mg, 0.362 mmol) in toluene (4 ml) was refluxed with stirring under an Ar atmosphere for 8 h. The solvent was removed off under reduced pressure and MeOH (4 ml) was added to the resulting residue. After stirring at 22 °C for 10 min, H_2SO_4 in MeOH (20% v/v, 0.27 ml, 1.01 mmol) was added at −18 °C and the mixture was stirred for 5 min. Saturated $NaHCO_3$-H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by PTLC [hexane–CH_2Cl_2 (1:2)] afforded spiro[1,3-dioxolane-2,1′(2*H*)-naphthalen]-4′(3′*H*)one (**80**, 17 mg, 46%) as a colorless syrup. GC–HRMS calcd for $C_{12}H_{12}O_3$: 204.0786. Found: 204.0787. GC–MS *m/z*: 204 (M^+, 26), 176 (35), 148 (100), 104 (52), 76 (36). IR ($CHCl_3$) cm^{-1}: 1689. ^1H NMR (90 MHz) δ: 2.33 (2H, t, $J=7$ Hz), 2.92 (2H, t, $J=7$ Hz), 4.19 (4H, s), 7.36–7.76 (3H, m), 8.05 (1H, br d, $J=7$ Hz).

4.6.3. Table 3, runs 3 and 4. The procedure for Table 3, run 3 was described as a representative. A slurry of **27**-*trans* (51 mg, 0.138 mmol), $PdCl_2(Ph_3P)_2$ (5 mg, 7.12 μmol), and Cs_2CO_3 (90 mg, 0.276 mmol) in benzene (4 ml) was refluxed with stirring under an Ar atmosphere for 6 h. After having been cooled in an ice bath, citric acid monohydrate (58 mg, 0.276 mmol) and H_2O were added and the pH of the whole was adjusted to ca. 6 with saturated $NaHCO_3$-H_2O. Extraction with CH_2Cl_2, usual work-up, and PTLC [hexane–CH_2Cl_2 (2:3)] provided (4a*R**,9a*S**,10*S**)-3,4,4a,9,9a,10-hexahydro-10-nitrospiro[anthracene-1(2*H*),2′-[1,3]dioxolane] (**81a**), (4a*R**,9a*S**,10*R**)-3,4,4a,9,9a,10-hexahydro-10-nitrospiro[anthracene-1(2*H*),2′-[1,3]dioxolane] (**81b**) and **67**-*trans* in order of increasing polarity.

Compound **81a**. Colorless prisms, mp 121–122.5 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.53; H, 6.70; N, 4.85. DI–HRMS calcd for $C_{16}H_{19}NO_4$: 289.1313. Found: 289.1313. DI–MS *m/z*: 289 (M^+, 4), 259 (3), 243 (35), 181 (72), 141 (22), 128 (34), 99 (100), 86 (20), 73 (20), 55 (15). IR ($CHCl_3$) cm^{-1}: 1555. ^1H NMR (300 MHz) δ: 1.26 (1H, dddd, $J=13$, 12.5, 12.5, 4 Hz), 1.41 (1H, ddd, $J=13$, 13, 4 Hz), 1.62 (1H, ddddd, $J=13$, 13, 13, 3.5, 3.5 Hz), 1.77 (1H, ddddd, $J=13$, 4, 4, 3, 3 Hz), 1.83–1.99 (3H, m), 2.55 (1H, dddd, $J=12.5$, 12.5, 10, 4 Hz), 2.86 (1H, dd, $J=16$, 5.5 Hz), 2.92 (1H, dd, $J=16$, 10 Hz), 4.01–4.06 (4H, m), 5.58 (1H, d, $J=10$ Hz), 7.12–7.22 (3H, m), 7.26 (1H, ddd, $J=7$, 7, 2 Hz).

Compound **81b**. Colorless needles, mp 136–137 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.49; H, 6.61; N, 4.94. DI–HRMS calcd for $C_{16}H_{19}NO_4$: 289.1313. Found: 289.1298. DI–MS *m/z*: 289 (M^+, 1), 259 (15), 243 (30), 181 (65), 141 (21), 128 (29), 99 (100), 86 (15), 73 (22), 55 (9). IR ($CHCl_3$) cm^{-1}: 1554. ^1H NMR (300 MHz) δ: 1.11 (1H, dddd, $J=13$, 13, 13, 4 Hz), 1.41 (1H, ddd, $J=13$, 13, 4 Hz), 1.64 (1H, ddddd, $J=13$, 13, 13, 3.5, 3.5 Hz), 1.73–1.99 (3H, m), 2.17 (1H, dddd, $J=12.5$, 12.5, 5, 4 Hz), 2.64 (1H, ddd, $J=12.5$, 10.5, 5.5 Hz), 2.80 (1H, dd, $J=17.5$, 10.5 Hz), 3.06 (1H, dd, $J=17.5$, 5.5 Hz), 5.68 (1H, d, $J=5$ Hz), 7.16 (1H, br dd, $J=7.5$, 7.5 Hz), 7.23 (1H, br d, $J=7.5$ Hz), 7.25 (1H, br d, $J=7.5$ Hz), 7.31 (1H, ddd, $J=7.5$, 7.5, 1.5 Hz).

4.6.4. (4a*S,9a*S**,10*S**)-3,4,4a,9,9a,10-Hexahydro-10-nitrospiro[anthracene-1(2*H*),2′-[1,3]dioxolane] (81c, Table 3, run 4).** Colorless syrup obtained from **27**-*cis* in Table 3, run 4 along with **67**-*cis*. DI–HRMS calcd for $C_{16}H_{19}NO_4$: 289.1313. Found: 289.1295. DI–MS *m/z*: 289 (M^+, 3), 259 (3), 243 (23), 181 (55), 141 (16), 128 (23), 99 (100), 86 (27), 73 (11), 55 (16). IR ($CHCl_3$) cm^{-1}: 1553. ^1H NMR (300 MHz) δ: 1.12–1.28 (1H, m), 1.50–1.63 (2H, m), 1.64–1.88 (3H, m), 2.45 (1H, ddd, $J=11.5$, 7, 4 Hz), ca. 2.78–2.88 (1H, m), 2.81 (1H, dd, $J=18$, 11.5 Hz), 3.04 (1H,

dd, J=18, 7 Hz), 3.86–4.05 (4H, m), 5.51 (1H, d, J=2.5 Hz), 7.18–7.37 (4H, m).

4.6.5. Table 3, runs 5 and 6. The procedure for Table 3, run 5 was described as a representative. A slurry of **43**-major (34 mg, 88.5 μmol), $PdCl_2(Ph_3P)_2$ (6 mg, 8.55 μmol), and Cs_2CO_3 (87 mg, 0.267 mmol) in *m*-xylene (4 ml) was refluxed with stirring under an Ar atmosphere for 6 h. After having been cooled in an ice bath, saturated NH_4Cl–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane–EtOAc (34:1)] afforded (4a*R**,9a*S**,10*S**)-3,4,4a,9,9a,10-hexahydro-10-methyl-10-nitrospiro[anthracene-1(2*H*),2′-[1,3]dioxolane] (**82**, 12.5 mg, 47%), 3,4,9,9a-tetrahydro-10-methylspiro[anthracene-1(2*H*),2′-[1,3]dioxolane] (**83**, 8 mg, 35%), and (4a*R**,9a*S**)-3,4,4a,9,9a,10-hexahydro-10-methylenespiro-[anthracene-1(2*H*),2′-[1,3]dioxolane] (**84**, 2 mg, 9%) in order of decreasing polarity.

Compound **82**. Colorless syrup. DI–HRMS calcd for $C_{17}H_{21}NO_4$: 303.1469. Found: 303.1470. DI–MS *m*/*z*: 303 (M^+, 1), 273 (3), 257 (39), 195 (94), 143 (26), 141 (24), 128 (23), 115 (18), 99 (100), 86 (16), 73 (15), 55 (16). IR ($CHCl_3$) cm^{-1}: 1539. ^1H NMR (300 MHz) δ: 1.28–1.43 (2H, m), 1.45–1.66 (2H, m), 1.69–1.80 (1H, m), 1.76 (3H, s), 1.90 (1H, br d, J=13 Hz), 2.86 (1H, ddd, J=12.5, 12, 4 Hz), 2.89 (1H, dd, J=17.5, 5.5 Hz), 3.04 (1H, dd, J=17.5, 11 Hz), 4.04 (4H, s), 6.97 (1H, br d, J=7.5 Hz), 7.12 (1H, br d, J=7.5 Hz), 7.16 (1H, br dd, J=7.5, 7.5 Hz), 7.22 (1H, ddd, J=7.5, 7.5, 1.5 Hz). NOE cross-peak was observed between methyl group at C-10 and H-9a in the NOESY spectrum.

Compound **83**. Colorless syrup. DI–HRMS calcd for $C_{17}H_{20}NO_2$: 256.1462. Found: 256.1458. DI–MS *m*/*z*: 256 (M^+, 11), 155 (12), 141 (11), 115 (8), 99 (100). ^1H NMR (90 MHz) δ: 1.43–2.18 (5H, m), 2.05 (3H, s), 2.53–3.11 (4H, m), 3.78–4.20 (4H, m), 7.02–7.40 (4H, m).

Compound **84**. Colorless syrup. DI–HRMS calcd for $C_{17}H_{20}NO_2$: 256.1462. Found: 256.1458. DI–MS *m*/*z*: 256 (M^+, 21), 228 (27), 213 (62), 194 (51), 141 (67), 128 (41), 115 (47), 112 (79), 99 (100), 86 (63), 55 (25), 41 (38). IR ($CHCl_3$) cm^{-1}: 1620. ^1H NMR (90 MHz) δ: 1.13–2.66 (8H, m), 2.66–3.08 (2H, m), 4.03 (4H, s), 5.04 (1H, d, J=2 Hz), 5.55 (1H, d, J=2 Hz), 6.99–7.34 (3H, m), 7.45–7.71 (1H, m).

4.6.6. Table 3, run 7. A slurry of **30** (42 mg, 0.109 mmol), $PdCl_2(Ph_3P)_2$ (7.5 mg, 10.7 μmol), and Cs_2CO_3 (107 mg, 0.328 mmol) in toluene (4 ml) was refluxed with stirring under an Ar atmosphere for 20 h. The same work-up as above left a residue (42 mg). The residue was treated with KOH and then with H_2SO_4 as for the procedure of Table 3, run 1 to yield **69**-*trans* (3 mg, 10%) and **69**-*cis* (1.5 mg, 5%) after PTLC [hexane- CH_2Cl_2 (1:2)]. The spectral data of both compounds have been described in Table 2, run 7.

4.6.7. Table 3, run 8. A slurry of **44** (37 mg, 0.100 mmol), $PdCl_2(Ph_3P)_2$ (7 mg, 9.97 mmol), and Cs_2CO_3 (98 mg, 0.301 mmol) in toluene (4 ml) was heated at 140 °C in a sealed tube under an Ar atmosphere for 22 h. The same work-up and PTLC [hexane–EtOAc (9:1)] afforded (4′a*R**,10′a*S**)-2′,3′,4′,4′a,10′,10′a-hexahydro-4′a-nitrospiro[1,3-dioxolane-2,9′(1′*H*)-phenanthrene] (**85**, 9.5 mg, 33%), 2′,3′,4′,10′-tetrahydrospiro[1,3-dioxolane-2,9′(1′*H*)-phenanthrene] (**87**, 3.5 mg, 14%), and crude **86** in order of decreasing polarity. The crude **86** was further purified by PTLC [hexane–benzene (1:3)] provided 2′,3′,10′,10′a-tetrahydrospiro[1,3-dioxolane-2,9′(1′*H*)-phenanthrene] (**86**, 10 mg, 41%).

Compound **85**. Colorless syrup. GC–MS *m*/*z*: 243 ($M^+ - NO_2$, 100), 199 (72), 170 (24), 157 (43), 141 (27), 129 (29), 128 (28), 115 (33), 45 (24). IR ($CHCl_3$) cm^{-1}: 1539. ^1H NMR (300 MHz) δ: 1.38–1.71 (6H, m), 1.86–1.99 (1H, m), 2.01 (1H, dd, J=13.5, 3.5 Hz), 2.18 (1H, dd, J=13.5, 12.5 Hz), 2.69 (1H, br d, J=15 Hz), 3.46 (1H, br dddd, J=12.5, 3.5, 3.5, 3.5 Hz), 4.05–4.35 (4H, m), 7.25 (1H, dd, J=7, 2 Hz), 7.34 (1H, ddd, J=7, 7, 2 Hz), 7.38 (1H, ddd, J=7, 7, 2 Hz), 7.53 (1H, dd, J=7, 2 Hz). ^{13}C NMR δ: 19.6, 22.7, 28.0, 33.6, 35.5, 36.6, 64.6, 66.0, 93.6, 106.2, 124.3, 126.5, 129.0, 129.6, 136.2, 136.7.

Compound **86**. Colorless syrup. GC–HRMS calcd for $C_{16}H_{18}O_2$: 242.1306. Found: 242.1299. GC–MS *m*/*z*: 242 (M^+, 100), 198 (66), 197 (70), 181 (36), 170 (42), 141 (26), 115 (38). IR ($CHCl_3$) cm^{-1}: 1635. ^1H NMR (90 MHz) δ: 1.14–2.41 (8H, m), 2.47–2.94 (1H, m), 3.96–4.39 (4H, m), 6.30–6.54 (1H, m), 7.14–7.44 (2H, m), 7.44–7.78 (2H, m).

Compound **87**. Colorless syrup. GC–HRMS calcd for $C_{16}H_{18}O_2$: 242.1306. Found: 242.1300. GC–MS *m*/*z*: 242 (M^+, 100), 198 (87), 170 (68), 141 (23), 115 (20), 45 (24). IR ($CHCl_3$) cm^{-1}: 1643. ^1H NMR (90 MHz) δ: 1.48–2.06 (4H, m), 2.06–2.64 (6H, m), 4.09 (4H, s), 7.06–7.58 (4H, m).

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References and notes

1. Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995.
2. (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478 and references therein. (b) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345–5348. (c) Fox, J. M.; Huang, X. H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370 and references therein. (d) Satoh, T.; Miura, M.; Nomura, M. *Organomet. Chem.* **2002**, *653*, 161–166. (e) For a recent review, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245.
3. (a) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807–4810. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *38*, 2367–2370. (c) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580 and references therein. (d) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.;

Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174 and references therein.
4. (a) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225. (b) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498–2500.
5. Intramolecular α-arylation of ketone: (a) Ueda, N.; Tokuyama, T.; Sakan, T. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2012–2014. (b) Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. *Tetrahedron Lett.* **1973**, 4519–4522. (c) Semmelhack, M. F.; Bargar, T. M. *J. Org. Chem.* **1977**, *42*, 1481–1482. (d) Snider, B. B.; Cole, B. M. *J. Org. Chem.* **1995**, *60*, 5376–5377.
6. Intermolecular α-arylation of ketone: (a) Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Saitoh, K.; Migita, T. *Chem. Lett.* **1982**, 939–940. (b) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831–6833. (c) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *J. Chem. Soc., Chem. Commun.* **1983**, 344–345. (d) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn* **1984**, *57*, 242–246. (e) Urabe, H.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 1355–1358. (f) McCague, R.; Kuroda, R.; Leclercq, G.; Stoessel, S. *J. Med. Chem.* **1986**, *29*, 2053–2059. (g) Negishi, E.; Akiyoshi, K. *Chem. Lett.* **1987**, 1007–1010. (h) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Stenson, P. H. *Tetrahedron* **1988**, *44*, 6387–6396. (i) Donnelly, D. M. X.; Finet, J.-P.; Stenson, P. H. *Heterocycles* **1989**, *28*, 15–18.(j) Hou, D.; Mas, J. L. US Patent 4992591, 1991; *Chem. Abstr.* **1991**, *115*, 28927z. (k) Pandey, G.; Krishna, A.; Girija, K.; Karthikeyan, M. *Tetrahedron Lett.* **1993**, *34*, 6631–6634. (l) Gao, P.; Portoghese, P. S. *J. Org. Chem.* **1995**, *60*, 2276–2278.
7. Arylation of 1,3-dicarbonyl compounds and their equivalents: (a) Bruggink, A.; McKillop, A. *Tetrahedron* **1975**, *31*, 2607–2619. (b) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507–2516. (c) Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 932–933. (d) Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* **1985**, 506–508. (e) Kobayashi, T.; Tanaka, M. *Tetrahedron Lett.* **1986**, *27*, 4745–4748. (f) Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *28*, 171–174. (g) Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4149–4151. (h) Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C.; Bellandi, P. *Tetrahedron* **1991**, *47*, 333–342. (i) Lloris, M. E.; Abramovitch, R. A.; Marquet, J.; Morenomanas, M. *Tetrahedron* **1992**, *48*, 6909–6916. (j) Donnelly, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1729–1735. (k) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606–7607.
8. (a) Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7577–7580. (b) Muratake, H.; Hayakawa, A.; Natsume, M. *Chem. Pharm. Bull.* **2000**, *48*, 1558–1566.
9. Recently Pd-catalyzed intermolecular α-arylation of aliphatic formyl group by use of tri-*tert*-butylphosphine has been reported: Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101–104.
10. Recently Pd-catalyzed intermolecular α-arylation of nitroalkane has been reported: Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106–111.
11. Muratake, H.; Natsume, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4646–4649.
12. A part of this paper was reported as preliminary communications: (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581–7582. (b) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355–2358.
13. Ripa, L.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 84–91.
14. Kozikowski, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, *32*, 3317–3320.
15. (a) Hays, S. J.; Novak, P. M.; Ortwine, D. F.; Bigge, C. F. *J. Med. Chem.* **1993**, *36*, 654–670. (b) Pal, S.; Mukhopadhyaya, J. K.; Ghatak, U. R. *J. Org. Chem.* **1994**, *59*, 2687–2694. (c) Bailey, W. F.; Doskapan, T.; Rampalli, S. *J. Org. Chem.* **2003**, *68*, 1334–1338.
16. (a) Godefroi, S. *J. Org. Chem.* **1963**, *28*, 1112–1116. (b) Pang, Y. P.; Kozikowski, A. P. *J. Org. Chem.* **1991**, *56*, 4499–4508.
17. (a) Taber, D. F. *J. Org. Chem.* **1976**, *41*, 2649–2650. (b) Taber, D. F.; Gunn, B. P.; Chiu, I.-C. In *Organic Syntheses*, *Collect. Vol. VII*; Wiley: New York, 1990; pp 249–250.
18. Stelion, K.; Poupart, M.-A. *J. Org. Chem.* **1985**, *50*, 4971–4973.
19. Snyder, L.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 7507–7515.
20. Barnes, R. A.; Hirschler, H. P.; Bluestein, B. R. *J. Am. Chem. Soc.* **1952**, *74*, 4091–4093.
21. Bruyère, D.; Gaignard, G.; Bouyssi, D.; Balme, G.; Lancelin, J-M. *Tetrahedron Lett.* **1997**, *38*, 827–830.
22. Wollenberg, R. H.; Miller, S. J. *Tetrahedron Lett.* **1978**, 3219–3222.
23. Julia, S.; Huynh, C.; Olivie, J. *Bull. Soc. Chim. Fr.* **1966**, 147–152.
24. Mitsuhashi, K.; Shiotani, S. *Chem. Pharm. Bull.* **1970**, *18*, 75–87.
25. Baker, L. *J. Chem. Soc.* **1948**, 974–979.
26. Comubert, E. *Bull. Soc. Chim. Fr.* **1954**, 531–533.
27. Adkins, H. *J. Am. Chem. Soc.* **1949**, *71*, 2965–2967.
28. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–4731.

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A new synthesis of amides and γ-lactones based on the conjugate addition of lithium enolate of amides to 1-chlorovinyl *p*-tolyl sulfoxides

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Abstract—Reaction of 1-chlorovinyl *p*-tolyl sulfoxides, which were synthesized from chloromethyl *p*-tolyl sulfoxide and ketones or aldehydes, with lithium enolate of *N*,*N*-dimethylacetamide gave the adducts in good to quantitative yields. The adducts were converted to several kinds of amides in high overall yields. Treatment of the adducts with trifluoroacetic anhydride in the presence of NaI resulted in the formation of γ-tolylsulfanylated γ-lactones in high yields. The scope and limitations of this method and the mechanism of the reactions are also discussed. These procedures offer a new and effective method for the synthesis of amides and γ-lactones having substituents on the β-carbon from *N*,*N*-dimethylacetamide with carbon elongation.

Carboxylic acids, esters, amides, and their derivatives are among the most important compounds in organic chemistry[1] including bioorganic[2,3] and synthetic organic chemistry. In view of their importance, development of new synthetic methods for these compounds has still been actively investigated in many laboratories worldwide.

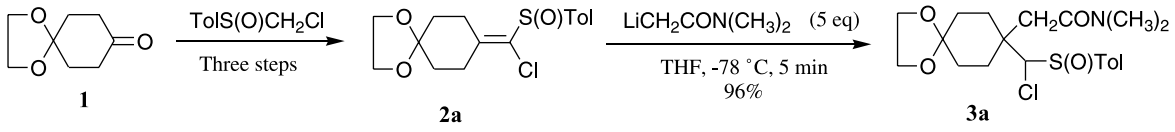
One method for obtaining the desired carboxylic acid derivatives is considered to be the elongation of carbons from simple acetates or acetamides. Recently, we reported a method for a synthesis of functionalized esters and lactones from acetates and their homologues with 1-chlorovinyl *p*-tolyl sulfoxides.[4] In continuation of our interest in the development of new synthetic methods by using 1-chlorovinyl *p*-tolyl sulfoxides,[5,6] we turned our attention to the reaction of 1-chlorovinyl *p*-tolyl sulfoxides with lithium enolate of *N*,*N*-dimethylacetamide and its homologues, and quite interesting results were obtained.

1. Results and discussion

1.1. The addition reaction of the lithium enolate of *N*,*N*-dimethylacetamide to 1-chlorovinyl *p*-tolyl sulfoxides

In previous studies, we have found that lithium ester enolates added to 1-chlorovinyl *p*-tolyl sulfoxides in high yields.[4] Based on this experience, we investigated the addition reaction of the vinylsulfoxides with the lithium enolate of *N*,*N*-dimethylacetamide (Scheme 1).

Thus, a THF solution of 1-chlorovinyl *p*-tolyl sulfoxide **2a**, derived from ketone **1** in three steps,[7] was added dropwise to a solution of 5 equiv of lithium enolate of *N*,*N*-dimethylacetamide (generated from *N*,*N*-dimethylacetamide with LDA) at −78 °C. An instantaneous reaction took place and the adduct **3a** was obtained as about a 5:3 mixture of two diastereomers in a quantitative yield. Encouraged by this



1 **2a** **3a**

Scheme 1.

Keywords: Amide; Amide enolate; Conjugate addition; γ-Lactone; Sulfoxide.
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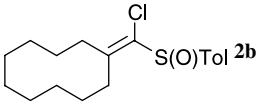
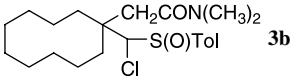
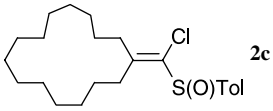
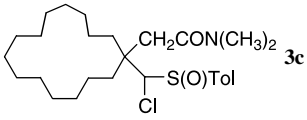
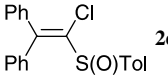
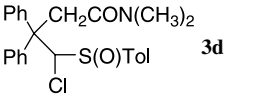
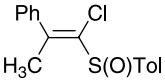
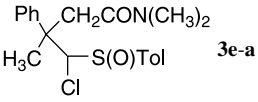
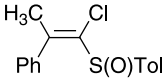
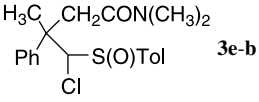
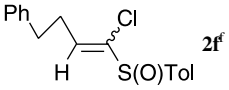
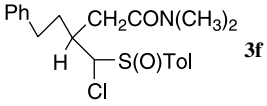
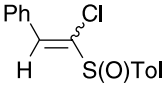
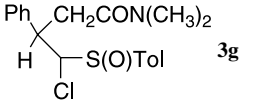
Table 1. Addition of lithium enolate of *N*,*N*-dimethylacetamide to 1-chlorovinyl *p*-tolyl sulfoxides **2**

Entry	2	Conditions[a]	Adduct 3	Yield (%)
1	 **2b**	−78 °C, 1.5 h	 **3b**	97[b]
2	 **2c**	−78 °C, 3 h	 **3c**	99[c]
3	 **2d**	−78 ~ −10 °C, 2 h	 **3d**	40[d]
4	 **2e**-*Z*	−78 ~ −10 °C, 2 h	 **3e-a**	86[d]
5	 **2e**-*E*	−78 ~ −10 °C, 2 h	 **3e-b**	22[d,e]
6	 **2f**[f]	−78 °C, 30 min	 **3f**	96[g]
7	 **2g**[f]	−78 °C, 30 min	 **3g**	99[h]

[a] Five equivalents of lithum enolate of *N*,*N*-dimethylacetamide was reacted with 1-chlorovinyl *p*-tolyl sulfoxides **2**.
[b] About 5:1 mixture of two diastereomers.
[c] About 10:1 mixture of two diastereomers.
[d] Single diastereomer.
[e] Starting material 75% was recovered.
[f] A mixture of two geometrical isomers was used in this reaction.
[g] A mixture of four diastereomers.
[h] About 3:1 mixture of two diastereomers.

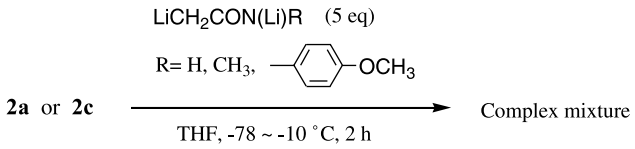
result, the addition reaction of lithium enolate of *N*,*N*-dimethylacetamide with 1-chlorovinyl *p*-tolyl sulfoxides (**2b**–**2g**) derived from ketones and aldehydes was investigated and the results are summarized in Table 1.

Interestingly, the addition reaction of the lithium enolate with the 1-chlorovinyl *p*-tolyl sulfoxides derived from cyclodecanone and cyclopentadecanone (**2b** and **2c**) was found to be sluggish compared to the reaction with **2a**; however, on prolonging the reaction time to 3 h, the desired adducts **3b** and **3c** were obtained in quantitative yields (entries 1 and 2).

The reaction with the 1-chlorovinyl *p*-tolyl sulfoxides **2d** and **2e**, derived from benzophenone and acetophenone, was found to be very sluggish, and warming the reaction mixture from −78 to −10 °C was required (entries 3–5). It is interesting to note that, in a previous study,[4] the addition reaction of lithium enolate of *tert*-butylacetate to **2d** and **2e** did not proceed at all and the starting sulfoxides were recovered. Conjugation of the phenyl group to the 1-chlorovinyl *p*-tolyl sulfoxides was thought to be the reason for these results.

Difference in reactivity between the geometrical isomers **2e**-*Z* and **2e**-*E* was observed (entries 4 and 5). The reason for this result is obscure at present. The addition reaction with the 1-chlorovinyl *p*-tolyl sulfoxides derived from alkyl aldehyde **2f** and aryl aldehyde **2g** is shown in entries 6 and 7. Both vinyl sulfoxides reacted with the lithium enolate at −78 °C within 30 min without any problem to give the adducts **3f** and **3g** in quantitative yields (entries 6 and 7). The adducts were usually a mixture of diastereomers; however, in the cases of the reaction with **2d** and **2e**, a single diastereomer was obtained (entries 3–5). The stereochemistry of both adducts has not yet been determined.

Next, the addition reaction of the dianions of acetamide, *N*-methylacetamide, and *N*-(4-methoxyphenyl)acetamide to 1-chlorovinyl *p*-tolyl sulfoxides **2a** and **2c** was examined (Scheme 2). The reaction of 5 equiv of these dianions with the vinyl sulfoxides **2a** or **2c** at −78 °C did not proceed at all. When the temperature of the reaction mixture was slowly allowed to warm to −10 °C, we observed decomposition of the vinyl sulfoxides and obtained only a complex mixture with no desired adduct.



Scheme 2.

The higher basicity of the dianions, compared with the lithium enolate of *N*,*N*-dimethylacetamide, was thought to be the reason for these results, because we have already observed that the reaction of the 1-chlorovinyl *p*-tolyl sulfoxides **2** with a highly basic reagent, such as lithium diisopropylamide, resulted in their decomposition.

1.2. Transformation of the carbon bearing a chlorine atom and a sulfinyl group in the adduct to a methyl group

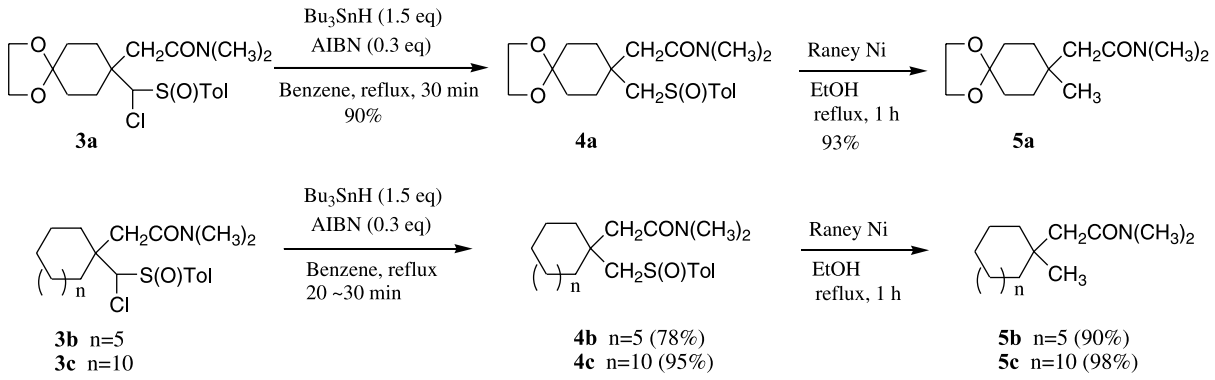
In order to transform the adducts to simple amides, reduction of the chlorine and sulfinyl groups was investigated (Scheme 3). First, **3a** was treated with Bu_3SnH in the presence of a catalytic amount of AIBN in refluxing benzene.[8] The desired reduction cleanly took place to afford the sulfoxide **4a** in 90% yield.

The sulfinyl group in **4a** was cleanly reduced with Raney nickel[9] in refluxing ethanol for 1 h to give **5a** in 93% yield. The other adducts **3b** and **3c** were converted to the reduced compounds having a methyl group at the β-position (**5b** and **5c**) in high overall yields. By these reactions, a new method for a synthesis of amides having a quaternary carbon at the β-position was realized starting from *N*,*N*-dimethylacetamide with carbon elongation.

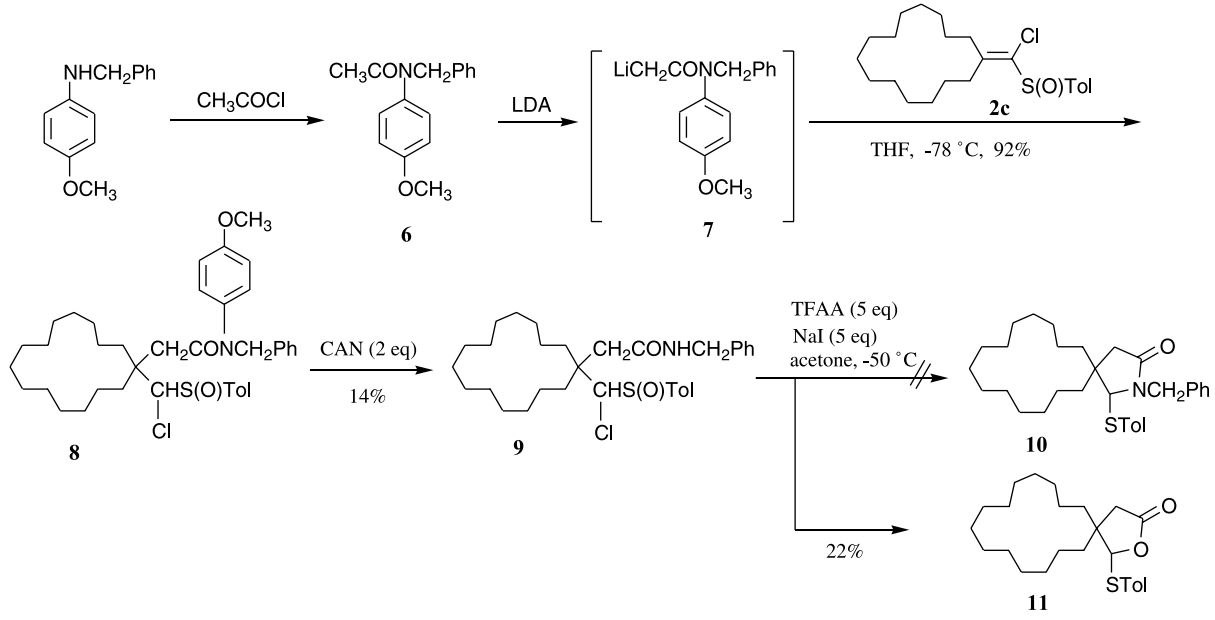
1.3. Trial to a synthesis of γ-lactams

Kita et al. reported a synthesis of β-lactams from β-amido sulfoxides via intramolecular Pummerer-type cyclization.[10] We attempted to synthesize γ-lactams from the adducts, γ-amido sulfoxides, by using a similar cyclization.

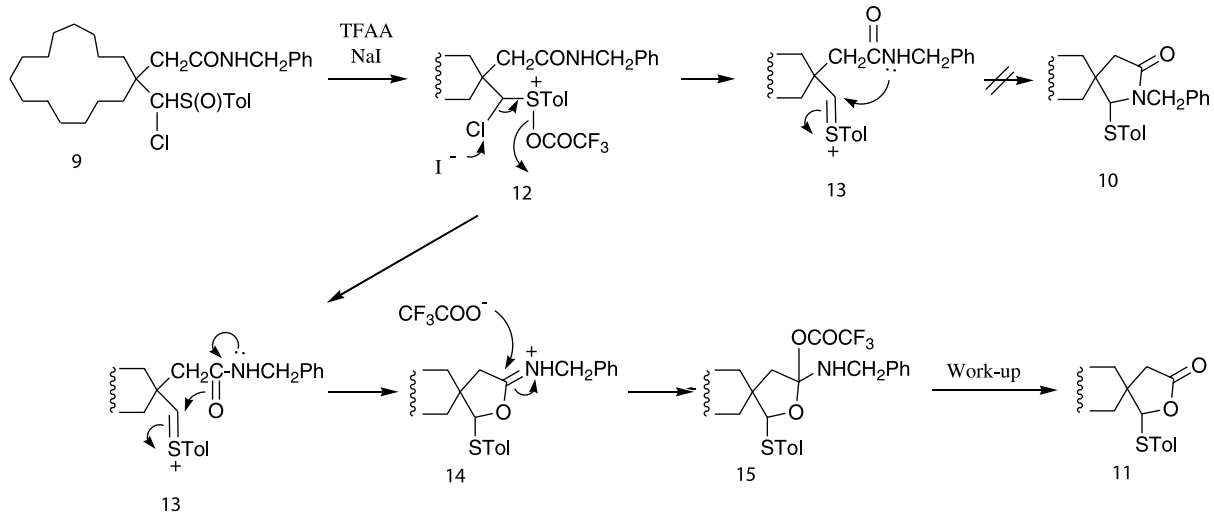
As already mentioned, the addition reaction of the dianions of *N*-mono-substituted acetamide and acetamide with 1-chlorovinyl *p*-tolyl sulfoxides failed (see Scheme 2). We synthesized *N*-benzyl-*N*-(4-methoxyphenyl)acetamide **6**



Scheme 3.



Scheme 4.



Scheme 5.

from *N*-benzyl *p*-anisidine, and the lithium enolate of amide **7**, derived from **6**, was reacted with **2c**. The addition reaction worked excellently to afford the adduct **8** in 92% yield (Scheme 4).

The 4-methoxyphenyl group in **8** was eliminated with ceric ammonium nitrate (CAN)[11] to afford the desired γ-amido sulfoxide **9**, though the yield was low. The amide **9** was treated with excess trifluoroacetic anhydride (TFAA) in the presence of NaI in acetone at −50 °C.[12] We obtained not the expected γ-lactam **10** but spiro-lactone having a *p*-tolylsulfanyl group at the γ-position **11** in 22% yield as a main product.

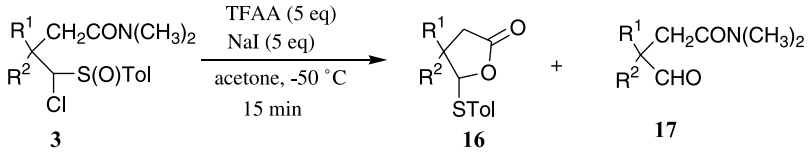
The presumed mechanism of this interesting reaction is shown in Scheme 5. First, the reaction of the sulfoxide **9** with TFAA gives an acyloxysulfonium ion **12**.[13] The iodide anion attacks the chlorine atom to afford thionium ion **13**. The anticipated reaction, attack of the nitrogen lone pair to the thionium ion, did not take place and no desired γ-lactam **10** was obtained. Instead, the thionium ion was attacked by the oxygen of the amide group to give an ether having iminium ion **14**. The trifluoroacetoxy anion then attacks the carbon of the iminium ion to afford **15**, which was hydrolyzed in the work-up process to give the γ-lactone **11**.

1.4. Synthesis of lactones from the adducts 3

As mentioned above, the Pummerer-type cyclization of γ-amido sulfoxide **9** was found to give γ-lactone **11**. From the presumed mechanism shown in Scheme 5, we expected that the treatment of the adducts **3** derived from *N*,*N*-dimethylacetamide with TFAA also gave lactones. In fact, treatment of the adduct **3a** with TFAA in the presence of NaI in acetone at −50 °C gave γ-lactone having a *p*-tolylsulfanyl group at the γ-position **16a** in 49% yield (Table 2, entry 1). The results of this reaction with the adducts **3c**–**3g** are summarized in Table 2.

As shown in Table 2, about 70–90% of γ-lactones **11**, **16a**, and **16d**–**16g** were obtained by this reaction. In some cases, aldehydes **17c**, **17f**, and **17g** were obtained as by-products.

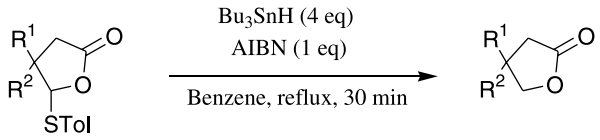
Table 2. Synthesis of γ-lactones **16** and *N*,*N*-dimethylamides having a formyl group at the β-position **17** from the adducts **3**



Entry	3			16 Yield	17 Yield
		R^1	R^2		
1	**3a**	-$(CH_2)_2$-C(O,O)-$(CH_2)_2$-		**16a**[a] 49	—[b]
2	**3c**	–$(CH_2)_{14}$–		**11**[a] 85	**17c** 13
3	**3d**	Ph	Ph	**16d** 75	—[b]
4	**3e-a**	Ph	CH_3	**16e**[c] 91	—[b]
5	**3f**	$PhCH_2CH_2$	H	**16f**[a] 81	**17f** 15
6	**3g**	Ph	H	**16g**[d] 68	**17g** 21

[a] See lit. 4.
[b] No aldehyde was obtained.
[c] About 3:1 inseparable mixture of diastereomers.
[d] About 5:1 inseparable mixture of diastereomers.

These aldehydes were thought to be produced form the competitive addition of the trifluoroacetoxy anion to the corresponding thionium ione **13** (see Scheme 5). Finally, the *p*-tolylsulfanyl group was reduced with Bu_3SnH in the presence of AIBN[14] to give γ-lactones **18** in high yields (Scheme 6).



16 **18**

16d	(R^1=Ph, R^2=Ph)	**18d**	99%
16e	(R^1=Ph, R^2=CH_3)	**18e**	99%
16g	(R^1=Ph, R^2=H)	**18g**	98%

Scheme 6. Reduction of the *p*-tolylsulfanyl group of **16** with Bu_3SnH.

In conclusion, we have developed a novel and versatile procedure for a synthesis of *N*,*N*-dimethylamides having a tertiary or a quaternary carbon at the β-position from 1-chlorovinyl *p*-tolyl sulfoxides and *N*,*N*-dimethylacetamide with carbon elongation. Pummerer-type cyclization of the adducts **3**, γ-amido sulfoxides, was found to give γ-lactones and by this reaction a novel synthesis of γ-lactones having a tertiary and a quaternary carbon at the β-position was realized.

2. Experimental

2.1. General

All melting points are uncorrected. IR spectra were measured with Perkin–Elmer Spectrum One FT-IR spectrometer. ^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNM-LA 300 and 500 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silica gel 60 (Merck) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry reagent and solvent, *N*,*N*-diisopropylamine and benzene were distilled from CaH_2 and THF was distilled from diphenylketyl. Acetone was dried over $CaSO_4$ and distilled before use. 1-Chlorovinyl *p*-tolyl sulfoxides **2** used in this study were synthesized from the corresponding ketones or aldehydes and chloromethyl *p*-tolyl sulfoxide as reported before.[4,5a]

2.1.1. 2-{8-[Chloro(*p*-tolylsulfinyl)methyl]-1,4-dioxaspiro-[4.5]dec-8-yl}-*N*,*N*-dimethylacetamide (3a). *N*,*N*-Dimethylacetamide (0.39 ml; 4.0 mmol) was added to a solution of LDA (4.0 mmol) in 4 ml of dry THF at −78 °C with stirring. The solution was stirred for 10 min, then a solution of **2a** (262 mg; 0.8 mmol) in THF (4 ml) was added. The solution was stirred for 5 min, then the reaction was quenched by adding sat. aq. NH_4Cl. The whole was extracted with AcOEt–hexane (1:1). The product was purified by silica gel column chromatography to afford **3a** (318 mg, 96%). Colorless oil (about 5:3 mixture of two diastereomers); IR (neat) 2938, 1637 (CO), 1494, 1454, 1400, 1262, 1143, 1109, 1051 (SO), 895, 812, 787, 714 cm^{-1}; ^{1}H NMR δ 1.65–1.75 (4H, m), 2.03–2.37 (4H, m), 2.41 (3H, s), 2.79–3.35 (2H, m), 2.96, 3.09 (each 1.12H, s, NCH_3), 2.98, 3.08 (each 1.88H, s, NCH_3), 3.95 (4H, s), 5.51 (0.38H, s), 5.80 (0.62H, s), 7.29 (2H, t, *J*=8.1 Hz), 7.49 (0.8H, d, *J*=8.1 Hz), 7.68 (1.2H, d, *J*=8.1 Hz). MS *m*/*z* (%) 413 (M^+, 0.4), 360 (7), 334 (2), 329 (2), 274 (100), 238 (68), 211 (72), 182 (12), 149 (23), 99 (52), 72 (64). Calcd for $C_{20}H_{28}ClNO_4S$: M, 413.1427. Found: *m*/*z* 413.1425.

2.1.2. 2-{1-[Chloro(*p*-tolylsulfinyl)methyl]cyclodecyl}-*N*,*N*-dimethylacetamide (3b). Main product: colorless oil; IR (neat) 2926, 1638 (CO), 1484, 1445, 1263, 1216, 1148, 1125, 1048 (SO), 1017, 811, 755 cm^{-1}; ^{1}H NMR δ 1.59–2.27 (18H, m), 2.41 (3H, s), 2.49 (1H, d, *J*=16.8 Hz), 2.96 (3H, s), 3.04 (3H, s), 3.22 (1H, d, *J*=16.8 Hz), 5.90 (1H, s), 7.29, 7.70 (each 2H, d, *J*=8.0 Hz). Minor product: colorless oil; IR (neat) 2924, 1639 (CO), 1482, 1399, 1260, 1088, 1060 (SO), 810, 754 cm^{-1}; ^{1}H NMR δ 1.62–2.22 (18H, m), 2.40 (3H, s), 2.70, 2.76 (each 1H, d, *J*=16.8 Hz), 2.95 (3H, s), 3.08 (3H, s), 5.55 (1H, s), 7.31 (2H, d, *J*=8.0 Hz), 7.53 (2H, d, *J*=8.0 Hz).

2.1.3. 2-{1-[Chloro(*p*-tolylsulfinyl)methyl]cyclopentadecyl}-*N*,*N*-dimethylacetamide (3c). Main product: colorless oil; IR (neat) 2927, 2856, 1644 (CO), 1494, 1461, 1398, 1265, 1141, 1084, 1052 (SO), 810, 787 cm^{-1}; ^{1}H NMR δ 1.25–1.87 (28H, m), 2.41 (3H, s), 2.53 (1H, d, *J*=16.8 Hz), 2.96 (3H, s), 3.05 (3H, s), 3.21 (1H, d, *J*=16.8 Hz), 5.81 (1H, s), 7.29, 7.69 (each 2H, d, *J*=8.3 Hz). MS *m*/*z* (%) 481 (M^+, 0.3), 427 (4), 395 (2), 323 (100), 295 (100), 294 (100), 246 (42), 238 (18). Calcd for $C_{27}H_{44}ClNO_2S$: M, 481.2781. Found: *m*/*z* 481.2768. Minor product: colorless oil; IR (neat) 2928, 2857, 1640 (CO), 1494, 1460, 1399, 1263, 1141, 1089, 1061 (SO), 810, 754 cm^{-1}; ^{1}H NMR δ 1.26–1.98 (28H m), 2.40 (3H, s), 2.69, 2.73 (each 1H, d, *J*=17.1 Hz), 2.94 (3H, s), 3.07 (3H, s), 5.49 (1H, s), 7.31 (2H, d, *J*=8.0 Hz), 7.52 (2H, d, *J*=8.0 Hz). MS *m*/*z* (%) 481 (M^+, 0.15), 342 (100), 306 (61), 294 (12), 139 (8), 72 (64). Calcd for $C_{27}H_{44}ClNO_2S$: M, 481.2781. Found: *m*/*z* 481.2782.

2.1.4. 4-Chloro-*N*,*N*-dimethyl-3,3-diphenyl-4-(*p*-tolylsulfinyl)butanamide (3d). Colorless crystals; mp 182–183 °C (AcOEt–hexane); IR (KBr) 2924, 1626 (CO), 1493, 1444, 1058 (SO), 814, 707 cm^{-1}; ^{1}H NMR δ 2.39 (3H, s), 2.41 (3H, s), 2.68 (3H, s), 3.30 (1H, d, *J*=13.4 Hz), 4.61 (1H, br d), 7.04 (1H, s), 7.21–7.24 (5H, m), 7.30 (2H, d, *J*=8.3 Hz), 7.44–7.47 (3H, m), 7.66–7.68 (2H, m), 7.84 (2H, d, *J*=8.0 Hz). MS *m*/*z* (%) 439 (M^+, 0.1), 422 (3) 353 (8), 300 (50), 264 (75), 253 (40), 234 (10), 191 (28), 178 (30), 139 (23), 115 (16), 91 (30), 72 (100). Calcd for $C_{25}H_{26}ClNO_2S$: M, 439.1373. Found: *m*/*z* 439.1369. Anal. Calcd for $C_{25}H_{26}ClNO_2S$: C, 68.24; H, 5.96; Cl, 8.06; N, 3.18; S, 7.29. Found: C, 67.92; H, 5.85; Cl, 7.97; N, 3.27; S, 7.24.

2.1.5. 4-Chloro-3,*N*,*N*-trimethyl-3-phenyl-4-(*p*-tolylsulfinyl)butanamide (3e-a). Colorless crystals; mp 127–128 °C (AcOEt–hexane); IR (KBr) 2923, 1619 (CO), 1495, 1399, 1088, 1054 (SO), 815, 707, 628 cm^{-1}; ^{1}H NMR δ 2.04 (3H, s), 2.41 (3H, s), 2.78 (3H, s), 2.85 (3H, s), 3.19, 3.23 (each 1H, d, *J*=15.9 Hz), 5.80 (1H, s), 7.27–7.36 (5H, m), 7.51

(2H, d, J=7.7 Hz), 7.77 (2H, d, J=7.9 Hz). MS m/z (%) 377 (M^+, 1), 360 (1.6), 341 (3), 324 (10), 291 (3), 279 (3), 238 (43), 218 (5), 202 (80), 190 (28), 139 (10), 129 (20), 91 (30), 72 (100). Calcd for $C_{20}H_{24}ClNO_2S$: M, 377.1216. Found: m/z 377.1208. Anal. Calcd for $C_{20}H_{24}ClNO_2S$: C, 63.56; H, 6.40; Cl, 9.38; N, 3.71; S, 8.48. Found: C, 63.55; H, 6.29; Cl, 9.31; N, 3.71; S, 8.39.

2.1.6. 4-Chloro-3,*N*,*N*-trimethyl-3-phenyl-4-(*p*-tolylsulfinyl)butanamide (3e-b). Colorless oil; IR (neat) 2925, 1639 (CO), 1495, 1399, 1084, 1051 (SO) cm^{-1}; ^1H NMR δ 1.80 (3H, s), 2.40 (3H, s), 2.93 (1H, d, J=16.2 Hz), 2.98 (6H, s), 3.95 (1H, d, J=16.2 Hz), 7.27–7.37 (3H, m), 7.44 (2H, t, J=7.6 Hz), 7.67–7.74 (4H, m). MS m/z (%) 377 (M^+, 0.3), 362 (0.4), 291 (4), 238 (22), 202 (30), 191 (15), 158 (5), 129 (18), 124 (17), 91 (40), 72 (100). Calcd for $C_{20}H_{24}ClNO_2S$: M, 377.1216. Found: m/z 377.1218.

2.1.7. 3-[Chloro(*p*-tolylsulfinyl)methyl]-*N*,*N*-dimethyl-5-phenylpentanamide (3f). One of the four diastereomers was isolated: colorless oil; IR (neat) 2927, 1645 (CO), 1495, 1455, 1400, 1052 (SO), 812, 753, 701 cm^{-1}; ^1H NMR δ 1.71–1.79 (1H, m), 2.23–2.30 (1H, m), 2.42 (3H, s), 2.51 (1H, dd, J=16.2, 9.8 Hz), 2.62 (1H, dd, J=16.2, 5.2 Hz), 2.74–2.84 (2H, m), 2.92 (3H, s), 2.96 (3H, s), 3.20–3.22 (1H, m), 4.91 (1H, d, J=2.2 Hz), 7.19–7.32 (7H, m), 7.70 (2H, d, J=8.3 Hz). MS m/z (%) 391 (M^+, 6), 374 (3), 337 (10), 305 (5), 252 (100), 215 (42), 129 (37), 91 (90), 72 (95), 65 (13). Calcd for $C_{21}H_{26}ClNO_2S$: M, 391.1373. Found: m/z 391.1375.

2.1.8. 4-Chloro-*N*,*N*-dimethyl-3-phenyl-4-(*p*-tolylsulfinyl)butanamide (3g). Colorless oil (about 3:1 diastereomeric mixture); IR (neat) 2927, 1643 (CO), 1495, 1455, 1400, 1244, 1142, 1084, 1048 (SO), 1016, 813, 755, 702 cm^{-1}; ^1H NMR δ 2.41 (3H, s), 2.87 (0.75H, s), 2.90 (2.25H, s), 2.92–3.33 (3H, m), 3.04 (3H, s), 4.75 (0.75H, d, J=3.4 Hz), 5.30 (0.25H, d, J=7.1 Hz), 7.28–7.63 (9H, m). MS m/z (%) 363 (M^+, trace), 224 (32), 188 (7), 160 (5), 140 (15), 115 (30), 91 (26), 72 (82). Calcd for $C_{19}H_{22}ClNO_2S$. M, 363.1060. Found: m/z 363.1057.

2.1.9. *N*,*N*-Dimethyl-2-{8-[(*p*-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]dec-8-yl}acetamide (4a). AIBN (37 mg; 0.23 mmol) was added to a solution of **3a** (315 mg; 0.76 mmol) and Bu_3SnH (0.31 ml; 1.14 mmol) in 15 ml of benzene. The atmosphere in the flask was replaced with Ar, and the reaction mixture was stirred and refluxed for 30 min. The benzene was evaporated and the residue was purified by silica gel column chromatography to give **4a** (259 mg; 90%) as a colorless oil; IR (neat) 2933, 1639 (CO), 1494, 1451, 1398, 1275, 1104, 1037 (SO), 1016, 938, 906, 788 cm^{-1}; ^1H NMR δ 1.61–2.10 (8H, m), 2.40 (3H, s), 2.73, 2.79 (each 1H, d, J=16.5 Hz), 2.96 (3H, s), 3.08 (3H, s), 3.21 (2H, s), 3.93 (4H, s), 7.30 (2H, d, J=8.0 Hz), 7.54 (2H, d, J=8.0 Hz). MS m/z (%) 379 (M^+, 0.6), 362 (20), 276 (8), 240 (97), 196 (12), 178 (3), 153 (12), 139 (5), 99 (10). Calcd for $C_{20}H_{29}NO_4S$: M, 379.1815. Found: m/z 379.1809.

2.1.10. *N*,*N*-Dimethyl-2-{1-[(*p*-tolylsulfinyl)methyl]cyclodecyl}acetamide (4b). Colorless oil; IR (neat) 2925, 2869, 1640 (CO), 1494, 1483, 1398, 1261, 1141, 1086, 1041 (SO), 812, 753 cm^{-1}; ^1H NMR δ 1.25–1.85 (18H, m), 2.40 (3H, s), 2.64, 2.69 (each 1H, d, J=16.5 Hz), 2.96 (3H, s), 3.04 (1H, d, J=13.7 Hz), 3.08 (3H, s), 3.21 (1H, d, J=13.5 Hz), 7.29, 7.57 (each 2H, d, J=8.0 Hz). MS m/z (%) 377 (M^+, 0.6), 360 (9), 291 (9), 274 (26), 238 (100), 139 (7), 109 (5), 87 (25), 72 (50). Calcd for $C_{22}H_{35}NO_2S$: M, 377.2386. Found: m/z 377.2378.

2.1.11. *N*,*N*-Dimethyl-2-{1-[(*p*-tolylsulfinyl)methyl]cyclopentadecyl}acetamide (4c). Colorless oil; IR (neat) 2929, 2857, 1644 (CO), 1494, 1460, 1042 (SO), 812, 787, 756 cm^{-1}; ^1H NMR δ 1.21–1.71 (28H, m), 2.40 (3H, s), 2.66, 2.72 (each 1H, d, J=16.5 Hz) 2.96 (3H, s), 3.08 (3H, s), 3.10, 3.21 (each 1H, d, J=13.7 Hz), 7.29, 7.56 (each 2H, d, J=8.0 Hz). MS m/z (%) 447 (M^+, 1), 430 (10), 344 (30), 308 (100), 306 (8), 137 (5), 124 (5), 87 (15), 72 (30). Calcd for $C_{27}H_{45}NO_2S$: M, 447.3171. Found: m/z 447.3168.

2.1.12. *N*,*N*-Dimethyl-2-(8-methyl-1,4-dioxaspiro[4.5]-dec-8-yl)acetamide (5a). A solution of **4a** (100 mg; 0.27 mmol) and excess of Raney Ni in EtOH was stirred and refluxed for 1 h. The Raney Ni was filtered off, and the filtrate was evaporated to give a residue, which was purified by silica gel column chromatography to afford **5a** (60.6 mg; 93%) as a colorless oil; IR (neat) 2931, 1638 (CO), 1509, 1397, 1246, 1101, 1036, 942 cm^{-1}; ^1H NMR δ 1.09 (3H, s), 1.46–1.71 (8H, m), 2.30 (2H, s), 2.94 (3H, s), 3.04 (3H, s), 3.93 (4H, s). MS m/z (%) 241 (M^+, 7), 226 (3), 196 (8), 179 (7), 154 (100), 139 (10), 99 (52), 87 (90), 72 (26). Calcd for $C_{13}H_{23}NO_3$: M, 241.1676. Found: m/z 241.1670.

2.1.13. *N*,*N*-Dimethyl-2-(1-methylcyclodecyl)acetamide (5b). Colorless oil; IR (neat) 2928, 1644 (CO), 1483, 1445, 1393, 1262, 1141 cm^{-1}; ^1H NMR δ 0.99 (3H, s), 1.37–1.55 (18H, m), 2.21 (2H, s), 2.94 (3H, s), 3.04 (3H, s). MS m/z (%) 239 (M^+, 0.5), 224 (10), 88 (7), 87 (100), 72 (15), 45 (12). Calcd for $C_{15}H_{29}NO$: M, 239.2249. Found: m/z 239.2252.

2.1.14. *N*,*N*-Dimethyl-2-(1-methylcyclopentadecyl)acetamide (5c). Colorless oil; IR (neat) 2929, 2856, 1645 (CO), 1462, 1393, 1260, 1126, 806, 754 cm^{-1}; ^1H NMR δ 1.0 (3H, s), 1.21–1.59 (28H, m), 2.22 (2H, s), 2.94 (3H, s), 3.03 (3H, s). MS m/z (%) 309 (M^+, 3), 87 (100), 72 (12), 55 (6), 45 (6). Calcd for $C_{20}H_{39}NO$: M, 309.3032. Found: m/z 309.3026.

2.1.15. *N*-Benzyl-2-{1-[chloro(*p*-tolylsulfinyl)methyl]-cyclopentadecyl}-*N*-(4-methoxyphenyl)acetamide (8). To a solution of acetyl chloride (1.27 mmol) in 13 ml of CH_2Cl_2 was added a solution of *N*-benzyl *p*-anisidine (213 mg; 1 mmol) in 1 ml of CH_2Cl_2 followed by Et_3N (2 mmol) and the solution was stirred at room temperature for 1 h. The reaction was quenched by adding sat. aq. NH_4Cl and the whole was extracted with CH_2Cl_2. The product was purified by silica gel column chromatography to afford **6** (255 mg; 99%). The amide **6** (646 mg; 2.5 mmol) in THF (6.5 ml) was added to a solution of LDA (2.5 mmol) in 3.5 ml of dry THF at −78 °C with stirring. The solution was stirred for 10 min, then a solution of **2c** (198 mg; 0.5 mmol) in THF (4 ml) was added. The solution was stirred for 15 min and the reaction was quenched by adding sat. aq. NH_4Cl. The whole was extracted with AcOEt. The product was purified by silica gel column chromatography to afford

8 (299 mg; 92%) as colorless crystals; mp 112–113 °C (AcOEt–CH_3CN); IR (KBr) 2928, 2855, 1651 (CO), 1511, 1401, 1249, 1049 (SO), 837 cm^{-1}; ^1H NMR δ 1.13–1.96 (28H, m), 2.24, 3.08 (each 1H, d, J=17.1 Hz), 2.43 (3H, s), 3.80 (3H, s), 4.84 (2H, s), 6.02 (1H, s), 6.83, 6.94 (each 2H, d, J=8.3 Hz), 7.23–7.27 (5H, m), 7.30, 7.74 (each 2H, d, J=8.3 Hz). MS *m/z* (%) 650 ($[M+H]^+$, 10), 510 (60), 474 (15), 437 (17), 255 (10), 213 (20), 212 (10), 122 (10), 91 (100). Calcd for $C_{39}H_{53}ClNO_3S$: M+H, 650.3434. Found: *m/z* 650.3436. Anal. Calcd for $C_{39}H_{52}ClNO_3S$: C, 72.03; H, 8.06; Cl, 5.45; N, 2.15; S, 4.93. Found: C, 71.70; H, 8.14; Cl, 5.36; N, 2.16; S, 4.94.

2.1.16. *N*-Benzyl-2-{1-[chloro(*p*-tolylsulfinyl)methyl]-cyclopentadecyl}acetamide (9). A solution of CAN (118 mg; 0.22 mmol) in 0.5 ml of water was added to a solution of **8** (70 mg; 0.11 mmol) in 1.35 ml CH_3CH_2CN at room temperature and the reaction mixture was stirred for five days at room temperature. The reaction was quenched by adding sat. aq. $NaHCO_3$ at 0 °C follwed by Na_2SO_3 (41 mg; 0.33 mmol). The suspension was filtered through a celite pad. The whole was extracted with AcOEt. The product was purified by silica gel column chromatography to afford **9** (8.1 mg; 14%) as an orange oil; IR (neat) 3326 (NH), 2928, 2856, 1651 (CO), 1542, 1458, 1041 (SO), 810 cm^{-1}; ^1H NMR δ 1.20–1.99 (28H, m), 2.40 (3H, s), 2.43 (1H, d, J=5.2 Hz), 2.50, 3.09 (each 1H, d, J=13.8 Hz), 4.45 (1H, dd, J=14.7, 5.8 Hz), 4.52 (1H, dd, J=14.7, 5.8 Hz), 4.91 (1H, s), 7.18–7.38 (7H, m), 7.43 (2H, d, J=8.0 Hz). MS *m/z* (%) 543 (M^+, trace), 385 (36), 368 (23), 136 (12), 91 (100). Calcd for $C_{32}H_{46}ClNO_2S$: M, 543.2938. Found: *m/z* 543.2941.

2.1.17. 2-(1-Formylcyclopentadecyl)-*N*,*N*-dimethylacetamide (17c). A solution of NaI (110 mg; 0.73 mmol) in 7.5 ml of dry acetone was stirred for 15 min at −55 °C. TFAA (0.103 ml; 0.73 mmol) was added dropwise to a solution of NaI with stirring at −55 °C and the solution was stirred for 15 min. The adduct **3c** (70 mg; 0.15 mmol) in 1.5 ml of dry acetone was added dropwise to the suspention of NaI and TFAA at −55 °C dropwise with stirring and the reaction mixture was stirred for 10 min. The reaction mixture turned from light yellow to black green in color. The reaction was quenched by adding sat. aq. $NaHCO_3$ followed by sat. aq. Na_2SO_3. The whole was extracted with ether–benzene. The organic layer was washed with sat. aq. $NaHCO_3$ and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography to give **11** (50 mg; 85%) and the aldehyde **17c** (6.1 mg; 13%). **17c**: colorless oil; IR (neat) 2930, 2858, 1722 (CHO), 1638 (CO), 1461, 1402, 1216, 757 cm^{-1}; ^1H NMR δ 1.17–1.69 (28H, m), 2.61 (2H, s), 2.91 (3H, s), 3.01 (3H, s), 9.68 (1H, s). MS *m/z* (%) 323 (M^+, 25), 294 (42), 279 (15), 252 (15), 238 (7), 224 (5), 196 (7), 168 (9), 140 (12), 127 (15), 95 (7), 87 (100), 72 (57). Calcd for $C_{20}H_{37}NO_2$: M, 323.2824. Found: *m/z* 323.2820.

2.1.18. 4,4-Diphenyl-5-(*p*-tolylsulfanyl)dihydrofuran-2-one (16d). Colorless oil; IR (neat) 2924, 1790 (CO), 1494, 1447, 1171, 953, 699 cm^{-1}; ^1H NMR δ 2.35 (3H, s), 3.12, 3.56 (each 1H, d, J=16.8 Hz), 6.34 (1H, s), 7.13–7.16 (4H, m), 7.28–7.37 (8H, m), 7.43 (2H, d, J=8.2 Hz). MS *m/z* (%) 360 (M^+, 25), 237 (100), 219 (30), 191 (10), 180 (50), 165 (35), 152 (15), 105 (40). Calcd for $C_{23}H_{20}O_2S$: M, 360.1184. Found: *m/z* 360.1181.

2.1.19. 4-Methyl-4-phenyl-5-(*p*-tolylsulfanyl)dihydrofuran-2-one (16e). Colorless oil (about 3:1 diastereomeric mixture); IR (neat) 2925, 1790 (CO), 1495, 1445, 1195, 970, 700 cm^{-1}; ^1H NMR δ 1.63 (2.3H, s), 1.64 (0.7H, s), 2.32 (0.7H, s), 2.33 (2.3H, s), 2.65, 3.19 (each 0.25H, d, J=16.8 Hz), 2.79, 3.05 (each 0.75H, d, J=16.8 Hz), 5.78 (0.75H, s), 5.79 (0.25H, s), 7.10–7.49 (9H, m). MS *m/z* (%) 298 (M^+, 50), 175 (100), 147 (8), 131 (67), 105 (57), 91 (45), 77 (20). Calcd for $C_{18}H_{18}O_2S$: M, 298.1028. Found: *m/z* 298.1030.

2.1.20. *N*,*N*-Dimethyl-3-formyl-5-phenylpentanamide (17f). Colorless oil; IR (neat) 2926, 2855, 1718 (CHO), 1638 (CO), 1509, 1455, 1400, 1243, 1145, 749, 701 cm^{-1}; ^1H NMR δ 1.76–1.83 (1H, m), 2.05–2.13 (1H, m), 2.44 (1H, dd, J=16.5, 4.9 Hz), 2.65–2.72 (2H, m), 2.78 (1H, dd, J=16.5, 8.3 Hz), 2.93 (3H, s), 3.01 (3H, s), 7.18–7.21 (3H, m), 7.27–7.30 (2H, m), 9.81 (1H, s). MS *m/z* (%) 233 (M^+, 3), 205 (8), 204 (8), 165 (18), 129 (100), 114 (38), 91 (58), 72 (78), 65 (10). Calcd for $C_{14}H_{19}NO_2$: M, 233.1418, Found: *m/z* 233.1407.

2.1.21. 4-Phenyl-5-(*p*-tolylsulfanyl)dihydrofuran-2-one (16g). Colorless oil (about 5:1 diastereomeric mixture); IR (neat) 2922, 1774 (CO), 1490, 1456, 1410, 1288, 1245, 1177, 1149, 947, 921, 830, 698 cm^{-1}; ^1H NMR δ 2.32 (0.5H, s), 2.35 (2.5H, s), 2.72 (1H, dd, J=17.7, 7.9 Hz), 2.89 (1H, dd, J=17.7, 9.3 Hz), 3.58 (0.83H, m), 4.09 (0.17H, m), 5.63 (0.83H, d, J=6.8 Hz), 6.03 (0.17H, J=6.7 Hz), 7.10–7.43 (9H, m). MS *m/z* (%) 284 (M^+, 41), 161 (100), 160 (7), 124 (47), 105 (62), 91 (58), 77 (30), 65 (10). Calcd for $C_{17}H_{16}O_2S$: M, 284.0872. Found: *m/z* 284.0862.

2.1.22. *N*,*N*-Dimethyl-4-oxo-3-phenylbutanamide (17g). Colorless oil; IR (neat) 2924, 1722 (CO), 1645, 1494, 1408, 1264, 1149, 879, 759 cm^{-1}; ^1H NMR δ 2.54 (1H, dd, J=16.5, 4.9 Hz), 2.94 (3H, s), 3.01 (3H, s), 3.25 (1H, dd, J=16.5, 8.9 Hz), 4.36 (1H, dd, J=8.9, 4.9 Hz), 7.22–7.38 (5H, m), 9.79 (1H, s). MS *m/z* (%) 205 (M^+, 7), 191 (35), 177 (100), 176 (7), 147 (12), 131 (11), 120 (10), 105 (58), 104 (36), 72 (90). Calcd for $C_{12}H_{15}NO_2$: M, 205.1103. Found: *m/z* 205.1099.

2.1.23. 4,4-Diphenyldihydrofuran-2-one (18d). AIBN (16 mg; 0.1 mmol) was added to a solution of **16d** (36 mg; 0.1 mmol) and Bu_3SnH (0.11 ml; 0.4 mmol) in 10 ml of benzene. The atmosphere in the flask was replaced with Ar and the reaction mixture was stirred and refluxed for 2 h. The benzene was evaporated and the residue was purified by silica gel column chromatography to give **18d** (23.6 mg; 99%) as colorless crystals; mp 105–106 °C (AcOEt–hexane); IR (KBr) 2964, 1781 (CO), 1177, 1022, 700 cm^{-1}; ^1H NMR δ 3.20 (2H, s), 4.84 (2H, s), 7.16–7.36 (10H, m). MS *m/z* (%) 238 (M^+, 28), 180 (100), 165 (40), 89 (15), 77 (10). Calcd for $C_{16}H_{14}O_2$: M, 238.0992. Found: *m/z* 238.0986. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.43; H, 5.65.

2.1.24. 4-Methyl-4-phenyldihydrofuran-2-one (18e). Colorless oil; IR (neat) 2965, 1778 (CO), 1170, 1022,

766, 702 cm^{-1}; ^1H NMR δ 1.53 (3H, s), 2.68, 2.92 (each 1H, d, $J=16.8$ Hz), 4.42, 4.43 (each 1H, d, $J=8.9$ Hz), 7.18–7.40 (5H, m). MS *m/z* (%) 176 (M^+, 20), 118 (100), 103 (13), 91 (11), 78 (9), 51 (7). Calcd for $C_{11}H_{12}O_2$: M, 176.0837. Found: *m/z* 176.0837.

2.1.25. 4-Phenyldihydrofuran-2-one (18g). Colorless crystals; mp 40–41 °C (AcOEt–hexane); IR (KBr) 2904, 1764 (CO), 1457, 1355, 1164, 1011, 761, 703 cm^{-1}; ^1H NMR δ 2.68 (1H, dd, $J=17.4$, 9.2 Hz), 2.93 (1H, dd, $J=17.4$, 8.8 Hz), 3.79 (1H, m), 4.27, 4.67 (each 1H, t, $J=8.9$ Hz), 7.23–7.39 (5H, m). MS *m/z* (%) 162 (M^+, 27), 104 (100), 91 (7), 78 (12), 51 (10), 28 (32). Calcd for $C_{10}H_{10}O_2$: M, 162.0680. Found: *m/z* 162.0681. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.75; H, 6.20.

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References and notes

1. Some monographs for the chemistry of carboxylic acids, amides, lactones, and their derivatives: (a) Patai, S. *The Chemistry of Carboxylic Acids and Esters*; Wiley: London, 1969. (b) Zabicky, J. *The Chemistry of Amides*; Wiley: London, 1970. (c) Patai, S. *The Chemistry of Acid Derivatives*; Wiley: Chichester, 1979; Part 1 and 2. (d) Sutherland, I. O., Ed.; Comprehensive Organic Chemistry; Pergamon: Oxford, 1979; Vol. 2; part 9. (e) Patai, S. *The Chemistry of Acid Derivatives*; Wiley: Chichester, 1992; Part 1 and 2.
2. Recent monographs and reviews for the chemistry and synthesis of α-amino acids: (a) *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman & Hall: London, 1985. (b) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (d) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (e) Sano, S. *Yakugaku Zasshi* **2000**, *120*, 28. (f) Sano, S.; Nagao, Y. *J. Syn. Org. Chem. Jpn* **2000**, *58*, 756. (g) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. (h) Beller, M.; Eckert, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1010.
3. Recent monograph and reviews for the chemistry and synthesis of β-amino acids: (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3. (c) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (d) Davies, S. G.; Ichihara, O. *J. Syn. Org. Chem. Jpn* **1997**, *55*, 26. (e) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813. (f) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991.
4. Satoh, T.; Sugiyama, S.; Kamide, Y.; Ota, H. *Tetrahedron* **2003**, *59*, 4327.
5. Some recent papers for the new synthetic methods by using 1-chlorovinyl *p*-tolyl sulfoxides: (a) Satoh, T.; Ota, H. *Tetrahedron* **2000**, *56*, 5113. (b) Satoh, T.; Yoshida, M.; Ota, H. *Tetrahedron Lett.* **2001**, *42*, 9241. (c) Satoh, T.; Sakamoto, T.; Watanabe, M. *Tetrahedron Lett.* **2002**, *43*, 2043. (d) Satoh, T.; Sugiyama, S.; Ota, H. *Tetrahedron Lett.* **2002**, *43*, 3033. (e) Satoh, T.; Yoshida, M.; Takahashi, Y.; Ota, H. *Tetrahedron: Asymmetry* **2003**, *14*, 281. (f) Satoh, T.; Wakasugi, D. *Tetrahedron Lett.* **2003**, *44*, 7517. (g) Ota, H.; Chyouma, T.; Iso, S.; Satoh, T. *Tetrahedron Lett.* **2004**, *45*, 3903. (h) Satoh, T.; Ogino, Y.; Nakamura, M. *Tetrahedron Lett.* **2004**, *45*, 5785.
6. An account for the new synthetic method by using 1-chlorovinyl aryl sulfoxides: Satoh, T. *Chem. Record* **2004**, *3*, 329.
7. (a) Satoh, T.; Takano, K.; Ota, H.; Someya, H.; Matsuda, K.; Koyama, M. *Tetrahedron* **1998**, *54*, 5557. (b) Satoh, T.; Kawashima, T.; Takahashi, S.; Sakai, K. *Tetrahedron* **2003**, *59*, 9599.
8. (a) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (b) Satoh, T.; Sato, T.; Oohara, T.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3973.
9. Mozingo, R. *Org. Syn. Coll. Vol. 3* **1965**, 181.
10. Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Matsumoto, K.; Fujita, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2405.
11. (a) Bravo, P.; Guidetti, M.; Viani, F.; Zanda, M.; Markovsky, A. L.; Sorochinsky, A. E.; Soloshonok, I. V.; Soloshonok, V. A. *Tetrahedron* **1998**, *54*, 12789. (b) Bravo, P.; Capelli, S.; Crucianelli, M.; Guidetti, M.; Markovsky, A. L.; Meille, S. V.; Soloshonok, V. A.; Sorochinsky, A. E.; Viani, F.; Zanda, M. *Tetrahedron* **1999**, *55*, 3025. (c) Fustero, S.; Pina, B.; Garcia de la Torre, M.; Navarro, A.; Ramirez de Arellano, C.; Simon, A. *Org. Lett.* **1999**, 977.
12. Bravo, P.; Piovosi, E.; Resnati, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1201.
13. (a) Block, E. *Reaction of Organosulfur Compounds*; Academic: New York, 1978; pp 154–162. (b) DeLucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157. (c) Padwa, A.; Gunn, D. E.; Osterhout, M. H. *Synthesis*, 1353. (d) Solladie, G.; Wilb, N.; Bauder, C. *Tetrahedron Lett.* **2000**, *41*, 4189.
14. (a) Gutierrez, C. G.; Stringham, R. A.; Nitasaka, T.; Glasscock, K. G. *J. Org. Chem.* **1980**, *45*, 3393. (b) Gutierrez, C. G.; Summerhays, L. R. *J. Org. Chem.* **1984**, *49*, 5206. (c) Watanabe, Y.; Araki, T.; Ueno, Y.; Endo, T. *Tetrahedron Lett.* **1986**, *27*, 5385. (d) Satoh, T.; Kubota, K. *Tetrahedron Lett.* **2000**, *41*, 2121.

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Antiplasmodial cembradiene diterpenoids from a Southwestern Caribbean gorgonian octocoral of the genus *Eunicea*

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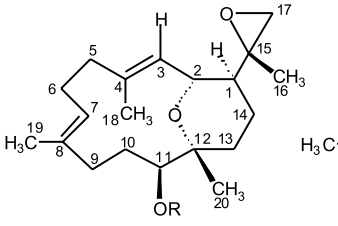
Abstract—Five new representatives of the cembrane class of marine natural products have been isolated as minor metabolites from an undescribed species of *Eunicea*, a sea whip collected near the Colombian Southwestern Caribbean Sea. The structure of the crystalline metabolite **1** was solved by single-crystal X-ray diffraction analysis. Structures could then be proposed for cembradienes **2**–**5** by comprehensive spectral analyses involving 2D NMR, IR, UV, and high-resolution mass spectrometry, as well as chemical interconversion studies. Compound **1** exhibited weak cytotoxicity in the NCI 3-cell line panel human cancer screening program, whereas compounds **1**, **2** and **4** displayed significant antiplasmodial activity against *Plasmodium falciparum*.

1. Introduction

Throughout the Caribbean Sea, sea whips of the genus *Eunicea* (family Plexauridae) constitute major inhabitants of the shallow water invertebrate fauna.[1] Since the early 1960s, these animals have been shown to be a prolific resource for many chemically complex diterpenoids of diverse molecular architecture, namely, cembrane lactones, dolabellanes, cubitanes, dilophols, and fuscols.[2] In this paper, we report the structures of five new cembranes, isolated from an undescribed Caribbean gorgonian species of the genus *Eunicea*. Compounds **1**–**4** are cembrane diterpenes characterized by the presence of an unprecedented ether linkage between C2/C12, and compound **5**, also a cembrane, possesses a conjugated diene, ketone, and epoxide functionalities. Although cembranes are the most commonly encountered class of secondary metabolites from *Eunicea* octocorals, many of the present compounds possess different functionalities from other *Eunicea* cembranes. Moreover, compounds isolated from this extract were found active in inhibiting the growth of *Plasmodium falciparum*, the parasite responsible for the most severe forms of malaria.[3]



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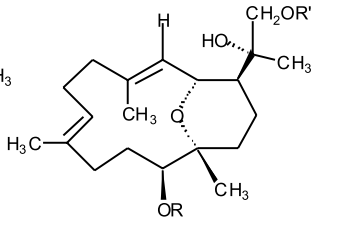

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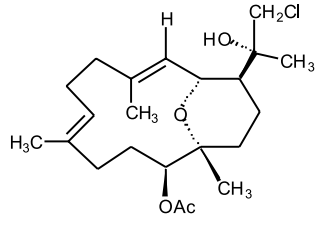

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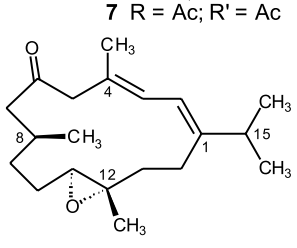

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Keywords: Diterpene; *Eunicea* sp.; Single-crystal X-ray analysis; Cytotoxicity; Antimalarial; Caribbean gorgonian octocoral.
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2. Results and discussion

Eunicea sp. was collected in 2002, as part of an expedition to Old Providence Island, in the Colombian Southwestern Caribbean Sea. Freshly collected animals were air-dried, stored frozen, and subsequently extracted with 1:1 CH_2Cl_2/MeOH. Compounds **1**–**5** were isolated by rapid elution silica gel chromatography of the crude hexane extract and purified by successive size-exclusion chromatography, normal- and reversed-phase silica gel column chromatography, and HPLC from the fractions containing the terpenoid constituents. Compounds **1**–**5** were minor components of *Eunicea* sp., each comprising less than 0.1% of the crude organic extract.

Compound **1**, the most abundant cembrane isolated, crystallized from 10:1 $CHCl_3$/MeOH after purification by reversed-phase HPLC. Data from HRFAB mass and ^{13}C NMR spectrometry (Table 2) established a molecular formula of $C_{22}H_{34}O_4$ for this compound. Evaluation of spectral information established the presence of a 1,1-disubstituted epoxide, a cyclic ether, and an acetate, which accounted for the four oxygen atoms in the molecular formula. ^{13}C NMR signals at δ 52.2 (CH_2) and 59.0 (C) along with ^1H NMR resonances (Table 1) at δ 2.59 (d, 1H, $J=4.6$ Hz), 2.49 (d, 1H, $J=4.6$ Hz), and 1.27 (s, 3H) showed that the methyl-bearing epoxide in **1** was terminal. ^{13}C NMR bands at δ 171.6 (C), 77.1 (CH), and 21.2 (CH_3), coupled with an IR absorption at 1732 cm^{-1} and bands in the ^1H NMR spectrum at δ 5.45 (d, 1H, $J=9.3$ Hz) and 2.01 (s, 3H), further indicated that compound **1** possessed a secondary acetate. The presence of two trisubstituted olefins was next established based upon signals in the ^{13}C NMR spectrum at δ 137.2 (C), 134.3 (C), 131.3 (CH), and 125.6 (CH), in conjunction with bands in the ^1H NMR spectrum at δ 5.40 (d, 1H, $J=10.3$ Hz) and 5.08 (dd, 1H, $J=3.3$, 8.9 Hz). These latter proton bands were allylically coupled, respectively, to two broadened resonances at δ 1.62 (s, 3H) and 1.51 (s, 3H), assigned to two olefinic methyls. Two other resonances in the ^{13}C NMR spectrum of **1** at δ 70.4 (CH) and 74.4 (C), together with the absence of absorption bands ascribable to hydroxyl groups in the IR, showed the molecule to possess an additional cyclic ether functionality. From these data, five of the six degrees of unsaturation in the molecular formula of **1** could be accounted for, demonstrating that **1** was mono-carbocyclic. Furthermore, the ring was determined to be 14-membered via subtraction of the recognized carbon substituents.

The relative positions and relative stereochemistries of all the substituents, and hence the final structure of **1**, were solved by using X-ray crystallographic methods. The X-ray drawing of compound **1** is shown in Figure 1 and was thus fully defined as 11(S^*)-acetoxy-2(R^*),12(R^*),15(S^*),17-diepoxy-(3*E*,7*E*)-1(S^*)-cembra-3,7-diene. The absolute stereochemistry was not defined in the X-ray experiment. Comprehensive analysis of 2D NMR data, including the results of ^1H–^1H COSY, NOESY, HMQC, and HMBC experiments, enabled the complete proton and carbon atoms assignment for compound **1** (Tables 1 and 2).

Once the structure of compound **1** was fully defined, structures for the remaining 2,12-epoxy-3,7-cembradienes **2**–**4** could be proposed based upon comparisons with compound **1**. Cembradiene **2** was isolated as a colorless oil, $[\alpha]_D^{20}$ +35.2° (*c* 1.2, $CHCl_3$), which analyzed for

Table 1. ^1H NMR assignments for compounds **1**–**5** in $CDCl_3$ [δ_H, mult, intgr, (*J* in Hz)][a]

Position	**1**[b]	**2**[b]	**3**[b]	**4**[b]	**5**[c]
1	1.48, m, 1H	1.52, m, 1H	1.70, m, 1H	1.82, m, 1H	
2	4.60, dd, 1H (9.8, 1.9)	4.50, dd, 1H (10.5, 2.5)	4.57, dd, 1H (10.5, 2.2)	4.68, dd, 1H (10.6, 2.3)	6.05, d, 1H (11.0)
3	5.40, d, 1H (10.3)	5.20, d, 1H (10.4)	5.48, d, 1H (10.3)	5.51, d, 1H (10.5)	6.21, d, 1H (10.7)
5α	2.02, d, 1H (4.1)	1.92, m, 1H	2.08, m, 1H	2.10, m, 1H	3.31, d, 1H (14.2)
5β	2.13, m, 1H	2.19, m, 1H	2.18, m, 1H	2.17, m, 1H	2.94, d, 1H (13.8)
6α	2.06, d, 1H (4.1 Hz)	2.04, m, 1H	2.05, m, 1H	2.05, m, 1H	
6β	2.36, dd, 1H (11.6, 4.2)	2.41, m, 1H	2.42, dd, 1H (8.4, 3.6)	2.46, m, 1H	
7α	5.08, dd, 1H (8.9, 3.3)	4.92, dd, 1H (9.1, 2.8)	5.14, d, 1H (8.3)	5.14, dd, 1H (10.3, 3.3)	1.98, m, 1H
7β					2.58, dd, 1H (13.1, 7.1)
8					2.26, m, 1H
9α	1.64, d, 1H (12.5)	2.04, m, 1H	1.68, m, 1H	1.70, t, 1H (2.6)	1.37, m, 1H
9β	1.84, dd, 1H (12.3, 7.2)	2.04, m, 1H	1.90, dd, 1H (10.5, 5.0)	1.91, t, 1H (2.6)	1.57, m, 1H
10α	1.46, m, 1H	1.23, m, 1H	1.68, m, 1H	1.71, m, 1H	1.68, m, 1H
10β	1.21, m, 1H	1.72, m, 1H	1.44, m, 1H	1.43, m, 1H	1.52, m, 1H
11	5.45, d, 1H (9.3)	3.86, d, 1H (9.1)	5.49, d, 1H (9.6)	5.53, d, 1H (9.4)	2.89, t, 1H (5.9)
13α	1.63, m, 1H	1.53, m, 1H	1.56, m, 1H	1.63, m, 1H	2.11, m, 1H
13β	1.42, m, 1H	1.79, m, 1H	1.56, m, 1H	1.49, m, 1H	1.49, m, 1H
14α	1.17, m, 1H	1.19, m, 1H	1.36, dd, 1H (7.3, 3.7)	1.21, m, 1H	2.47, m, 1H
14β	1.56, dd, 1H (7.0, 4.0)	1.19, m, 1H	1.71, dd, 1H (7.3, 3.7)	1.58, m, 1H	2.08, m, 1H
15					2.36, m, 1H
16	1.27, s, 3H	1.34, s, 3H	1.15, s, 3H	1.27, s, 3H	1.11, d, 3H (6.7)
17α	2.59, d, 1H (4.6)	2.66, d, 1H (4.6)	3.63, d, 1H (11.5)	3.56, d, 1H (11.2)	1.04, d, 3H (6.8)
17β	2.49, d, 1H (4.6)	2.56, d, 1H (4.6)	3.36, d, 1H (11.3)	3.48, d, 1H (11.2)	
18	1.62, s, 3H	1.65, s, 3H	1.65, s, 3H	1.67, s, 3H	1.79, s, 3H
19	1.51, s, 3H	1.56, s, 3H	1.56, s, 3H	1.57, s, 3H	0.96, d, 3H (6.3)
20	1.02, s, 3H	1.03, s, 3H	1.07, s, 3H	1.06, s, 3H	1.19, s, 3H
22	2.01, s, 3H		2.07, s, 3H	2.07, s, 3H	

[a] Chemical shift values are in ppm relative to TMS. Spectra were recorded at 25 °C. Proton assignments were aided by ^1H–^1H COSY, HMQC, HMBC, and NOESY experiments.
[b] ^1H (300 Hz) NMR data.
[c] ^1H (500 MHz) NMR data.

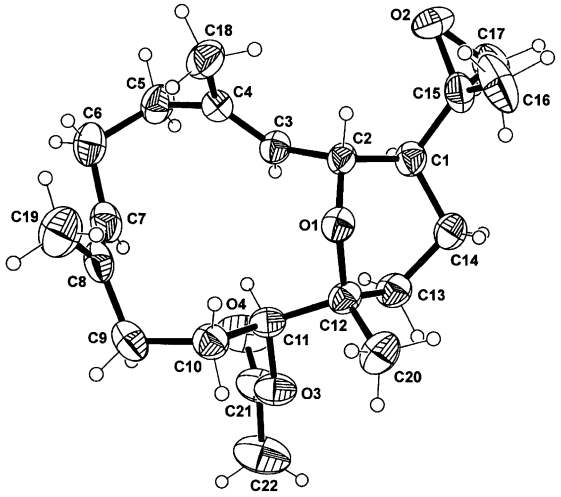


Figure 1. X-ray crystal structure of compound **1** with 30% thermal probability ellipsoids.

$C_{20}H_{32}O_3$ by HRFABMS and ^{13}C NMR methods. Comparison of ^1H and ^{13}C NMR spectra (Tables 1 and 2) showed that **2** possessed the same diepoxy-cembradiene framework as compound **1**. In addition, the IR spectrum of **2** showed a strong hydroxyl absorption at 3452 cm^{-1} but lacked a carbonyl absorption band. Although the chemical shifts of some proton resonances were different, proton NMR COSY experiments showed very similar coupling patterns between **2** and **1**, suggesting that the same carbons were oxygenated. Acetylation of **2**, under normal conditions, provided the mono-acetate **1** in good yield, thus establishing the close structural relationship between these natural products.

A related mono-acetate, **3**, was also isolated as an oil that analyzed for $C_{22}H_{36}O_5$ by HRESIMS and ^{13}C NMR spectrometry, one oxygen and two hydrogen atoms more than in the molecular formula of **1**. NMR spectral data for **3** were very similar to those obtained from **1** suggesting that the two compounds had the same skeletal arrangement and a similar oxygenation pattern. The only significant difference was the downfield shift of the C17 protons by 0.87–1.04 ppm in the ^1H NMR spectrum of **3** (Table 1). Also, the absence of resonance bands near δ 59.0 (C) and 52.2 (CH_2) indicated the lack in this compound of an oxirane ring, a feature found in **1**. Therefore, compound **3** was concluded to be the corresponding glycol derivative of **1**. A 2D-NOESY NMR experiment allowed the stereochemistries of the asymmetric centers to be defined (Fig. 2). For instance, NOESY correlations for H2/H_2-17 and H_3-16, H1/H_2-17, H14β/H_3-16 and H_3-20, and H7/H11 indicated that H2, H_3-16 and H_3-20 were β-oriented and H1 and H11 were α-oriented. As was the case with the previous compounds, the high field ^{13}C chemical shifts of the C18 and C19 carbon signals (δ 15.0 and 16.4, respectively) indicated the *E* configuration for the Δ^3 and Δ^7 double bonds. A chemical correlation study confirmed the close structural relationship between cembradienes **1** and **3**. Base hydrolysis of **1** with LiOH cleaved the oxirane ring to afford a single product, triol **6**, which upon acetylation afforded di-acetate **7** in excellent overall yield. The spectral characteristics of the latter material were determined to be identical in all respects with those of **7** produced upon acetylation of natural isolate **3**. These conversions established the C15(S^*) stereochemical assignment of cembradiene **3** unequivocally and also suggested that **3** might be an artifact produced from **1** by epoxide ring opening. The overall relative configurations of compound **3** are thus 1(S^*),2(R^*),3*E*,7*E*,11(S^*),12(R^*) and 15(S^*).

A molecular formula of $C_{22}H_{35}O_4Cl$, estimated from LREIMS and ^{13}C NMR data, was confirmed for **4** by HREIMS. The intensity of the $[M+2]^+$ isotope peak and the occurrence of a fragment ion corresponding to

Table 2. ^{13}C NMR Assignments for compounds **1–5** in $CDCl_3$ [δ_C (mult)][a]

Position	**1**[b]	**2**[b]	**3**[b]	**4**[b]	**5**[c]
1	46.9 (CH)	47.2 (CH)	48.1 (CH)	47.2 (CH)	148.5 (C)
2	70.4 (CH)	70.2 (CH)	68.8 (CH)	68.5 (CH)	117.9 (CH)
3	131.3 (CH)	131.9 (CH)	131.3 (CH)	131.6 (CH)	125.2 (CH)
4	137.2 (C)	136.6 (C)	137.3 (C)	136.8 (C)	130.3 (C)
5	39.8 (CH_2)	40.0 (CH_2)	39.8 (CH_2)	38.9 (CH_2)	53.4 (CH_2)
6	26.0 (CH_2)	25.9 (CH_2)	26.1 (CH_2)	26.1 (CH_2)	210.7 (C)
7	125.6 (CH)	124.8 (CH)	125.6 (CH)	125.7 (CH)	49.5 (CH_2)
8	134.3 (C)	135.7 (C)	134.4 (C)	134.4 (C)	28.7 (CH)
9	35.0 (CH_2)	35.9 (CH_2)	35.1 (CH_2)	35.1 (CH_2)	33.5 (CH_2)
10	29.7 (CH_2)	29.4 (CH_2)	26.6 (CH_2)	26.6 (CH_2)	24.6 (CH_2)
11	77.1 (CH)	76.3 (CH)	77.2 (CH)	77.2 (CH)	60.5 (CH)
12	74.4 (C)	75.5 (C)	74.4 (C)	74.2 (C)	61.0 (C)
13	26.7 (CH_2)	31.3 (CH_2)	30.1 (CH_2)	30.0 (CH_2)	35.9 (CH_2)
14	17.8 (CH_2)	18.1 (CH_2)	17.0 (CH_2)	18.0 (CH_2)	25.1 (CH_2)
15	59.0 (C)	59.1 (C)	74.5 (C)	74.2 (C)	32.2 (CH)
16	18.9 (CH_3)	18.9 (CH_3)	21.7 (CH_3)	20.2 (CH_3)	21.3 (CH_3)
17	52.2 (CH_2)	52.4 (CH_2)	67.7 (CH_2)	53.5 (CH_2)	23.0 (CH_3)
18	14.9 (CH_3)	14.9 (CH_3)	15.0 (CH_3)	15.0 (CH_3)	17.3 (CH_3)
19	16.3 (CH_3)	16.5 (CH_3)	16.4 (CH_3)	16.3 (CH_3)	20.3 (CH_3)
20	20.3 (CH_3)	19.1 (CH_3)	20.3 (CH_3)	20.2 (CH_3)	18.7 (CH_3)
21	171.6 (C)		171.6 (C)	171.6 (C)	
22	21.2 (CH_3)		21.2 (CH_3)	21.6 (CH_3)	

[a] Chemical shift values are in ppm relative to TMS. Spectra were recorded at 25 °C. Atom multiplicities were obtained from DEPT NMR experiments. Assignments were aided by ^1H–^1H COSY, HMQC, HMBC, and NOESY experiments.
[b] ^{13}C (75 Hz) NMR data.
[c] ^{13}C (125 MHz) NMR data.

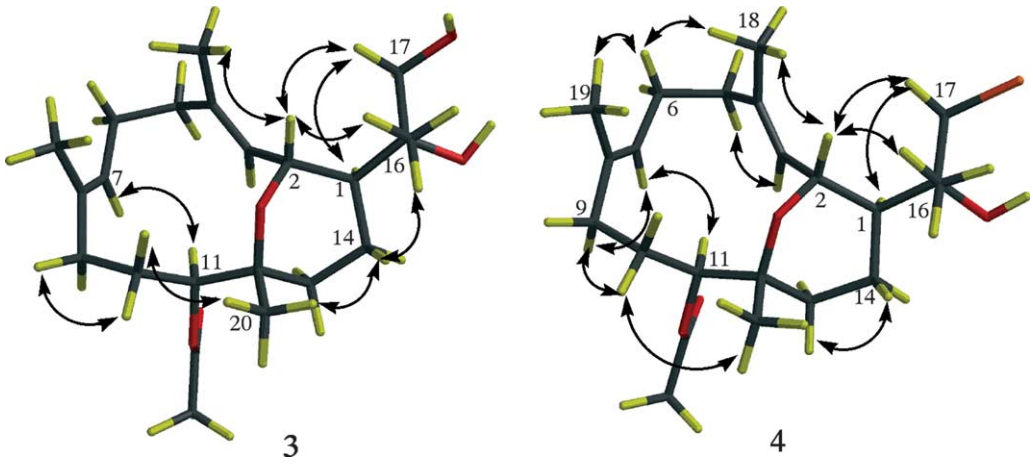
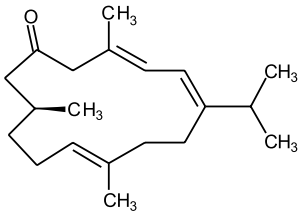


Figure 2. Selected NOESY correlations and relative configurations for cembradienes **3** and **4**.

$[M-35]^+$ were strong indications of the presence of a chlorine atom in **4**. Like **3**, compound **4** showed IR absorptions that indicated the presence of OH, olefin, and ester functionalities. The ^1H and ^{13}C NMR spectra of **4** were almost identical to those of **3** (see Tables 1 and 2), the only major difference being the upfield shift of C17 by 14.2 ppm in the ^{13}C NMR spectrum of **4** (Table 2). This information suggested that the chlorine atom in **4** was located at C17 and that, otherwise, these two compounds possessed identical molecular constitutions. The presence of an acetate and a 2-(1-chloro-2-propanol) alkyl side chain in **4** could be argued from the ion fragments at *m/z* 338 (11%) and *m/z* 246 (20%) in the LREI mass spectrum, due to the sequential loss of acetic acid and α-chloroacetone, respectively, from the molecular ion species at *m/z* 398 (3%). The relative stereochemistry of **4** was determined to be identical to that of **3** on the basis of 2D-NOESY data (Fig. 2). The structure of **4** was correlated chemically with that of **1** upon regioselective ring-opening of the epoxide with a mixture of LiCl/AcOH for 4 days at 25 °C.[4] After workup, we obtained halohydrin **4** in high yield. The rigorous assignment of the NMR spectra of **4** (see Tables 1 and 2) was established by application of the same 2D NMR techniques described earlier. It is conceivable that chlorohydrin **4** may be derived artificially from **1** during the extraction of the gorgonian through acid-catalyzed cleavage of the epoxide. However, since CH_2Cl_2, not $CHCl_3$, was used during the animal extraction, plus the fact that the chlorine in **4** is attached to the least substituted C17 carbon, suggest that **4** may indeed be a natural product.[5]

Compound **5** was isolated as an oil by repeated C_{18} silica gel column chromatography and reversed-phase HPLC (20% H_2O in MeOH) and found to analyze for $C_{20}H_{32}O_2$ by HREIMS and ^{13}C NMR spectroscopy. The carbonyl signals at δ 210.7 (C) in the ^{13}C NMR spectrum (Table 2) and the corresponding absorption band at 1703 cm^{-1} in the IR spectrum established the presence of a ketone. Two oxygen-bearing carbon atoms at δ 61.0 (C) and 60.5 (CH) illustrated **5** to possess an epoxide, which accounted for the remaining oxygen atom in the molecular formula. Four low-field carbon bands at δ 148.5 (C), 130.3 (C), 125.2 (CH), and 117.9 (CH) showed the molecule to contain two double bonds, thus compound **5** was bicyclic. Also, in contrast to the lack of UV absorption from compounds **1**–**4**, the UV spectrum of **5** in MeOH showed maxima at 202, 245, and 282 nm. Careful examination of ^1H and ^{13}C NMR spectra, in combination with ^1H–^1H COSY, HMQC, and HMBC NMR experiments, revealed **5** to possess a 1*E*, 3*E*-1,1,4,4-tetrasubstituted diene unit.[6] These 2D NMR experiments (all the carbon and proton resonances were unambiguously assigned, see Tables 1 and 2) confidently connected all of the partial structures and thus revealed the full planar structure of **5**. Thus, cembradiene **5** has an isopropyl group at C1, two conjugated double bonds (Δ^1 and Δ^3), a secondary methyl at C8, a ketone at C6, and a *E*-trisubstituted epoxide across C11,12.

Interestingly, the NMR spectral data for **5** were very similar to those reported from **8**, a known compound isolated by Fenical and co-workers from the Caribbean sea whip *Eunicea calyculata* collected off the Tobago Cays, eastern Caribbean Sea.[7] Compound **5**, however, had an epoxy group, as indicated by ^1H NMR signals at δ 2.89 (t, 1H, J= 5.9 Hz) and 1.19 (s, 3H) and the above-mentioned ^{13}C NMR signals. The combined EIMS and NMR spectral data and the close similarity of the rest of the ^1H and ^{13}C NMR spectra of **5** with those of **8**, led to the assignment of the former as the C11,12-epoxy derivative of **8**. Assuming the α-orientation for H8 as in **8**, the *E*-trisubstituted epoxy group was assigned the α-configuration on the basis of weak, but very diagnostic NOEs, between H8 and the signals at δ 6.21 (H3) and 1.19 (H_3-20) plus the observation that the carbon atom shifts of the epoxide in **5** are highly comparable with those of a closely related epoxi-cembradiene of known relative stereochemistry.[8] The lack of an NOE between H_3-20 and H11 indicated the *E* configuration of the epoxide. Except for the optical rotation, UV data, and ^{13}C NMR assignments for C11 and C12, the spectral properties of compound **5** were very similar to those of compound **9**, recently isolated from *Eunicea tourneforti* collected off the coast of St Thomas, US Virgin Islands.[9] From these data, in particular the different polarimetric properties and distinct UV absorption maxima, we surmise that compound **9** (reported with incomplete relative stereochemistry as shown) and cembradiene **5** should be diastereomeric.



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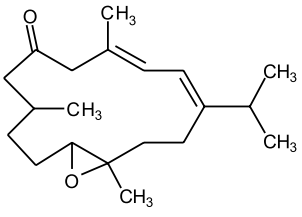

9

Cembradienes **1**, **4**, and **5** were tested for their inhibitory activity toward the growth of *Mycobacterium tuberculosis*, but were deemed inactive (% of inhibition at 6.25 μg/mL = 9, 37, and 35%, respectively). Likewise, compound **1** was not active against the influenza A, HSV-1, HSV-2, HCMV, or VZV viruses. On the other hand, **1**, **2**, and **4** were active against *Plasmodium falciparum* W2 (chloroquine-resistant) strain with IC_{50} values of 23, 15, and 16 μg/mL, respectively. Cembradiene **1** was also evaluated in a 3-cell line panel consisting of the MCF7 breast cancer, NCI-H460 non-small cell lung cancer, and SF-268 (CNS). Results from the one dose primary anticancer assay showed a lack of significant cytotoxicity as the percent of growth of the treated cells when compared to the untreated control cells was approximately 83, 44, and 106%, respectively.

3. Experimental

3.1. General

The melting point was determined with an electrothermal IA 9000 digital melting apparatus. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz, with a Bruker Avance DRX-500 spectrometer or at 300 and 75 MHz, with a Bruker DPX-300 spectrometer, with TMS as internal standard. IR and UV spectra were measured with a Nicolet Magna FT-IR 750 spectrophotometer and a Shimadzu UV–VIS spectrophotometer (UV-2401PC), respectively. EI, FAB, and HRESI mass spectrometry analyses were performed by the Mass Spectrometry Laboratory of the University of Illinois at Urbana-Champaign. Optical rotations were measured with a Rudolph Autopol® IV automatic polarimeter. All solvents used were either spectral grade or were distilled from glass prior to use. Silica gel (35–75 mesh), C_{18} silica gel, and Bio-Beads SX-3 were used for column chromatography, and pre-coated silica gel GF_{254} plates were used for TLC and were visualized by heating the plates sprayed with 5% H_2SO_4 in EtOH. HPLC separations were carried out on 10 mm × 25 cm reversed-phase Ultrasphere ODS or polar bonded-phase Ultrasphere Cyano 5 μ columns. All HPLC separations were monitored simultaneously by refractive index and UV absorption. The percentage yield of each compound is based on the weight of the MeOH/CH_2Cl_2 crude extract.

3.2. Biological material

Medium to large colonies (0.5–1.3 m) of the gorgonian coral *Eunicea* sp. (order Gorgonacea, family Gorgoniidae, phylum Cnidaria) were collected by SCUBA at depths of 75–85 ft from the coral reefs off Old Providence Island (March, 2002), Colombia located off the Nicaraguan shelf in the Southwestern Caribbean Sea. A voucher specimen (No. *Eunicea* sp. 2) has been deposited at the Chemistry Department of the University of Puerto Rico, Río Piedras campus. The specimens collected corresponded to tall and bushy colonies up to 1.3 m in height composed of thin branches of 3–5 mm in diameter or lesser at the branch tips. They have numerous low calyx disposed uniformly with a noticeable lower tip. The middle layer sclerites are blunt and usually less than 1 mm in length; they have a diagnostic characteristic for this species which is a dark core in the sclerite as well as noteworthy ornamentations. The axial layer was composed by a diverse array of ornate forms of capstans and spindles usually purple-colored and up to 0.11–0.17 mm in length. The polyp armature is composed of ornate sclerites (0.14–0.32 mm in length) as well as little flat rods (0.06–0.12 mm). The surface layer has tiny and foliate club sclerites of 0.07–0.11 mm in length but mostly with small sizes. Although *Eunicea* sp. resembles externally its sister species *E. fusca*, the calyx are uniform in the former and differences in sclerites are very evident. For instance, the clubs sclerites and the axial layer ones are remarkably reduced in *Eunicea* sp. It is certain that *Eunicea* sp. is an undescribed species. According to the previous description this species is the same species studied by Cóbar et al.[10,11] Nonetheless, the specimens from Old Providence Island tend to be darker when dried.

3.3. Extraction and isolation

The gorgonian specimens were partially air-dried, freeze-dried, and then kept frozen prior to extraction. The dried animal (1.7 kg) was blended with a mixture of 1:1 CH_2Cl_2/MeOH (5×4 L) and, after filtration, the combined extracts were concentrated in vacuo to afford a gummy green residue (74.4 g). The crude extract was suspended in water (1 L) and extracted successively with hexane (4×2 L), CH_2Cl_2 (4×2 L), and EtOAc (3×2 L). The hexane extract (45.7 g) was chromatographed on a large silica gel column by stepwise elution with 100% hexane, hexane/EtOAc mixtures (100–0%), and then 100% MeOH. Fractions were pooled based on their TLC and NMR profile to yield 15 primary fractions, I–XV. Fraction VIII (2.2 g) was purified successively by size exclusion chromatography (Bio-Beads SX-3, toluene), normal-phase column chromatography (silica gel with 1% acetone in hexane), reversed-phase column chromatography (C_{18} silica gel with 1:1 MeOH/H_2O), and finally by reversed-phase HPLC with a mixture of 4:1 MeOH/H_2O as eluant. Compound **1** was isolated pure as white crystals (30 mg, 0.04%). The penultimate fraction obtained from 30% hexane/EtOAc [fraction XIV (1.5 g)] was purified by successive size exclusion on a Bio-Beads SX-3 column eluted with toluene followed by column chromatography over silica gel (10% acetone in hexane) and cyano polar bonded-phase HPLC (5% isopropanol in hexane) to afford compound **2** (10 mg, 0.013%). Compound **3** (1.3 mg, 0.0017%) was obtained after repeated size exclusion (toluene) and HPLC (2% isopropanol in hexane) chromatography of the last fraction obtained from 50% hexane/EtOAc [fraction XV (0.28 g)]. Fraction X (0.6 g) was chromatographed successively on a silica gel column by stepwise elution from 50:1 to 30:1 hexane/acetone, then on a silica gel column eluted with a 125:1 mixture of hexane/isopropanol, and finally by polar

bonded-phase HPLC (95:5 hexane/isopropanol) to afford compound **4** (5.9 mg, 0.0079%). Separation and purification of fraction VI (0.56 g) by silica gel flash column chromatography [stepwise elution from 80:1 to 50:1 hexane/EtOAc] followed by repeated C_{18} silica gel column chromatography and reversed-phase HPLC (each eluted with 20% H_2O in MeOH) afforded pure compound **5** (4.0 mg, 0.0054%).

3.3.1. 11(S^*)-Acetoxy-2(R^*),12(R^*),15(S^*),17-diepoxy-(3*E*,7*E*)-1(S^*)-cembra-3,7-diene (1). White crystalline solid; mp 85.5–85.8 °C; $[\alpha]_D^{20}$ +70.5° (*c* 1.2, $CHCl_3$); IR (film) 3035, 2981, 2927, 1732, 1660, 1456, 1372, 1242, 1175, 1041, 1024, 957, 871 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) (see Table 1); HRFABMS *m/z* $[M+1]^+$ 363.2534 (calcd for $C_{22}H_{35}O_4$, 363.2535).

3.3.2. 11(S^*)-Hydroxy-2(R^*),12(R^*),15(S^*),17-diepoxy-(3*E*,7*E*)-1(S^*)-cembra-3,7-diene (2). Colorless oil; $[\alpha]_D^{20}$ +35.2° (*c* 1.2, $CHCl_3$); IR (film) 3452, 3043, 2949, 2926, 1622, 1448, 1377, 1221, 1041, 1018, 992, 900, 870 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) (see Table 1); EIMS *m/z* 320 $[M]^+$ (4), 301 (6), 289 (3), 262 (5), 241 (9), 161 (24), 151 (36), 133 (43), 121 (52), 93 (89), 61 (100); HRFABMS *m/z* $[M]^+$ 320.2346 (calcd for $C_{20}H_{32}O_3$, 320.2351).

3.3.3. 11(S^*)-Acetoxy-15(S^*),17-dihydroxy-2(R^*),12(R^*)-epoxy-(3*E*,7*E*)-1(S^*)-cembra-3,7-diene (3). Colorless oil; $[\alpha]_D^{20}$ +78.0° (*c* 1.0, $CHCl_3$); IR (film) 3418, 2974, 2928, 2854, 1732, 1651, 1456, 1437, 1371, 1238, 1086, 1040, 993, 958, 932, 878, 859 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) (see Table 1); HRESIMS *m/z* $[M+Na]^+$ 403.2477 (calcd for $C_{22}H_{36}O_5Na$, 403.2460).

3.3.4. 11(S^*)-Acetoxy-15(S^*)-hydroxy-17-chloro-2(R^*),12(R^*)-epoxy-(3*E*,7*E*)-1(S^*)-cembra-3,7-diene (4). Colorless oil; $[\alpha]_D^{20}$ +77.4° (*c* 1.0, $CHCl_3$); IR (film) 3450, 2978, 2941, 2858, 1729, 1659, 1455, 1434, 1371, 1245, 1075, 1043, 990, 961, 932, 857, 736, 636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) (see Table 1); EIMS *m/z* 400 $[M+2]^+$ (1), 398 $[M]^+$ (3), 363 (2), 338 (11), 265 (13), 246 (20), 227 (25), 191 (29), 149 (100), 133 (60), 93 (94), 81 (61); HREIMS *m/z* $[M]^+$ 398.2233 (calcd for $C_{22}H_{35}O_4Cl$, 398.2224).

3.3.5. (1*E*,3*E*)-11(S^*),12(S^*)-Epoxy-8(S^*)-cembra-1,3-diene-6-one (5). Colorless oil; $[\alpha]_D^{20}$ +27.0° (*c* 1.0, $CHCl_3$); IR (film) 2956, 2927, 2865, 1703, 1617, 1461, 1371, 1252, 1057 cm^{-1}; UV (MeOH) λ_{max} 202 nm (ε 12,100), 245 nm (ε 5890), 282 nm (ε 3390); ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) (see Table 1); EIMS *m/z* 304 $[M]^+$ (7), 261 (7), 189 (5), 136 (28), 121 (43), 85 (66), 83 (100), 69 (26); HREIMS *m/z* $[M]^+$ 304.2404 (calcd for $C_{20}H_{32}O_2$, 304.2402).

3.4. Acetylation of compound 2

A solution of compound **2** (2.0 mg, 0.006 mmol) in a mixture of Ac_2O (0.3 mL) and pyridine (0.7 mL) was stirred at 25 °C overnight. Excess reagents were removed by evaporation in vacuo. The ^1H and ^{13}C NMR data and TLC retention time of the product obtained were identical with those of the natural product **1**.

3.4.1. Base hydrolysis of cembradiene 1. A suspension of **1** (5 mg, 0.014 mmol) in 3% aqueous LiOH (1 mL) was heated at 55 °C for 24 h. After cooling, 0.1 N HCl (5 mL) was added to the mixture which was then extracted with EtOAc (3×10 mL). The combined EtOAc layer was washed with brine, dried over Na_2SO_4, and evaporated to give triol **6** (3 mg, 64% yield): colorless oil; IR (film) 3413, 3337, 2962, 2923, 2856, 1444, 1289, 1007, 912 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, *J* in Hz) δ 4.42 (t, 1H, *J*=9.2 Hz, H2), 5.25 (d, 1H, *J*=9.1 Hz, H3), 5.07 (br d, 1H, H7), 3.50 (dd, 1H, *J*=6.3, 3.2 Hz, H11), 1.36 (s, 3H, H_3-16), 3.80 (d, 1H, *J*=9.3 Hz, H17α), 3.73 (d, 1H, *J*=9.3 Hz, H17β), 1.64 (s, 3H, H_3-18), 1.68 (s, 3H, H_3-19), 1.14 (s, 3H, H_3-20); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.6 (CH, C1), 75.2 (CH, C2), 124.0 (CH, C3), 139.9 (C, C4), 39.5 (CH_2, C5), 26.8 (CH_2, C6), 127.2 (CH, C7), 136.0 (C, C8), 36.0 (CH_2, C9), 24.3 (CH_2, C10), 80.1 (CH, C11), 79.0 (C, C12), 34.3 (CH_2, C13), 17.6 (CH_2, C14), 74.3 (C, C15), 23.7 (CH_3, C16), 79.7 (CH_2, C17), 15.3 (CH_3, C18), 17.1 (CH_3, C19), 23.7 (CH_3, C20); LRESIMS *m/z* 361 $[M+Na]^+$, 339 $[M+1]^+$, 321 $[M+1-H_2O]^+$, 303 $[M+1-2H_2O]^+$, 285 $[M+1-3H_2O]^+$.

3.4.2. Acetylation of triol 6. Compound **6** (3 mg, 0.009 mmol) was acetylated with Ac_2O (1.5 mL) and pyridine (10 drops) at 25 °C for 24 h. After removal of excess reagents by rotoevaporation under reduced pressure, the crude material was purified by silica gel flash column chromatography (hexane–acetone, 30:1) to give 2 mg (53.4%) of pure di-acetate **7**: colorless oil; IR (film) 3483, 2931, 1733, 1242, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, *J* in Hz) δ 4.68 (dd, 1H, *J*=9.8, 1.9 Hz, H2), 5.45 (d, 1H, *J*=10.3 Hz, H3), 5.15 (dd, 1H, *J*=8.9, 3.3 Hz, H7), 5.52 (d, 1H, *J*=9.3 Hz, H11), 1.21 (s, 3H, H_3-16), 4.01 (d, 1H, *J*=11.3 Hz, H17α), 3.92 (d, 1H, *J*=11.4 Hz, H17β), 1.57 (s, 3H, H_3-18), 1.57 (s, 3H, H_3-19), 1.06 (s, 3H, H_3-20), 2.07 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.1 (CH, C1), 68.5 (CH, C2), 131.8 (CH, C3), 136.7 (C, C4), 39.9 (CH_2, C5), 26.1 (CH_2, C6), 125.6 (CH, C7), 134.4 (C, C8), 35.1 (CH_2, C9), 26.7 (CH_2, C10), 77.2 (CH, C11), 74.2 (C, C12), 30.1 (CH_2, C13), 17.9 (CH_2, C14), 73.9 (C, C15), 20.2 (CH_3, C16), 68.4 (CH_2, C17), 14.9 (CH_3, C18), 16.3 (CH_3, C19), 19.6 (CH_3, C20), 171.0 (C, $COCH_3$), 171.7 (C, $COCH_3$), 20.9 (CH_3, $COCH_3$), 21.3 (CH_3, $COCH_3$); LRESIMS *m/z* 461 $[M+K]^+$.

3.5. Acetylation of cembradiene 3

A solution of compound **3** (2 mg, 0.005 mmol) in a mixture of Ac_2O (0.5 mL) and pyridine (0.5 mL) was stirred at 25 °C overnight. Excess reagents were removed by evaporation in vacuo. The ^1H and ^{13}C NMR data and TLC retention time of the product obtained were identical with those of di-acetate derivative **7**.

3.6. Regioselective ring-opening of cembradiene epoxide 1[4]

A mixture of compound **1** (4 mg, 0.011 mmol), LiCl (0.7 mg, 0.017 mmol), and AcOH (1 drop) in THF (1 mL)

was stirred at 25 °C for 4 days. The reaction mixture was diluted with H_2O, extracted with $CHCl_3$ (3×10 mL), and then concentrated under reduced pressure. The crude product mixture then underwent silica gel flash column chromatography (elution with hexane–acetone, 50:1) to afford pure compound **4** (2 mg, 69%) and unreacted cembradiene **1** (1.5 mg). The spectral data and TLC retention time of the sole reaction product were identical with those of the natural isolate **4**.

3.7. Single-crystal X-ray diffraction analysis of compound 1

A colorless plate crystal of compound **1** was obtained from a 10:1 $CHCl_3$/MeOH solution. The crystal belongs to the orthorhombic crystal system, space group is $P2_12_12_1$ (N0.19) with $a=9.686(2)$ Å, $b=11.484(2)$ Å, $c=58.068(10)$ Å, $V=6459(2)$ Å^3, $\rho_{calc}=1.118$ mg m^{-3}, $\lambda=0.71073$ Å, μ(Mo Kα)$=0.075$ mm^{-1}, $F_{000}=2376$, $T=298(2)$ K. Data collection yielded 23,283 reflections resulting in 7222 unique, averaged reflections, 5734 with $I>2\sigma(I)$, θ range: 0.70–22.34. Full-matrix least-squares refinement led to a final R and R (all) values of 0.0514 and 0.0467, and GOF=1.083. Intensity data were measured on a Siemens SMART 1K CCD diffractometer. CCDC-242917 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

3.8. Anti-malaria inhibition bioassay

Compounds **1**, **2**, and **4** were tested for anti-malarial activity against a chloroquine resistant *Plasmodium falciparum* strain using a novel fluorometric method, based in the intercalation of the fluorochrome PicoGreen® in the parasite DNA, as described by Corbett et al.[12]

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References and notes

1. Bayer, F. M. The Shallow-Water Octocorallia of the West Indian Region, Martinus Nijhoff, The Hague, 1961.
2. Rodríguez, A. D. *Tetrahedron* **1995**, *51*, 4571–4618.
3. (a) Greenwood, B.; Mutabingwa, T. *Nature* **2002**, *415*, 670–672. (b) Ridley, R. G. *Science* **1999**, *285*, 1502–1503.
4. Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*, 3021–3024.
5. The HCl-catalyzed cleavage of epoxide **1** would be expected to yield as the major product a chlorohydrin with the halogen attached to C15, not C17. For an example of such an artificially-derived chlorohydrin stemming from the acid-catalyzed cleavage of a cembranoid epoxide, see: Rodríguez, A. D.; Li, Y.; Dhasmana, H.; Barnes, C. L. *J. Nat. Prod.* **1993**, *56*, 1101–1113.
6. Bowden, B. F.; Coll, J. C.; Hicks, W.; Kazlauskas, R.; Mitchell, S. J. *Aust. J. Chem.* **1978**, *31*, 2707–2712.
7. Shin, J.; Fenical, W. *J. Org. Chem.* **1991**, *56*, 1227–1233.
8. Bowden, B. F.; Coll, J. C.; Tapiolas, D. M. *Aust. J. Chem.* **1983**, *36*, 2289–2295.
9. Marville, K. I.; McLean, S.; Reynold, W. F.; Tinto, W. F. *J. Nat. Prod.* **2003**, *66*, 1284–1287.
10. Cóbar, O. M.; Rodríguez, A. D.; Padilla, O. L.; Sánchez, J. A. *J. Org. Chem.* **1997**, *62*, 7183–7188.
11. Shi, Y.-P.; Rodríguez, A. D.; Padilla, O. L. *J. Nat. Prod.* **2001**, *64*, 1439–1443.
12. Corbett, Y.; Herrera, L.; González, J.; Cubilla, L.; Capson, T.; Colley, P. D.; Kursar, T. A.; Romero, L. I.; Ortega-Barria, E. *J. Trop. Med. Hyg.* **2004**, *70*, 119–124.

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Synthesis of pure stereoisomers of benzo[*b*]thienyl dehydrophenylalanines by Suzuki cross-coupling. Preliminary studies of antimicrobial activity

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Abstract—Several benzo[*b*]thienyldehydrophenylalanines were synthesized from pure stereoisomers of the methyl ester of *N*-(*tert*-butoxycarbonyl)-β-bromodehydrophenylalanine as an extension of our previously reported method for the synthesis of dehydrotryptophan analogues to dehydrophenylalanine derivatives. The latter were obtained in high yields by *N*-deprotection and bromination of *N*,*N*-bis-(*tert*-butoxycarbonyl)-(*Z*)-dehydrophenylalanine using TFA and NBS. This was carried out in two steps or in a one pot procedure resulting in different *E*/*Z* ratios. These compounds were coupled under Suzuki cross-coupling conditions [$Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O] with several boronic benzo[*b*]thienyl acids in good to high yields maintaining the stereochemistry of the starting materials. The best yields were obtained when the boronic acid was in position 7 of the benzo[*b*]thiophene and with the *E* isomer of the brominated dehydrophenylalanine. In some cases it was possible to increase the lower yields by changing the Pd source to $PdCl_2(PPh_3)_2$. A model dipeptide was prepared coupling a benzo[*b*]thienyldehydrophenylalanine with the methyl ester of alanine. Preliminary antimicrobial studies were performed with both isomers of one of the β, β-diaryldehydroalanines obtained. The results show that the compounds are selective and very active (very low MICs) against Gram positive bacteria (*B. cereus* and *B. subtilis*) the *Z*-isomer being more active. The compounds are also active against *Candida albicans* presenting similar MICs.

1. Introduction

Dehydroamino acids have been found in several natural peptides from microbial or marine sources. The incorporation of α,β-dehydroamino acids constitutes a valuable tool in structure-activity relationship (SAR) studies, due to the conformational constraints they impose. These restrained analogues of amino acids mainly dehydrophenylalanine and dehydrotyrosine have been introduced in peptide sequences to probe the preferred orientations of these residues once bound to the receptors.[1] These molecules can also be very useful as pharmaceutical probes towards various proteases, namely HIV-proteases.[2]

The dehydrophenylalanine residue as a constrained phenylalanine mimic has gained much importance, in particular, because of its turn inducing as well as helix-forming propensity.[3] Studies have indicated that the α,β-double bond of dehydroamino acids does not in itself cause reversal in the peptide backbone and the preferred conformation of a dehydropeptide may be decided by the nature of the β-substituents. Thus, different dehydroamino acids can be used to introduce different kinds of constraints in peptides.[4]

Recently, we have been interested in the synthesis of new β-substituted dehydroamino acids either by Michael additions[5] or by palladium catalyzed cross-couplings.[6a–c] The fluorescence studies performed on β-benzo[*b*]thienyldehydroamino acids already prepared by us showed that some of them can also be used as fluorescent probes.[6c]

Here we describe the synthesis of benzo[*b*]thienyldehydrophenylalanines using Suzuki cross-coupling[7] of several boronic benzo[*b*]thienyl acids with pure stereoisomers of a β-bromodehydrophenylalanine derivative. Two of the β, β-diaryldehydroalanines obtained were tested for antimicrobial activity and showed to be active with low minimal inhibitory concentration (MIC). The insertion of this type of compounds in peptides was demonstrated preparing a model dipeptide using DCC/HOBt.

Keywords: Amino acids; Dehydrophenylalanines; Benzo[*b*]thiophenes; Suzuki coupling; Palladium; Antimicrobial.
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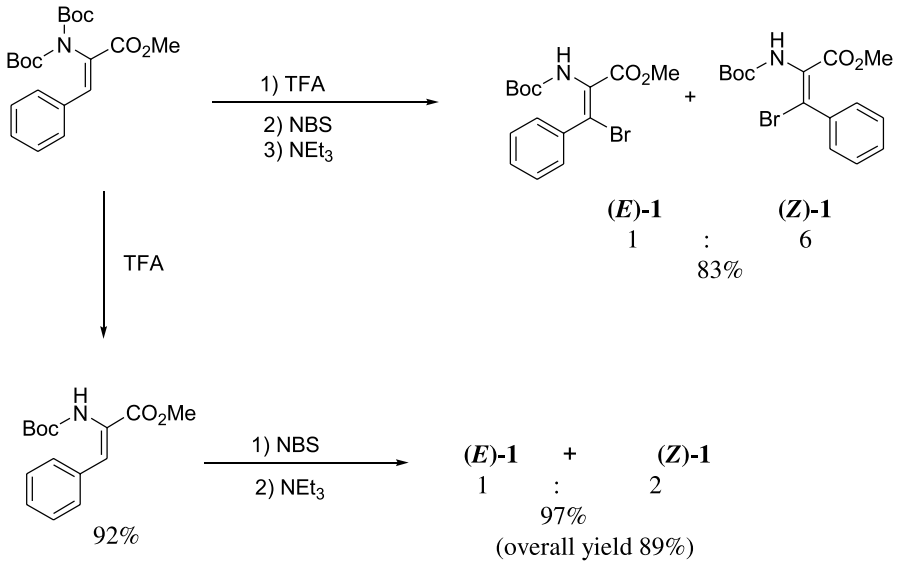


Scheme 1. Synthesis of compound (*E*)-**1** and (*Z*)-**1** in two steps or in a one pot procedure.

2. Results and discussion

The methyl ester of *N*,*N*-bis-(*tert*-butoxycarbonyl)-(*Z*)-dehydrophenylalanine[5] (Boc_2-ΔPhe-OMe) was N-monodeprotected[5] with TFA and β-brominated with NBS followed by treatment with NEt_3 to give the methyl ester of *N*-(*tert*-butoxycarbonyl)-β-bromodehydrophenylalanine [Boc-ΔPhe(β-Br)-OMe)] as a 1:2 E/Z mixture in an overall

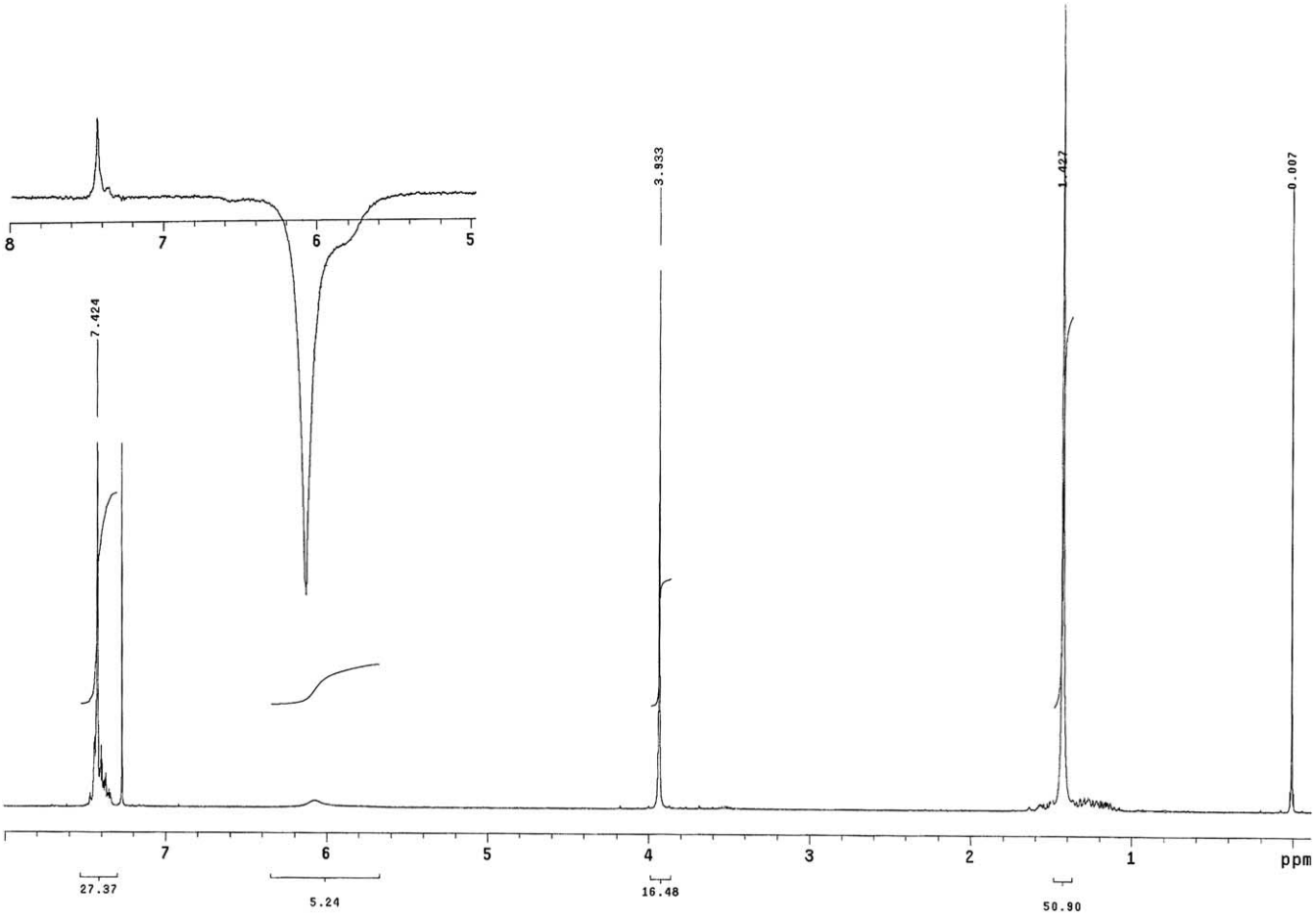


Figure 1. ^1H NMR spectrum ($CDCl_3$) of (*E*)-**1** and NOE difference experiment irradiating the α-NH and observing the effect on the signal of the phenyl protons.

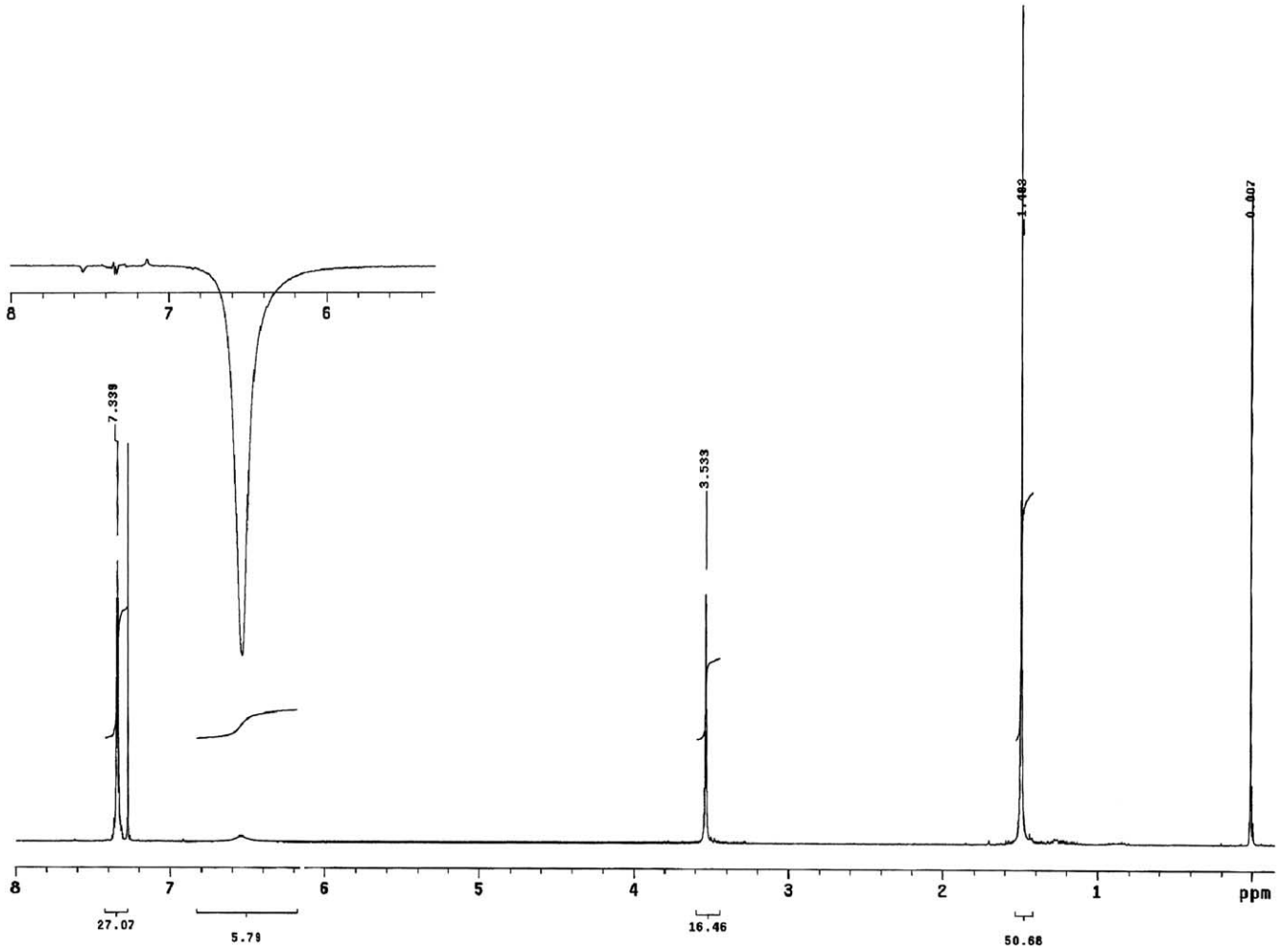


Figure 2. ^{1}H NMR spectrum ($CDCl_3$) of (*Z*)-**1** and NOE difference experiment irradiating the α-NH.

yield of 89%. The same reactions performed in a one pot procedure gave the products in a similar yield but resulted in a higher selectivity towards the *Z* isomer (1:6 *E*/*Z*) (Scheme 1). These results are similar to those obtained by us in the bromination of dehydroaminobutyric acid.[6a]

The stereochemistry of (*E*) and (*Z*)-**1** was determined by NOE difference experiments irradiating the α-NH and observing a NOE effect on the signal of the phenyl protons of (*E*)-**1** (Fig. 1) while for compound (*Z*)-**1** this was not observed (Fig. 2).

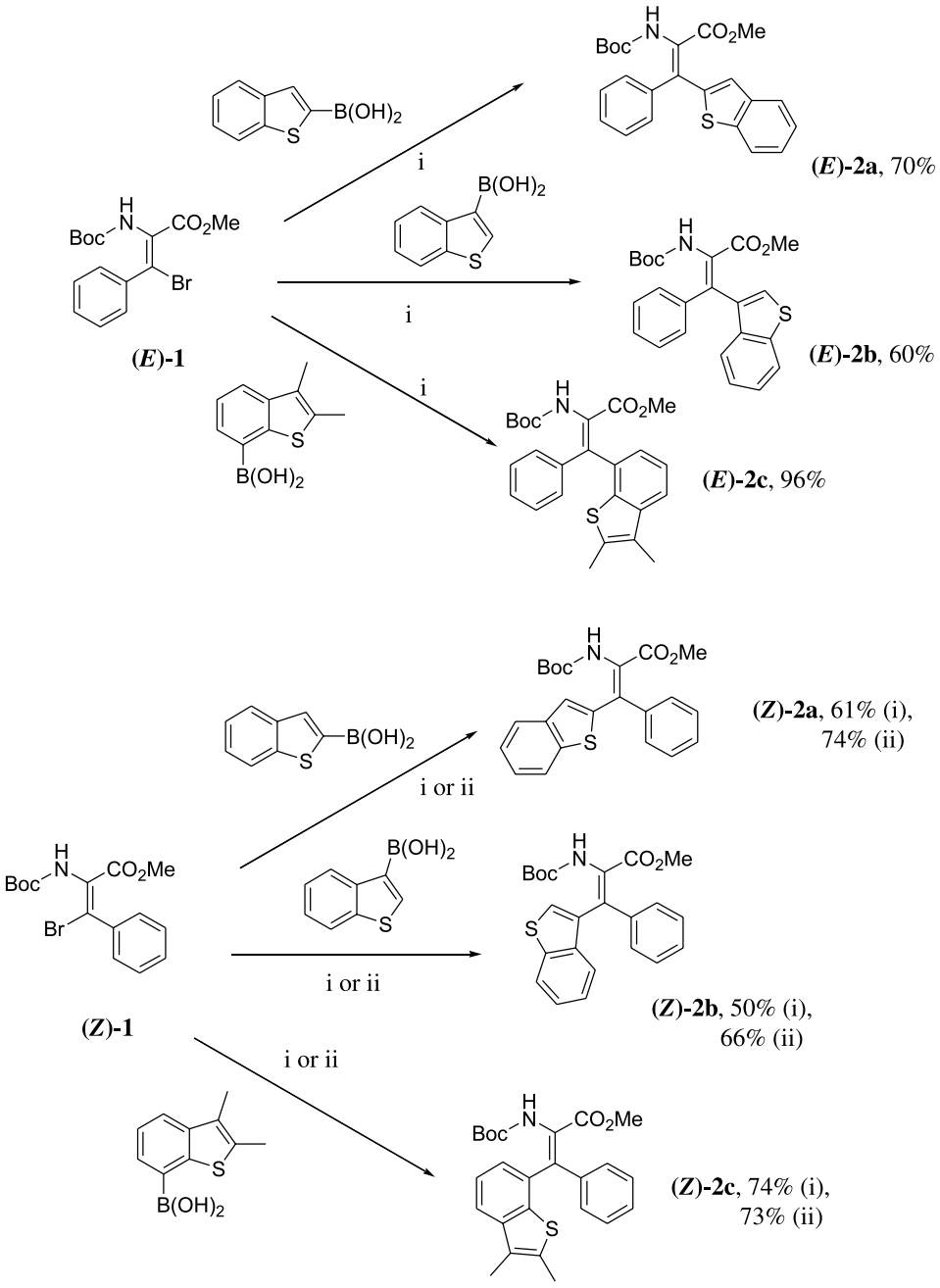
The pure stereoisomers (*E*) and (*Z*)-**1** were coupled with several boronic benzo[*b*]thienyl acids under Suzuki cross-coupling conditions[6a] to give β-benzo[*b*]thienyldehydrophenylalanines in good to high yields (Scheme 2). NOE difference experiments irradiating the α-NH confirmed that the coupled products maintained the stereochemistry of the starting materials.

The best yields were obtained when the boronic acid was in position 7 of the benzo[*b*]thiophene moiety. In all cases using the same catalytic conditions (i), the higher yields were obtained from compound (*E*)-**1** which can be due to the lower steric hindrance of this derivative.

In order to increase the yields of the *Z* isomers, another palladium catalyst [$PdCl_2(PPh_3)_2$], that had already given good results in the synthesis of β,β-bis-(benzo[*b*]thienyl)-dehydroalanines from a β,β-dibromodehydroalanine derivative, was used.[6c] In these conditions (ii), when the boronic acids are in the thiophene ring the yields increased from 61 to 74% in the synthesis of (*Z*)-**2a** and from 50 to 66% in the synthesis of (*Z*)-**2b**. This increase was not observed in the synthesis of compound (*Z*)-**2c** which was obtained in similar yields using both catalytic systems (Scheme 2).

A dipeptide was prepared from (*E*)-**2b** by C-deprotection and coupling with the methyl ester of alanine using DCC/HOBt (Scheme 3). This result in the synthesis of a model dipeptide shows that our β,β-diaryldehydroamino acids can be inserted into peptides.

A screening of antibacterial activities using two Gram negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and two Gram positive bacteria (*Bacillus subtilis* and *Bacillus cereus*) and antifungal activity using *Candida albicans* as a representative of fungi was assessed for compounds (*Z*)-**2c** and (*E*)-**2c**. The MIC (in μg/mL) was determined (Table 1) using an adaptation of agar streak

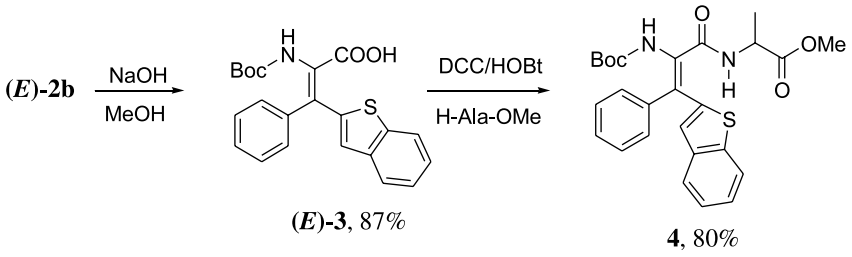


Scheme 2. Synthesis of compounds (*E*)-**2a–c** and (*Z*)-**2a–c** under Suzuki cross-coupling conditions. (i) $Pd(PPh_3)_4$ (10 mol%), Na_2CO_3 (2 equiv), boronic acid (1.3 equiv), DME/H_2O (4:1), 90 °C, 3–5 h. (ii) Same conditions but using $PdCl_2(PPh_3)_2$ (10 mol%).

dilution method based on radial diffusion.[8] In the same conditions, different concentrated solutions of Ampicillin (antibacterial) and Cyclohexamide (antifungal) were used as standards. The MIC was considered to be the lowest concentration of the tested compound which inhibits growth of bacteria or fungi on the plate. The compounds tested were inactive against the Gram- bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). The diameters of the inhibition zones corresponding to the MICs for the Gram+ bacteria and for *C. albicans* are presented in Table 1.

From the inspection of Table 1 it is possible to conclude that the compounds tested are active against *B.cereus*, *B.subtilis* and *C. albicans* presenting MICs very much lower than those obtained with Ampicillin (antibacterial) and Cyclohexamide (antifungal).

Compound (*Z*)-**2c** shows lower MICs than (*E*)-**2c** for Gram+ bacteria but the results against *C. albicans* are similar for both isomers. These results indicate that the compounds are selective and very active (very low MICs) against the Gram+ bacteria tested and against a representative of fungi, thus showing very interesting antimicrobial properties.



Scheme 3. Synthesis of dipeptide **4** from (*E*)-**2b** and the methylester of alanine.

Table 1. Antimicrobial activity of compounds (*Z*)-**2c** and (*E*)-**2c**

Compounds	MIC (μg/mL) (zone of inhibition in mm)		
	Bacillus cereus CECT148	*Bacillus subtilis* CECT498	*Candida albicans* CECT 1394
(*E*)-**2c**	0.125 (13)	0.125 (15)	0.125 (6)
(*Z*)-**2c**	1.25×10^{-3} (15)	1.25×10^{-3} (11)	0.125 (5)
Ampicillin	3.13 (13)	12.5 (10)	—
Cyclohexamide	—	—	12.5 (5)

CECT—Spanish type culture collection of Valencia University.

3. Conclusion

Several β,β-diaryldehydroamino acids in the benzo[*b*]thiophene series were synthesized in good to high yields from pure stereoisomers of a β-bromodehydrophenylalanine derivative and benzo[*b*]thienylboronic acids using C–C palladium-catalyzed cross-couplings. From the results obtained we can conclude that the *E* isomer of the β-brominated dehydrophenylalanine (*E*)-**1** is more reactive under Suzuki cross coupling conditions then the *Z* isomer. It is also possible to conclude that the 7-benzo[*b*]thienylboronic acid is the most reactive, and its reactivity does not depend on the Pd source. The insertion of this type of compounds in peptides was tested preparing a model dipeptide in high yield. Preliminary antimicrobial studies were performed using both isomers of one of the β,β-diaryldehydroalanines obtained. The results show that the compounds are selective and very active (very low MICs) against Gram+bacteria (*B. cereus* and *B. subtilis*), the *Z*-isomer being more active. The compounds are also active against *Candida albicans* presenting similar MICs.

4. Experimental

4.1. General

Melting points (°C) were determined in a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus at 300 and 75.4 MHz, respectively. ^{1}H–^{1}H spin–spin decoupling and DEPT θ 45° were used. Chemical shifts are given in ppm and coupling constants in Hz. MS and HRMS data were recorded by the mass spectrometry service of the University of Vigo, Spain. Elemental analysis was performed on a LECO CHNS 932 elemental analyser.

The reactions were monitored by thin layer chromatography (TLC). Column chromatography was performed on Macherey-Nagel silica gel 230–400 mesh. Petroleum ether refers to the boiling range 40–60 °C. When solvent gradient was used, the increase in polarity was made from neat petroleum ether to mixtures of ether/petroleum ether, increasing 10% of ether each time until the isolation of the product.

4.2. Synthesis of Boc-(*E*)-ΔPhe(β-Br)-OMe (*E*)-1 and Boc-(*Z*)-ΔPhe(β-Br)-OMe (*Z*)-1

Boc-ΔPhe-OMe[5] (1.39 g, 5.00 mmol) was dissolved in dichloromethane (0.1 M) and 1.2 equiv of *N*-bromosuccinimide (0.980 g, 5.50 mmol) were added with vigorous stirring. After reacting for 16 h, triethylamine (1.5 equiv) was added and stirring continued for an additional hour. Dicloromethane (50 mL) was added and the organic phase was washed with water and brine (3×30 mL each). After drying over $MgSO_4$ the extract was taken to dryness at reduced pressure to give (*E*)-**1** and (*Z*)-**1** (1.73 g, 97%) as a 1:2 mixture. The diastereomers were separated by column chromatography using solvent gradient from neat petroleum ether to 20% diethyl ether/petroleum ether to give (*Z*)-**1** mp 101–103 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$): 1.49 (9H, s, CH_3 Boc), 3.53 (3H, s, OCH_3), 6.55 (1H, s, αNH), 7.34 (5H, br s, ArH). ^{13}C NMR ($CDCl_3$): 28.06 ($C(CH_3)_3$), 52.43 (OCH_3), 82.10 ($OC(CH_3)_3$), 128.21 (CH), 128.41 (C), 128.94 (CH), 129.11 (CH), 129.31 (C), 137.39 (C), 151.89 (C=O), 163.47 (C=O) ppm. Anal. Calcd for $C_{15}H_{18}NO_4Br$ (356.22): C, 50.58; H, 5.09; N, 3.93. Found: C, 50.61; H, 5.12; N, 4.01. (*E*)-**1** mp 80–81 °C (from petroleum ether). ^{1}H NMR ($CDCl_3$): 1.43 (9H, s, CH_3 Boc), 3.93 (3H, s, OCH_3), 6.08 (1H, s, αNH), 7.43 (5H, br s, ArH). ^{13}C NMR ($CDCl_3$): 28.01 ($C(CH_3)_3$), 52.58 (OCH_3), 82.00 ($OC(CH_3)_3$), 128.58 (C), 128.94 (CH), 129.04 (CH), 129.47 (CH), 136.50 (C), 151.56 (C=O), 164.55 (C=O) ppm. Anal. Calcd for $C_{15}H_{18}NO_4Br$ (356.22): C, 50.58; H, 5.09; N, 3.93. Found: C, 50.74; H, 5.21; N, 4.09.

One pot procedure. Boc_2-ΔPhe-OMe[5] (1.86 g, 5.00 mmol) was dissolved in dichloromethane (0.1 M) and 2% of TFA was slowly added with vigorous stirring. The reaction was monitored by TLC and when no starting material was detected (≈1 h) 1.2 equiv of *N*-bromosuccinimide (1.34 g,

7.50 mmol) were added. After reacting for 16 h triethylamine (15.0 mmol) was added and stirring continued for an additional hour. Dichoromethane was added (50 mL) and the organic phase was then washed with water and brine (2×30 mL each). After drying over $MgSO_4$, the extract was taken to dryness at reduce pressure to afford a 1:6 mixture of (*E*)-**1** and (*Z*)-**1** (1.48 g, 83%).

4.3. General procedure for Suzuki cross couplings

To a solution of compound (*E*)-**1** or (*Z*)-**1** in DME/water (4:1), benzo[*b*]thienylboronic acids (1.1 equiv), Na_2CO_3 (2 equiv) and $Pd(PPh_3)_4$ (10 mol%) were added and the mixture was heated at 90 °C while the reaction was monitored by TLC. The DME was removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL). The organic layer was then washed with water and brine (3×5 mL) dried with $MgSO_4$ and the solvent evaporated at reduce pressure to give an oil which was submitted to column chromatography.

4.3.1. Boc-(*E*)-ΔPhe(β-benzo[*b*]thien-2-yl)-OMe ((*E*)-2a). The procedure described above was applied using compound (*E*)-**1** (107 mg, 0.300 mmol) and the 2-benzo-[*b*]thienylboronic acid (0.330 mmol, 59.0 mg) and heating for 3 h 30 min. Column chromatography using a solvent gradient from pure petroleum ether to 30% diethyl ether in petroleum ether, gave compound (*E*)-**2a** (86.0 mg, 70%) as an oil. Recrystallization from diethyl ether/petroleum ether afforded light yellow crystals, mp 97–99 °C. ^{1}H NMR ($CDCl_3$): 1.46 (9H, s, CH_3 Boc), 3.69 (3H, s, OCH_3), 6.17 (1H, br s, NH), 7.16 (1H, s, ArH), 7.29–7.43 (7H, m, ArH), 7.69–7.74 (2H, m, ArH) ppm. ^{13}C NMR ($CDCl_3$): 28.09 ($C(CH_3)_3$), 52.58 (OCH_3), 81.77 ($OC(CH_3)_3$), 122.05 (CH), 123.60 (CH), 124.33 (CH), 124.43 (CH), 124.55 (CH), 127.44 (C), 128.83 (CH), 129.02 (CH), 129.62 (CH), 137.33 (C), 139.31 (C), 140.72 (C), 141.97 (C), 152.12 (C=O), 166.01 (C=O) ppm. Anal. Calcd for $C_{23}H_{23}NO_4S$ (409.50): C, 67.46; H, 5.66; N, 3.42; S, 7.83. Found: C, 67.25; H, 5.93; N, 3.39; S, 7.36.

4.3.2. Boc-(*Z*)-ΔPhe(β-benzo[*b*]thien-2-yl)-OMe ((*Z*)-2a). The procedure described above was applied using compound (*Z*)-**1** (107 mg, 0.300 mmol) and the 2-benzo-[*b*]thienylboronic acid (59.0 mg, 0.330 mmol) and heating for 5 h. Column chromatography using a solvent gradient from pure petroleum ether to 30% diethyl ether in petroleum ether, gave compound (*Z*)-**2a** (75.0 mg, 61%) as an oil. Recrystallization from diethyl ether/petroleum ether afforded colourless crystals, mp 123–124 °C. ^{1}H NMR ($CDCl_3$): 1.52 (9H, s, CH_3 Boc), 3.49 (3H, s, OCH_3), 6.55 (1H, br s, NH), 7.08 (1H, s, ArH), 7.28–7.41 (7H, m, ArH), 7.67–7.76 (1H, m, ArH), 7.80–7.83 (1H, m, ArH) ppm. ^{13}C NMR ($CDCl_3$): 28.15 ($C(CH_3)_3$), 51.96 (OCH_3), 81.59 ($OC(CH_3)_3$), 122.01 (CH), 123.57 (C), 124.00 (CH), 124.59 (CH), 125.31 (CH), 125.87 (C), 127.80 (CH), 128.07 (CH), 128.24 (CH), 129.38 (CH), 138.79 (C), 138.85 (C), 140.77 (C), 152.84 (C=O), 165.89 (C=O) ppm. Anal. Calcd for $C_{23}H_{23}NO_4S$ (409.50): C, 67.46; H, 5.66; N, 3.42; S, 7.83. Found: C, 67.58; H, 5.74; N, 3.48; S, 7.70. The procedure described above using 0.5 mmol of (*Z*)-**1** and using $PdCl_2(PPh_3)_2$ gave compound (*Z*)-**2a** (150 mg, 74%).

4.3.3. Boc-(*E*)-ΔPhe(β-benzo[*b*]thien-3-yl)-OMe ((*E*)-2b). The procedure described above was applied using compound (*E*)-**1** (178 mg, 0.500 mmol) and the 3-benzo-[*b*]thienylboronic acid (98.0 mg, 0.550 mmol) and heating for 3 h. Column chromatography using a solvent gradient from pure petroleum ether to 30% diethyl ether in petroleum ether, gave compound (*E*)-**2b** (112 mg, 60%) as an oil. Recrystallization from diethyl ether/petroleum ether afforded colourless crystals, mp 171–172 °C. ^{1}H NMR ($CDCl_3$): 1.48 (9H, s, CH_3 Boc), 3.46 (3H, s, OCH_3), 6.33 (1H, br s, NH), 7.19 (1H, d, J=7.8 Hz, ArH), 7.26–7.40 (8H, m, ArH), 7.81 (1H, d, J=7.5 Hz, ArH) ppm ^{13}C NMR ($CDCl_3$): 28.09 ($C(CH_3)_3$), 52.09 (OCH_3), 81.46 ($OC(CH_3)_3$), 122.49 (CH), 123.21 (CH), 124.08 (CH), 124.30 (CH), 125.63 (CH), 127.57 (C), 128.45 (CH), 128.89 (CH), 129.20 (CH), 131.94 (C), 134.59 (C), 136.75 (C), 138.09 (C), 139.81 (C), 152.54 (C=O), 166.34 (C=O) ppm. Anal. Calcd for $C_{23}H_{23}NO_4S$ (409.50): C, 67.46; H, 5.66; N, 3.42; S, 7.83. Found: C, 67.30; H, 5.94; N, 3.51; S, 7.64.

4.3.4. Boc-(*Z*)-ΔPhe(β-benzo[*b*]thien-3-yl)-OMe ((*Z*)-2b). The procedure described above was applied using compound (*Z*)-**1** (107 mg, 0.300 mmol) and the 3-benzo-[*b*]thienylboronic acid (59.0 g, 0.330 mmol) and heating for 3 h. Column chromatography using a solvent gradient from pure petroleum ether to 30% diethyl ether in petroleum ether, gave compound (*Z*)-**2b** (62.0 mg, 50%) as an oil. Recrystallization from diethyl ether/petroleum ether afforded colourless crystals, mp 139–140 °C. ^{1}H NMR ($CDCl_3$): 1.40 (9H, s, CH_3 Boc), 3.61 (3H, s, OCH_3), 5.92 (1H, br s, NH), 7.16–7.20 (2H, m, ArH), 7.27–7.44 (6H, m, ArH), 7.58 (1H, d, J=8.1 Hz, ArH), 7.90 (1H, d, J=8.1 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$): 28.07 ($C(CH_3)_3$), 52.13 (OCH_3), 81.38 ($OC(CH_3)_3$), 122.79 (CH), 123.25 (C), 124.67 (CH), 124.82 (CH), 127.22 (C), 128.05 (CH), 128.17 (CH), 128.41 (CH), 128.70 (CH), 134.16 (C), 136.84 (C), 139.39 (C), 140.12 (C), 152.73 (C=O), 166.18 (C=O) ppm. Anal. Calcd for $C_{23}H_{23}NO_4S$ (409.50): C, 67.46; H, 5.66; N, 3.42; S, 7.83. Found: C, 67.53; H, 5.79; N, 3.50; S, 7.72. The procedure described above using $PdCl_2(PPh_3)_2$ gave compound (*Z*)-**2b** (81.0 mg, 66%).

4.3.5. Boc-(*E*)-ΔPhe(β-2,3-dimethylbenzo[*b*]thien-7-yl)-OMe ((*E*)-2c). The procedure described above was applied using compound (*E*)-**1** (178 mg, 0.500 mmol) and the 2,3-dimethyl-7-benzo[*b*]thienylboronic acid (113 mg, 0.550 mmol) and heating for 4 h 30 min. Column chromatography using a solvent gradient from pure petroleum ether to 30% diethyl ether in petroleum ether, gave compound (*E*)-**2c** (209 mg, 96%) as an oil. Recrystallization from petroleum ether afforded colourless crystals, mp 152–154 °C. ^{1}H NMR ($CDCl_3$): 1.47 (9H, s, CH_3 Boc), 2.26 (3H, s, $ArCH_3$), 2.36 (3H, s, $ArCH_3$), 3.41 (3H, s, OCH_3), 6.24 (1H, br s, NH), 7.15 (1H, br d, J=6.9 Hz, ArH), 7.31–7.36 (6H, m, ArH), 7.53 (1H, dd, J=8.1, 0.9 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$): 11.41 (CH_3), 13.63 (CH_3), 28.13 ($C(CH_3)_3$), 51.99 (OCH_3), 81.27 ($OC(CH_3)_3$), 120.89 (CH), 123.71 (CH), 124.47 (CH), 126.70 (C), 127.06 (C), 128.06 (C), 128.45 (CH), 128.76 (CH), 129.67 (CH), 133.50 (C), 134.48 (C), 136.60 (C), 138.07 (C), 141.48 (C), 152.70 (C=O), 166.03 (C=O) ppm. Anal. Calcd for $C_{25}H_{27}NO_4S$

(437.55): C, 68.62; H, 6.22; N, 3.20; S, 7.33. Found: C, 68.64; H, 6.44; N, 3.29; S, 7.02.

4.3.6. Boc-(*Z*)-ΔPhe(β-2,3-dimethylbenzo[*b*]thien-7-yl)-OMe ((*Z*)-2c). The procedure described above was applied using compound (*Z*)-**1** (178 mg, 0.500 mmol) and the 2,3-dimethyl-7-benzo[*b*]thienylboronic acid (113 mg, 0.550 mmol) and heating for 4 h 30 min. Column chromatography using a solvent gradient from pure petroleum ether to 30% diethyl ether in petroleum ether, gave compound (*E*)-**2c** (162 mg, 74%) as an oil. Recrystallization from petroleum ether afforded colourless crystals, mp 140–142 °C. ^{1}H NMR ($CDCl_3$): 1.42 (9H, s, CH_3 Boc), 2.31 (3H, s, $ArCH_3$), 2.42 (3H, s, $ArCH_3$), 3.60 (3H, s, OCH_3), 5.89 (1H, br s, NH), 7.08–7.21 (3H, m, ArH), 7.23–7.30 (3H, m, ArH), 7.38 (1H, t, J=8.1 Hz, ArH), 7.59 (1H, d, J=8.1 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$): 11.46 (CH_3), 13.67 (CH_3), 28.08 ($C(CH_3)_3$), 52.19 (OCH_3), 81.14 ($OC(CH_3)_3$), 121.26 (CH), 124.38 (CH), 125.33 (CH), 126.99 (C), 127.93 (CH), 128.08 (CH), 128.78 (CH), 129.69 (C), 132.00 (C), 134.87 (C), 137.87 (C), 138.59 (C), 141.78 (C), 152.67 (C=O), 166.30 (C=O) ppm. Anal. Calcd for $C_{25}H_{27}NO_4S$ (437.55): C, 68.62; H, 6.22; N, 3.20; S, 7.33. Found: C, 68.54; H, 6.35; N, 3.24; S, 7.05. The procedure described above using $PdCl_2(PPh_3)_2$ gave compound (*Z*)-**2c** (160 mg, 73%).

4.4. Synthesis of the model dipeptide Boc-(*E*)-ΔPhe-(β-benzo[*b*]thien-2-yl)-Ala-OMe

4.4.1. Synthesis of Boc-(*E*)-ΔPhe-(β-benzo[*b*]thien-2-yl)-OH ((*E*)-3). To a solution of Boc-*E*-ΔPhe(β-benzo[*b*]thien-2-yl)-OMe (0.34 mmol, 137 mg) in dioxane (3 mL), 1 equiv of NaOH 1 M was added. The solution was left stirring for 18 h at rt (the reaction was followed by TLC until no starting material was detected). The reaction mixture was acidified to pH 2–3 with $KHSO_4$ 1 M and the solid formed filtered. Crystallization from ethyl acetate/*n*-hexane afforded compound (*E*)-**3** (117 mg, 87%) as a light yellow solid, mp 189–191 °C (from ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): 1.43 (9H, s, CH_3 Boc), 6.18 (1H, s, NH), 7.29–7.40 (8H, m, ArH), 7.70–7.73 (2H, m, ArH) ppm. ^{13}C NMR ($CDCl_3$): 28.08 ($C(CH_3)_3$), 82.01 ($OC(CH_3)_3$), 114.48 (C), 122.09 (CH), 123.87 (CH), 124.38 (CH), 124.72 (CH), 125.23 (CH), 126.32 (C), 128.95 (CH), 129.02 (CH), 129.58 (CH), 137.46 (C), 139.36 (C), 141.05 (C), 141.34 (C), 151.32 (C=O), 152.56 (C=O) ppm.

4.4.2. Synthesis of Boc-(*E*)-ΔPhe-(β-benzo[*b*]thien-2-yl)-Ala-OMe (4). To a solution of Boc-(*E*)-ΔPhe(β-benzo-[*b*]thien-2-yl)-OH (0.20 mmol, 79.0 mg) in acetonitrile (5 mL), HOBt (0.22 mmol, 34 mg) and DCC (0.22 mmol, 44 mg) were added with vigorous stirring at 0 °C. After 15 min, HCl,H-Ala-OMe (0.2 mmol, 28 mg) and NEt_3 (0.2 mmol, 0.03 mL) were added. The reaction was left stirring for 18 h at rt. The urea was removed by filtration and the solvent removed at reduced pressure. The oily residue was dissolved in ethyl acetate (15 mL) and the solution washed with $KHSO_4$ 1 M (3×5 mL), $NaHCO_3$ 1 M (3×5 mL) and brine (3×5 mL). The organic layer was dried with $MgSO_4$ and solvent removed at reduced pressure giving an oil which was submitted to column chromatography with diethyl ether/petroleum ether (2:1). Compound **4** was isolated as a white solid (74 mg, 80%), mp 168–169 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$): 1.10 (3H, d, J=7.2 Hz, βCH_3 Ala), 1.44 (9H, s, CH_3 Boc), 3.43 (3H, s, OMe), 4.54–4.63 (1H, m, αCH Ala), 6.06 (1H, s, NH), 6.42 (1H, d, J=7.5 Hz, NH), 7.27–7.41 (8H, m, ArH), 7.73–7.78 (2H, m, ArH) ppm. ^{13}C NMR ($CDCl_3$): 17.82 (CH_3), 28.13 ($C(CH_3)_3$), 48.33 (CH), 52.17 (OMe), 81.52 ($OC(CH_3)_3$), 122.07 (CH), 123.57 (C), 123.67 (CH), 124.45 (CH), 124.56 (CH), 125.18 (CH), 128.73 (CH), 128.96 (CH), 129.54 (CH), 131.11 (C), 137.50 (C), 139.44 (C), 140.82 (C), 141.44 (C), 152.16 (C=O), 164.29 (C=O), 172.60 (C=O) ppm. Anal. Calcd for $C_{26}H_{28}N_2O_5S$ (480.58): C, 64.98; H, 5.87; N, 5.83; S, 6.67. Found: C, 64.94; H, 5.95; N, 5.82; S, 6.66.

4.5. In vitro antimicrobial activity

Suspensions of the microorganism were prepared to contain approximately 10^8 cfu/mL and the plates were inoculated. A stock solution of the synthesized compound (1000 μg/mL) in DMSO was prepared and graded dilutions of the tested compounds were incorporated in a cavity (depth 3 mm, diameter 4 mm) made in the center of the Petri dish (nutrient agar for antibacterial activity and sabouraud dextrose agar medium for antifungal activity). The plates were incubated at 37 °C (for bacteria) and at 30 °C (for fungi) for 24 h in duplicate. Positive control using only inoculation and negative control using only DMSO in the cavity were carried out.

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References and notes

1. Sagan, S.; Josien, H.; Karoyan, P.; Brunissen, A.; Chassaing, G.; Lavielle, S. *Bioorg. Med. Chem.* **1996**, *4*, 2167–2178 and references cited therein.
2. Prabhakaran, E. N.; Nandy, J. P.; Shukla, S.; Tewari, A.; Kumar Das, S.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6461–6466 and references cited therein.
3. Sastry, T. V. R. S.; Banerji, B.; Kumar, S. K.; Kunwar, A. C.; Das, J.; Nandy, J. P.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 7621–7625 and references cited therein.
4. Siddiqui, M. Z. *Int. J. Biol. Macromol.* **1999**, *26*, 17–21 and references cited therein.
5. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3167–3173.
6. (a) Silva, N. O.; Abreu, A. S.; Ferreira, P. M. T.; Monteiro, L. S.; Queiroz, M.-J.R.P. *Eur. J. Org. Chem.* **2002**, 2524–2528. (b) Abreu, A. S.; Silva, N. O.; Ferreira, P. M. T.; Queiroz, M.-J.R.P. *Eur. J. Org. Chem.* **2003**, 1537–1544. (c) Abreu, A. S.; Silva, N. O.; Ferreira, P. M. T.; Queiroz, M.-J.R.P. *Eur. J. Org. Chem.* **2003**, 4792–4796.

7. For reviews see (a) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.
8. (a) Rameshkumar, N.; Ashokkumar, M.; Subramanian, E. H.; Ilavarasan, R.; Sridhar, S. K. *Eur. J. Med. Chem.* **2003**, *38*, 1001–1004. (b) Queiroz, M.-J.; Agathe Begouin, R. P.; Ferreira, I. C. F. R.; Kirsch, G.; Calhelha, R. C.; Barbosa, S.; Estevinho, L. M. *Eur. J. Org. Chem.* **2004**, 3679–3685.

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Anti-selective and regioselective aldol addition of ketones with aldehydes using MgI_2 as promoter

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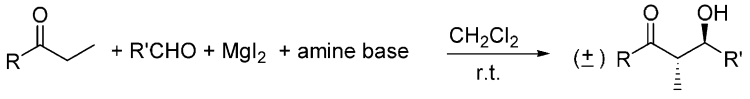
Abstract—The first example of a direct aldehyde–ketone coupling using the secondary amine piperidine as base in the presence of MgI_2 to generate high selectivity of anti-aldol products from unmodified ethyl ketones in high yield is reported. The coupling reactions were carried out in a one-pot reaction by mixing four reaction components at room temperature. In the case of unsymmetrical ketones, addition was made to the less hindered α-side.

1. Introduction

The stereoselective synthesis of anti-aldol products from unmodified ethyl ketones is of great interest to organic chemists,[1] especially in the area of natural product synthesis. Several methodologies have been reported that use boron reagents or metal complexes in the presence of a tertiary amine to convert unmodified ethyl ketones to enolates that then react with aldyhydes to form anti-aldol products. For example, the use of dicyclohexylboron chloride and triethylamine produce high selectivity for *E*-enolates and correspondingly high selectivity for the anti-aldol products;[2] this two step process requires hydrogen peroxide oxidation of the boron intermediate to obtain free aldol products. An alternative aldol coupling reaction eliminated this oxidation step by using ytterbium trifluoromethanesulfonate and a tertiary amine;[3] however, high anti-aldol products were produced only when sterically hindered aldehydes such as trimethylacetaldehyde were employed as the electrophilic acceptor. $TiCl_4$ has also been used as a reaction promoter with a tertiary amine;[4] however only when special unmodified ketones were used could high anti-aldol product ratios be realized. All of the previously mentioned approaches have their individual weaknesses, some of which include long reaction times, using air and moisture-sensitive reagents,[2] two step reactions that require enolate to be formed before aldehyde can be added,[2–4] and the random *anti*/*syn* selectivity of products.[3,4] Because of these weaknesses, the development of a general method for synthesizing anti-aldol products from unmodified ethyl ketones is needed.

Here we describe a direct method for the stereoselective coupling of aromatic and non-aromatic aldehydes with unmodified ethyl ketones to generate anti-aldol products. In the presence of stoichiometric quantities of MgI_2, the reaction of ethyl ketones with aldehydes at room temperature results in high yields of anti-3-hydroxy ketones (Scheme 1). In the case of unsymmetrical ketones, addition is made to the less hindered α-side.

We have recently reported that MgI_2 is a well-suited Lewis acid for the carbon–carbon bond forming reaction during the synthesis of β-iodo Baylis–Hillman adducts.[5] MgI_2 is thought to serve as a Lewis acid as well as an iodine source for Michael-type additions of α,β-acetylenic ketones or



Scheme 1.

Keywords: Piperidine; Anti-aldol reaction; Magnesium iodide; Ethyl ketone.
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esters. The initial ketone is proposed to be converted to an active β-iodo allenolate intermediate, which in turn reacts with an aldehyde to yield β-iodo Baylis–Hillman adducts. In an attempt to broaden the scope of this reaction, MgI_2 was combined with tertiary amines to determine if such a combination would promote formation of Mg-enolates directly from the original ketone. When 1.0 equiv of benzaldehyde, MgI_2, propiophenone, and diisopropylethylamine were added at room temperature in dichloromethane the aldol product 1,3-diphenyl-3-hydroxy-2-methylpropanone was generated within 30 min with a yield of 80%. This yield was optimized to 95% by using 1.3 equiv of diisopropylethylamine, 1.2 equiv of propiophenone, and 1.0 equiv of benzaldehyde.

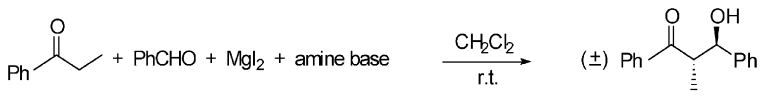
The diasteroselectivity of the initial reaction was modest (*anti*/*syn*=72/28) with negligible differences observed when the reaction temperature or solvent system was changed. Elevated reaction temperatures slightly improved the *anti*/*syn* ratio (70/30 at 0 °C and 74/26 at 40 °C) while the alternative solvents (benzene and toluene) had no effect on diasteroselectivity. Both diethyl ether and THF were unsuitable solvents, which required a reaction time of more than 10 h and gave rise to less then 10% yield within a 2 h reaction period. Other metal salts and organometallics including $MgBr_2$, $Mg(OTf)_2$, $MgCl_2$, $SnCl_4$, $Sn(OTf)_2$ was either much less active or inert. In fact, Choji Kashima[6] had already reported in 1998 using $MgBr_2$ in combination with *i*-Pr_2NEt mediates the aldol addition of *N*-acylpyrazoles to aldehydes and in some cases this system gives products with high anti-selectivity. This system was not suitable for the present reaction conditions. For example, when propiophenone was reacted with benzaldehyde in the presence of *i*-Pr_2NEt with $MgBr_2$ as the promoter, the *anti*/*syn* ratio of the product was 70/30. When piperidine was used as the amine base, less than 10% of the desired product was obtained after a 24 h period when propiophenone was reacted with benzaldehyde in the presence of $MgBr_2$ as the promoter. A survey of various tertiary amines was also met with limited success (Table 1); therefore we explored the possibility of using secondary amines as an amine base in the reaction. All of the secondary amines that were tested resulted in aldol products with increased anti-selectivity. The secondary amine piperidine proved to be the best suited for promoting the desired diastereoselectivity (Table 1).

Using the secondary amine piperidine as a base for improved selectivity, we examined various symmetric and asymmetrical ketones that can undergo an aldol reaction. In the first reaction listed, propiophenone coupled with benzaldehyde in the presence of piperidine (1.2 equiv) and MgI_2 (1.1 equiv) in a 93/7 *anti*/*syn* ratio resulted in a 35% product yield within 30 min; a 95/5 *anti*/*syn* ratio with a 91% yield was realized when the reaction was allowed to go to completion over 2 h period using 1.5 equiv piperidine and 1.4 equiv MgI_2. Other aromatic aldehydes resulted in high diasteroselectivity (entries 2, 3 and 4, Table 2) within the 2 h reaction time, although product selectivity diminished when aliphatic aldehydes were employed (entries 5 and 6, Table 2). The anti-product was exclusively obtained when the bulkier aliphatic aldehyde trimethylacetaldehyde was used as an electrophilic acceptor (entry 7, Table 2). Cyclohexanone gave modest diasteroselectivity (entry 8 and 9, Table 2). The relatively low diasteroselectivity was also observed when 3-pentanone was reacted with benzaldehyde (entry 10, Table 2).

With regard to unsymmetrical ketones, both piperidine and the tertiary amines *N*,*N*-diisopropylethylamine and *N*-ethylpiperidine are well suited for producing aldol products with the same ratio of regioselectivity. However, in order to obtain reasonable yields, longer reaction times (2 h) and higher MgI_2 loading (1.4 equiv) are needed when piperidine is used as the base for the reaction. For example, the reaction of 3-methyl-2-butanone (1.4 equiv) with benzaldehyde (1.0 equiv) in the presence of MgI_2 (1.4 equiv) and piperidine (1.5 equiv) required 2 h for completion at room temperature with an 85% yield of expected products and regioselectivity 100:0. However, the same reaction took only 30 min to complete when *N*,*N*-diisopropylethylamine or *N*-ethylpiperidine was used in place of piperidine as the base for the reaction. Another advantage for using *N*,*N*-diisopropylethylamine or *N*-ethylpiperidine as the base for the reaction is that the amount of MgI_2 and starting ketone can be reduced to 1.2 equiv with no decrease in yield (entry 11–16, Table 3).

The *anti*/*syn* selectivities listed in Table 2 were measured by ^1H NMR spectroscopic analyses of the crude product mixture. In all cases, the carbinol proton signals for *anti* and *syn*-isomers were clearly distinguishable with the proton for

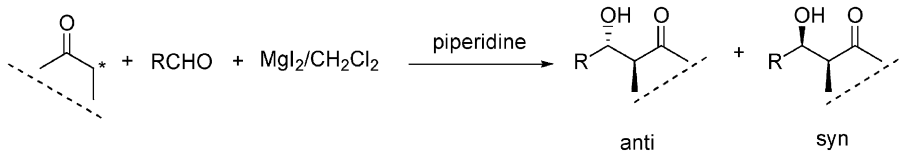
Table 1. Effect of amine bases for *anti*/*syn* selectivity

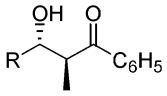
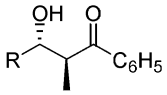
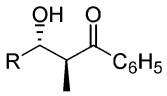
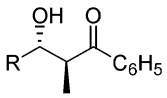
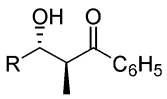
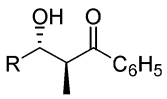
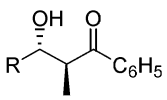
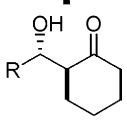
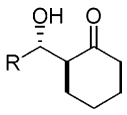
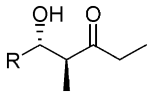


Entry	Amine base	Reaction time (min)	*anti*/*syn* selectivity[a]	Yield[b] (%)
1	Et_3N	30	72/28	90
2	*i*-Pr_2NEt	30	73/27	95
3	Bu_3N	30	76/24	92
4	*N*-ethylpiperidine	30	71/29	92
5	Pyrrolidine	240	82/18	50
6	2,2,6,6-Tetramethylpiperidine	30	80/20	90
7	Piperidine	120	95/5	91
8	DABCO	120	75/25	82
9	Pyridine	120	–	<10

[a] The isomeric ratio was determined by analysis of 300 MHz ^1H NMR spectra of crude products.
[b] Yields after purification by column chromatography.

Table 2. Anti-selective aldol addition of ketones with aldehydes using piperidine as base



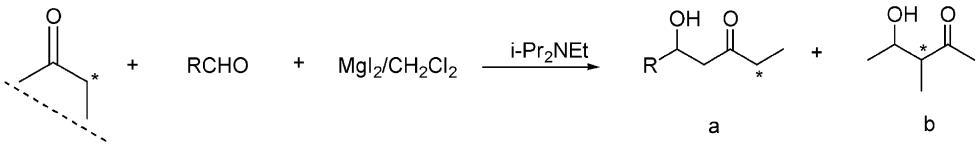
Entry	Ketone	R	Product		*anti*/*syn*[a]	Yield[b] (%)
1	Propiophenone	C_6H_5		**1**	95/5	91
2	Propiophenone	4-FC_6H_4		**2**	94/6	92
3	Propiophenone	4-BrC_6H_4		**3**	90/10	90
4	Propiophenone	4-MeC_6H_4		**4**	92/8	88
5	Propiophenone	$C_6H_5CH{=}CH$		**5**	88/12	92
6	Propiophenone	$CH_3CH{=}CH$		**6**	84/16	90
7	Propiophenone	$(CH_3)_3C$–		**7**	100/0	82
8	Cyclohexanone	C_6H_5		**8**	77/23	68
9	Cyclohexanone	4-ClC_6H_4		**9**	76/24	70
10	3-Pentanone	C_6H_5		**10**	76/24	70[c]

[a] Ratios were determined by ^{1}H NMR ($CDCl_3$, 300 MHz) on the crude products.
[b] Yields after purification by column chromatography.
[c] Two stereoisomers were inseparable.

the *anti*-isomer upfield relative to the proton for the *syn* isomer. In addition, they also appear in different vicinal coupling constants; for *anti*-isomers these numbers are approximately 8 Hz and *syn* isomers less than 5 Hz.

In order to better understand the mechanisms involved in this reaction, we designed an experiment to track the reaction intermediates. We added diisopropylethylamine (1.2 equiv) into a mixture of propiophenone (1.0 equiv) and MgI_2 (1.0 equiv) dissolved in $CDCl_3$, after stirring at room temperature for 1 h; the mixture was directly taken for ^{1}H NMR analysis. Unfortunately, the Mg-enolate was not observed due to the total formation of the propiophenone self-condensation aldol product. However, when diisopropylethylamine in the above reaction was replaced with piperidine (1.2 equiv) and stirred for 1 h at room temperature, we observed the Mg-enolate of propiophenone in its ^{1}H NMR spectrum, in which the *Z*-enolate vinyl proton showed as a quartet at δ 3.46 ppm and the *E*-enolate as a quartet at δ 4.13 ppm. The ratio of *Z*/*E* was 78/22, based on its ^{1}H NMR spectrum analysis. Also, from its ^{1}H NMR analysis, only 5 mol% of propiophenone was converted into Mg-enolate intermediate when stored at room temperature for 24 h. The reaction is therefore a 'balanced reaction' with aldehydes essential for the reaction to go to completion within 2 h. This raises an important question; can the reaction be carried out via the enamine pathway? We have experimental evidence that suggests that the reaction is more likely to follow the Mg-enolate pathway. (1) Propiophenone (1.0 equiv) and MgI_2 (1.0 equiv) were dissolved in anhydrous $CDCl_3$ and piperidine (1.2 equiv) was added via a syringe under a nitrogen atmosphere. After

Table 3. Regioselective aldol addition of unsymmetrical ketones with aldehydes using *N*,*N*-diisopropylethylamine as base



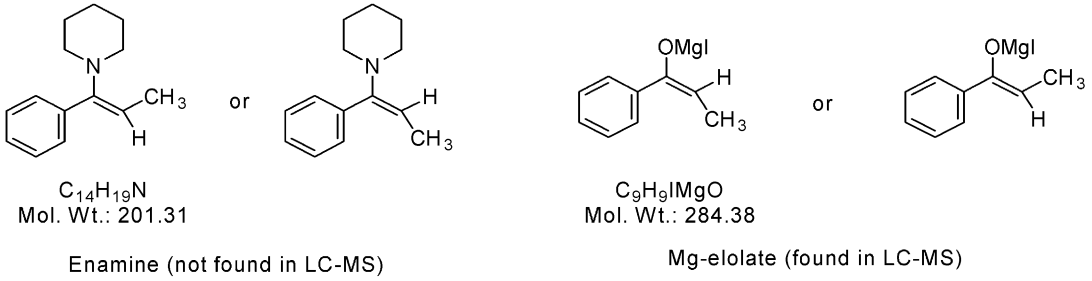
Entry	Ketone	R	Product	Ratio *a*/*b*[a]	Yield[b] (%)
11	2-Butanone	4-$PhCH_2OC_6H_4$	**11**	96/4	85
12	2-Butanone	2-Naphthyl	**12**	98/2	86
13	3-Methyl-2-butanone	C_6H_5	**13**	100/0	90
14	3-Methyl-2-butanone	2-Naphthyl	**14**	100/0	91
15	4-Phenyl-2-butanone	$C_6H_5CH{=}CH$	**15**	90/10	81[c]
16	4-Phenyl-2-butanone	4-$PhCH_2OC_6H_4$	**16**	98/2	85

[a] Ratios were determined by ^1H NMR ($CDCl_3$, 300 MHz) on the crude products.
[b] Yields after purification by column chromatography.
[c] Two regioisomers were inseparable.

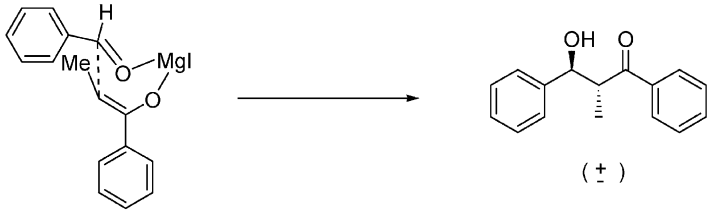
stirring 2 h at room temperature, the solution was filtered through a short silicon gel pad and the filtrate directly injected into an LC-MS. No enamine peak was observed from the LC-MS analysis (Scheme 3). (2). When piperidine was replaced with 2,2,6,6-Tetramethylpiperidine in the above reaction an Mg-enolate peak was observed with a molecular weight of 284 (Scheme 2).

Since the *Z*-enolate was formed predominantly, the well-known chair Zimmerman–Traxler transition state cannot be adopted; however, the Evans' 'boat–metal transition state'[7] can be employed to satisfactorily explain our results (Scheme 3).

In conclusion, we present here the first example of using a secondary amine as a base in combination with MgI_2 to perform direct aldehyde–ketone coupling to generate high anti-aldol products in high yield. Aldol coupling reactions were carried out in a one-pot reaction by mixing the four reaction components at room temperature under the protection of nitrogen gas. This is in contrast to the recently reported Lewis acid mediated aldol addition of



Scheme 2. LC-MS confirmed the intermediates in MgI_2 promoted anti-aldol reaction.



Scheme 3. Boat transition state for MgI_2 promoted anti-aldol reaction.

unsymmetrical ketones using $TiCl_4$[8] to generate high *syn* selective products. In fact, we observed that $TiCl_4$ as an aldol promoter was limited in its scope to stimulate aldol additions with aliphatic ketones. For example, when the aromatic ketone propiophenone was tested as a substrate to react with benzaldehyde, less than a 10% yield of the corresponding *syn* product was observed after 16 h at room temperature.[9] With this new MgI_2 promoting system, both aromatic and aliphatic ketones are suitable for direct coupling to generate anti-products without the formation of activated silyl enol ether.

2. Experimental

2.1. General

All reactions were conducted at room temperature in a flask (10.0 mL) with magnetic stirring. Dichloromethane was dried and freshly distilled from calcium hydride under the nitrogen atmosphere. Other commercial chemicals were used without further purification and their stoichiometrics were calculated based on the reported purities from the manufacturers. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). ^{1}H NMR spectra were recorded on a Varian 500 MHz NMR spectrometer. Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet) and m (multiplet). ^{13}C NMR spectra were recorded at 125 MHz using $CDCl_3$ as the solvent and the internal reference. Chemical shifts are given in ppm from tetramethylsilane. GC spectra were recorded at hp 6890 with hp 5973 Mass Selective Detective. Mass spectra were recorded with a JEOL JMS-D300 mass spectrometer using direct inlet electron impact ionization (70 eV). The Mass Spectroscopy Laboratory at the Crompton Corporation and University of Texas at Austin conducted high-resolution Mass spectral analysis.

2.1.1. General procedure A (Table 2). Anti-aldol addition with unmodified ketones using piperidine as base. Dichloromethane (5.0 mL), aldehyde (1.0 mmol, 1.0 equiv), ketone (1.4 mmol, 1.4 equiv), and magnesium iodide (1.4 mmol, 398.0 mg, 98% purity) were added to a dry 25 mL flask. The resulting mixture was protected by nitrogen gas and at room temperature piperidine (1.5 mmol, 0.147 mL) was added dropwise via a syringe. The resulting mixture was stirred for 2 h at room temperature and quenched by the addition of dilute 2 N HCl (4.0 mL). Dichloromethane was completely evaporated and 8.0 mL of ethyl acetate was added to the mixture. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate two more times (2×8.0 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. Purification was carried out by column chromatography [hexane (saturated with acetonitrile, up layer)/ethyl acetate=10:1] to give the pure anti-product.

Compound **1**. 218 mg, 91%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3488 (s), 3456 (s), 1676 (s), 1456 (s), 1215 (s), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.98 (m, 2H), 7.57 (tt, J=7.5, 1.0 Hz, 1H), 7.34–7.49 (m, 6H), 7.29 (tt, J=7.5, 1.5 Hz, 1H), 4.99 (dd, J=8.0, 4.5 Hz, 1H), 3.83 (qn, J=7.5 Hz, 1H), 2.98 (d, J=4.5 Hz, OH), 1.07 (d, J=7.5 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 204.9, 142.2, 136.7, 133.3, 128.6×2, 128.4×2, 128.4×2, 127.9,126.7×2, 76.7, 47.9, 15.7; MS: (EI, 70 eV) 222 (M−H_2O, 100), 207 (40), 193 (6.6), 179 (16), 145 (10), 105 (69.8), 91 (14), 77 (52), 51 (19); HRMS: cald for $C_{16}H_{16}O_2$: 240.115; found: 240.112.

Compound **2**. 238 mg, 92%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3609 (m), 3489 (m), 1674 (s), 1604 (s), 1510 (s), 1448 (m), 1215 (s), 1157 (s), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.96 (m, 2H), 7.57 (tt, J=7.5, 1.0 Hz, 1H), 7.47 (m, 2H), 7.38 (m, 2H), 7.04 (m, 2H) 4.98 (dd, J=8.0, 4.5 Hz, 1H), 3.78 (qn, J=7.5 Hz, 1H), 3.08 (d, J=4.5 Hz, OH), 1.07 (d, J=7.5 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 205.0, 163.5, 161.6, 138.2, 136.8, 133.6, 128.9×2, 128.6×2, 128.5, 115.6, 115.4, 76.2, 48.3, 15.9; MS: (EI, 70 eV) 240 (M−H_2O, 100), 225 (41), 211 (5), 197 (9), 163 (9), 133 (33), 105 (91), 77 (61); HRMS: cald for $C_{16}H_{15}O_2F$: 258.1056; found: 258.1051.

Compound **3**. 287 mg, 90%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3606 (m), 3485 (m), 1680 (s), 1598 (s), 1456 (s), 1206 (s), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.94 (m, 2H), 7.57 (tt, J=7.5, 1.0 Hz, 1H), 7.47 (m, 4H), 7.28 (m, 2H), 4.95 (dd, J=8.0, 4.5 Hz, 1H), 3.77 (qn, J=7.5 Hz, 1H), 3.14 (d, J=5.0 Hz, OH), 1.08 (d, J=6.0 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 204.6, 141.2, 136.4, 133.4, 131.5×2, 128.7×2, 128.4×2, 128.3×2, 121.6, 76.1, 47.7, 15.6; MS: (EI, 70 eV) 302 (71) 301 (43), 300 (M−H_2O, 75), 284 (25), 221 (46), 178 (15), 144 (16) 115 (68), 105 (100), 77 (66); HRMS: cald for $C_{16}H_{15}O_2Br$: 318.0255; found: 318.0251. Data for *syn*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.95 (m, 2H), 7.61 (tt, J=7.0, 1.5 Hz, 1H), 7.52–7.46 (m, 4H), 7.31–7.28 (m, 2H), 5.21 (t, J=2.4 Hz, 1H), 3.76 (d, J=2.1 Hz, 1H, OH), 3.64 (dq, J=7.3, 3.0 Hz, 1H), 1.16 (d, J=7.3 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 205.4, 140.9, 135.3, 133.7, 131.2×2, 128.9×2, 128.5×2, 127.7×2, 121.1, 72.4, 46.7, 11.2.

Compound **4**. 224 mg, 88%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3614 (m), 3501 (m), 1678 (s), 1609 (s), 1514 (s), 1218 (s), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.99 (m, 2H), 7.56(tt, J=7.5, 1.0 Hz, 1H), 7.46 (m, 2H), 7.29 (m, 2H), 7.16 (m, 2H), 4.95 (dd, J=8.0, 4.5 Hz, 1H), 3.81 (qn, J=7.5 Hz, 1H), 2.89 (d, J=4.5 Hz, OH), 2.34 (s, 3H) 1.04 (d, J=7.5 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 204.9, 139.2, 137.6, 136.8, 133.2, 129.1×2, 128.6×2, 128.4×2, 126.6×2, 76.6, 47.9, 21.1, 15.6; MS: (EI, 70 eV) 236 (M−H_2O, 54), 221 (100), 207 (6), 193 (8), 178 (7), 144 (13), 105(42) 91 (12), 77 (34); HRMS: cald for $C_{17}H_{18}O_2$: 254.1307; found: 254.1310.

Compound **5**. 244 mg, 92%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3608 (w), 3065 (w), 1676 (s), 1600 (m), 1451 (m), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.99 (m, 2H), 7.58(tt, J=7.5, 1.0 Hz, 1H), 7.47 (m, 2H), 7.37 (m, 2H), 7.30 (t, J=7.4 Hz, 2H), 7.24 (t, J=7.4 Hz, 1H), 6.68 (d, 16.0 Hz, 1H), 6.28 (dd, J=16.0, 7.5 Hz, 1H), 4.61 (q, J=6.5 Hz, 1H), 3.71 (qn, J=7.2 Hz, 1H), 3.04 (d, J=5.6 Hz, OH), 1.27 (d, J=7.2 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 204.7, 136.5, 136.5, 133.4, 132.1, 129.6×2,

128.7×2, 128.5×2, 128.4×2, 127.8, 126.5, 75.3, 46.3, 15.4; MS: (EI, 70 eV) 248 (M−H_2O, 52), 175 (9), 134 (87), 132 (28), 106 (11), 105 (100) 91 (18), 77 (71); HRMS: cald for $C_{18}H_{18}O_2$: 266.1307; found: 266.1311.

Data for *syn*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.98 (d, J=8.0 Hz, 2H), 7.61 (t, J=8 Hz, 1H), 7.50 (t, J=8.0 Hz, 2H), 7.39 (d, J=7.5 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.24 (t, J=7.5 Hz, 1H), 6.73 (d, J=16.0 Hz, 1H), 6.26 (dd, J=16.0, 6.0 Hz, 1H), 4.83–4.79 (m, 1H), 3.65 (dq, J=7.0, 3.5 Hz, 1H), 3.34 (d, J=2.5 Hz, OH), 1.32 (d, J=7.0 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 205.3, 136.7, 135.7, 133.6, 131.2, 129.1×2, 128.7×2, 128.5×2, 127.7×2, 126.5×2, 72.0, 45.4, 11.7.

Compound **6**. 183 mg, 90%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3610 (w), 3604 (w), 1671 (s), 1446 (m), 1211 (m), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.96 (m, 2H), 7.60–7.56 (m, 1H), 7.50–7.46 (m, 2H), 5.77 (dq, J=15.1, 6.0 Hz, 1H), 5.54 (ddq, J=15.1, 7.2, 1.1 Hz, 1H), 4.53 (m, 1H), 3.53 (q, J=7.2 Hz, 1H), 2.74 (d, J=6.0 Hz, OH), 1.71 (dd, J=7.2, 1.1 Hz, 3H), 1.18 (d, J=7.4 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 204.9, 136.7, 133.2, 131.5, 128.9×2, 128.7×2, 128.4, 75.3, 46,2, 17.7, 15.3; MS: (EI, 70 eV) 186 (M−H_2O, 78), 148 (8), 135 (15), 134 (100), 133 (61), 105 (91), 78 (5), 71 (26); HRMS: cald for $C_{13}H_{16}O_2$: 204.115; found: 204.110. Data for *syn*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.94 (d, J=7.5 Hz, 2H), 7.61–7.57 (m, 1H), 7.49 (t, J=7.5 Hz, 2H), 5.78 (ddq, J=15.0, 6.5, 1.5 Hz, 1H), 5.55 (ddq, J=15.0, 6.5, 1.5 Hz, 1H), 4.52 (t, J=5.0 Hz, 1H), 3.54 (dq, J=7.3, 3.5 Hz, 1H), 2.98 (s, 1H, OH), 1.71 (d, J=6.5 Hz, 3H), 1.27 (d, J=7.3 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 205.2, 136.1, 133.3, 130.8, 128.7×2, 128.4×2, 127.8, 72.5, 45.5, 17.7, 11.8.

Compound **7**. 180 mg, 82%, a colorless oil. IR: ($CHCl_3$) 3610 (w), 3500 (w), 1711 (s), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.96 (m, 2H), 7.59 (m, 1H), 7.50 (m, 2H), 4.73 (d, J=9.0 Hz, OH), 3.80 (dq, J=7.5, 2 Hz, 1H), 3.43 (dd, J=9.0, 2.0 Hz, 1H), 1.45 (d, J=7.0 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR: (125 MHz, $CDCl_3$) 208.2, 136.3, 133.6, 128.8×2, 128.1×2, 84.9, 37.5, 36.2, 26.80×3, 18.9; HRMS: cald for $C_{14}H_{20}O_2$: 220.1463; found: 220.1459.

Compound **8**. 139 mg, 68%, a white solid, mp: 40–42 °C. Data for *anti*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.36–7.27 (m, 5H), 4.78 (dd, J=9.2, 2.4 Hz, 1H), 3.98(d, J=2.4 Hz, OH), 2.64–2.58 (m, 1H), 2.50–2.45 (m, 1H), 2.40–2.31 (m, 1H), 2.10–2.03 (m, 1H), 1.81–1.74 (m, 1H), 1.71–1.46 (m, 3H), 1.34–1.22 (m, 1H); ^{13}C NMR: (125 MHz, $CDCl_3$) 215.5, 140.8, 128.2×2, 127.8, 126.9×2, 74.6, 57.3, 42.6, 30.7, 27.7, 24.6; HRMS: cald for $C_{13}H_{16}O_2$: 204.115; found: 204.119. Data for *syn*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.36–7.21 (m, 5H), 5.39 (m, 1H), 3.05 (d, J=2.1 Hz, 1H), 2.62–2.57 (m, 1H), 2.47–2.43 (m, 1H), 2.42–2.32 (m, 1H), 2.11–2.06 (m, 1H), 1.87–1.82 (m, 1H), 1.75–1.60 (m, 3H), 1.57–1.43 (m, 1H); ^{13}C NMR: (125 MHz, $CDCl_3$) 214.9, 141.3, 128.1×2, 126.8, 125.5×2, 70.5, 57.1, 42.6, 27.9, 25.9, 24.8.

Compound **9**. 167 mg, 70%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3591 (w), 3077 (w), 1771 (s), 1452 (s), 1209 (m), 902 (m); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.34–7.30 (m, 2H), 7.28–7.24 (m, 2H), 4.76 (dd, J=8.5, 2.5 Hz, 1H), 3.98 (d, J=3.0 Hz, OH), 2.60–2.52 (m, 1H), 2.51–2.45 (m, 1H), 2.40–2.31 (m, 1H), 2.13–2.02 (m, 1H), 1.82–1.77 (m, 1H), 1.72–1.62 (m, 1H), 1.61–1.51 (m, 2H), 1.33–1.22 (m, 1H); ^{13}C NMR: (125 MHz, $CDCl_3$) 215.3, 139.4, 133.5, 128.5×2, 128.3×2, 74.1, 57.3, 42.6, 30.74, 27.7, 24.7; MS: (EI, 70 eV) 220 (M−H_2O, 36), 140 (52), 132 (100), 104 (44), 89 (31); HRMS: cald for $C_{13}H_{15}O_2Cl$: 238.0761; found: 238.0766. Data for *syn*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.32–7.29 (m, 2H), 7.27–7.22 (m, 2H), 5.35 (m, 1H), 3.04 (d, J=3.0 Hz, OH), 2.60–2.52 (m, 1H), 2.49–2.41 (m, 1H), 2.41–2.32 (m, 1H), 2.13–2.06 (m, 1H), 1.89–1.82 (m, 1H), 1.73–1.64 (m, 3H), 1.57–1.47 (m, 1H); ^{13}C NMR: (125 MHz, $CDCl_3$) 214.6, 139.9, 132.6, 128.3×2, 127.1×2, 70.11, 57.0, 42.6, 27.9, 25.9, 24.8.

Compound **10**. 134 mg, 70%, a colorless oil, inseparable; ^{1}H NMR: (500 MHz, $CDCl_3$) 7.40–7.20 (m, 5H), 5.03 (d, J=4.0 Hz, 0.24H, *syn*-isomer), 4.74 (d, J=8.1 Hz, 0.76H, *anti*-isomer), 2.83 (dq, J=7.2, 4.0 Hz, 1H), 2.20–2.55 (m, 2H), 1.07 (d, J=7.2 Hz, 3H), 0.99 (t, J=7.0 Hz, 3H).

2.1.2. General procedure B (Table 3). Regio selective aldol addition with unmodified ketones using *N*,*N*-diisopropylethylamine as base. Dichloromethane (5.0 mL), aldehyde (1.0 mmol, 1.0 equiv), ketone (1.2 mmol, 1.2 equiv), and magnesium iodide (1.2 mmol, 340.0 mg, 98% purity) were added to a dry 25 mL flask. The resulting mixture was protected by nitrogen gas and at room temperature *N*,*N*-diisopropylethylamine (1.3 mmol, 0.226 mL) was added dropwise via a syringe. The resulting mixture was stirred for 30 min at room temperature and quenched by addition of dilute 2 N HCl (4.0 mL). Dichloromethane was completely evaporated and 8.0 mL of ethyl acetate was added to the mixture. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate two more times (2×8.0 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. Purification was carried out by column chromatography (hexane/ethyl acetate=10:1) to give the pure product.

Compound **11**. 241 mg, 85%, a colorless oil. Major isomer: mp: 80–82 °C. IR: ($CHCl_3$) 3609 (s), 3514 (w), 3019 (m), 1678 (s), 1214 (s), 969 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.45–7.40 (m, 2H), 7.40–7.35 (m, 2H), 7.34–7.30 (m, 1H), 7.29 (m, 2H), 6.97–6.92 (m, 2H), 5.13–5.08 (dt, J=9.5, 3 Hz, 1H), 5.05 (s, 2H), 3.27 (d, J=3.0 Hz, OH), 2.88–2.72 (m, 2H), 2.44 (q, J=7.5 Hz, 2H), 1.06 (t, J=7.5 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 212.1, 158.5, 137.1, 135.5, 128.8×2, 128.2, 127.6×2, 127.1×2, 115.1×2, 70.2, 69.8, 50.8, 37.1, 7.7; MS: (EI, 70 eV) 266 (M−H_2O, 16), 212 (8), 153 (0.6), 105 (0.3), 91 (100), 65 (13); HRMS: cald for $C_{18}H_{20}O_3$: 284.3550; found: 284.3556.

Compound **12**. 196 mg, 86%, a colorless oil; Major isomer: mp: 58–60 °C. IR: ($CHCl_3$) 3607 (w), 3551 (w), 3001 (w), 1675 (s), 1521 (m), 969 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.85–7.80 (m, 4H), 7.49–7.44 (m, 3H), 5.33 (dt, J=8.5, 2.5 Hz, 1H), 3.49 (d, J=3.0 Hz, OH), 2.97–2.84 (m, 2H), 2.47 (q, J=7.5 Hz, 2H), 1.07 (t, J=7.5 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 211.8, 140.2, 133.2, 132.9, 128.3, 127.9, 127.6, 126.1, 125.8, 124.3, 123.7, 70.1, 50.6, 36.8, 7.4; MS:

(EI, 70 eV) 210 (M−H_2O, 38), 181 (100), 152 (46), 127 (8), 126 (6); HRMS: cald for $C_{15}H_{16}O_2$: 228.1412; found: 228.1416.

Compound **13**. 173 mg, 90%, a colorless oil. IR: ($CHCl_3$) 3605 (w), 3514 (w), 2956 (m), 1699 (s), 1514 (m), 1066 (m), 973 (m); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.37–7.31 (m, 4H), 7.29–7.24 (m, 1H), 5.13 (dt, J=9.0, 3.5 Hz, 1H), 3.54 (d, J=3.5 Hz, OH), 2.92–2.78 (m, 2H), 2.62–2.52 (m, 1H), 1.08 (dd, J=7.0, 1.5 Hz, 6H); ^{13}C NMR: (125 MHz, $CDCl_3$) 215.1, 142.9, 128.4×2, 127.5, 125.5×2, 69.8, 48.7, 41.4, 17.7×2; MS: (EI, 70 eV) 174 (M−H_2O, 1), 159 (2), 135 (3), 119 (100), 105 (6), 91 (4); HRMS: cald for $C_{12}H_{16}O_2$: 192.1150; found: 192.1154.

Compound **14**. 220 mg, 91%, a white solid; mp: 54–56 °C. IR: ($CHCl_3$) 3609 (w) 3600 (s), 3000 (m), 1699 (s), 1467 (m), 1386 (m), 1221 (s), 1035 (s), 858 (m); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.84–7.79 (m, 4H), 7.48–7.42 (m, 3H), 5.29 (dt, J=8.5, 3.5 Hz, 1H), 3.65 (d, J=3.0 Hz, OH), 2.97–2.85 (m, 2H), 2.62–2.52 (m, 1H), 1.08 (dd, J=7.0, 1.5 Hz, 6H); ^{13}C NMR: (125 MHz, $CDCl_3$) 215.1, 140.3, 133.2, 132.8, 128.2, 127.9, 127.5,126.1, 125.7, 124.2, 123.7, 70.0, 48.6, 41.4, 17.8×2; MS: (EI, 70 eV) 224 (M−H_2O, 23), 181 (100), 152 (41), 127 (7), 115 (1); HRMS: cald for $C_{16}H_{18}O_2$: 242.1307; found: 242.1302.

Compound **15**. 227 mg, 81%, a colorless oil, inseparable; ^{1}H NMR: (300 MHz, $CDCl_3$) 7.40–7.15 (m, 10H), 6.40 (dd, J=16.0, 1.1 Hz, 1H), 6.17 (dd, J=16.0, 6.1 Hz, 1H), 4.75 (m, 0.9H), 4.41 (m, 0.1H), 3.07 (d, J=3.7 Hz, OH), 3.0–2.85 (m, 2H), 2.84–2.75 (m, 2H), 2.74–2.67 (m, 2H).

Compound **16**. 300 mg, 83%, a white solid; mp: 87–89 °C. IR: ($CHCl_3$) 3608 (w), 3512 (w), 2945 (w), 1680 (S), 1600 (m), 1289 (m), 1211 (m), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.42–7.35 (m, 4H), 7.34–7.14 (m, 8H), 6.96–6.92 (m, 2H), 5.08 (dt, J=9.0, 3.0 Hz, 1H), 5.05 (s, 2H), 3.15 (d, J=3.0 Hz, OH), 2.90 (t, J=7.5 Hz, H), 2.88–2.70 (m, 4H); ^{13}C NMR: (125 MHz, $CDCl_3$) 210.3, 158.3, 140.6, 136.9, 135.2, 128.5×2, 128.5×2, 128.2×2 127.9, 127.4×2, 126.9×2, 126.2, 114.8×2, 70.0, 69.5, 51.2, 45.1, 29.4; MS: (EI, 70 eV) 342 (M−H_2O, 10), 212 (18), 181 (1), 152 (1), 91 (100), 65 (25); HRMS: cald for $C_{24}H_{24}O_3$: 360.1725; found: 360.1728.

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References and notes

1. (a) Heathcock, C. H. In Comprehensive Organic Synthesis, Trost B. M., Ed.; Pergamon: Oxford, 1991; Vol. 1, pp 181–237. (b) Kim, B. M.; Williams, S. F.; Masamune, S. In Comprehensive Organic Synthesis, Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, pp 239–275.
2. (a) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441–3442. (b) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1992**, *57*, 3767–3772.
3. Fukuzawa, S. I.; Tsuchimoto, T.; Kanai, T. *Bull. Chem. Soc. Jpn* **1994**, *67*, 2227–2232.
4. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.
5. (a) Wei, H. X.; Hu, J. L.; Purkiss, D. W.; Paré, P. W. *Tetrahedron Lett.* **2003**, *44*, 949–952. (b) Wei, H. X.; Chen, D. J.; Xu, X.; Li, G.; Paré, P. W. *Tetrahedron: Asymmetry* **2003**, *14*, 971–974.
6. Kashima, C.; Fukuchi, I.; Takahashi, K.; Fukusaka, K.; Hosomi, A. *Heterocycles* **1998**, *47*, 357–365.
7. Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127–1130.
8. Mahrwald, R.; Gundogan, B. *J. Am. Chem. Soc.* **1998**, *120*, 413–414.
9. Procedure for reacting propiophenone with benzaldehyde (see Ref. 8): benzaldehyde (0.1 mL, 1.0 mmol) and propiophenone (0.13 mL, 1.0 mmol) were dissolved in 2.0 mL of anhydrous toluene. Under a nitrogen atmosphere and at room temperature, 0.1 mL (0.1 mmol, 1.0 M solution in toluene, Aldrich) of $TiCl_4$ was added dropwise via a syringe to the solution. The solution was stirred for an additional 16 h at room temperature. The ^{1}H NMR of the crude mixture showed that less than 10% of benzaldehyde was converted to an aldol product. This conclusion was based on the comparison of peak integrations of the carbinol proton of aldol the product (5.23 ppm) with the benzaldehyde proton (10.01 ppm).

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Synthesis of *N*-aryl-aza-crown ethers via Pd-catalyzed amination reactions of aryl chlorides with aza-crown ethers

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Abstract—The $Pd_2(dba)_3$/P(*i*-$BuNCH_2CH_2)_3N$ (**1**) catalyst system effectively catalyzes the coupling of aza-crown ethers with electronically diverse aryl chlorides, affording *N*-aryl-aza-crown ethers in good yields. The $Pd_2(dba)_3$/P(*i*-$BuNCH_2)_3CMe$ (**2**) catalyst system containing the more constrained bicyclic triaminophosphine is useful for aryl chlorides possessing base-sensitive ester, nitro, and nitrile functional groups.

1. Introduction

The chemistry of *N*-aryl-aza-crown ether derivatives is attracting significant interest because of the utility of these compounds in synthesizing fluoroionophores in which, for example, a fluorescent aryl moiety is covalently linked to the nitrogen of an aza-crown ether.[1] These molecules can serve as sensitive and selective sensors of cations by binding them in the crown ether, thereby modifying the intensity and/or the energy of the signal of the fluorophore. Pyridine-functionalized aza-crown ethers have also been used as a scaffold for self-assembly in supramolecular chemistry.[2] Traditional approaches to the preparation of *N*-aryl-aza-crown ethers include nucleophilic aromatic substitution of activated aryl halides with aza-crown ethers under high pressure conditions,[3] or manipulation of functional groups on aniline precursors.[4] However, these approaches suffer from one or more of the following problems that impede accessibility to this important class of compounds: stringent conditions, multiple step syntheses, low yields, and limited substrate scope.

In recent years, palladium-catalyzed Buchwald–Hartwig amination reactions of aryl halides with amines have emerged as a method of choice for C–N bond forming processes.[5–7] In this respect, Witulski et al.[8] have developed a Pd/PPh_3 and a Pd/P(*o*-tol)$_3$ catalyst system for the coupling of aryl and heteroaryl bromides with aza-crown ethers. However, this method was limited to electron-poor aryl and heteroaryl bromides. Interestingly, the use of P(*t*-Bu)$_3$,[7] a popular ligand for Pd-catalyzed amination reactions, gave inferior results probably because of its steric bulk.

An improvement to the above protocol was described by Zhang and Buchwald[9] who achieved cross-coupling of aryl bromides with aza-crown ethers using a catalyst system comprised of $Pd_2(dba)_3$ and biphenyl-based monophosphine ligands with NaO-*t*-Bu as the base. Although electronically diverse and also *ortho*-substituted aryl bromides could be employed in these reactions, limitations still existed. For example, the authors noted that poor yields of *N*-aryl-aza-crown ethers were obtained when weak bases such as Cs_2CO_3 or K_3PO_4 were used in place of NaO-*t*-Bu, thus precluding the introduction of various base-sensitive functional groups into the aryl substrate. A particularly important apparent limitation was that no examples employing aryl chlorides as the coupling partner were reported. Aryl chlorides are cheaper and are available in wider diversity than bromides or iodides, and their applicability in coupling with aza-crown ethers would constitute a significant advance, especially since aza-crown ethers are currently quite expensive. We report here a general and efficient method for the synthesis of *N*-aryl-aza-crown ethers via a palladium-catalyzed amination reaction of aryl chlorides that occurs in the presence of bicyclic triaminophosphine ligands **1** and **2**.

Our recent explorations in palladium-catalyzed cross coupling reactions have established that electron-rich and commercially available proazaphosphatrane **1** (Fig. 1), first synthesized in our laboratories, serves as an excellent ligand

Keywords: Proazaphosphatrane; *N*-Aryl-aza-crown ether; Buchwald–Hartwig amination; Palladium; Bicyclic triaminophosphine.
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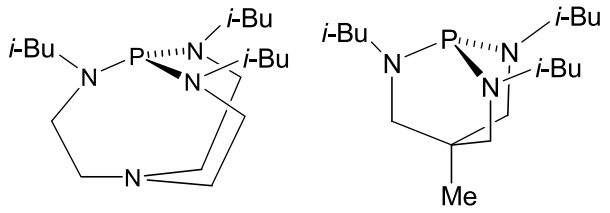


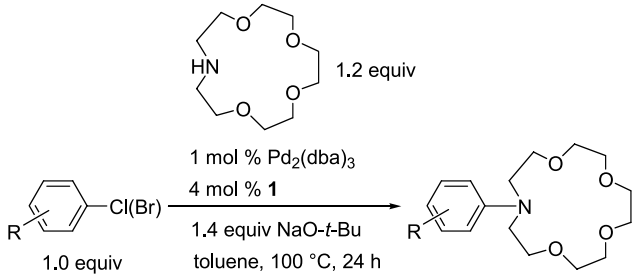
1 2

Figure 1. Bicyclic triaminophosphine ligands.

in Suzuki,[10] Buchwald–Hartwig amination,[11] Stille,[12] and *alpha*-arylation[13] reactions. Notoriously unreactive aryl chlorides can also be employed in these transformations. We have also developed a new bicyclic triaminophosphine ligand **2** (Fig. 1) for which we have demonstrated utility in Buchwald–Hartwig amination reactions.[14] It was noted that ligand **2** is especially useful for substrates with functionalities that require a weak base such as Cs_2CO_3.

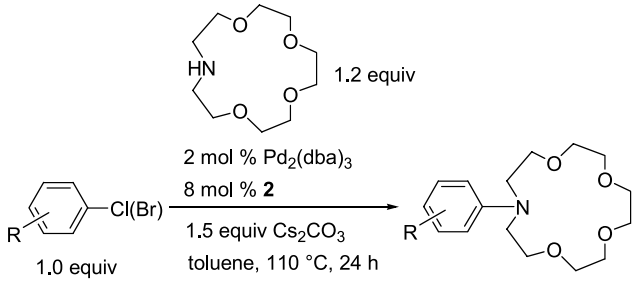
2. Results and discussion

We initially investigated the coupling of commercially available 1-aza-15-crown-5 with aryl chlorides. After brief experimentation, we established that a variety of aryl chlorides can be coupled with 1-aza-15-crown-5 using 1 mol% $Pd_2(dba)_3$ and 4 mol% ligand **1** in toluene at 100 °C (Scheme 1) in the presence of NaO-*t*-Bu as the base.



Scheme 1. Conditions for $Pd_2(dba)_3$/**1**-catalyzed synthesis of *N*-aryl-aza-crown ethers.

Not surprisingly, aryl chlorides possessing an ester, nitro or nitrile group did not fare well in this approach. For these substrates, however, conditions developed by us utilizing **2** as the ligand in the presence of the mild base Cs_2CO_3 proved to be gratifyingly efficacious (Scheme 2).



Scheme 2. Conditions for $Pd_2(dba)_3$/**2**-catalyzed synthesis of *N*-aryl-aza-crown ethers possessing base-sensitive functional groups.

The potential and scope of this methodology is illustrated in Table 1 by the reaction of a variety of aryl chlorides and bromides with 1-aza-15-crown-5. It is seen in this table that electronically diverse aryl chlorides as well as bromides can be coupled successfully in good to excellent yields with the aza-crown ether. Using the $Pd_2(dba)_3$/**1** catalyst system (2 mol% Pd), electron-poor 4-chlorobenzotrifluoride afforded the desired product in 86% yield (entry 1). Electron-neutral 4-chlorotoluene also reacted efficiently (80% product yield, entry 5). Electron-rich 4-chloroanisole, a more challenging substrate, also functioned as a substrate, providing the desired *N*-aryl-aza-crown ether in moderate yield (50%, entry 7). The *meta*-substituted aryl chloride, 3-chloroanisole also coupled, giving a 66% product yield (entry 6). Notably, 2-chloropyridine and less reactive 3-chloropyridine were also successfully coupled (entries 8 and 9). The coupling shown in entry 9 is particularly impressive, because to date, no catalyst system has been reported for the coupling of 3-halopyridines with aza-crown ethers. Under these conditions, electron-neutral and electron-rich aryl bromides also participated in the process (entries 11–13).

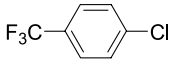
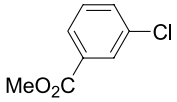
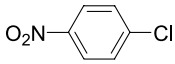
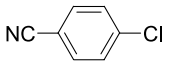
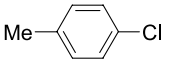
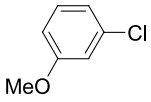
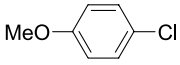
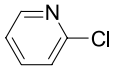
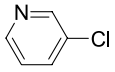
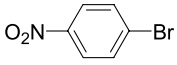
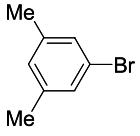
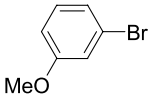
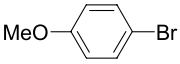
As mentioned earlier, the $Pd_2(dba)_3$/**2** catalyst system in the presence of the weak base Cs_2CO_3 was employed (4 mol% Pd) for substrates with base-sensitive functional groups. Thus, methyl-3-chlorobenzoate (73%, entry 2), 4-chloronitrobenzene (81%, entry 3), 4-chlorobenzonitrile (56%, entry 4), and 4-bromonitrobenzene (87%, entry 10) were all aminated under our standard conditions. For the reaction of 4-bromonitrobenzene, however, 2 mol% of Pd was sufficient for the coupling to occur in high yield.

Although ligands **1** and **2** are slightly air- and moisture-sensitive, they can be easily handled without the need for a glove-box using standard Schlenk techniques. Because of the moisture sensitivity of NaO-*t*-Bu and Cs_2CO_3, these reagents were stored and weighed inside the glove-box. However, we have established that the weighing of the aforementioned reagents inside the glove-box is not an absolute requirement. Thus when a sample of one of these reagents was taken from material stored inside the glove-box and weighed outside the glove-box with manipulations carried out using Schlenk techniques, amination reactions proceeded with almost equal efficiency (see parenthesized yields in entries 3, 6, and 11 of Table 1). The same procedure was also applied to other ingredients, that is, $Pd_2(dba)_3$, aryl chloride, toluene, and aza-crown ether.

The present methodology is not without its limitations, however. For example, *ortho*-substituted aryl chlorides did not couple with 1-aza-15-crown-5 to an appreciable extent and *ortho*-substituted aryl bromides provided only trace amounts of products.

We have also applied a biphenyl based aminophosphine ligand **3** (Buchwald's ligand) to synthesize the target compounds from aryl chlorides (Table 2). Using the protocol of Buchwald [i.e., 1 mol% of $Pd_2(dba)_3$ and 6 mol% of **3** (3L/Pd)], 4-chloroanisole and 4-chlorotoluene efficiently reacted with 1-aza-15-crown-5, affording the desired products in 61% (entry 1, Table 2) and 79% yields (entry 2, Table 2), respectively. However, when aryl chlorides with functional groups such as nitro and ester

Table 1. $Pd_2(dba)_3$/**1** or **2**-catalyzed synthesis of *N*-aryl-aza-crown ethers from aryl chlorides

Entry	Aryl halide	Ligand	mol% Pd	Base	Yield (%)[a]
1		**1**	2	NaO-*t*-Bu	80[b]
2		**2**	4	Cs_2CO_3	73[c]
3		**2**	4	Cs_2CO_3	81[c] (79)[d]
4		**2**	4	Cs_2CO_3	56[c]
5		**1**	2	NaO-*t*-Bu	80[b]
6		**1**	2	NaO-*t*-Bu	66[b] (61)[d]
7		**1**	2	NaO-*t*-Bu	50[b]
8		**1**	2	NaO-*t*-Bu	76[b]
9		**1**	2	NaO-*t*-Bu	51[b]
10		**2**	2	Cs_2CO_3	87[c]
11		**1**	2	NaO-*t*-Bu	82[b] (81)[d]
12		**1**	2	NaO-*t*-Bu	68[b]
13		**1**	2	NaO-*t*-Bu	60[b]

[a] Isolated yields (average of two runs).
[b] For reaction conditions, see Scheme 1.
[c] For reaction conditions, see Scheme 2.
[d] Yields in parenthesis refer to the same reaction performed without the use of glove-box (see text).

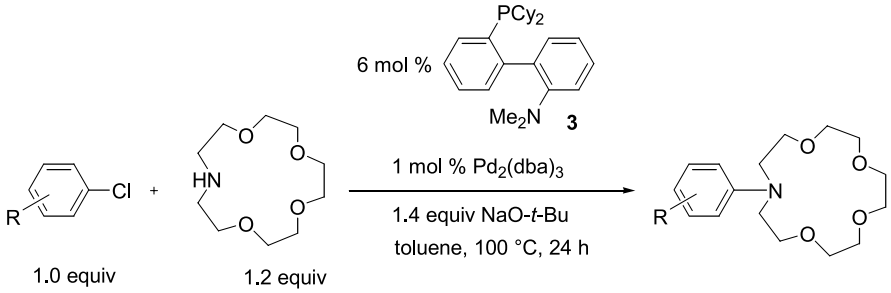
were employed in the presence of Cs_2CO_3 as the base, the corresponding products were obtained in only poor yields (entries 3 and 4, Table 2). As demonstrated above, the coupling of these substrates can be best carried out using ligand **2**.

We have extended our methodology based on the $Pd_2(dba)_3$/**1** catalyst system to the arylation of a second aza-crown ether, namely, 1-aza-18-crown-6 and the results are summarized in Table 3. Using unactivated and deactivated aryl chlorides, bromides, and iodides, yields obtained were in the range of 51–55% (entries 1–4). For an aryl iodide, only 1 mol% of Pd was used.

3. Conclusions

The synthesis of various *N*-aryl-aza-crown ethers was readily achieved via palladium-catalyzed amination of aryl chlorides, bromides, and iodides in which the catalyst system consists of $Pd_2(dba)_3$ and one of the bicyclic triaminophosphine ligands **1** or **2**, the choice depending on the nature of the aryl substrate. Using this approach, the reaction is tolerant of a variety of functional groups. To the best of our knowledge, our protocol is the first reported for coupling aryl chlorides with aza-crown ethers. We have also demonstrated the utility of Buchwald's ligand in the reactions involving aryl chlorides.

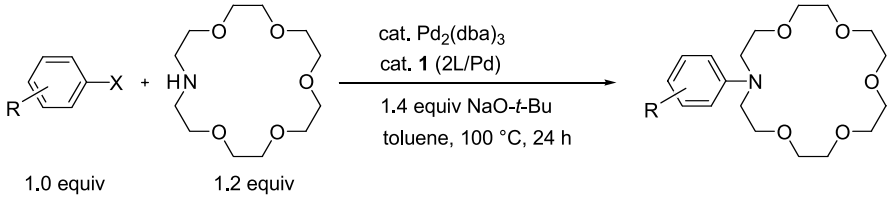
Table 2. Synthesis of *N*-aryl-aza-crown ethers from aryl chlorides using Buchwald's protocol

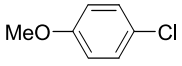
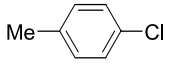
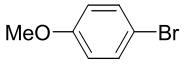
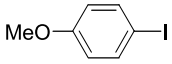


Entry	R	Yield (%)[a]
1	4-OMe	61
2	4-Me	79
3	4-NO_2	44[b,c]
4	3-CO_2Me	26[b,c]

[a] Isolated yields (average of two runs).
[b] 2 mol% of $Pd_2(dba)_3$ and 12 mol% of **3** were used.
[c] Cs_2CO_3 was used as the base.

Table 3. $Pd_2(dba)_3$/**1**-catalyzed coupling of aryl halides with 1-aza-18-crown-6



Entry	Aryl halide	mol% Pd	Yield (%)[a]
1		2	51
2		2	52
3		1.8	54
4		1	55

[a] Isolated yields (average of two runs).

4. Experimental

4.1. General methods

$Pd_2(dba)_3$, NaO-*t*-Bu, and Cs_2CO_3 were purchased from Aldrich and used without further purification. Toluene was collected from a Grubbs type solvent purification system. All other reagents were commercially available and are used as received. Ligands **1**[15] and **2**[14] were prepared according to previously reported procedures, although **1** is commercially available from Aldrich and Strem Chemicals. For convenience, stock solutions of **1** and **2** in toluene (2 mM) were prepared and stored under argon outside the glove-box. All reactions were performed under an atmosphere of argon in oven-dried glassware. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, unless otherwise noted. Elemental analyses were performed by Desert Analytics (Tucson, Arizona, USA). Mass spectra were recorded on a Kratos MS 50 instrument. The yields reported are isolated yields and are the average of two runs.

4.2. General procedure for the coupling of aryl halides with aza-crown ethers using the $Pd_2(dba)_3$/1 or $Pd_2(dba)_3$/2 catalyst system (Tables 1 and 3)

An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (0.5–2 mol%, see Tables 1 and 3), an appropriate aza-crown ether (1.2 mmol), and NaO-*t*-Bu (1.4 mmol) or Cs_2CO_3 (1.5 mmol) inside a glovebox. If the aryl halide (1.0 mmol) was a solid, it was also added at this time. The flask was capped with a rubber septum and removed from the glove box. Ligand **1** or **2** (2–8 mol%) was then added via syringe from a stock solution

(2 mM in toluene). Aryl halide (if a liquid, 1.0 mmol) and toluene (3 mL) were then successively added via syringe. The reaction mixture was heated at the temperature indicated (see Tables 1 and 3) for 24 h. The mixture was then cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography using initially 10% ethyl acetate/hexanes and then ethyl acetate as eluents.

4.3. General procedure for the coupling of aryl chlorides with 1-aza-15-crown-5 using Buchwald's catalyst system (Table 2)

Inside a glovebox, an oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (1 mol%), 1-aza-15-crown-5 (1.2 mmol), ligand **3** (6 mol%), and NaO-*t*-Bu (1.4 mmol). The flask was capped with a rubber septum and removed from the glove box. Then aryl chloride (1.0 mmol) and toluene (3 mL) were successively added via syringe and the reaction mixture was heated at 100 °C for 24 h. The mixture was cooled to room temperature, adsorbed onto silica gel and then purified by column chromatography using initially 10% ethyl acetate/hexanes, followed by ethyl acetate as eluents.

4.4. References for known compounds and spectroscopic data for unknown compounds

4.4.1. *N*-(4-Trifluoromethylphenyl)-1-aza-15-crown-5 (Table 1, entry 1). The ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.[9]

4.4.2. *N*-(3-Carbomethoxyphenyl)-1-aza-15-crown-5 (Table 1, entry 2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.19 (m, 3H), 6.85–6.82 (m, 1H), 3.86 (s, 3H), 3.76–3.58 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 147.8, 131.3, 129.4, 117.0, 116.0, 112.3, 71.5, 70.4, 70.3, 68.6, 52.7, 52.2. HRMS *m/z* Calcd for $C_{18}H_{27}NO_6$: 353.18384. Found: 353.18430. Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.19; H, 7.65. Found: C, 61.34; H, 7.81.

4.4.3. *N*-(4-Nitrophenyl)-1-aza-15-crown-5 (Table 1, entries 3 and 10). The ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.[8a]

4.4.4. *N*-(4-Cyanophenyl)-1-aza-15-crown-5 (Table 1, entry 4). The ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.[16]

4.4.5. *N*-(4-Methylphenyl)-1-aza-15-crown-5 (Table 1, entry 5 and Table 2, entry 2). The ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.[17]

4.4.6. *N*-(3-Methoxyphenyl)-1-aza-15-crown-5 (Table 1, entries 6 and 12). The ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.[9]

4.4.7. *N*-(4-Methoxyphenyl)-1-aza-15-crown-5 (Table 1, entries 7 and 13, and Table 2, entry 1). The ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.[9]

4.4.8. *N*-(2-Pyridinyl)-1-aza-15-crown-5 (Table 1, entry 8). ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J=3.5 Hz, 1H), 7.34 (t, J=7.1 Hz, 1H), 6.49–6.42 (m, 2H), 3.72–3.57 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 148.0, 137.2, 111.6, 106.0, 71.4, 70.4, 70.2, 69.3, 51.2. HRMS *m/z* Calcd for $C_{15}H_{24}N_2O_4$: 296.17361. Found: 296.17410. Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.81; H, 8.11. Found: C, 60.67; H, 8.31.

4.4.9. *N*-(3-Pyridinyl)-1-aza-15-crown-5 (Table 1, entry 9). ^1H NMR (400 MHz, $CDCl_3$): δ 8.08–8.05 (m, 1H), 7.90 (d, J=4.3 Hz, 1H), 7.09–7.06 (m, 1H), 6.94–6.92 (m, 1H), 3.74–3.55 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 137.3, 134.2, 123.8, 118.2, 71.5, 70.5, 70.2, 68.4, 52.5. HRMS *m/z* Calcd for $C_{15}H_{24}N_2O_4$: 296.17361. Found: 296.17410. Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.81; H, 8.11. Found: C, 60.98; H, 7.97.

4.4.10. *N*-(3,5-Dimethylphenyl)-1-aza-15-crown-5 (Table 1, entry 11). The ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.[9]

4.4.11. *N*-(4-Methoxyphenyl)-1-aza-18-crown-6 (Table 3, entries 1, 3, and 4). ^1H NMR (300 MHz, $CDCl_3$): δ 6.82–6.70 (m, 4H), 3.74–3.56 (m, 27H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8, 142.4, 115.1, 114.4, 71.03, 70.99, 70.8, 69.0, 56.0, 52.4. HRMS *m/z* Calcd for $C_{19}H_{31}NO_6$: 369.21514. Found: 369.21580. Anal. Calcd for $C_{19}H_{31}NO_6$: C, 61.79; H, 8.40. Found: C, 61.63; H, 8.33.

4.4.12. *N*-(4-Methylphenyl)-1-aza-18-crown-6 (Table 3, entry 2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, J=8.4 Hz, 2H), 6.62 (d, J=8.5 Hz, 2H), 3.70–3.56 (m, 24H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.0, 130.0, 125.2, 112.1, 71.1, 71.08, 71.0, 70.9, 69.1, 51.7, 20.4. HRMS *m/z* Calcd for $C_{19}H_{31}NO_5$: 353.22022. Found: 353.22100. Anal. Calcd for $C_{19}H_{31}NO_5$: C, 64.59; H, 8.78. Found: C, 64.67; H, 8.67.

Acknowledgements

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References and notes

1. (a) Lohr, H.-G.; Vogtle, F. *Acc. Chem. Res.* **1985**, *18*, 65. (b) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515.
2. Chi, K.-W.; Addicott, C.; Stang, P. J. *J. Org. Chem.* **2004**, *69*, 2910.
3. (a) Matsumoto, K.; Hashimoto, M.; Toda, M.; Tsukube, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2497. (b) Ciobanu, M.; Matsumoto, K. *Liebigs Ann.* **1997**, 623.
4. (a) Crochet, P.; Malval, J.-P.; Lapouyade, R. *Chem. Commun.* **2000**, 289. (b) Hirano, T.; Kikuchi, K.; Urano, Y.; Higuchi, T.; Nagano, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 1052. (c) Lednev,

I. K.; Hester, R. E.; Moore, J. N. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 1551. (d) Liu, R. C. W.; Fung, P.-S.; Xue, F.; Mak, T. C. W.; Ng, D. K. P. *J. Chem. Res. (S)* **1998**, 414.

5. (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.
6. (a) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley: Weinheim, Germany, 2000. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.
7. (a) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (b) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617.
8. (a) Witulski, B. *Synlett* **1999**, 1223. (b) Witulski, B.; Zimmerman, Y.; Dacros, V.; Desvergne, J.-P.; Bassani, D. M.; Bouas-Laurent, H. *Tetrahedron Lett.* **1998**, *39*, 4807. (c) Witulski, B.; Weber, M.; Bergstrasser, U.; Desvergne, J.-P.; Bassani, D. M.; Bouas-Laurent, H. *Org. Lett.* **2001**, *3*, 1467.
9. Zhang, X.-X.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 8027.
10. Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921.
11. (a) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452. (b) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815. (c) Urgaonkar, S.; Verkade, J. G. *Adv. Synth. Catal.* **2004**, *346*, 611.
12. (a) Su, W.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2004**, *6*, 1421. (b) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.*, in press.
13. (a) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. (b) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003.
14. Urgaonkar, S.; Xu, J.-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.
15. Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 467.
16. Letard, J. F.; Lapouyade, R.; Rettig, W. *Pure Appl. Chem.* **1993**, *65*, 1705.
17. Lu, X.; Zhong, R.; Liu, S.; Liu, Y. *Polyhedron* **1997**, *16*, 3865.

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Pyridinium *N*-2′-pyridylaminide: synthesis of 3-aryl-2-aminopyridines through an intramolecular radical process

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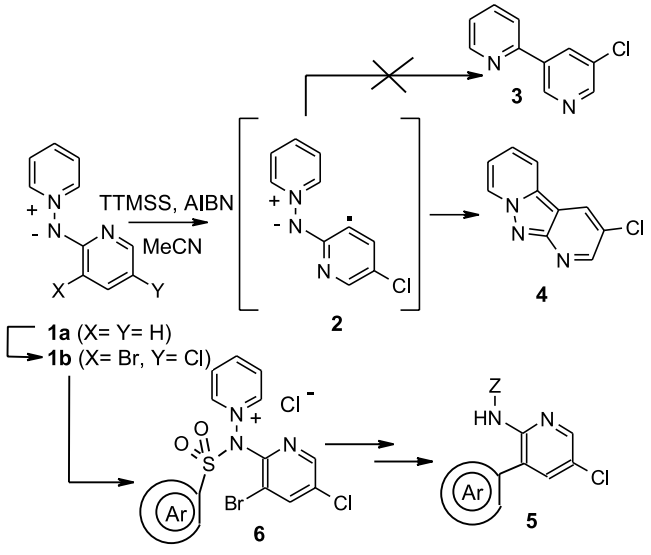
Abstract—Tris(trimethylsilyl)silane (TTMSS) and azobisisobutironitrile (AIBN) promote the intramolecular heteroarylation of arenesulfonamides with pyridyl radicals under thermal conditions. The arenesulfonamides are easily prepared from pyridinium *N*-2′-pyridylaminide. The heteroarylation process involves pyridyl radical cyclization and *ipso* substitution.

1. Introduction

Azinium *N*-ylides, a subgroup of mesomeric betaines, are interesting compounds due to their dipolar character, as well as to their biological properties and synthetic applications.[1,2] During the past few years our research group has been interested in the chemistry of pyridinium *N*-2′-pyridylaminide, **1a** (Scheme 1), a stable heterocyclic betaine, that has a π-deficient pyridinium fragment attached to a π-excessive 2-iminopyridine moiety. This compound has proven to be a versatile scaffold in a wide range of transformations. Thus, for example, the preparation of 3-or 3,5-halogenated 2-alkyl aminopyridines from **1a** can be carried out by an easy and selective halogenation at the iminopyridine moiety (for supply, for example **1b**, Scheme 1), followed by regioselective *N*-alkylation at the aminide nitrogen and final reduction of N–N bond.[3]



Scheme 1.

During the course of our studies on the intramolecular arylation of **1b**, we evaluated the behavior of the pyridyl radical **2** (Scheme 1). The ultimate goal was the preparation of bipyridine **3** by a reaction pathway involving a exo/endo-*trig* cyclization, followed by N–N bond breaking, as previously described.[3d] Compound **3**, however, was not detected and instead, the tricyclic derivative **4** was obtained in moderate yield.[4] Following the same target in the development of a preparation of bipyridines and related biaryls by intramolecular radical arylation (i.e., **5**, Scheme 1), we decided to prepare salt **6** in order to explore the feasibility of an intramolecular free radical *ipso*-substitution of the corresponding arenesulfonamides by pyridyl radicals, according to the methodology described by Motherwell and col.[5] This well-established method, based on aryl radical cyclizations, has been applied to the synthesis of biaryls and arylheterocycles. However, to the best of our knowledge, references concerning the use of heteroaryl radicals in such a method have not been published to date. Indeed, from a general point of view, the cyclization of pyridyl radicals has scarcely been exploited in synthesis.[6]

Keywords: Arylation; Biaryls; *Ipso*-substitution mechanism; Radicals and radical reaction; Tris(trimethylsilyl)silane.
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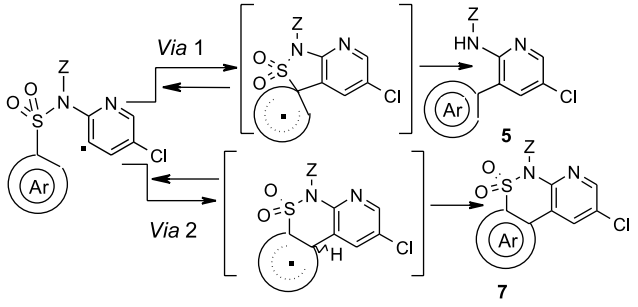
On the other hand, reductive cyclization of *N*-(2-haloaryl)arenesulfonamides has been studied by Motherwell in the first instance, in the presence of tributyltin hydride/AIBN,[5] which later obviated the need for tin derivatives by using arenesulfonylaminobenzene-diazonium salts and $TiCl_3$.[7] More recently, Togo and Ryokawa reported a similar tin-free cyclization of bromoaryl arenesulfonamides, using 1,1,2,2 tetraphenyl disilane, in the presence of AIBN.[8]

The 1,5-*ipso*-substitution approach to biaryls compounds **5** is shown in Scheme 2, via 1, while via 2, shows the alternative 1,6-cyclization to yield the by-products **7**. Both of processes occur according to the reaction mechanism described by Motherwell and colleagues.[5]

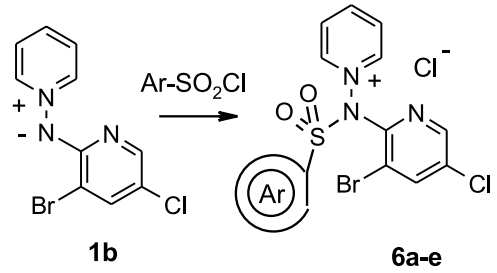


Scheme 2.

As a continuation of our interest in inter- and intramolecular radical heteroarylations of aromatic substrates, using Tris(trimethylsilyl)silane (TTMSS)/AIBN, under reductive conditions, we wish to report our preliminary results concerning pyridyl radical cyclizations, onto arenesulfonamide derivatives, using *N*-2′-pyridylaminide, **1a**, as starting material.

2. Results and discussion

Pyridyl-substituted aminide **1b** (Scheme 3),[3c] was reacted with the corresponding aryl sulfonyl chlorides to produce *N*-[(3-bromo-5-chloro-pyridin-2-yl)arenesulfonamido] pyridinium chlorides **6**. Best results were obtained for compounds **6a–e** (Table 1, entries 1–5) by addition, at room temperature, of a solution of corresponding aryl sulfonyl chloride (3 equiv) in acetone (15 mL) to a stirred solution of **1b** (1 equiv) in acetone (5 mL). Stirring was then maintained for 24 h (method A). The method, however, did not produce detectable yields of **6** with other aryl sulfonyl chlorides such as 2,4,6-trimethylbenzenesulfonyl chloride,



Scheme 3.

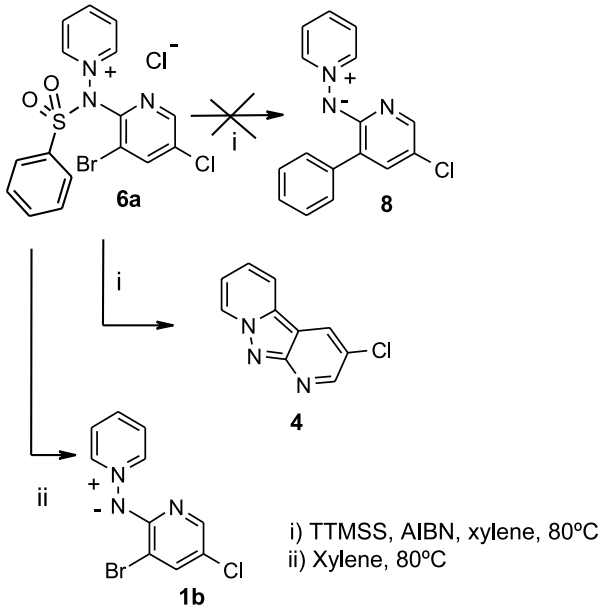
Table 1. Arenosulfonamides salts **6** were obtained

Entry	Compound	Ar[a]	Yield (%)
1	**6a**	C_6H_5	79
2	**6b**	4-Me–C_6H_4	66
3	**6c**	4-MeO–C_6H_4	46
4	**6d**	4-Cl–C_6H_4	53
5	**6e**	4-NO_2–C_6H_4	65

[a] Method A: aryl sulfonyl chloride (3 equiv) in acetone (15 mL) to a stirred solution of **1b** (1 equiv) in acetone (5 mL), stirring was then maintained for 24 h.

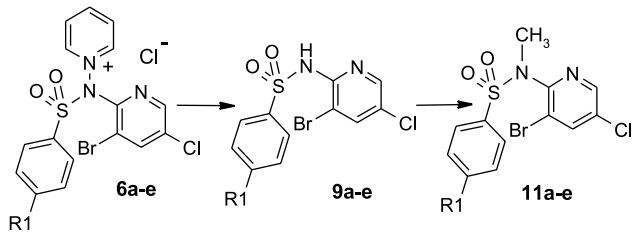
quinoline 8-sulfonyl chloride or thiophene-2-sulfonyl chloride, even refluxing toluene for 48 h (method B).

Having obtained substrates **6**, initial experiments on pyridyl radical cyclization were undertaken on **6a**, bearing in mind the results of previous work on the intramolecular process.[4] Thus, as indicated in Scheme 4, the very slow dropwise addition (syringe pump) of a solution of TTMSS (2 equiv) and AIBN (2 equiv) to a solution of **6a** in benzene/acetonitrile did not generate detectable yields of **8** and only poor yields of tricyclic derivative **4** could be obtained. Similar results were found when the reaction was carried out in *m*-xylene, which was used as an alternative to avoid the use of benzene.[8] As a result, the suggested reaction mechanism would involve N–S fission and subsequent 5-*exo*/*endo*-*trig* cyclization, or alternatively radical cyclization followed by desulfonylation, both consistent with the formation of ylide **1b** in the absence of TTMSS and AIBN (Scheme 4).[4]



Scheme 4.

Cyclization of compound **6a** did not seem to be an efficient process, so N–N reduction of **6** was performed. The use of a two molar excess of reducing agents [method C, **6** (0.5 mmol), Pt/C 5% (240 mg), formic acid 96% (1.6 mL, 40 mmol), triethylamine (15 mL, 108 mmol)] on the previously described method,[3c] gave *N*-unsubstituted compounds **9**. These results are shown in Scheme 5 and Table 2. The process, when applied to pyridinium salts **6a–d**,



Scheme 5.

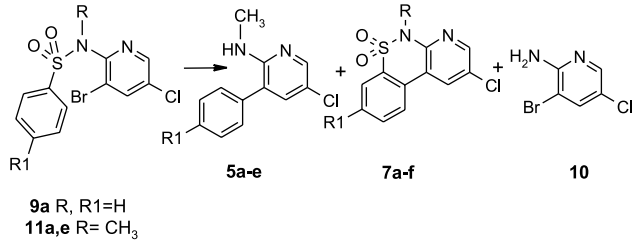
Once again, application of the radical cyclization process, under similar experimental conditions, to **9a**, which has a N–H free sulfonamide, did not generate the rearranged biaryl **5**. In this case, only the cyclization **7f** and the reduction products **10** were obtained in moderate yields, a situation in agreement with the results reported for other radical arylations,[5,8] (see Scheme 6 and Table 3, entry 10). As an alternative, compounds **11** were prepared by *N*-methylation with methyl iodide/potassium carbonate (method E). Results are summarized in Scheme 5 and Table 2.

Table 2. Compounds **9** and **11** were obtained

Entry	R_1	Starting material	**9**, Yield (%)	Method	**11**, Yield (%)	Method
1	H	**6a**	70	C[a]	72	E[b]
2	CH_3	**6b**	82	C[a]	60	E[b]
3	OCH_3	**6c**	54	C[a]	96	E[b]
4	Cl	**6d**	54	C[a]	71	E[b]
5	NO_2	**6e**	4	C[a]	61	E[b]
6	NO_2	**6e**	70	D[c]		

[a] Method C: **6** (0.5 mmol), Pt/C 5% (240 mg), formic acid 96% (1.6 mL,40 mmol), triethylamine (15 mL, 108 mmol)), 0–4 °C.
[b] Method E: **9** (5 mmol), K_2CO_3 (10 mmol), MeI (15 mmol) in acetone (20 mL), RT, 24 h.
[c] Method D: **6e** (0.5 mmol) in EtOH (6 mL), Et_3B (1 M, 0.85 mL), RT, 24 h.

produced arenesulfonamides **9a–d** (Table 2, entries 1–4) in good yields. As expected, reduction of **6e**, ($R_1=NO_2$) produced simultaneous reduction of the nitro group and only 4% of compound **9e** was isolated (entry 5). Finally, the product **9e** was satisfactorily obtained (70%), in the presence of BEt_3/EtOH, at room temperature (entry 6, method D). The process, probably, involves in situ generation of ethoxydiethylborane as previously described.[9]



Scheme 6.

Optimal conditions for radical *ipso*-substitution with TTMSS and AIBN were studied and the results are shown in Scheme 6 and Table 3. AIBN (2 mmol) in *m*-xylene (10 mL) was added dropwise over 20 h to a stirred solution, at 80 °C, of **11a** (0.5 mmol) and TTMSS (2 mmol) in *m*-xylene (2 mL). After 7 h, additional TTMSS (2 mmol) was added in one portion. When the addition was complete, the mixture was stirred at the same temperature, for a further 24 h. In this case, cyclized **7a** (48%) and the desired compound **5a** (25%) were obtained (Table 3, entry 1, method F). Similar results were observed on slow addition of TTMSS (entry 2, method G). The best results were obtained by slow addition (29 h) of a solution of AIBN (2 mmol) and TTMSS (4 mmol) in *m*-xylene (10 mL) to a stirred solution, at 80 °C, of **11a** (0.5 mmol) in *m*-xylene (2 mL) (entry 3, method H). The reaction did not go to completion (40% starting material was recovered

Table 3. Compounds **5** and 7 were obtained

Entry	R_1	Starting material	**5**, Yield (%)	**7**, Yield (%)	**10**, Yield (%)	Method
1	H	**11a**	25	48	—	F[a]
2	H	**11a**	28	34		G[b]
3	H	**11a**	67	20	—	H[c]
4	H	**11a**	11	40		I[d]
5	H	**11a**	17	57		J[e]
6	CH_3	**11b**	63	18		H[c]
7	OCH_3	**11c**	60	13		H[c]
8	Cl	**11d**	50	20		H[c]
9	NO_2	**11e**	33	—		H[c]
10	H	**9a**		33	7	H[c]

[a] Method F: AIBN (2 mmol) in *m*-xylene (10 mL) was added over 20 h to a stirred solution at 80 °C, of **11a** (0.5 mmol) and TTMSS (2 mmol) in *m*-xylene (2 mL); after 7 h, TTMSS (2 mmol) in one portion was added, 80 °C for futher 24 h.
[b] Method G: AIBN (2 mmol) and TTMSS (4 mmol) in *m*-xylene (10 mL) was added over 20 h to a stirred solution at 80 °C of **11a** (0.5 mmol) in *m*-xylene (2 mL), 80 °C for futher 24 h.
[c] Method H: AIBN (2 mmol) and TTMSS (4 mmol) in *m*-xylene (10 mL) was added over 29 h to a stirred solution at 80 °C of **11** (0.5 mmol) in *m*-xylene (2 mL), 80 °C for futher 24 h.
[d] Method I: AIBN (2 mmol) and TTMSS (2 mmol) in *m*-xylene (10 mL) was added over 29 h to a stirred solution at 80 °C of **11a** (0.5 mmol) in *m*-xylene (2 mL), 80 °C for futher 24 h.
[e] Method J: AIBN (2 mmol) and TTMSS (4 mmol) in *m*-xylene (20 mL) was added over 29 h to a stirred solution at 80 °C of **11a** (0.5 mmol) in *m*-xylene (2 mL), 80 °C for futher 24 h.

unchanged) when only 2 equiv of TTMSS (1 mmol) were used (entry 4, method I). When the reaction was carried out in more diluted conditions (entry 5, method J) only 17% yield of substituted compound **5a** was detected.

Method H was also applied to compounds **11b–e** and the results are summarized in Table 3 (entries 6–9). When the reaction was carried out using **11e** as the starting material (entry 9), the reaction mixture appeared very complex and only **5e** was obtained, albeit in poor yield. In general terms, the presence of an electron-withdrawing substituents in the *para*-position of the sulfonyl group led to lower yields in the *ipso*-substitution product (entries 8 and 9, Table 3). In contrast, an electron-donating substituent on the benzenesulfonyl moiety produced higher yields of derivatives **5**. Additionally, the π-excessive character of 2-azinylimino-pyridine moiety on the heterocyclic side, seems to facilitate the rearrangement to biaryls, both effects being in agreement with previously reported *ipso*-substitutions in arenesulfonamides.[8]

3. Conclusions

Pyridinium *N*-2′-pyridylaminide is a suitable starting material to produce halo pyridin-2-yl benzenesulfonamides through halogenation, sulfonylation and N–N reduction in very mild conditions. The method, combined with *N*-methylation and cyclization, by a radical *ipso*-substitution mechanism, in the presence of TTMSS/AIBN, yields 3-aryl-2-aminopyridines in good yield. In agreement with previously reported observations, the presence of electron-donating substituents on both aromatics rings seems to facilitate the rearrangement to biaryls.

4. Experimental

General methods. All experiments were carried out under a dry argon atmosphere, with solvents freshly distilled under anhydrous conditions, unless stated otherwise. All chemicals were purchased from the Aldrich Chemical Company and Fluka, and were used without further purification. ^{1}H, ^{13}C NMR and decoupled spectra were recorded on a Varian UNITY 300 MHz or VARIAN UNITY PLUS 500 MHz spectrometer. Mass spectra were recorded on a VG AutoSpec (Micromass Instruments). Elemental analysis was performed on a LECO instruments CHNS-932. Pyridinium *N*-aminides **1a**[3b] and **1b**[3c] have been previously described.

4.1. Reaction de aminide 1b with arene sulfonyl chlorides

General method, method A. To a solution of aminide **1b** (0.285 g, 1 mmol) in acetone (5 mL) was added the corresponding sulfonyl chloride (3 mmol for compounds **6a**,**b**,**d**,**e** and 6 mmol for compound **6c**) The mixture was stirred at room temperature until starting material could not be detected by TLC (24 h for compounds **6a–d** and only 1 h for compound **6e**). The resulting solid was filtered off and washed with dry acetone.

4.1.1. *N*-[Benzenesulfonyl-(3′-bromo-5′-chloro-pyridin-2-yl)amino] pyridinium chloride 6a. White solid (364 mg, 79%), mp 170–175 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.34 (d, 2H, J=6.2 Hz), 8.90 (t, 1H, J=8.0 Hz), 8.65 (d, 1H, J=1.8 Hz), 8.58 (d, 1H, J=1.8 Hz), 8.45 (at, 2H, J=7.7 Hz), 7.98 (t, 1H, J=7.6 Hz), 7.82 (d, 2H, J=7.6 Hz), 7.76 (at, 2H, J=7.6 Hz); MS (ESI) *m*/*z* (relative intensity) 424, 426, 428 [(M^+) 92, 100, 41], 284, 286, 288 (23, 30, 8); Anal. Calcd for $C_{16}H_{12}BrCl_2N_3O_2S$ 461.17: C, 41.67; H, 2.62; N, 9.11; S, 6.95%. Found: C, 41.93; H, 2.77; N, 9.41; S, 6.84%.

4.1.2. *N*-[(3′-Bromo-5′-chloro-pyridin-2-yl)(toluene-4″-sulfonyl)-amino] pyridinium chloride 6b. White solid (314 mg, 66%), mp 175–180 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.18 (d, 2H, J=5.5 Hz), 8.76 (t, 1H, J=7.8 Hz), 8.52 (d, 1H, J=2.2 Hz), 8.44 (d, 1H, J=2.2 Hz), 8.12 (dd, 2H, J=7.8, 5.5 Hz), 7.56 (d, 2H, J=8.4 Hz), 7.44 (d, 2H, J=8.4 Hz) 2.43 (s, 3H); MS (ESI) *m*/*z* (relative intensity) 438, 440, 442 [(M^+) 96, 100, 41], 284, 286, 288 (16, 21, 5); Anal. Calcd for $C_{17}H_{14}BrCl_2N_3O_2S$ 475.19: C, 42.97; H, 2.97; N, 8.84; S, 6.75%. Found: C, 42.93; H, 2.78; N, 8.61; S, 6.84%.

4.1.3. *N*-[(3′-Bromo-5′-chloro-pyridin-2-yl)(4″-methoxy-benzenesulfonyl)-amino] pyridinium chloride 6c. White solid (319 mg, 65%), mp 115–120 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.31 (dd, 2H, J=5.5, 1.2 Hz), 8.88 (tt, 1H, J=6.7, 1.2 Hz), 8.65 (d, 1H, J=2.2 Hz), 8.56 (d, 1H, J=2.2 Hz), 8.26 (dd, 2H, J=6.7, 5.5 Hz), 7.74 (d, 2H, J=7.1 Hz), 7.22 (d, 2H, J=7.1 Hz), 4.00 (s, 3H); MS (ESI) *m*/*z* (relative intensity) 454, 456, 458 [(M^+) 73, 100, 31], 284, 286, 288 (9, 11, 3); Anal. Calcd for $C_{17}H_{14}BrCl_2N_3O_3S$ 491.19: C, 41.57; H, 2.87; N, 8.55; S, 6.82%. Found: C, 41.63; H, 2.70; N, 8.31; S, 6.85%.

4.1.4. *N*-[(3′-Bromo-5′-chloro-pyridin-2-yl)(4″-chloro-benzenesulfonyl)-amino] pyridinium chloride 6d. White solid (263 mg, 53%), mp 115–120 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.36 (d, 2H, J=6.3 Hz), 8.92 (t, 1H, J=7.7 Hz), 8.66 (d, 1H, J=1.3 Hz), 8.58 (d, 1H, J=1.3 Hz), 8.30 (dd, 2H, J=7.7, 6.3 Hz), 7.80 (m, 4H); MS (ESI) *m*/*z* (relative intensity) 458, 460, 462 [(M^+) 83, 100, 76], 284, 286, 288 (16, 21, 5); Anal. Calcd for $C_{16}H_{11}BrCl_3N_3O_2S$ 495.61: C, 38.78; H, 2.24; N, 8.48; S, 6.47%. Found: C, 38.68; H, 2.50; N, 8.38; S, 6.66%.

4.1.5. *N*-[(3′-Bromo-5′-chloro-pyridin-2-yl)(4″-nitro-benzenesulfonyl)-amino] pyridinium chloride 6e. White solid (329 mg, 65%), mp 115–120 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.40 (dd, 2H, J=6.6, 1.1 Hz), 8.94 (tt, 1H, J=7.8, 1.1 Hz), 8.66 (d, 1H, J=2.1 Hz), 8.62 (d, 1H, J=2.1 Hz), 8.56 (d, 2H, J=6.9 Hz), 8.30 (dd, 2H, J=7.8, 6.6 Hz), 8.10 (d, 2H, J=6.9 Hz); MS (ESI) *m*/*z* (relative intensity) 469, 471, 473 [(M^+) 72, 100, 35], 284, 286, 288 (26, 33, 10); Anal. Calcd for $C_{16}H_{11}BrCl_2N_4O_4S$ 506.16: C, 37.97; H, 2.19; N, 11.07; S, 6.34%. Found: C, 38.09; H, 2.26; N, 11.38; S, 6.55%.

4.2. Reduction of substituted *N*-arenesulfonyl *N*-(3′-bromo-5′-chloro-pyridin-2-yl) pyridinium chlorides

General method, method C. Platinum on charcoal (5%) (240 mg) was suspended in a solution of the pyridinium salts (0.5 mmol) in CH_3CN (12 mL) and cooled in an ice

bath. A solution of formic acid (96%, 1.6 mL) in CH_3CN (5 mL) and then triethylamine (15 mL) in the same solvent (12 mL) were added dropwise. The resulting suspension was allowed to warm up to room temperature and filtered through Celite. The filtrate was evaporated and the residue dissolved in water, made basic with solid K_2CO_3 and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and evaporated to dryness. The corresponding benzenesulfonamide was purified by flash chromatography and crystallization from diethyl ether/hexanes.

4.2.1. *N*-(3-Bromo-5-chloro-pyridin-2-yl)benzenesulfonamide 9a. The general procedure (method C) using **6a** (231 mg) as the starting pyridinium salt gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (80:20), $R_f \approx 0.48$], a white solid (122 mg, 70%), mp 146–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, 2H, $J=7.4$ Hz), 8.10 (d, 1H, $J=2.1$ Hz), 7.75 (d, 1H, $J=2.1$ Hz), 7.58 (t, 1H, $J=8.0$ Hz), 7.48 (dd, 2H, $J=8.0$, 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 145.2, 141.8, 140.1, 133.4, 133.0, 128.6, 128.4, 107.0; MS (EI) *m/z* (relative intensity) 346, 348, 350 [(M^+), 0.4, 0.6, 0.2], 281, 283, 285 (27, 35, 9), 77 (100); Anal. Calcd for $C_{11}H_8BrClN_2O_2S$ 347.62: C, 38.01; H, 2.32; N, 8.06; S, 9.22%. Found: C, 37.72; H, 2.56; N, 7.88; S, 9.16%.

4.2.2. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-methyl-benzenesulfonamide 9b. The general procedure (method C) using **6b** (238 mg) as the starting pyridinium salt gave, after flash chromatography and crystallization [silica gel, hexanes/ethyl acetate (70:30), $R_f \approx 0.28$], a white solid (148 mg, 82%), mp 136–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, 1H, $J=2.1$ Hz), 7.98 (d, 2H, $J=8.2$ Hz), 7.74 (d, 1H, $J=2.1$ Hz), 7.62 (bs, 1H), 7.28 (d, 2H, $J=$ 8.2 Hz), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 145.2, 144.3, 140.0, 136.0, 129.2, 128.5, 125.1, 106.7, 21.7; MS (EI) *m/z* (relative intensity) 360, 362, 364 [(M^+), 0.4, 0.6, 0.1], 295, 297, 299 (57, 74, 18), 91 (100); Anal. Calcd for $C_{12}H_{10}BrClN_2O_2S$ 361.65: C, 39.85; H, 2.79; N, 7.75; S, 8.87%. Found: C, 39.65; H, 2.83; N, 7.48; S, 8.40%.

4.2.3. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-methoxy-benzenesulfonamide 9c. The general procedure (method C) using **6c** (246 mg) as the starting pyridinium salt gave, after flash chromatography and crystallization [silica gel, hexanes/ethyl acetate (70:30), $R_f \approx 0.45$], a white solid (102 mg, 54%), mp 155–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 1H, $J=2.0$ Hz), 8.02 (d, 2H, $J=$ 8.9 Hz), 7.70 (d, 1H, $J=2.0$ Hz), 6.92 (d, 2H, $J=8.9$ Hz), 5.00 (bs, 1H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 163.4, 146.5, 145.2, 140.0, 134.6, 130.7, 125.5, 113.7, 106.6, 55.5; MS (EI) *m/z* (relative intensity) 311, 313, 315 (74, 100, 27), 171 (27), 107 (11), 77 (86); Anal. Calcd for $C_{12}H_{10}BrClN_2O_3S$ 377.65: C, 38.17; H, 2.67; N, 7.42; S, 8.49%. Found: C, 38.33; H, 2.77; N, 7.41; S, 8.24%.

4.2.4. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-chloro-benzenesulfonamide 9d. The general procedure (method C) using **6d** (248 mg) as the starting pyridinium salt gave, after flash chromatography and crystallization [silica gel, hexanes/ethyl acetate (70:30), $R_f \approx 0.37$], a white solid (103 mg, 54%) mp 145–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 1H, $J=2.0$ Hz), 8.05 (d, 2H, $J=8.5$ Hz), 7.74 (d, 1H, $J=2.0$ Hz), 7.44 (d, 2H, $J=8.5$ Hz), 5.00 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 145.2, 140.3, 139.9, 137.7, 130.0, 128.9, 126.0, 106.9; MS (EI) *m/z* (relative intensity) 315, 317, 319 (61, 100, 46), 111 (73), 75 (43); Anal. Calcd for $C_{11}H_7BrCl_2N_2O_2S$ 382. 06: C, 34.58; H, 1.85; N, 7.33; S, 8.39%. Found: C, 34.75; H, 1.90; N, 7.37; S, 8.01%.

4.2.5. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-nitro-benzenesulfonamide 9e. The general procedure (method C) using **6e** (253 mg) as the starting pyridinium salt gave, after flash chromatography and crystallization (silica gel, hexanes/ethyl acetate (70:30), $R_f \approx 0.31$), a white solid (8 mg, 4%). *Method D*. Compound **6e** (0.5 mmol, 253 mg) was dissolved in EtOH (6 mL). The solution was flushed with argon and stirred at room temperature. A solution of triethylborane in hexane (1.0 M, 0.85 mL, 0.85 mmol) was then added dropwise. After stirring for 2 h at room temperature, air (0.85 mL) was added with a syringe and stirring was maintained at the same temperature for further 24 h. Purification by flash chromatography and crystallization furnished **9e** (137 mg, 70%), mp 202–203 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, 2H, $J=6.8$ Hz), 8.32 (d, 2H, $J=6.8$ Hz), 8.11 (d, 1H, $J=2.4$ Hz), 7.79 (d, 1H, $J=$ 2.4 Hz), 7.68 (bs, 1H); MS (EI) *m/z* (relative intensity) 326, 328, 330 (76, 100, 26), 282 (35), 248 (23), 208 (53), 76 (41); Anal. Calcd for $C_{11}H_7BrClN_3O_4S$ 392.62: C, 33.65; H, 1.80; N, 10.70; S, 8.17%. Found: C, 33.32; H, 1.84; N, 10.47; S, 7.98%.

4.3. Reaction of arenesulfonamides with iodomethane

General method, method E: To a dispersion of corresponding *N*-unsubstituted arenesulfonamide **9a–e** (5 mmol) and potassium carbonate (10 mmol, 1.38 g) in acetone (20 mL), was added iodomethane (15 mmol, 0.93 mL). The mixture was stirred at room for 24 h and all starting material was consumed (TLC analysis). Purification by flash chromatography furnished a white solid, which was crystallized from hexanes.

4.3.1. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-*N*-methyl-benzenesulfonamide 11a. The general procedure (method E) using **9a** (1.738 g) as starting material gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (70:30), $R_f \approx 0.86$], a white solid (1.310 g, 72%), mp 145–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, 1H, $J=2.3$ Hz), 8.02 (d, 1H, $J=2.3$ Hz), 7.83 (d, 2H, $J=7.5$ Hz), 7.62 (t, 1H, $J=7.3$ Hz), 7.52 (dd, 2H, $J=7.5$, 7.3 Hz), 3.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 144.1, 139.7, 135.3, 131.0, 129.6, 126.6, 126.4, 119.9, 34.8; MS (EI) *m/z* (relative intensity) 295, 297, 299 (61, 80, 20), 221 (25), 77 (100); Anal. Calcd for $C_{12}H_{10}BrClN_2O_2S$ 361.65: C, 39.85; H, 2.79; N, 7.75; S, 8.87%. Found: C, 40.10; H, 2.97; N, 7.70; S, 8.64%.

4.3.2. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′,*N*-dimethyl-benzene sulfonamide 11b. The general procedure (method E) using **9b** (1.808 g) as the starting material gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (70:30), $R_f \approx 0.90$], a white solid (1.126 g, 60%), mp 120–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27

(d, 1H, $J=2.4$ Hz), 8.02 (d, 1H, $J=2.4$ Hz), 7.69 (d, 2H, $J=8.2$ Hz), 7.30 (d, 2H, $J=8.2$ Hz), 3.04 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 145.9, 143.7, 141.5, 134.1, 131.3, 129.2, 128.4, 121.8, 36.7, 21.6; MS (EI) *m/z* (relative intensity) 309, 311, 313 (50, 66, 17), 91 (100); Anal. Calcd for $C_{13}H_{12}BrClN_2O_2S$ 375.67: C, 41.56; H, 3.22; N, 7.46; S, 8.54%. Found: C, 41.40; H, 3.39; N, 7.20; S, 8.71%.

4.3.3. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-methoxy-*N*-methyl-benzenesulfonamide 11c. The general procedure (method E) using **9c** (1.888 g) as the starting material gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (70:30), $R_f \approx 0.40$], a white solid (1.194 g, 61%), mp 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, 1H, $J=2.2$ Hz), 7.99 (d, 1H, $J=2.2$ Hz), 7.72 (d, 2H, $J=8.8$ Hz), 6.95 (d, 2H, $J=8.8$ Hz), 3.84 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 151.2, 146.1, 141.6, 131.3, 130.6, 121.8, 113.8, 109.0, 55.4, 36.6; MS (EI) *m/z* (relative intensity) 325, 327, 329 (67, 96, 33), 171 (56), 107 (99), 92 (71), 77 (100); Anal. Calcd for $C_{13}H_{12}BrClN_2O_3S$ 391.67: C, 39.87; H, 3.09; N, 7.15; S, 8.19%. Found: C, 40.06; H, 3.13; N, 7.12; S, 7.92%.

4.3.4. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-chloro-*N*-methyl-benzenesulfonamide 11d. The general procedure (method E) using **9d** (1.910 g) as the starting material gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (70:30), $R_f \approx 0.64$], a white solid (1.406 g, 71%), mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, 1H, $J=2.2$ Hz), 7.98 (d, 1H, $J=2.2$ Hz), 7.75 (d, 2H, $J=8.5$ Hz), 7.46 (d, 2H, $J=8.5$ Hz), 3.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 146.1, 141.7, 139.4, 135.9, 131.6, 129.8, 128.9, 121.7, 36.6; MS (EI) *m/z* (relative intensity) 329, 331, 333 (53, 86, 40), 111 (100), 75 (90); Anal. Calcd for $C_{12}H_9BrCl_2N_2O_2S$ 396.09: C, 36.39; H, 2.29; N, 7.07; S, 8.10%. Found: C, 36.07; H, 2.37; N, 7.06; S, 7.10%.

4.3.5. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-*N*-methyl-4′-nitro-benzenesulfonamide 11e. The general procedure (method E) using **9e** (1.910 g) as the starting material gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (70:30), $R_f \approx 0.83$], a white solid (1.951 g, 96%), mp 137–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, 2H, $J=8.7$ Hz), 8.26 (d, 1H, $J=2.2$ Hz), 8.02 (m, 3H), 3.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 150.2, 146.4, 143.4, 142.1, 132.3, 129.8, 123.9, 121.8, 37.0; MS (EI) *m/z* (relative intensity) 340, 342, 344 (78, 100, 29), 219, 221, 22 (63, 75, 19), 190, 192, 194 (30, 44, 17); Anal. Calcd for $C_{12}H_9BrClN_3O_4S$ 406.64: C, 35.44; H, 2.23; N, 10.33; S, 7.89%. Found: C, 35.27; H, 2.33; N, 10.12; S, 7.91%.

4.4. Radical reaction of arenesulfonamides

General method, method H. A solution of TTMSS (0.498 g, 2 mmol) and AIBN (0.328 g, 2 mmol) in *m*-xylene (10 mL) was added dropwise by a syringe pump during 29 h to a stirred solution of appropriate arenesulfonamide (**9a** or **11a–e**, 0.5 mmol) in *m*-xylene (2 mL), at 80 °C (bath temperature). Stirring was maintained at the same temperature for further 24 h, after which the starting material had been consumed (TLC analysis). The solution was concentrated and the crude mixture was separated by flash chromatography [silicagel, hexanes/ethyl acetate (70:30)], yielding the pure compounds.

4.4.1. (5-Chloro-3-phenyl-pyridin-2-yl)-methyl amine 5a and 3-chloro-10-methyl-10H-9-thia-1,10-diaza-phenanthrene 9,9-dioxide 7a. The general procedure (method H) using **11a** as the starting sulfonamide (181 mg) gave a mixture of products. After separation by flash chromatography, pure compounds **5a** and **7a** were obtained. **5a** yellow oil, $R_f \approx 0.39$ (73 mg, 67%); ^{1}H NMR (500 MHz, CD_3OD) δ 7.98 (d, 1H, $J=2.5$ Hz), 7.51 (dd, 1H, $J=7.8$, 7.3 Hz), 7.44 (tt, 1H, $J=7.3$, 1.4 Hz), 7.42 (dd, 1H, $J=7.8$, 1.4 Hz), 2.87 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 155.2, 144.0, 136.6, 136.5, 130.1, 129.1, 128.7, 128.1, 124.4, 118.7, 28.9; MS (EI) *m/z* (relative intensity) 218, 220 [(M^+) 11, 4], 202 (2), 217, 219 (20, 4), 128 (31), 111 (24), 82 (66), 58 (100). **7a** White solid, $R_f \approx 0.61$ (28 mg, 20%, diethyl ether/hexanes), mp 138–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, 1H, $J=2.4$ Hz), 8.28 (d, 1H, $J=2.4$ Hz), 8.09 (dd, 1H, $J=7.9$, 1.3 Hz), 7.94 (d, 1H, $J=8.1$ Hz), 7.77 (ddd, 1H, $J=8.1$, 7.1, 1.3 Hz), 7.67 (dd, 1H, $J=7.9$, 7.1 Hz) 3.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 147.3, 133.8, 132.6, 132.4, 129.4, 128.8, 126.7, 125.1, 122.4, 118.5, 28.7; MS (EI) *m/z* (relative intensity) 280, 282 (16, 6), 215, 217 (100, 37), 73 (16); Anal. Calcd for $C_{12}H_9ClN_2O_2S$ 280.73: C, 51.34; H, 3.23; N, 9.98; S, 11.42%. Found: C, 51.33; H, 2.95; N, 10.06; S, 11.56%.

4.4.2. (5-Chloro-3-*p*-tolyl-pyridin-2-yl)-methyl-amine 5b and 3-chloro-6,10-dimethyl-10H-9-thia-1,10-diaza-phenanthrene 9,9-dioxide 7b. The general procedure (method H) using **11b** as the starting sulfonamide (188 mg) gave a mixture of products. After separation by flash chromatography, pure compounds **5b** and **7b** were obtained. **5b** yellow oil, $R_f \approx 0.73$ (74 mg, 63%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.92 (d, 1H, $J=2.5$ Hz), 7.27 (m, 4H), 7.24 (d, 1H, $J=2.5$ Hz), 2.83 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 149.1, 144.8, 139.3, 137.5, 134.7, 130.8, 129.6, 121.9, 119.8, 28.9, 21.2; MS (EI) *m/z* (relative intensity) 231, 232 [(M^+) 26, 11], 231, 233 (44, 21), 103 (13). **7b** White solid, $R_f \approx 0.65$ (26 mg, 18%, diethyl ether/hexanes), mp 137–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, 1H, $J=2.4$ Hz), 8.25 (d, 1H, $J=2.4$ Hz), 7.96 (d, 1H, $J=8.1$ Hz), 7.71 (bs, 1H, w ½=2 Hz), 7.45 (dd, 1H, $J=8.1$, 2.0 Hz), 3.60 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 147.1, 143.5, 132.3, 131.3, 130.2, 128.8, 126.6, 125.4, 122.5, 118.5, 28.4, 21.9; MS (EI) *m/z* (relative intensity) 294, 296 [(M^+) 17, 3], 229, 231 (100, 30); Anal. Calcd for $C_{12}H_{11}ClN_2O_2S$ 294.76: C, 52.97; H, 3.76; N, 9.50; S, 10.88%. Found: C, 52.76; H, 4.01; N, 9.55; S, 10.83%.

4.4.3. [5-Chloro-3-(4-methoxy-phenyl)-pyridin-2-yl]-methyl-amine 5c and 3-chloro-6-methoxy-10-methyl-10H-9-thia-1,10-diaza-phenanthrene 9,9-dioxide 7c. The general procedure (method H) using **11c** as the starting sulfonamide (196 mg) gave a mixture of products. After separation by flash chromatography, pure compounds **5c** and **7c** were obtained. **5c** yellow oil, $R_f \approx 0.55$ (75 mg, 60%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.91 (d, 1H, $J=$

2.5 Hz), 7.29 (d, 2H, $J=8.8$ Hz), 7.22 (d, 1H, $J=2.5$ Hz), 7.01 (d, 2H, $J=8.8$ Hz), 3.82 (s, 3H), 2.83 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 161.2, 156.8, 144.8, 137.6, 131.1, 129.8, 125.5, 119.9, 115.7, 30.6, 24.2; MS (EI) *m/z* (relative intensity) 248, 250 [($M^+ +1$) 73, 24], 247, 249 [(M^+) 100, 41]. **7c** White solid, $R_f \approx 0.39$ (20 mg, 13%, diethyl ether/hexanes), mp 174–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, 1H, $J=2.4$ Hz), 8.21 (d, 1H, $J=2.4$ Hz), 8.00 (d, 1H, $J=8.8$ Hz), 7.33 (d, 1H, $J=2.4$ Hz), 7.15 (dd, 1H, $J=8.8$, 2.4 Hz), 3.97 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 148.2, 147.5, 132.5, 132.4, 130.9, 126.6, 124.7, 118.4, 115.2, 109.9, 55.8, 28.3; MS (EI) *m/z* (relative intensity) 311, 313 [($M^+ +1$) 4, 2], 310, 312 [(M^+) 23, 9], 246, 248 (16, 5), 245, 247 (100, 34), 231 (21), 202 (22); Anal. Calcd for $C_{13}H_{11}ClN_2O_3S$ 310.76: C, 50.24; H, 3.57; N, 9.01; S, 10.32%. Found: C, 50.40; H, 3.64; N, 9.22; S, 10.56%.

4.4.4. [5-Chloro-3-(4-chloro-phenyl)-pyridin-2-yl]-methyl-amine 5d and 3,6-dichloro-10-methyl-10H-9-thia-1,10-diaza-phenanthrene 9,9-dioxide 7d. The general procedure (method H) using **11d** as the starting sulfonamide (198 mg) gave a mixture of products. After separation by flash chromatography, pure compounds **5d** and **7d** were obtained. **5d** yellow oil, $R_f \approx 0.71$ (58 mg, 46%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.97 (d, 1H, $J=2.4$ Hz), 7.48 (d, 2H, $J=8.5$ Hz), 7.38 (d, 2H, $J=8.5$ Hz), 7.28 (d, 1H, $J=2.4$ Hz), 2.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 145.6, 137.7, 136.4, 135.2, 131.5, 130.3, 124.1, 119.9, 28.9; MS (EI) *m/z* (relative intensity) 252, 254 [(M^+) 15, 10], 251, 253 (25, 11), 71 (64), 69 (100), 73 (63). **7d** White solid, $R_f \approx 0.68$ (34 mg, 21%, diethyl ether/hexanes), mp 137–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ 8.44 (d, 1H, $J=1.2$ Hz), 8.21 (d, 1H, $J=1.4$ Hz), 7.98 (d, 1H, $J=8.4$ Hz), 7.87 (d, 1H, $J=1.2$ Hz), 7.61 (dd, 1H, $J=8.4$, 1.4 Hz), 3.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 148.0, 139.3, 132.6, 132.3, 130.7, 129.6, 127.0, 125.2, 124.2, 117.6, 28.6; MS (EI) *m/z* (relative intensity) 314, 316 [(M^+) 13, 10], 249, 251 (100, 65); Anal. Calcd for $C_{12}H_8Cl_2N_2O_2S$ 315.18: C, 45.73; H, 2.56; N, 8.89; S, 10.17%. Found: C, 45.94; H, 2.66; N, 8.79; S, 9.98%.

4.4.5. [5-Chloro-3-(4-nitro-phenyl)-pyridin-2-yl]-methyl-amine 5e. The general procedure (method H) using **11e** as the starting sulfonamide (203 mg) gave a after purification by flash chromatography, only pure compound **5e**. Yellow solid, $R_f \approx 0.54$ (43.5 mg, 33%, hexanes), mp 128–130 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.00 (d, 1H, $J=2.5$ Hz), 7.62 (d, 2H, $J=8.4$ Hz), 7.49 (d, 2H, $J=8.4$ Hz), 7.36 (d, 1H, $J=2.5$ Hz), 2.88 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 156.3, 148.6, 145.6, 137.9, 137.7, 130.3, 127.4, 121.7, 120.0, 28.9; MS (EI) *m/z* (relative intensity) 263, 265 [(M^+) 3, 1], 248 (100), 247 (55); Anal. Calcd for $C_{12}H_{10}ClN_3O_2$ 263.69: C, 54.66; H, 3.82; N, 15.94%. Found C, 54.94; H, 3.88; N, 16.17%.

4.4.6. 3-Chloro-10H-9-thia-1,10-diaza-phenanthrene 9,9-dioxide 7f and *N*-(5-chloro-pyridin-2-yl)benzene-sulfonamide 10. The general procedure (method H) using **9a** as unsubstituted sulfonamide (174 mg) gave a mixture of products. After separation by flash chromatography, pure compounds **7f** and **10** were obtained. **7f** pale yellow solid, $R_f \approx 0.66$ (44 mg, 33%, diethyl ether/hexanes), mp >250 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (d, 1H, $J=2.3$ Hz), 8.37 (d, 1H, $J=7.1$ Hz), 8.36 (d, 1H, $J=2.3$ Hz), 7.94 (dd, 1H, $J=7.4$, 1.8 Hz), 7.75 (m, 2H), 4.50 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.6, 148.8, 135.2, 133.0, 131.3, 129.6, 127.5, 124.7, 121.9, 117.0, 108.2; MS (EI) *m/z* (relative intensity) 267, 269 [($M^+ +1$) 9, 4], 266, 268 [(M^+) 62, 24], 203, 205 (19, 9), 202, 204 (100, 52), 140 (69), 113 (31); Anal. Calcd for $C_{11}H_7ClN_2SO_2$ 266.71: C, 49.54; H, 2.65; N, 10.50, S, 12.02%. Found C, 49.66; H, 2.84; N, 10.71; S, 11.86%. **10** white solid, $R_f \approx 0.62$ (10 mg, 7%, hexanes), mp 156–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, 1H, $J=2.3$ Hz), 8.20 (bs, 1H), 7.81 (d, 2H, $J=7.1$ Hz), 7.62 (dd, 1H, $J=8.5$, 2.3 Hz), 7.55 (d, 1H, $J=8.5$ Hz), 7.44 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 146.9, 139.5, 138.7, 133.3, 133.0, 129.2, 127.0, 113.0; MS (EI) *m/z* (relative intensity) 268, 270 [(M^+) 3, 1], 203, 205 (60, 21), 77 (100); Anal. Calcd for $C_{11}H_9ClN_2O_2S$ 268.72: C, 49.17; H, 3.38; N, 10.42; S, 11.93%. Found: C, 48.97; H, 3.65; N, 10.46; S, 12.07%.

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References and notes

1. Ollis, D. W.; Stanforth, S. P. *Tetrahedron* **1985**, *41*, 2239–2339.
2. Sliva, W. *Heterocycles* **1991**, *32*, 2241–2272, and references cited therein.
3. (a) Vaquero, J. J.; Alvarez-Builla, J. *Adv. Nitrogen Heterocycl.* **2000**, *4*, 159–250. (b) Carceller, R.; García-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **1993**, *34*, 2019–2020. (c) Burgos, C.; Delgado, F.; García-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **1995**, *51*, 8649–8654. (d) García de Viedma, A.; Martínez-Barrasa, V.; Burgos, C.; Izquierdo, M. L.; Alvarez-Builla, J. *J. Org. Chem.* **1999**, *64*, 1007–1010. (e) Martínez-Barrasa, V.; Delgado, F.; Burgos, C.; García-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2000**, *56*, 2481–2490. (f) Reyes, M. J.; Burgos, C.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 1093–1097.
4. Núñez, A.; García de Viedma, A.; Martínez-Barrasa, V.; Burgos, C.; Alvarez-Builla, J. *Synlett* **2002**, 1093–1096.
5. (a) Motherwell, W. B.; Pennell, A. M. K. *J. Chem. Soc., Chem. Commun.* **1991**, 877–879. (b) da Mata, M. L.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 137–140. (c) da Mata, M. L.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 141–144.
6. (a) Shankaran, K.; Sloan, C. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 6001–6004. (b) Snieckus, V. *Bull. Soc. Chim. Fr.* **1988**, 66–78. (c) Harrowven, D. *Tetrahedron Lett.* **1993**, *34*, 5653–5656. (d) Jones, K.; Fiumana, A. *Tetrahedron Lett.* **1996**, *37*, 8049–8052. (e) Jones, K.; Escudero-Hernández, M. L. *Tetrahedron* **1998**, *54*, 2275–2280. (f) Nadin, A.; Harrison, T. *Tetrahedron Lett.* **1999**, *40*, 4073–4076. (g) Jones, K.; Fiumana,

A.; Escudero-Hernández, M. L. *Tetrahedron* **2000**, *56*, 397–406.
7. Bonfand, E.; Forslund, L.; Motherwell, W. B.; Vazquez, S. *Synlett* **2000**, 475–478.
8. Ryokawa, A.; Togo, H. *Tetrahedron* **2001**, *57*, 5915–5921.
9. (a) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604–8605. (b) Chen, K. M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923–1926.

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Cerium ammonium nitrate: a new catalyst for regioselective protection of glycols

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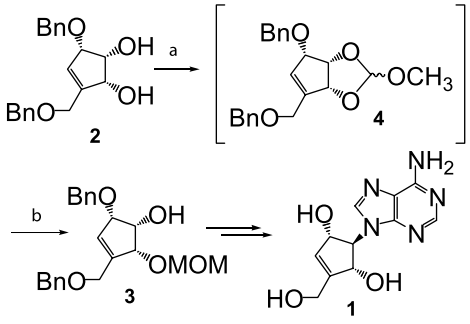
Abstract—The regioselective introduction of a methoxymethyl (MOM) group on different type of glycols via an orthoester intermediate was investigated. The novelty presented in this study is the use of ceric ammonium nitrate instead of the previously employed camphorsulfonic acid as catalyst. The monoprotection reaction was revealed to be highly selective when the glycol moiety was in the presence of an ether functionality.

1. Introduction

The selective monoprotection of polyhydroxylated compounds has been subject of research for many years because of its importance in the synthesis of complex natural products and their corresponding analogues.[1,2] In addition, the occurrence of 1,2-diols in macrolides, nucleosides and carbohydrates has led to the development of many protective groups of different stability to a range of reagents. For example, the selective protection of primary hydroxyl group versus a secondary alcohol,[3,4] the regioselective silylation of nucleosides,[5,6] and the selective monoprotection of carbohydrates[7] are some motivating cases in which regioselectivity may be necessary.

In the course of the enantioselective synthesis of (+)-neplanocin F (**1**), a synthetic challenge was the regioselective protection of the secondary allylic hydroxyl group over the secondary homoallylic hydroxyl group of the advanced synthetic intermediate **2**.[8] This problem was solved with the use of a methoxymethyl (MOM) protecting group that was able to discriminate between the allylic and homoallylic hydroxyl groups of a particular glycol. There were only two examples of this one-pot reaction reported in the literature based on orthoester formation of the corresponding diol by treatment with trimethyl orthoformate followed by in situ diisobutyl aluminum hydride reductive cleavage in methylene chloride at low temperature.[9,10] The former case illustrates the introduction of a MOM moiety onto the less sterically hindered hydroxyl group of a glycol.[9] In contrast to this report, a similar method describes the selective protection of a secondary alcohol with MOM groups in the presence of a primary alcohol.[10] These results suggested that the regioselectivity of this one pot reaction was strongly modulated by the nature of the substituents in the vicinity of the diol moiety. When **2** was reacted under these monoprotection conditions, in the presence of camphorsulfonic acid as catalyst as previously described,[9,10] only unreacted starting material was recovered. However, if the reaction is carried out employing cerium (IV) ammonium nitrate (CAN) instead of camphorsulfonic acid smoothly affords the desired MOM derivative **3** via the orthoester **4** (Scheme 1).[8] The use of a strong oxidant such as CAN as catalyst constitutes a surprising novelty for this type of reaction.[8]



Scheme 1. Reagents and conditions: (a) trimethyl orthoformate, CH_2Cl_2, CAN, rt, 2 h; (b) DIBAL, −78 °C 1 h→0 °C 10 min, 66%.

Keywords: Glycols; Regioselective monoprotection; Methoxymethyl protecting group; Diisobutyl aluminum hydride.
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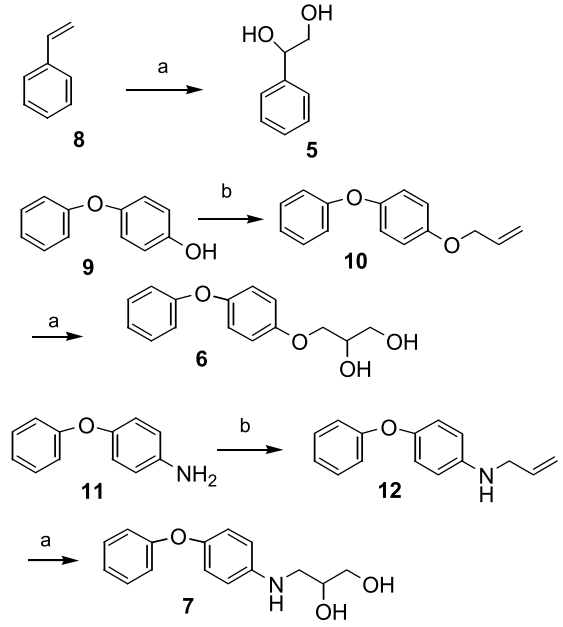
Consequently, it seems of interest to explore its scope as a general monoprotective protocol to introduce one MOM unit in glycols with vanishing environmental differences.

2. Results and discussion

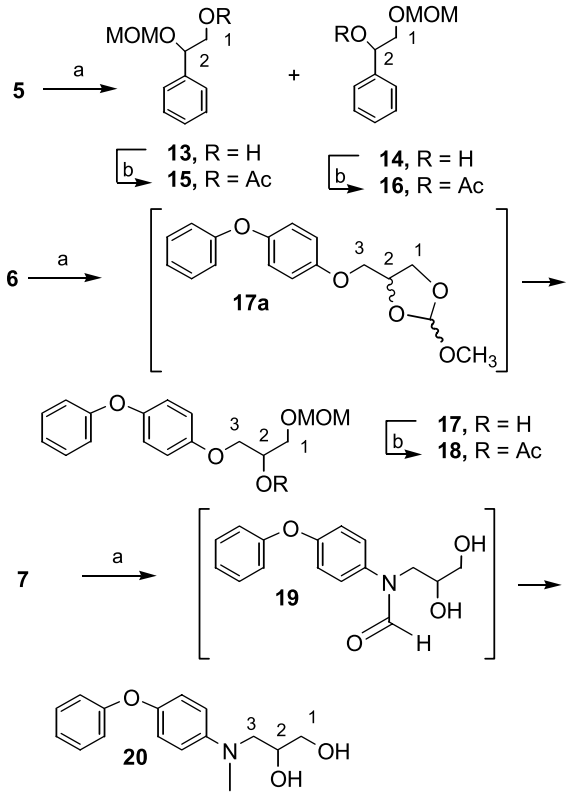
In order to investigate the reliability of this reaction, the syntheses of simple models that would mimic complex natural products were considered. Then, glycols possessing both a primary and a secondary alcohol were the first type of diols studied. The rationale for selecting the target glycols was to investigate the influence of a heteroatom in the vicinity of the glycol moiety on selectivity. The introduction of this heteroatom as an ether or amine functionality was motivated by their ability to coordinate with the aluminum atom of the diisobutyl aluminum hydride reagent improving selectivity. For this purpose, three glycols were envisioned (compounds **5**–**7**). Compound **5**, has no hetereoatoms in its chemical structure other than those of the glycol group and compounds **6** and **7** possess ether and amino groups at the α-carbon, respectively. Glycol **5** was straightforwardly prepared from styrene (**8**) via a perhydroxylation reaction[11] by treatment with potassium osmate and potassium ferricyanide in 90% yield. In a similar way, compound **6** was prepared from readily available 4-phenoxyphenyl allyl ether **10**, which in turn was prepared from 4-phenoxyphenol as described in a similar yield.[12,13] The nitrogen-containing derivative **7** was analogously prepared from 4-phenoxyaniline (compound **11**) via the allyl amine **12** (Scheme 2).

The monoprotection of glycol **5** exhibited low regioselectivity employing either CAN or CSA as catalysts. In the first case, compounds **13** and **14** were obtained in a (1.7:1) ratio favoring **13** in 81% overall yield. The regiochemistry observed for this reaction may be explained as a consequence of the hydride attack by the less hindered side of the corresponding orthoester intermediate. The chemical structure of **13** and **14** was unambiguously characterized by NMR analysis of their corresponding acetates **15** and **16**, respectively. For example, the peak centered at 4.90 ppm as a double of doublets in **13** corresponding to H-1 shifted downfield to 5.97 ppm in the acetyl derivative **15** with the same multiplicity. A similar behavior was experienced when **14** was acetylated. H-2 of **14** appeared as a multiplet centered at 3.69 ppm. This signal shifted downfield in the acetylated product **16**. This peak was observed as a double of doublets centered at 4.88 ppm. In addition, the use of the common catalyst (CSA) for this type of reaction slowed down the reaction rate as well as impaired the reaction yield without changing regioselectivity (Scheme 3).

The stereochemistry of this one-pot reaction was very encouraging when glycol **6** was used as a substrate. Certainly, **6** was reacted with trimethyl orthoformate in the presence of CAN to afford the corresponding orthoester intermediate that on reaction with DIBAL at −78 °C afforded solely the monoprotective MOM derivative **17** in 90% yield. Interestingly, when CSA was used as catalyst a similar high regioselectivity was observed but the reaction yield was lower (67% yield). In order to confirm the formation of this product, **17** was treated with acetic anhydride to yield **18**. The position of the MOM protecting group was confirmed by ^{1}H NMR analysis. The signal assigned to H-2 in **17**, which appeared as a sextet centered at 4.17 ppm, shifted downfield 1.15 ppm in **18**. The



Scheme 2. Reagents and conditions: (a) $K_2OsO_4 \cdot 2H_2O$, K_2CO_3, $K_3Fe(CN)_6$, py, *tert*-butanol–water, 90% for **5**, 87% for **6**, 89% for **7**; (b) Refs. 12,13 for **10**, KOH, $CH_2{=}CHCH_2Cl$, DMSO, rt, 72 h, 81% for **12**.



Scheme 3. Reagents and conditions: (a) i. trimethyl orthoformate, CH_2Cl_2, CAN (CSA), rt, 2 h, ii. DIBAL, −78 °C 1 h→0 °C 10 min, 81% for **13/14** (1.7:1) ratio, 32% if CSA was employed, 90% (CAN) or 67% (CSA) for **17**, 20% (CAN) for **20**; (b) Ac_2O, py, rt, 16 h, 94% for **15/16**, 97% for **18**.

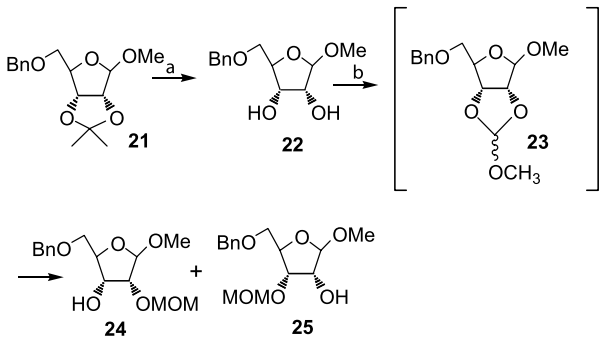
regiochemistry of this reaction was quite in agreement with our previous results on compound **2** that, under these conditions, gave rise to **3** as a single regioisomer (Scheme 3).[8] In addition, this result confirms a Block's previous work about the selective introduction of a MOM protecting group on a closely related compound.[14] Moreover, the neighboring group participation of an etherified oxygen atom has also been observed in ring-opening reaction on dioxolane-type acetals.[15,16] In addition, it has been reported that the configuration of the acetalic carbon atom strongly modulates the regiochemistry of closely related ring-cleavage reactions.[17,18] The exocyclic substituents of those acetals are two significantly different groups in size such as a phenyl (or naphtyl) group and a hydrogen atom. Therefore, the spatial orientation of the bulkier group can avoid coordination with the hydride donor through van der Waals forces, so the hydride attack occurs by the less hindered face of the molecule. In our case, the configuration of the orthoester intermediate **17a** that leads to **17** had no influence on regioselectivity. The proton NMR spectrum of this orthoester precursor showed the presence of both diastereomers as an equimolecular mixture. The characteristic peaks of this orthoester were observed as singlets at 5.80 and 5.83 ppm for the acetalic proton and at 3.35 and 3.36 ppm for the methoxy group of both diastereomers, respectively. Hence, the regioselectivity of this one-pot reaction is controlled by the presence of the vicinal ether functionality regardless of the acetalic-type carbon configuration.

The attempts for the regioselective introduction of one unit of a MOM protective group when the nitrogen-containing glycol **7** was used as a substrate were unsuccessful. It was not possible to isolate the corresponding mono-MOM derivative. Under these reaction conditions, the main product was the *N*-methyl derivative **20**. Apparently, the presence of the nitrogen atom in glycol **7** avoids formation of the corresponding orthoester intermediate. Interestingly, when diisobutyl aluminium hydride was not added to the reaction mixture, the formyl amide **19** was formed instead of the expected orthoester. Apparently, this transacetylation reaction may be catalyzed by CAN acting as a Lewis acid. Therefore, generation of the *N*-methyl derivative **20** can be rationalized by simple reduction of amide **19** by treatment with diisobutyl aluminium hydride (Scheme 3).

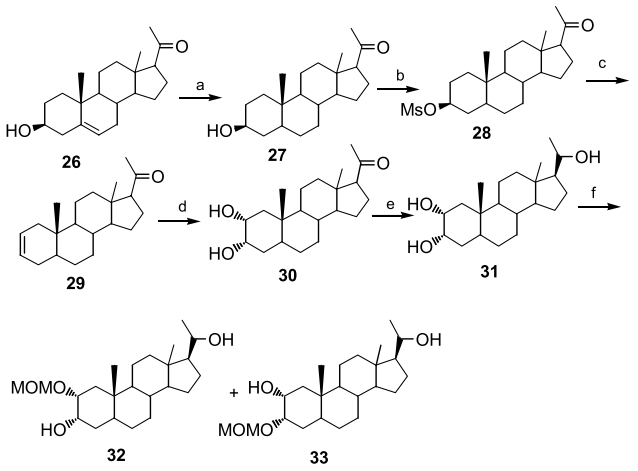
The free hydroxyl groups of methyl ribofuranoside **22** could not be regioselectively protected under this one-pot procedure as expected. The β-oriented methyl glycoside and benzyloxy groups prevent the aluminum atom of the DIBAL reagent to coordinate discriminatorily with any of the oxygen atoms present either at the anomeric center or at the C-5 position. Thus, **22** treated with trimethyl orthoformate followed by reductive ring opening with diisobutyl aluminium hydride afforded the respective MOM derivatives **24** and **25** in a (1:1) ratio. In this case, CAN also increased the reaction rate compared with CSA: 1 h after addition of diisobutyl aluminium hydride for CAN versus 5 h for CSA. At this point a valuable question rose. What is the role either of CAN or CSA? The orthoester intermediate **23** was isolated by reaction of **22** with trimethyl orthoformate employing CAN as catalyst without further addition of diisobutyl aluminium hydride. Interestingly, on treatment with diisobutyl aluminium hydride **23** was not converted into **24** and **25** in the absence of CAN, but produced the expected MOM derivatives, **24** and **25**, when this catalyst is present. That is, the catalyst is not only required for catalyzing the orthoester formation but is also essential for the reaction to complete. These results strongly suggested that CAN undoubtedly acts as a Lewis acid by catalyzing the second step of this reaction. To strength this idea, it has also been observed that the well-known electron acceptor 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) behaves as a Lewis acid in acetal removal reactions.[19,20] Compound **22** was readily prepared from **21** by isopropyliden cleavage by treatment with acetic acid, which was straightforwardly prepared from D-ribose (Scheme 4).[21]

A very similar behavior was observed when pregnan derivative **31** was employed as a substrate. In this case, only a poor selectivity was observed due to the lack of a vicinal heteroatom to coordinate with the aluminum atom present at the diisobutyl aluminium hydride reagent. Accordingly, **31** was reacted under these reaction conditions to produce **32** and **33** in a (1:1.5) ratio. Once again the absence of a heteroatom in the vicinity of the glycol group has a marked effect on regioselectivity. The use of CAN increased the reaction rate as well; in this case CAN resulted to be 3.5-fold faster than CSA. **31**, was synthesized starting from pregnenolone (**26**). Therefore, pregnenolone was treated with hydrogen in the presence of 10% palladium on activated carbon to give **27** quantitatively, which on reaction with mesyl chloride followed by an elimination reaction by treatment with lithium bromide in *N*,*N*-dimethylformamide at 120 °C[22] afforded exclusively the desired Δ-2 alkene **29** in good yield. This reaction occurred with high regioselectivity, the corresponding Δ-3 alkene was not detected. **29** was perhydroxylated by treatment with osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide[23] to afford exclusively the α-glycol **30** in 70% yield. The stereochemical course of the reaction can be justified by the presence of the angular methyl group that blocks the β-face of the A ring. Finally, **30** was treated with diisobutyl aluminium hydride to give the 20-*S* isomer **31** with high diastereoselectivity in 97% yield (Scheme 5).

On the other hand, **38**, which contains an α-oriented glycol group at the C-1 and C-2 positions as well as a vicinal α-methoxy group at the C-3 position, could be regioselectively protected at C-1 as a MOM derivative **39** but in low

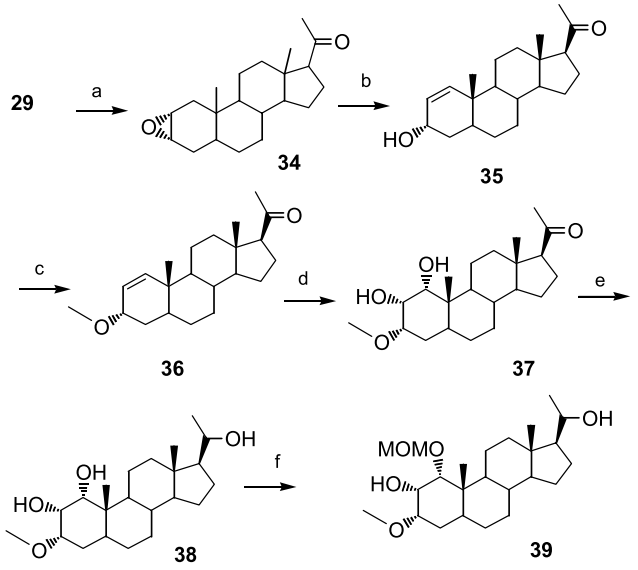


Scheme 4. Reagents and conditions: (a) 60% AcOH, 50 °C, 40 h, 63%; (b) i. trimethyl orthoformate, CH_2Cl_2, CAN, rt, 2 h, ii. DIBAL, −78 °C 1 h→ 0 °C 10 min, 92%.



Scheme 5. Reagents and conditions: (a) H_2, 10% Pd/C, EtOH, 100%; (b) ClMs, py, 0 °C, 90 min; (c) LiBr, DMF, 120 °C, 2 h, 64% from **27**; (d) $K_2OsO_4 \cdot 2H_2O$, K_2CO_3, $K_3Fe(CN)_6$, py, *tert*-butanol–water, 70%; (e) DIBAL, Cl_2CH_2, −78 °C, 45 min, 97%; (f) i. trimethyl orthoformate, CH_2Cl_2, CAN (CSA), rt, 2 h, ii. DIBAL, −78 °C 1 h→0 °C 10 min, 38% for **32** (CAN), 55% for **33** (CAN), 32% for **32** (CSA), 37% for **33** (CSA).

yields either with CAN or CSA. Compound **39** was unstable on standing but the fact that the presence of the methoxy group that is able to coordinate with the reducing agent strengthens the assumption that an oxygen atom in the surroundings of the glycol is required to warrant high regioselectivity. In connection with the reaction rate, once again CAN was more efficient than CSA as catalyst (2 h for CAN versus 4 h for CSA). **38** was prepared starting from **29** as illustrated in Scheme 6. Therefore, **29** treated with *m*-chloroperbenzoic acid gave rise to the α-epoxy derivative **34** in 59% yield, which on reaction with diphenyldiselenide[24] and sodium borohydride followed by treatment with *t*-butylhydroperoxide was converted into **35** in 48% yield. Compound **35** treated with sodium hydride and iodomethane led to the α-methoxy derivative **36** in 53% yield that was reacted with osmiun tetroxide/*N*-methylmorpholine-*N*-oxide to afford the corresponding α-1,2-glycol **37** in 52% yield. Finally, the target molecule **38** was obtained by treatment with diisobutyl aluminium hydride in 92% yield (Scheme 6).



Scheme 6. Reagents and conditions: (a) *m*-CPBA, Cl_2CH_2, 0 °C→rt, 1 h, 59%; (b) i. PhSeSePh, $NaBH_4$, EtOH–THF (1:1), reflux, 6 h, ii. 70% ^{t}BuOOH, reflux, 1 h, 48%; (c) NaH, IMe, THF, 0 °C, 53%; (d) $K_2OsO_4 \cdot 2H_2O$, K_2CO_3, $K_3Fe(CN)_6$, py, *tert*-butanol–water, 52%; (e) DIBAL, Cl_2CH_2, −78 °C, 1 h, 92%; (f)) i. trimethyl orthoformate, CH_2Cl_2, CAN, rt, 2 h, ii. DIBAL, −78 °C 1 h→0 °C 10 min, 17%.

In conclusion, we studied the scope of this interesting one-pot monoprotection reaction that employs ceric ammonium nitrate as catalyst. The use of CAN resulted in better yields than the employment of camphorsulfonic acid. Moreover, CAN notably accelerated the rate of the reaction compared with CSA in all cases but no differences in regioselectivity was observed between both catalysts. In addition, the presence of a heteroatom in the vicinity of a specific glycol such as oxygen had a profound effect on regioselectivity. It is worth to point out that hydride attack did not proceed in the absence of catalyst once the orthoester was formed. These evidences indicated that CAN is not only required to catalyze orthoester formation but is also essential for hydride attack to take place. Therefore, in this reaction, CAN works as a Lewis acid regardless its strong oxidant properties. Efforts to study the potential use of this reaction in more complex models as well as to investigate the reaction mechanism in detail are currently being pursued in our laboratory.

3. Experimental

3.1. General

Unless otherwise noted, all reagents were commercially available. All moisture sensitive reactions were performed under dry atmosphere of argon and all the glassware used in air and/or moisture sensitive reactions was flame-dried. Methylene chloride was distilled from P_2O_5 and stored over 4 Å molecular sieves.

Nuclear magnetic resonance spectra were recorded using a Bruker AC-200 MHz or a Bruker AM-500 MHz spectrometers. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. The ^{1}H NMR spectra are referenced with respect to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at 7.26 ppm. Coupling constants are reported in Hertz. ^{13}C NMR spectra were fully decoupled and are referenced to the middle peak of the solvent $CDCl_3$ at 77.0 ppm. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet.

Melting points were determined using a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded using a Nicolet Magna 550 spectrometer. Low-resolution mass spectra were obtained on a VG TRIO 2 instrument in electron impact mode at 70 eV (direct inlet).

Column chromatography was performed on silica gel 60 (230–240 mesh) and analytical TLC was performed on commercial 0.2 mm aluminum coated silica gel plates (Kieselgel 60 F_{254}) and visualized by UV light (254 nm) or by immersion in ethanolic 5% H_2SO_4. Elemental analyses were conducted by Atlantic Microlab Inc., Norcross, Georgia.

3.1.1. 1-Phenyl-ethane-1,2-diol (5). A mixture of styrene (compound **8**; 500 mg, 4.80 mmol), *tert*-butanol–water (1:1) (20 mL), pyridine (3.8 μL, 0.05 mmol), potassium ferricyanide (10.9 g, 14.40 mmol), potassium carbonate (284 mg, 14.40 mmol), and potassium osmate dihydrate (3.6 mg, 0.01 mmol) was stirred at room temperature for 24 h. An aqueous saturated solution of sodium bisulfite was added until no evolution of bubbles was observed. The aqueous phase was extracted with ethyl acetate (5×10 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using hexane–EtOAc (3:2) as eluent to afford 597 mg (90% yield) of pure glycol **5** as a white solid: R_f 0.13 (3:2, hexane–ethyl acetate); mp 63–64 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37 (m, 5H), 4.82 (m, 1H), 3.72 (m, 2H), 2.58 (broad s, 1H), 2.14 (broad s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.5, 128.5, 128.0, 126.1, 74.7, 68.1.

3.1.2. 3-(4-Phenoxy-phenoxy)propane-1,2-diol (6). A mixture of compound **10** (500 mg, 2.21 mmol), *t*-butanol/water (1:1) (20 mL), pyridine (1.8 μL, 0.02 mmol), potassium ferricyanide (2.18 g, 6.64 mmol), potassium carbonate (1.10 g, 6.64 mmol) and potassium osmate dihydrate (1.6 mg, 0.005 mmol) was stirred at room temperature for 48 h. The reaction mixture was quenched as depicted for the preparation of compound **5**. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (2:3) as eluent to afford 500 mg (87% yield) of pure diol **6** as a white solid: R_f 0.21 (hexane–EtOAc, 1:1); mp 86–87 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (m, 2H), 6.96 (m, 7H), 4.11 (sxt, J=4.9 Hz, 1H), 4.04 (m, 2H), 3.87 (dd, J=11.2, 3.9 Hz, 1H), 3.87 (dd, J=11.2, 5.4 Hz, 1H), 2.79 (broad s, 1H), 2.26 (broad s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.2, 154.6, 150.7, 129.6, 122.6, 120.7, 117.7, 115.6, 70.4, 69.7, 63.6; MS (*m*/*z*, relative intensity) 260 (M^+, 28), 186 (100). Anal. calcd for $C_{15}H_{16}O_4$: C 69.22, H 6.20. Found: C 69.23, H 6.07.

3.1.3. *N*-Allyl [4-phenoxy]aniline (12). To a solution of *p*-phenoxyaniline (2.0 g, 10 mmol) in dimethylsulfoxide (20 mL) was added potassium hydroxide (2.5 g, 10 mmol). The mixture was stirred at room temperature for 10 min. Then, allyl chloride (0.9 mL, 10 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 72 h. The mixture was partitioned between water (50 mL) and methylene chloride (50 mL). The aqueous phase was extracted with methylene chloride (2×30 mL). The combined organic layers were washed with a saturated solution of sodium chloride (5×50 mL), dried ($MgSO_4$), and the solvent was removed. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (199:1) as eluent to afford 2.05 g (81% yield) of pure compound **12** as a colorless oil: R_f 0.36 (hexane–EtOAc, 17:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (m, 2H), 6.93 (m, 5H), 6.61 (d, J=9.2 Hz, 2H), 5.97 (ddt, J=17.2, 10.4, 5.1 Hz, 1H), 5.29 (dd, J=17.2, 1.5 Hz, 1H), 5.18 (dq, J=10.0, 1.5 Hz, 1H), 3.76 (dt, J=6.0, 2.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.1, 147.8, 144.7, 135.5, 129.7, 122.0, 121.2, 117.1, 116.3, 114.0, 47.1; MS (*m*/*z*, relative intensity) 225 (M^+, 77), 198 (21), 184 (54), 129 (36), 77 (100).

3.1.4. 3-(4-Phenoxy-phenylamino)propane-1,2-diol (7). A solution of compound **12** (408 mg, 1.81 mmol) in *tert*-butanol–tetrahydrofuran–water (10:3:1; 5.0 mL) was treated with *N*-methylmorpholine-*N*-oxide (233 mg, 1.99 mmol) and osmiun tetroxide (10 mg). The mixture was stirred at room temperature overnight. The reaction mixture was quenched by addition of an aqueous saturated solution of sodium bisulfite (5.0 mL) and was extracted with methylene chloride (3×15 mL). The combined organic phases were washed with brine (3×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (6:1) as eluent to afford 420 mg (89% yield) of compound **7** as a brown solid: R_f 0.10 (1:1, hexane–EtOAc); mp 84–86 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H, aromatic protons), 6.96 (m, 5H, aromatic protons), 6.67 (m, 2H, aromatic protons), 3.99 (m, 1H, H-2), 3.82 (dd, J=11.2, 3.9 Hz, 1H, H-1_a), 3.67 (dd, J=11.2, 5.9 Hz, 1H, H-1_b), 3.30 (dd, J=13.9, 5.8 Hz, 1H, H-3_a), 3.19 (dd, J=13.9, 5.6 Hz, 1H, H-3_b), 2.55 (broad s, 2H, *OH*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.8, 148.8, 144.8, 129.4, 122.0, 121.0, 117.0, 114.4, 70.3, 64.6, 47.1; MS (*m*/*z*, relative intensity) 259 (M^+, 22), 198 (100).

3.1.5. 2-Methoxymethoxy-2-phenyl-ethanol (13); 2-methoxymethoxy-1-phenyl-ethanol (14). *Method A*. A solution of compound **5** (108 mg, 0.78 mmol) in anhydrous methylene chloride (10 mL) was treated with trimethyl orthoformate (120 μL, 1.08 mmol) in the presence of cerium ammonium nitrate (5 mg) under argon atmosphere. The reaction mixture was stirred at room temperature for 2 h and then was cooled at −78 °C. Then, diisobutyl aluminium hydride was added (1.0 mL, 5.40 mmol). The mixture was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to 0 °C and was stirred for additional 10 min. The reaction was worked up by addition of an aqueous 1.0 N solution of hydrochloric acid (2 mL) and an aqueous saturated solution of sodium and potassium tartrate (10 mL). The resulting mixture was extracted with methylene chloride (3×10 mL). The combined organic layers were washed with brine (2×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (1:1) as eluent to give 115 mg (81% yield) of a mixture of regioisomers **13** and **14** in a (1:1.7) ratio as a colorless oil. Compound **13**: R_f 0.36 (hexane–EtOAc, 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.90 (dd, J=8.5, 3.0 Hz, 1H), 4.69 (m*AB*, 2H), 3.79 (dd, J=10.6, 3.1 Hz, 1H), 3.79 (dd, J=10.6, 8.4 Hz, 1H), 3.38 (s, 3H). Compound **14**: R_f 0.44 (3:2, hexane–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.70 (m, 1H), 4.66 (m*AB*, 2H), 3.69 (m, 2H), 3.40 (s, 3H).

Method B. A solution of compound **5** (88 mg, 0.64 mmol) in anhydrous methylene chloride (10 mL) was treated as described in method A but employing camphorsulfonic acid (CSA, 5 mg) instead of ceric ammonium nitrate as catalyst. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (1:1) as eluent to afford 37 mg (32% yield) of a mixture of regioisomers **13** and **14** in a (1:1.6) ratio.

3.1.6. (2-Methoxymethoxy-2-phenyl)ethyl) acetate (15); [(2-methoxymethoxy-1-phenyl)ethyl] acetate (16). To a

solution of a mixture of compounds **13** and **14** (42 mg) in pyridine (1.0 mL) was added acetic anhydride (0.5 mL). The reaction mixture was stirred at room temperature overnight. Then, an aqueous 5% solution of hydrochloric acid was added and the mixture was stirred for an additional hour. The reaction mixture was partitioned between water (2.0 mL) and ethyl acetate (5.0 mL). The organic phase was washed with 5% HCl (2 mL) and brine (2×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (9:1) to afford 48 mg (94%) of an 1.2:1 ratio of a mixture of acetates **15** and **16** as a colorless oil. Compound **15**: R_f 0.53 (hexane–EtOAc, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.97 (dd, J=7.7, 4.4 Hz, 1H), 4.63 (m*AB*, 2H), 3.86 (dd, J=11.0, 7.7 Hz, 1H), 3.75 (dd, J=11.0, 4.4 Hz, 1H), 3.31 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.5, 128.5, 128.3, 126.7, 96.4, 74.6, 69.9, 55.3, 21.2. Compound **16**: R_f 0.45 (hexane–EtOAc, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (m, 5H), 4.88 (dd, J=6.5, 5.1 Hz, 1H), 4.61 (m*AB*, 2H), 4.26 (m*AB*, 2H), 3.39 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.8, 128.6, 128.4, 127.1, 94.3, 75.6, 67.7, 55.4, 20.9.

3.1.7. 1-Methoxymethoxy-3-(4-phenoxy-phenoxy)propan-2-ol (17). A solution of compound **6** (230 mg, 0.88 mmol) in anhydrous methylene chloride (20 mL) was treated as depicted for the preparation of compound **13** (Method A). The crude product was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (4:1) to afford 240 mg (90% yield) of pure compound **17** as a colorless oil: R_f 0.48 (hexane–EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 2H), 6.98 (m, 7H), 4.70 (m*AB*, 2H), 4.17 (sxt, J=5.0 Hz, 1H), 4.02 (d, J=5.5 Hz, 2H), 3.79 (dd, J=10.5, 4.1 Hz, 1H), 3.72 (dd, J=10.5, 5.9 Hz, 1H), 3.40 (s, 3H), 2.80 (d, J=4.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.2, 154.7, 150.4, 129.5, 122.4, 120.6, 117.6, 115.5, 96.7, 69.4, 69.3, 69.1, 55.3; MS (*m*/*z*, relative intensity) 304 (M^+, 13), 186 (48), 45 (100). Anal. calcd for $C_{17}H_{20}O_5$: C 67.09, H 6.62. Found: C 67.00, H 6.70.

A solution of diol **6** (230 mg, 0.88 mmol) in anhydrous methylene chloride (20 mL) was treated as depicted for compound **13** (method B). The product was purified by column chromatography (silica gel) employing hexane–EtOAc (4:1) as eluent to give 180 mg (67% yield) of pure **17** as a colorless oil.

3.1.8. 2-Methoxy-4-(4-phenoxyphenoxymethyl)-[1,3]-dioxolane (17a). A solution of compound **6** (25 mg, 0.10 mmol) in anhydrous methylene chloride (5 mL) was treated with trimethyl orthoformate (21 μL, 0.20 mmol) and CAN (5 mg) under argon atmosphere. The mixture was stirred at room temperature for 2 h. The reaction was worked up by addition of an aqueous saturated solution of sodium bicarbonate (5 mL). The mixture was extracted with methylene chloride (3×5 mL). The combined organic layers were washed with water (2×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by preparative TLC eluting with hexane–EtOAc (3:2) to afford 29 mg (95% yield) of **17a** as an equimolecular diastereomeric mixture as colorless oils: R_f 0.69, 0.66 (hexane–EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.05 (m, 1H), 6.97 (m, 4H), 6.89 (m, 2H), 5.83, 5.80 (s, 1H), 4.65, 4.53 (p, J=6.5 Hz, 1H), 4.25, 4.20 (m, 2H), 4.04 (m, 2H), 4.04, 3.96 (m, 2H), 3.36, 3.35 (s, 3H).

3.1.9. 1-Methoxymethoxy-3-(4-phenoxy-phenoxy)propan-2-yl Acetate (18). To a solution of compound **17** (56 mg, 0.18 mmol) in pyridine (1 mL) was added acetic anhydride (0.5 mL) as depicted for compounds **15** and **16**. After the usual workup, the product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (19:1) to afford 62 mg (97% yield) of pure compound **18** as a colorless oil: R_f 0.75 (hexane–EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, J=7.9 Hz, 2H), 7.04 (t, J=7.6 Hz, 1H), 6.96 (d, J=8.9 Hz, 2H), 6.94 (d, J=8.7 Hz, 2H), 6.89 (d, J=9.1 Hz, 2H), 5.32 (p, J=5.0 Hz, 1H), 4.65 (m*AB*, 2H), 4.15 (dd, J=10.2, 5.0 Hz, 1H), 4.12 (dd, J=10.2, 5.2 Hz, 1H), 3.82 (m*AB*, 2H), 3.36 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 158.3, 154.7, 150.7, 129.6, 122.6, 120.7, 117.7, 115.8, 96.6, 71.0, 66.8, 65.8, 55.3, 21.0; MS (*m*/*z*, relative intensity) 346 (M^+, 5), 186 (9), 161 (54), 131 (38), 71 (32), 45 (100). Anal. calcd for $C_{19}H_{22}O_6$: C 65.88, H 6.40. Found: C 66.17, H 6.62.

3.1.10. *N*-(2,3-Dihydroxy-propyl)-*N*-(4-phenoxyphenyl)-formamide (19); 3-[methyl-(4-phenoxy-phenyl)-amino]-propane-1,2-diol (20). A solution of compound **7** (80 mg, 0.31 mmol) in methylene chloride (10 mL) was treated as described for the preparation of **13** (Method A). The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (4:1) to afford 16 mg (20% yield) of compound **20** as a colorless oil. In an independent experiment, compound **19** was isolated as a white solid in 90% yield when DIBAL was not added to the reaction mixture. Compound **19**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.37 (m, 2H), 7.17 (m, 3H), 7.03 (d, J=Hz, 2H), 3.93 (dd, J=15.9, 8.2 Hz, 1H), 3.87 (m, 2H), 3.66 (m, 1H), 3.59 (dd, J=11.6, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 157.0, 156.4, 135.9, 130.0, 126.4, 124.0, 119.42, 119.37, 70.1, 63.6, 49.2. Compound **20**: R_f 0.25 (hexane–EtOAc, 2:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.96 (m, 5H), 6.82 (m, 2H), 4.02 (ddt, J=8.0, 5.0, 3.4 Hz, 1H), 3.80 (dd, J=11.4, 3.3 Hz, 1H), 3.58 (dd, J=11.4, 5.1 Hz, 1H), 3.39 (dd, J=14.3, 8.1 Hz, 1H), 3.25 (dd, J=14.7, 5.1 Hz, 1H), 2.94 (s, 3H), 2.09 (broad s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.7, 147.1, 142.6, 129.5, 122.2, 120.8, 117.4, 115.1, 69.4, 64.3, 56.9, 39.9; MS (*m*/*z*, relative intensity) 273 (M^+, 9), 212 (100), 197 (17).

3.1.11. Methyl 5-benzyloxy-β-D-ribofuranoside (22). Protected D-ribose derivative **21** (900 mg, 3.06 mmol) was treated with 60% acetic acid (5 mL). The reaction mixture was stirred at 50 °C for 40 h. The solvent was evaporated and the product was purified by column chromatography (silica gel) employing hexane–EtOAc (7:3) as eluent to afford 450 mg (63% yield) of pure compound **22** as a yellowish oil: R_f 0.15 (hexane–EtOAc, 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H, aromatic protons), 4.83 (s, 1H, H-1), 4.59 (m*AB*, 2H, OCH_2Ph), 4.19 (t, J=5.7 Hz, 1H, H-3), 4.09 (q, J=5.7 Hz, 1H, H-4), 4.00 (d, J=4.8 Hz, 1H, H-2), 3.63 (dd, J=10.0, 5.9 Hz, 1H, H-5$_a$), 3.60 (dd, J=10.0, 5.5 Hz, 1H, H-5$_b$), 3.33 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9 (C-1′), 128.4 (C-3′), 127.8

(C-4′), 127.7 (C-2′), 108.3 (C-1), 81.8 (C-4), 75.1 (C-2), 73.5 (O*C*H$_2$Ph), 73.0 (C-3), 71.9 (C-5), 55.1 (O*C*H$_3$).

3.1.12. Methyl 5-benzyloxy-2,3-*O*-methoxymethylidene-β-D-ribofuranoside (23). A solution of compound **22** (110 mg, 0.43 mmol) in anhydrous methylene chloride (10 mL) was treated with trimethyl orthoformate (95 μL, 0.87 mmol) in the presence of ceric ammonium nitrate (30 mg) and the mixture was stirred at room temperature for 2 h. The solution was quenched by addition of an aqueous saturated solution of sodium bicarbonate (10 mL). The mixture was extracted with methylene chloride (3×10 mL). The combined organic layers were washed with water (2×10 mL), dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (19:1) to afford 90 mg (71% yield) of pure orthoester **23** as a colorless oil: R_f 0.61 (hexane–EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (M, 5H), 5.86 (s, 1H), 4.97 (s, 1H), 4.81 (d, J=6.0 Hz, 1H), 4.67 (d, J=6.0 Hz, 1H), 4.55 (m*AB*, 2H), 4.39 (dist t, J=7.2 Hz, 1H), 3.54 (dd, J=9.7, 6.4 Hz, 1H), 3.48 (dd, J=9.7, 8.2 Hz, 1H), 3.30 (s, 3H), 3.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 128.4, 127.7, 117.4, 108.7, 84.6, 84.1, 81.5, 73.3, 70.7, 54.8, 51.4.

3.1.13. Methyl 5-benzyloxy-2-methoxymethoxy-β-D-ribofuranoside (24); methyl 5-benzyloxy-3-methoxymethoxy-β-D-ribofuranoside (25). A solution of compound **22** (125 mg, 0.50 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method A). Once DIBAL was added, the mixture was stirred at −78 °C for 1 h. After the usual workup, the product was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (4:1) to give 135 mg (92% yield) of an equimolecular mixture of alcohols **24** and **25** as a colorless oil: Compound **24**: R_f 0.23 (hexane–EtOAc, 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.91 (s, 1H), 4.78 (s, 2H), 4.61 (m*AB*, 2H), 4.18 (m, 1H), 4.07 (m, 1H), 3.95 (d, 1H), 3.69–3.54 (m, 4H), 3.43 (s, 3H), 3.35 (s, 3H), 2.67 (s, 1H). Compound **25**: R_f 0.23 (3:2, hexane–ethyl acetate), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.87 (s, 1H), 4.68 (s, 2H), 4.60 (m*AB*, 2H), 4.18 (m, 2H), 4.07 (m, 1H), 3.69–3.54 (m, 2H), 3.37 (s, 3H), 3.34 (s, 3H), 2.67 (s, 1H).

A solution of compound **22** (125 mg, 0.50 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method B). After DIBAL addition, the mixture was stirred at −78 °C for 5 h. Purification of the product afforded 50 mg (34% yield) of an equimolecular mixture of compounds **24** and **25**.

3.1.14. 3α-Hydroxy-5α-pregnan-20-one (27). A solution of pregnenolone (compound **26**; 10.0 g, 31.60 mmol) in absolute ethanol (600 mL) was treated with hydrogen at atmospheric pressure in the presence of 10% palladium on activated carbon (1.0 g). The reaction mixture was stirred at room temperature for 4 h. The mixture was filtered through a celite column and the solvent was evaporated to afford 10.1 g (100% yield) of compound **27** as a white solid. The product was used as such in the next step without further purification: R_f 0.27 (hexane–EtOAc, 7:3), mp 182–185 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.58 (m, 1H), 2.51 (m, 1H), 2.10 (s, 3H), 0.79 (s, 3H), 0.59 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.5, 71.3, 63.9, 56.7, 54.2, 44.8, 44.3, 39.1, 38.1, 37.0, 35.5, 35.3, 32.0, 31.5, 28.9, 28.6, 24.4, 22.8, 21.3, 13.5, 12.3; MS (*m*/*z*, relative intensity) 318 (M^+, 40), 300 (25), 215 (37), 55 (100).

3.1.15. 3α-Methanesulphonyl-5α-pregn-2-en-20-one (28). To a solution of compound **27** (10.1 g, 31.60 mmol) in pyridine (100 mL) at 0 °C was added methanesulphonyl chloride (3.05 mL, 39.19 mmol) and the mixture was stirred at this temperature for 1.5 h. The reaction was quenched by addition of aqueous solution of 5% hydrochloric acid. The mixture was extracted with methylene chloride (3×70 mL) and the combined organic layers were washed with 5% HCl (3×50 mL), brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated to afford crude compound **28**, which was used as such in the next step. An analytical sample was purified by column chromatography (silica gel) for characterization employing hexane–EtOAc (19:1) as eluent to afford pure compound **28** as a white solid: mp 110–112 °C; R_f 0.38 (hexane–EtOAc, 7:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.62 (m, 1H), 2.99 (s, 3H), 2.49 (m, 1H), 2.10 (s, 3H), 0.82 (s, 3H), 0.60 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.5, 81.9, 63.7, 56.5, 53.9, 44.8, 44.2, 38.9, 38.8, 36.8, 35.4, 35.3, 35.1, 31.8, 31.5, 28.6, 28.3, 24.3, 22.8, 21.2, 13.4, 12.1; MS (*m*/*z*, relative intensity) 396 (M^+, 19), 378 (22), 300 (27), 215 (58), 79 (100).

3.1.16. 5α-Pregn-2-en-20-one (29). A solution of compound **28** in anhydrous *N*,*N*-dimethylformamide (100 mL) was treated with lithium bromide (9.93 g, 114.31 mmol). The reaction mixture was stirred at 120 °C for 2 h and the mixture was allowed to cool to 0 °C, and water (100 mL) was added. The mixture was extracted with ethyl acetate (3×100 mL). The organic phase was washed with brine (50 mL) and water (2×50 mL), dried (Na_2SO_4) and the solvent was evaporated in vacuo. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (49:1) as eluent to afford 6.08 g (64% yield from **27**) of pure compound **29** as a white solid: mp 90–92 °C, R_f 0.56 (hexane–EtOAc, 9:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.59 (m, 2H), 2.51 (m, 1H), 2.11 (s, 3H), 0.74 (s, 3H), 0.60 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.7, 125.9, 125.8, 63.8, 56.7, 53.9, 44.2, 41.4, 39.7, 39.1, 35.6, 34.6, 31.8, 31.6, 30.2, 28.6, 24.4, 22.7, 20.9, 13.4, 11.7; MS (*m*/*z*, relative intensity) 300 (M^+, 21), 285 (8), 257 (10), 246 (21), 215 (18), 55 (100).

3.1.17. 2α,3α-Dihydroxy-5α-pregnan-20-one (30). To a solution of compound **29** (309 mg, 1.03 mmol) in *tert*-butanol–tetrahydrofuran–water (10:3:1, 5 mL) was added *N*-methylmorpholine-*N*-oxide (132 mg, 1.13 mmol) and osmiun tetroxide (10 mg). The reaction mixture was stirred at room temperature overnight. Then, the reaction was quenched by addition of an aqueous saturated solution of sodium bisulfite (5 mL). The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic phases were washed with an aqueous saturated solution of sodium bisulfite (5 mL), brine (2×5 mL), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (7:3) to afford 237 mg (70% yield) of compound **30** as a white solid: mp 190–193 °C; R_f 0.26

(hexane–EtOAc, 3:7); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.96 (m, 1H), 3.82–3.72 (m, 1H), 2.53 (m, 1H), 2.11 (s, 3H), 0.80 (s, 3H), 0.60 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.8, 69.2, 69.0, 63.7, 56.6, 54.3, 44.3, 40.9, 39.0, 38.1, 36.9, 34.8, 34.2, 31.7, 31.5, 27.5, 24.4, 22.8, 20.8, 13.4, 12.4; MS (*m*/*z*, relative intensity) 334 (M^+, 55), 316 (82), 298 (25), 231 (44), 55 (100).

3.1.18. (20*S*)-2α,3α-Dihydroxy-5α-pregnan-20-ol (31). To a solution of diol **30** (564 mg, 1.69 mmol) in anhydrous methylene chloride (80 mL) cooled at −78 °C was added dropwise a solution of diisobutyl aluminium hydride (0.66 mL, 3.71 mmol) in methylene chloride (3 mL) under an argon atmosphere. The reaction mixture was stirred at −78 °C for 45 min. Then, the reaction was quenched by addition of 5% aqueous hydrochloric acid (10 mL) and an aqueous saturated solution of sodium potassium tartrate (20 mL). The aqueous layer was extracted with methylene chloride (2×30 mL). The combined organic layers were washed with brine (2×20 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (7:3) to give 550 mg (97% yield) of compound **31** as a white solid: mp 200–203 °C, R_f 0.33 (hexane–EtOAc 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (m, 1H), 3.78–3.69 (m, 2H), 1.13 (d, J=6.2 Hz, 3H), 0.81 (s, 3H), 0.74 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.5, 69.3, 69.1, 58.6, 55.9, 54.3, 42.6, 41.0, 40.1, 38.2, 37.0, 34.7, 34.2, 31.9, 27.7, 25.7, 24.5, 23.6, 20.8, 12.6, 12.4; MS (*m*/*z*, relative intensity) 336 (M^+, 1), 318 (27), 250 (31), 232 (91), 45 (100).

3.1.19. (20*S*)-3α-Hydroxy-2α-methoxymethoxy-5α-pregnan-20-ol (32); (20*S*)-2α-hydroxy-3α-methoxymethoxy-5α-pregnan-20-ol (33). A solution of compound **31** (105 mg, 0.31 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method A). Once DIBAL addition, the mixture was stirred at −78 °C for 2 h. After the usual workup, the product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (7:3) to afford 45 mg (38% yield) of compound **32** and 64 mg (55% yield) of compound **33** as white solids. Compound **32**: mp 138–140 °C, R_f 0.37 (hexane–EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (m*AB*, 2H, OCH_2OCH_3), 4.02 (m, 1H, H-3), 3.69 (m, 2H, H-2, H-20), 3.38 (s, 3H, OCH_3), 1.12 (d, J=6.2 Hz, 3H, H-21), 0.80 (s, 3H, H-19), 0.74 (m, 3H, H-18); ^{13}C NMR (50 MHz, $CDCl_3$) δ 94.7 (OCH_2O), 74.8 (C-2), 70.6 (C-20), 67.7 (C-3), 58.6 (C-17), 55.9 (C-14), 55.5 (OCH_3), 54.2 (C-9), 42.5 (C-13), 40.1 (C-12), 38.2 (C-5), 38.2 (C-1), 36.8 (C-10), 34.7 (C-8), 33.7 (C-4), 31.8 (C-7), 27.6 (C-6), 25.6 (C-16), 24.4 (C-15), 23.6 (C-21), 20.8 (C-11), 12.6 (C-18), 12.4 (C-19); MS (*m*/*z*, relative intensity) 381 (M^+, 1), 318 (23), 45 (100). Anal. calcd for $C_{23}H_{40}O_4$: C 72.59, H 10.59. Found: C 70.13, H 10.59. Compound **33**: mp 183–185 °C, R_f 0.25 (hexane–EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (d, J=6.6 Hz, 1H, OCH_aHOCH_3), 4.70 (d, J=6.6 Hz, 1H, OCH_bHOCH_3), 3.82 (m, 1H, H-3), 3.72 (m, 1H, H-20), 3.64 (m, 1H, H-2), 3.42 (s, 3H, OCH_3), 1.13 (d, J=5.9 Hz, 3H, H-21), 0.81 (s, 3H, H-19), 0.74 (m, 3H, H-18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 96.8 (OCH_2O), 78.7 (C-3), 70.5 (C-20), 68.5 (C-2), 58.6 (C-17), 56.0 (C-14), 55.7 (OCH_3), 54.4 (C-9), 42.6 (C-13, C-1), 40.1 (C-12), 39.1 (C-5), 36.9 (C-10), 34.7 (C-8), 33.4 (C-4), 32.0 (C-7), 27.8 (C-6), 25.7 (C-16), 24.5 (C-15), 23.6 (C-21), 20.8 (C-11), 12.6 (C-18), 12.5 (C-19); MS (*m*/*z*, relative intensity) 381 (M^+, 2), 349 (6), 302 (7), 45 (100). Anal. calcd. for $C_{23}H_{40}O_4.0.4H_2O$: C 71.29, H 10.61. Found C 71.29, H 10.44.

A solution of compound **31** (100 mg, 0.30 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method B). Once addition of DIBAL was performed, the reaction mixture was stirred at −78 °C for 7 h. After the usual workup, the product was purified by column chromatography (silica gel) employing hexane–EtOAc (7:3) as eluent to afford 36 mg (32% yield) of compound **32** and 42 mg (37% yield) of compound **33** as white solids.

3.1.20. 2α,3α-Epoxy-5α-pregnan-20-one (34). To a solution of compound **29** (5.2 g, 17.3 mmol) in methylene chloride (300 mL) cooled at 0 °C was added dropwise a solution of 80% *m*-chloroperbenzoic acid (4.48 g, 25.9 mmol) in methylene chloride (200 mL). The reaction mixture was stirred at room temperature for 1 h, and then it was washed with an aqueous saturated solution of sodium bicarbonate (3×100 mL). The organic phase was dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (99:1) as eluent to afford 3.15 g (59% yield) of compound **34** as a white solid: mp 153–154 °C; R_f 0.24 (hexane–EtOAc, 9:1), ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.12 (m, 2H), 2.51 (m, 1H), 2.11 (s, 3H), 0.75 (s, 3H), 0.59 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 63.8, 56.5, 53.9, 52.4, 50.9, 44.0, 38.9, 38.3, 36.2, 35.6, 33.7, 31.6, 31.5, 29.0, 28.3, 24.4, 22.8, 20.9, 13.3, 13.0; MS (*m*/*z*, relative intensity) 316 (M^+, 19), 298 (25), 213 (24), 55 (100). Anal. calcd for $C_{21}H_{32}O_2 \cdot 2$EtOAc: C 70.70, H 9.82. Found C 70.25, H 10.19.

3.1.21. 3α-Hydroxy-5α-pregn-1-en-20-one (35). To a solution of diphenyldiselenide (3.11 g, 9.95 mmol) in a (1:1) mixture of absolute ethanol–tetrahydrofuran (50 mL) cooled at 0 °C under argon atmosphere was added sodium borohydride portionwise until the yellow solution turned clear. Then, a solution of compound **34** (3.15 g, 9.95 mmol) in tetrahydrofuran (20 mL) was added and the reaction mixture was refluxed for 6 h. The mixture was cooled at 0 °C and 70% *t*-butylhydroperoxide (17 mL, 119.4 mmol) was added dropwise. The reaction mixture was refluxed for an additional hour, and it was quenched by addition of water (100 mL). The aqueous layer was extracted with ethyl acetate (2×70 mL). The combined organic phases were washed with brine (2×40 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (19:1) to afford 1.51 g (48% yield) of pure compound **35** as a white solid: mp 130–132 °C; R_f 0.31 (hexane–EtOAc, 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (d, J=10.0 Hz, 1H, H-1), 5.67 (m, 1H, H-2), 4.11 (m, 1H, H-3), 2.53 (m, 1H, H-17), 2.11 (s, 3H, H-21), 0.80 (s, 3H, H-19), 0.63 (m, 3H, H-18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 140.2, 126.2, 64.4, 63.7, 56.8, 50.9, 44.3, 39.0, 38.9, 38.0, 35.8, 34.8, 31.9, 31.5, 27.9, 24.4, 22.8, 21.1, 13.8, 13.5; MS (*m*/*z*, relative intensity) 316 (M^+, 8), 298 (4), 246 (9), 43 (100). Anal. calcd for $C_{21}H_{32}O_2$: C 79.70, H 10.19. Found C 79.51, H 10.32.

3.1.22. 3α-Methoxy-5α-pregn-1-en-20-one (36). To a solution of compound **35** (1.51 g, 4.77 mmol) in anhydrous tetrahydrofuran (50 mL) was added sodium hydride (460 mg, 9.54 mmol) and iodomethane (3 mL, 47.7 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature for 48 h. The reaction was quenched by addition of an aqueous saturated solution of ammonium chloride (20 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (19:1) as eluent to afford 830 mg (53% yield) of pure compound **36** as a white solid: mp 69–72 °C; R_f 0.84 (hexane–EtOAc, 15:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.08 (d, J=10.1 Hz, 1H), 5.70 (d, J=10.1, 4.2 Hz, 1H), 3.57 (m, 1H), 3.36 (s, 3H), 2.53 (m, 1H), 2.11 (s, 3H), 0.80 (s, 3H), 0.62 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.7, 140.5, 124.0, 73.3, 63.7, 56.8, 56.3, 50.7, 44.3, 39.3, 39.0, 38.0, 35.8, 31.8, 31.5, 30.8, 27.9, 24.4, 22.8, 21.1, 13.8, 13.6; MS (*m*/*z*, relative intensity) 330 (M^+, 33), 301 (11), 246 (7), 203 (11), 85 (100). Anal. calcd for $C_{22}H_{34}O_2$: C 79.95, H 10.37. Found C 79.98, H 10.34.

3.1.23. 1α,2α-Dihydroxy-3α-methoxy-5α-pregnan-20-one (37). To a solution of compound **36** (157 mg, 0.48 mmol) in a (10:3:1) mixture of *tert*-butanol–tetrahydrofuran–water (5 mL) were added *N*-methylmorpholine-*N*-oxide (67 mg, 0.57 mmol) and osmiun tetroxide (10 mg). The reaction mixture was stirred at room temperature overnight. The reaction was worked up by addition of an aqueous saturated solution of sodium bisulfite (5 mL). The mixture was extracted with ethyl acetate (3×10 mL) and the organic phase was washed with saturated solution of $NaHSO_3$ (5 mL) and brine (2×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (3:2) to afford 81 mg (52% yield) of pure compound **37** as a white solid: mp 190–193 °C, R_f 0.45 (hexane–EtOAc, 2:3), ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (m, 1H, H-2), 3.56 (m, 1H, H-1), 3.48 (m, 1H, H-3), 3.35 (s, 3H, OCH_3), 2.50 (m, 1H, H-17), 2.10 (s, 3H, H-21), 0.94 (s, 3H, H-19), 0.59 (m, 3H, H-18); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.8, 79.0, 75.5, 72.4, 63.9, 56.6, 56.6, 55.3, 43.9, 42.1, 39.4, 38.0, 35.1, 31.8, 31.4, 28.0, 27.9, 24.6, 24.2, 22.6, 13.3, 8.3; MS (*m*/*z*, relative intensity) 364 (M^+, 13), 346 (29), 332 (15), 314 (23), 81 (100). Anal. calcd for $C_{21}H_{32}O_4$: C, 72.49; H, 9.95. Found: C, 72.08; H, 9.92.

3.1.24. (20*S*)-1α,2α-Dihydroxy-3α-methoxy-5α-pregnan-20-ol (38). To a solution of diol **37** (80 mg, 0.22 mmol) in anhydrous methylene chloride (10 mL) cooled at −78 °C was added dropwise a 0.96 M solution of diisobutyl aluminium hydride (0.50 mL) in anhydrous methylene chloride under argon atmosphere. The reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of a 5% aqueous solution of hydrochloric acid (5 mL) and an aqueous saturated solution of sodium potassium tartrate (5 mL). The aqueous layer was extracted with methylene chloride (3×10 mL), and the combined organic phases were washed with brine (2×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (1:1) as eluent to give 74 mg (92% yield) of triol **38** as a white solid: mp 165–169 °C; R_f 0.25 (hexane–EtOAc, 2:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (m, 1H), 3.70 (m, 1H), 3.56 (m, 1H), 3.48 (m, 1H), 3.35 (s, 3H), 1.12 (d, J=6.2 Hz), 0.96 (s, 3H), 0.74 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 79.0, 75.5, 72.4, 70.6, 58.7, 56.7, 55.8, 55.4, 42.1, 40.4, 38.1, 35.0, 31.9, 28.2, 28.0, 25.5, 24.7, 24.3, 23.5, 12.5, 8.4. Anal. calcd for $C_{22}H_{38}O_4 \cdot 1/3$EtOAc: C 70.79, H 10.35. Found: C 71.17, H 9.81.

3.1.25. (20*S*)-2α-Hydroxy-1α-methoxymethoxy-3α-methoxy-5α-pregnan-20-ol (39). A solution of compound **38** (26 mg, 0.071 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method A). After DIBAL addition, the mixture was stirred at −78 °C for 2 h. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (7:3) as eluent followed by further purification by preparative TLC eluting with hexane–EtOAc (1:1) to afford 15 mg of unreacted starting material and 5 mg (17% yield) of compound **39** as a white solid: R_f 0.36 (hexane–EtOAc, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.72 (m*AB*, 2H), 4.08 (m, 1H), 3.72 (m, 1H), 3.51 (m, 1H), 3.42 (s, 3H), 3.35 (s, 3H), 3.33 (m, 1H), 1.12 (d, J=6.2 Hz), 1.02 (s, 3H), 0.74 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 97.4, 85.3, 78.7, 77.2, 70.4, 58.8, 56.7, 55.8, 55.4, 42.1, 42.0, 40.7, 38.5, 35.5, 31.8, 28.0, 25.4, 24.7, 23.8, 23.5, 12.6, 9.1.

A solution of compound **38** (150 mg, 0.41 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method B). After DIBAL addition, the reaction mixture was stirred at −78 °C for 4 h. The residue was purified as depicted before affording 115 mg of the starting material (76%) and 2 mg (1% yield) of compound **39**.

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Supplementary data

General methods and ^{1}H and ^{13}C NMR spectra for all new compounds. DEPT spectra for compounds **6**, **7**, **17**, **19**, **20**, **22**, **32**–**36**, and **38**. ^{1}H–^{1}H COSY spectra for compounds **7**, **22**, **35**, and **37**. ^{1}H–^{13}C 2D correlation spectra for compounds **22**, **32**, **33**, and **37**.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.09.097.

References and notes

1. Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed; Wiley: New York, 1999; pp 17–200.

2. Nicolaou, K. C.; Sorensen, E. J. In *Classics in Total Synthesis*; VCH: Weinheim, 1996.
3. Oikawa, M.; Wada, A.; Okazaki, F.; Kusumoto, S. *J. Org. Chem.* **1996**, *61*, 4469–4475.
4. Bailey, W. F.; Zarcone, L. M. J.; Rivera, A. D. *J. Org. Chem.* **1995**, *60*, 2532–2536.
5. Ogilvie, K. K.; Hakimelahi, G. H.; Proba, Z. A.; McGee, D. P. C. *Tetrahedron Lett.* **1982**, *23*, 1997–2000.
6. Ogilvie, K. K.; McGee, D. P. C.; Boisvert, S. M.; Hakimelahi, G. H.; Proba, Z. A. *Can. J. Chem.* **1983**, *61*, 1204–1209.
7. Chauchan, K.; Wheelan, P.; Murphy, R. C.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 5050–5056.
8. Comin, M. J.; Leitofuter, J.; Rodriguez, J. B. *Tetrahedron* **2002**, *58*, 3129–3136.
9. Friesen, R. W.; Vanderwal, C. *J. Org. Chem.* **1996**, *61*, 9103–9110.
10. Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947–1950.
11. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X.-Z. *J. Org. Chem.* **1992**, *57*, 2768–2771.
12. Schvartzapel, A. J.; Fichera, L.; Esteva, M.; Rodriguez, J. B.; Gros, E. G. *Helv. Chim. Acta* **1995**, *78*, 1207–1214.
13. Schvartzapel, A. J.; Zhong, L.; Docampo, R.; Rodriguez, J. B.; Gros, E. G. *J. Med. Chem.* **1997**, *40*, 2314–2322.
14. Block, M. H. *Tetrahedron Lett.* **1992**, *33*, 8149–8150.
15. Hajkó, J.; Borbás, A.; Lipták, A.; Kajtár-Peredy, M. *Carbohydr. Res.* **1991**, *216*, 413–420.
16. Borbás, A.; Hajkó, J.; Kajtár-Peredy, M.; Lipták, A. *J. Carbohydr. Chem.* **1993**, *12*, 191–200.
17. Lipták, A.; Borbás, A.; Jánossy, L.; Szilágyi, L. *Tetrahedron Lett.* **2000**, *41*, 4949–4953.
18. Lipták, A. *Tetrahedron Lett.* **1976**, *17*, 3551–3554.
19. Desruet, M.-D.; Morin, C.; Ogier, L. *Carbohydr. Res.* **1997**, *301*, 225–229.
20. García Fernández, J. M.; Ortiz Mellet, C.; Moreno Marín, A.; Fuentes, J. *Carbohydr. Res.* **1995**, *274*, 263–268.
21. Mashhood, S.; Ramesh, K.; Borchardt, R. T. *Tetrahedron Lett.* **1990**, *31*, 1509–1512.
22. Holysz, R. P. *J. Am. Chem. Soc.* **1953**, *75*, 4432–4437.
23. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973–1976.
24. Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697–2699.

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Design and synthesis of intramolecular hydrogen bonding systems. Their application in metal cation sensing based on excited-state proton transfer reaction

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Abstract—We reported the design and synthesis of a new type of metal-cation probes, 3-hydroxy-4-(1,4,7,10-tetraoxa-13-azacyclopentadec-13-ylmethyl)naphthalene-2-carbaldehyde (**1a**) and its single hydrogen-bond analogue 1-(1,4,7,10-tetraoxa-13-azacylopentadec-13-ylmethyl)-2-naphthol (**2a**), in which 1-aza-15-crown-5 ether in combination with the naphthol oxygen acts as a receptor, while the mechanism of excited-state intramolecular proton transfer (ESIPT) is exploited as a signal transducer. The association constant of $(2.5\pm0.5)\times10^4$, $(3.8\pm0.4)\times10^4$, $(5.5\pm0.5)\times10^3$ and $(1.2\pm0.3)\times10^4$ M^{-1} for the formation of **1a**/Na^+, **1a**/Ca^{2+}, **2a**/Na^+ and **2a**/Ca^{2+} complexes, respectively, in CH_3CN plus drastic fluorescence changes due to the fine-tuning of ESIPT reaction upon complexation, lead **1a** and **2a** to be highly sensitive fluorescent sensors. The results add a new class into the category of metal-cation probes, with the perspective of designing ESIPT systems capable of sensing bio-analytes.

1. Introduction

Due to its importance in fundamental research, the excited state intramolecular proton transfer (ESIPT) process has received considerable attention.[1] The ESIPT reaction generally incorporates transfer of a hydroxyl (or amino) proton to the carbonyl oxygen (or pyridinic nitrogen) through a pre-existing six or five membered ring hydrogen bonding (HB) configuration. The resulting proton-transfer tautomer, which generally possesses a vast difference in electronic configuration from its corresponding normal species, exhibits a large Stokes shifted fluorescence. This unusual photophysical property has led to versatile applications such as the development of laser dyes,[2,3] probes for solvation environments,[4,5] ultraviolet stabilizers[6] and radiation hard-scintillator counters,[7] etc.

Recently, we have applied 1-[(diethylamino)methyl]-3-hydroxy-2-naphthaldehyde (DMHN) possessing dual HB sites (conformers **A** and **B**, see Scheme 1) to study the competitive ESIPT dynamics.[8] Despite a near degeneracy in the ground electronic state, conformers **A** and **B** undergo entirely different ESIPT dynamics, resulting in a zwitterion ($\lambda_{max}\sim485$ nm) and a keto-tautomer ($\lambda_{max}\sim730$ nm) emission, respectively. From the application viewpoint, one intriguing concept is to design ESIPT systems capable of capturing analytes and selectively blocking one HB site. The result may drastically alter the ESIPT pathway, and the associated photophysics can thus be exploited as a new type of sensor for molecule/metal-ion recognition. On this basis, we have designed 3-hydroxy-4-(1,4,7,10-tetraoxa-13-azacyclopentadec-13-ylmethyl)naphthalene-2-carbaldehyde (**1a**) and its single HB analogue 1-(1,4,7,10-tetraoxa-13-azacylopentadec-13-ylmethyl)-2-naphthol (**2a**). **1a** and **2a** were synthesized from the condensation between 3-hydroxy-naphthalene-2-carbaldehyde (3HN) (or 2-naphthol for **2a**) and 1-aza-15-crown-5 ether via a modified Mannich reaction depicted in Scheme 2, in which 3HN was prepared from the reduction of 3-hydroxy-2-naphthoic acid methyl ester. Both prove to be highly sensitive fluorescent sensors based on the mechanism incorporating metal cation fine-tuning ESIPT reaction, adding a new class into the category of metal-cation probes.[9,10]

Keywords: Hydrogen bonding; Metal-cation probes; Excited state intramolecular proton transfer reaction; Receptors.
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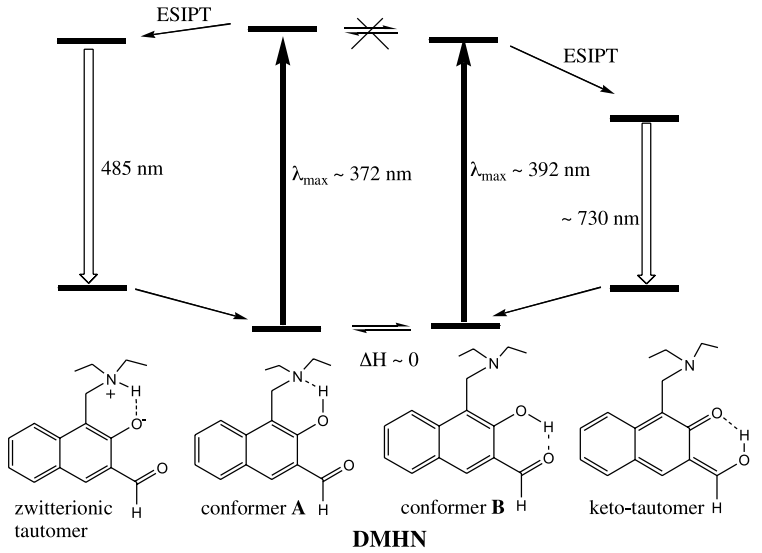
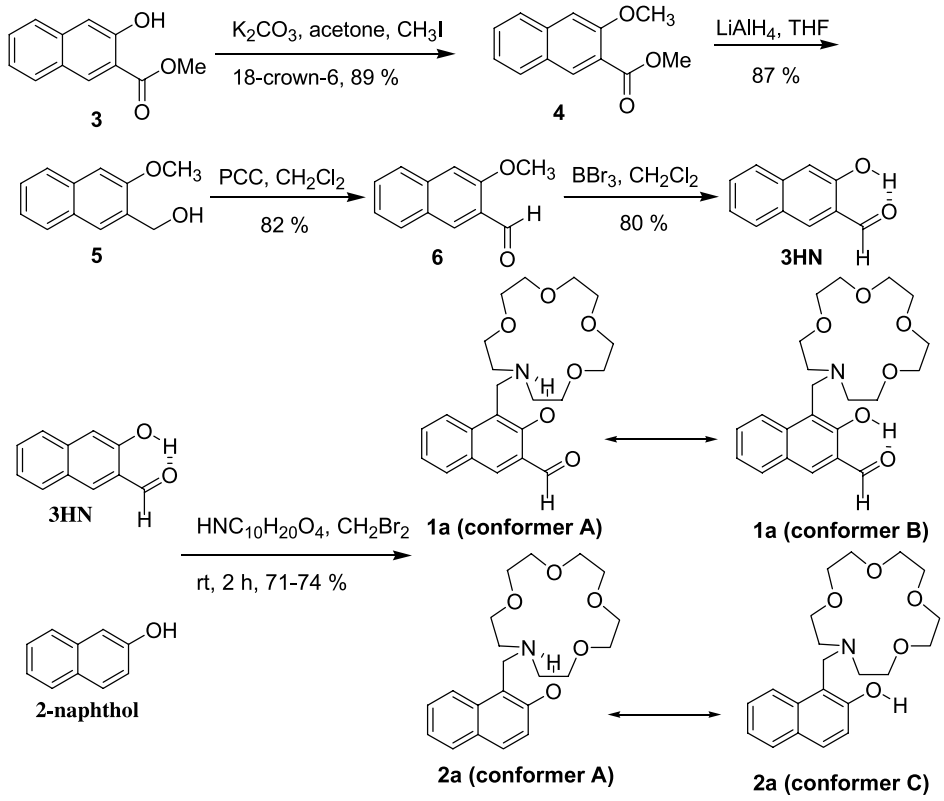


Scheme 1. The proposed competitive ESIPT mechanism for DMHN in aprotic solvents.[8] It should be noted that the rate of interconversion between conformers **A** and **B** in the excited state is too slow to compete with the proton transfer process. Thus, each hydrogen-bonding conformer undergoes independent ESIPT process.



Scheme 2. The synthetic scheme for compounds **1a** and **2a**, and their possible conformers.

2. Experimental

2.1. General

All reactions were performed under nitrogen atmosphere. Solvents were distilled from appropriate drying agents prior to use. Commercially available reagents were used without further purification unless otherwise stated. All reactions were monitored by TLC with Macherey-Nagel pre-coated glassic sheets (0.20 mm with fluorescent indicator UV_{254}). Compounds were visualized with UV light at 254 and 365 nm. Flash column chromatography was carried out using silica gel from Merck (230–400 mesh). ^{1}H NMR and ^{13}C NMR in $CDCl_3$ were recorded using a Varian (Unity Plus 400) spectrometer at 400 and 100 MHz, respectively. FAB-mass spectroscopy were collected on a JMS-700 double focusing mass spectrometer (JEOL, Tokyo, Japan) with a resolution of 3000 and 8000 for LR and HR

FAB-mass spectra. The source accelerating voltage was operated at 10 kV with Xe gun for FAB-mass spectra, using 3-nitrobenzyl alcohol as matrix.

2.1.1. 3-Methoxy-naphthalene-2-carboxylic acid methyl ester (4). To a suspension of potassium carbonate (2.7 g, 19.8 mmol) in acetone (10 mL) was added 2-hydroxy-3-naphthoic acid methyl ester (2.0 g, 9.9 mmol) and catalyst amount of 18-crown-6 ether (0.3 g, 1.0 mmol), followed by addition of methyl iodide (2.1 g, 14.9 mmol) under nitrogen. The reaction mixture was subjected to reflux for 12 h. The mixture was cooled and the solvent was removed via reduced pressure. The product was then extracted with CH_2Cl_2. Subsequently, the organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed in vacuum. The residue was purified by column chromatography (eluent: EtOAc/hexane (1:10 v/v)), yielding compound **4**, (1.9 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.9 (s, 3H), 3.98 (s, 3H), 7.18 (s, 1H), 7.34 (td, J=8.0, 1.2 Hz, 1H), 7.50 (td, J=8.0, 1.2 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.79 (d, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.3 (CH_3), 56.0 (CH_3), 106.7 (CH), 114.9 (C), 121.6 (C), 124.3 (CH), 126.3 (CH), 127.4 (C), 128.3 (CH), 128.5 (CH), 132.6 (CH), 135.9 (C), 155.5 (C), 166.5 (C); IR (neat) 3062, 2956, 2837, 1732, 1640, 1590, 1507, 1470, 1428, 1337 cm^{-1}; FAB-MS *m/z* (rel intensity) 217 (M^++1, 100%); HRMS (FAB) Calcd for $C_{13}H_{12}O_3$ 216.0786, found 216.0788.

2.1.2. (3-Methoxy-naphthalen-2-yl)-methanol (5). To a suspension of $LiAlH_4$ (0.7 g, 17.13 mmol) in dry THF (40 mL) was added 3-Methoxy-naphthalene-2-carboxylic acid methyl ester (1.9 g, 8.7 mmol) in dry THF (10 mL) in ice bath. The mixture was stirred at room temperature for 6 h. The reaction was then quenched with water. The product extracted from CH_2Cl_2 was washed with water and dried with $MgSO_4$. After filtration CH_2Cl_2 was removed by a rotavapor under reduced pressure and the residue was purified by column chromatography (eluent: EtOAc/hexane (1:5 v/v)), affording compound **5** as a white solid (1.4 g, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 1H), 3.96 (s, 3H), 4.81 (s, 2H), 7.11 (s, 1H), 7.33 (td, J=7.8, 1.0 Hz, 1H), 7.42 (td, J=8.0, 1.0 Hz, 1H), 7.71–7.76 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.4 (CH_2), 62.5 (CH_3), 105.1 (CH), 123.8 (CH), 126.2 (CH), 126.3 (CH), 127.4 (CH), 127.5 (CH), 128.5 (C), 130.3 (C), 134.0 (C), 155.7 (C); IR (neat) 3590, 3406, 3058, 2952, 1644, 1608, 1512, 1465, 1436, 1401, 1340 cm^{-1}; FAB-MS *m/z* (rel intensity) 188 (M^+, 100%); HRMS (FAB) Calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0839.

2.1.3. 3-Methoxy-naphthalene-2-carbaldehyde (6). A solution of (3-methoxy-naphthalen-2-yl)-methanol (1.3 g 6.7 mmol) in CH_2Cl_2 was added dropwise at 0 °C to a mixture of pyridinium chlorochromate (PCC, 2.2 g 10.0 mmol), sodium acetate (0.8 g 10.0 mmol) and 4 Å molecular sieve (2.2 g) in CH_2Cl_2. The mixture was stirred for 40 min under inert atmosphere. The solvent was removed under reduced pressure, and the residue was dissolved in ether and filtered. The product was purified by column chromatography. Elution with EtOAc/hexane (1:10 v/v) afforded compound **6** as yellow oil (1.0 g, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.01 (s, 3H), 7.17 (s, 1H), 7.36 (td, J=8.0, 1.0 Hz, 1H), 7.52 (td, J=8.0, 1.0 Hz, 1H), 7.72 (d, J=8.0 Hz, 1H), 7.86 (d, J=7.6 Hz, 1H), 8.34 (s, 1H), 10.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.8 (CH_3), 106.1 (CH), 124.3 (CH), 125.3 (C), 126.2 (CH), 127.4 (C), 128.8 (CH), 129.5 (CH), 130.6 (CH), 137.1 (C), 157.0 (C), 189.4 (CH); IR (KBr) 3064, 2994, 2880, 1700, 1632, 1602, 1470, 1434, 1406, 1346 cm^{-1}; FAB-MS *m/z* (rel intensity), 187 (M^++1, 100%); HRMS (FAB) Calcd for $C_{12}H_{10}O_2$ 186.0681, found 186.0684.

2.1.4. 3-Hydroxy-naphthalene-2-carbaldehyde (3HN). Under inert atmosphere, a solution of BBr_3 (0.52 g, 3.2 mmol) in anhydrous CH_2Cl_2 (5 mL) was added at 0 °C to a solution of 3-methoxynaphthalene-2-carbaldehyde (0.5 mg, 2.7 mmol) in anhydrous CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 1 h, and then the reaction was quenched with 1 N $NaHCO_3$ aqueous solution. The product was extracted with CH_2Cl_2, and the resulting organic layers were dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude mixture was purified by column chromatography (eluent: EtOAc/hexane (1:20 v/v)), yielding 3HN in 0.37 mg (80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (s, 1H), 7.36 (t, J=8.4 Hz, 1H), 7.55 (t, J=8.4 Hz, 1H), 7.70 (d, J=8.4 Hz, 1H), 7.85 (d, J=8.4 Hz, 1H), 8.13 (s, 1H), 10.06 (s, 1H), 10.30 (s, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 111.9 (CH), 122.1 (C), 124.3 (CH), 126.6 (CH), 127.3 (C), 129.2 (CH), 130.1 (CH), 137.7 (CH), 138.0 (C), 155.6 (C), 196.4 (CH); IR (KBr) 3256, 3064, 2985, 2856, 1674, 1518, 1458, 1417, 1388, 1358, 1308 cm^{-1}; FAB-MS *m/z* (rel intensity) 172 (M^+, 100%); HRMS (FAB) Calcd for $C_{11}H_8O_2$ 172.0524, found 172.0528.

2.1.5. 3-Hydroxy-4-(1,4,7,10-tetraoxa-13-azacyclopentadec-13-ylmethyl)naphthalene-2-carbaldehyde (1a). A mixture of 1-aza-15-crown-5 ether (0.6 g, 2.8 mmol) and dibromomethane (1.1 g, 11.4 mmol) was stirred at room temperature for 4 h under inert atmosphere. A solution containing 3-hydroxy-naphthalene-2-carbaldehyde (0.1 g, 0.71 mmol) in CH_2Cl_2 (2 mL) was added and the mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure, and the residue was dissolved in diethyl ether and filtered. The product was purified by column chromatography (eluent: methanol/dichloromethane (2:98 v/v)), yielding compound **1a** as yellow oil (203.1 mg, 0.5 mmol, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.90 (t, J=5.2 Hz, 4H), 3.60–3.73 (m, 16H), 4.25 (s, 2H), 7.28 (t, J=8.0 Hz, 1H), 7.49 (t, J=8.2 Hz, 1H), 7.82 (d, J=8.8 Hz, 2H), 8.23 (s, 1H), 10.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.6 (CH_2), 54 (CH_2), 68.7 (2×CH_2), 70.3 (4×CH_2), 70.8 (2×CH_2), 114.1 (C), 121.3 (CH), 123.2 (CH), 124.4 (C), 127.0 (C), 129.0 (CH), 130.4 (CH), 130.9 (CH), 135.9 (C), 157.4 (C), 191.6 (CH); IR (KBr) 3418, 3058, 2873, 1692, 1668, 1630, 1622, 1458, 1399, 1364 cm^{-1}; FAB-MS *m/z* (rel intensity) 404 (M^++1, 100%); HRMS (FAB) Calcd for $C_{22}H_{29}NO_6$ 403.1995, found 403.1999; Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.44; H, 7.29; N, 3.47.

2.1.6. 1-(1,4,7,10-Tetraoxa-13-azacyclopentadec-13-ylmethyl)-2-naphthol (2a). A mixture of 1-aza-15-crown-5 ether (0.6 g, 2.8 mmol) and dibromomethane (1.9 g, 11.0 mmol) was stirred at room temperature for 4 h under inert atmosphere. A solution of 2-naphthol (0.1 g,

0.69 mmol) in CH_2Cl_2 (1 mL) was added and the mixture was stirred at room temperature for 5 h. After removing CH_2Cl_2 under reduced pressure, the residue was dissolved in diethyl ether and filtered. The product was then purified by column chromatography (eluent: ethyl acetate/hexane (1:1 v/v)), yielding compound **2a** (194.1 mg, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.93 (t, J=5.2 Hz, 4H), 3.60–3.71 (m, 16H), 4.27 (s, 2H), 7.08 (d, J=8.8 Hz, 1H), 7.25 (t, J=6.8 Hz, 1H), 7.41 (td, J=7.6, 1.2 Hz, 1H), 7.65 (d, J=8.4, 1.6 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.82 (d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 54.3 (CH_2), 54.7 (CH_2), 68.8 (CH_2), 70.3 (CH_2), 70.3 (4×CH_2), 70.7 (CH_2), 111.9 (C), 119.3 (CH), 120.8 (CH), 122.2 (CH), 126.1 (CH), 128.3 (C), 128.7 (CH), 128.0 (CH), 132.6 (C), 156.4 (C); IR (KBr, neat) (cm^{-1}): 3488, 3060, 2874, 1676, 1626, 1602, 1526, 1474, 1410, 1353, 1272, 1238, 1128; FAB-MS m/z (rel intensity) 376 (M^++1, 100%); HRMS (FAB) Calcd for $C_{21}H_{29}NO_5$ 375.2046, found 375.2049; Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 65.15; H, 7.76; N, 3.77.

2.2. Spectroscopy and dynamics measurements

Steady-state absorption and emission spectra were recorded by a Hitachi (U-3310) spectrophotometer and an Edinburgh (FS920) fluorimeter, respectively. The excitation light source of the fluorimeter has been corrected by the Rodamine B spectrum. In addition, the wavelength-dependent characteristics of the monochromator and photomultiplier have been calibrated by recording the scattered light spectrum of the corrected excitation light from a diffused cell in the range of 220–700 nm.

For determining fluorescence quantum yields and relaxation dynamics of the studied compounds, sample solutions were degassed by three freeze-pump-thaw cycles under vigorous stirring condition. Quinine sulfate/1.0 N H_2SO_4 was used as a reference for the quantum yield measurement, assuming a yield of 0.564 with 360 nm excitation. Nanosecond lifetime studies were performed by an Edinburgh FL 900 photon-counting system with a hydrogen-filled/or a nitrogen lamp as the excitation source. Data were analyzed using the nonlinear least squares procedure in combination with an iterative convolution method, which allows partial removal of the instrument time broadening and consequently renders a temporal resolution of ~200 ps. A Suntex SP-701 pH-meter was used for the pH titration study.

3. Results and discussion

Similar to that of conformer **A** in DMHN,[8] the emission of **1a** revealed strong solvent-polarity dependence, being red shifted from 505 nm in cyclohexane to 585 nm in CH_3CN. The spectral shift of the fluorescence upon increasing solvent polarity depends on the difference in permanent dipole moments between ground (μ_g) and excited (μ_e) states, which can be quantitatively expressed based on Lippert equation[11] expressed in Eq. 1

$$\tilde{\nu}_f = \tilde{\nu}_f^{vac} - \left(\frac{2|\vec{\mu}_e - \vec{\mu}_g|^2}{hca_0^3}\right)\left(\frac{\varepsilon - 1}{2\varepsilon + 1}\right) \quad (1)$$

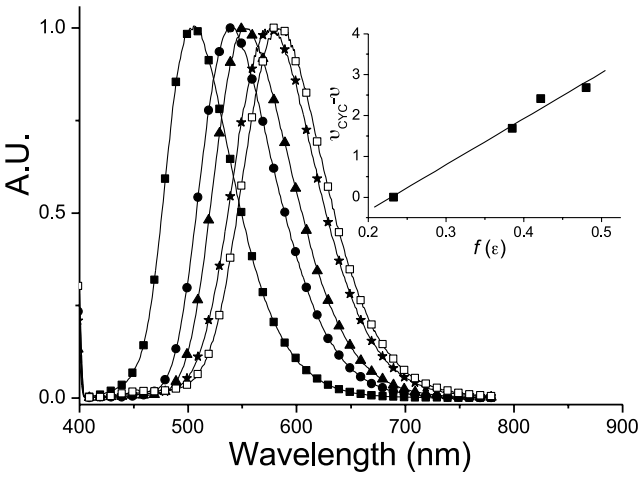


Figure 1. The emission spectra of **1a** in cyclohexane (–■–), benzene (–●–), ethyl acetate (–▲–), dichloromethane (–★–) and acetonitrile (–□–). The emission intensity has been normalized. Insert: the plot of $\tilde{\nu}_f^{cyc} - \nu_f$ versus $f(\varepsilon)=(\varepsilon-1)/(2\varepsilon+1)$ in various solvents.

where a_0 and ε denote the cavity radius and solvent dielectric constant, respectively, $\tilde{\nu}_f$ and $\tilde{\nu}_f^{vac}$ represent the fluorescence peak frequency (in cm^{-1}) in solvent studied and in vacuum, respectively. In this study, $\tilde{\nu}_f^{vac}$ can be replaced by the peak frequency in cyclohexane ($\tilde{\nu}_f^{cyc}$) if one neglects the induced dipole interaction. As shown in the insert of Figure 1, the plot of $\tilde{\nu}_f^{cyc} - \nu_f$ versus $f(\varepsilon)=(\varepsilon-1)/(2\varepsilon+1)$ is sufficiently linear, and a slope of as large as 11,200 cm^{-1} is deduced. a_0 in Eq. 1 was estimated to be 6.4 Å via the Hartree Fock theories with 6-31G(d′,p′) basis sets. Accordingly, the change in dipole moment between ground and excited states was deduced to be as large as 17.2 debye.

The results lead us to ascribe the 585 nm emission in CH_3CN to a zwitterionic species resulting from O–H···N→ $O^-\cdots HN^+$ ESIPT. In contrast to the existence of conformers **A** and **B** for DMHN, as supported by the significant difference between absorption and excitation spectrum monitored at zwitterion emission,[8] the excitation spectrum of **1a** in CH_3CN is identical to the absorption spectrum. The results indicate that the O–H···N intramolecular HB conformer **A** is the dominant species in **1a**. Further support was given by the lack of resolution of any keto-tautomer emission at >700 nm predicted according to the ESIPT mechanism in conformer **B** of DMHN.[8] The more stable conformer **A** in **1a** can qualitatively be rationalized by additional HB interactions between –O–H and ether oxygens. This viewpoint is also supported by a semi-empirical PM3 approach (see Fig. 2), estimating conformer **A** of **1a** to be energetically lower than conformer **B** by ~1.6 kcal/mol. In addition, the dipole moment of 5.52 debye calculated for conformer **A** of **1a** is larger than that of **B** (3.75 debye). Accordingly, it is reasonable to expect the dominant conformer **A** in the strong polar solvent such as CH_3CN.

The corresponding absorption and fluorescence titration spectra in CH_3CN upon the addition of Na^+ to **1a** are shown in Figures 3 and 4, respectively. Table 1 lists the

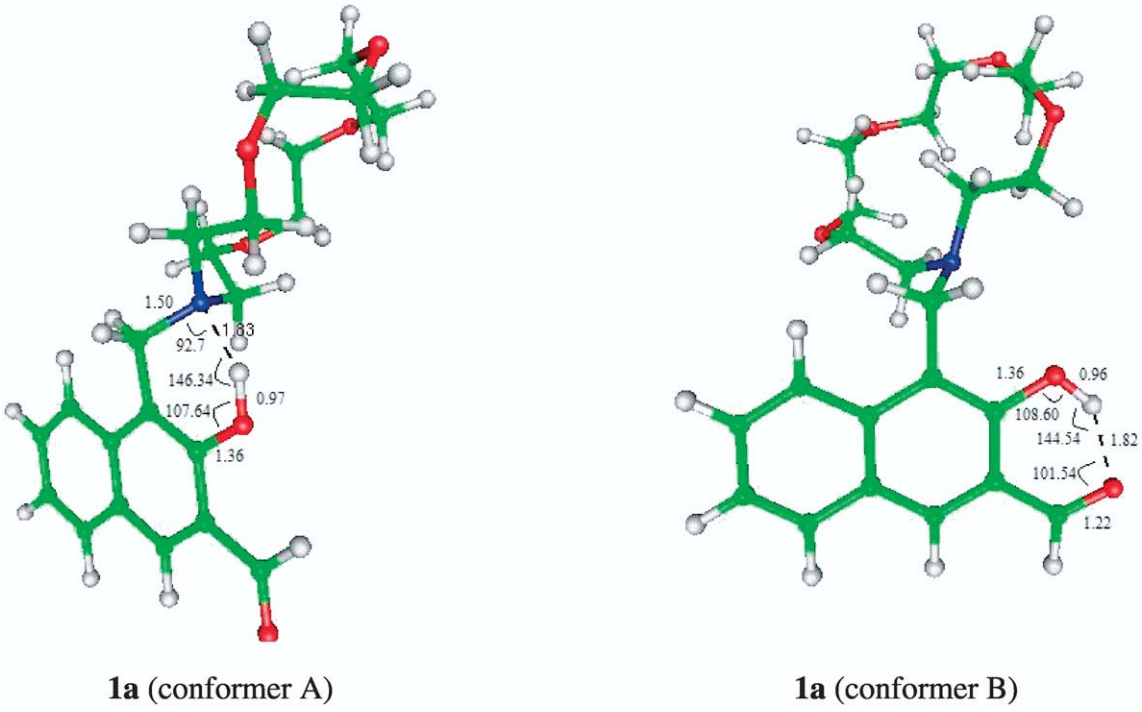


Figure 2. Two geometry-optimized (PM3 method) hydrogen-bonding conformers of **1a**, and the respective critical bond distance (in Å) and angle (in degree) involved in the intramolecular hydrogen bond.

photopysical properties of **1a** and **2a** and their associated metal ion complexes in CH_3CN. Increasing the $[Na^+]$ led to a hypsochromic shift of the absorption profile, in which the appearance of isosbestic points at ~360 and 315 nm verifies a two-species equilibrium. Thus, the plot of the relationship between the measured absorbance A as a function of the added $NaClO_4$ concentration, C_g, can be expressed by Eq. 2[12]

$$\frac{A_0}{A-A_0}=\left(\frac{\varepsilon_M}{\varepsilon_c-\varepsilon_M}\right)\left[\frac{1}{K_a[C_g]}+1\right] \quad (2)$$

where ε_M and ε_c are molar extinction coefficients of **1a** and **1a**/Na^+ complex, respectively, at a selected wavelength. A_0 denotes the absorbance of the free **1a** at that specific wavelength. The 1:1 **1a**/Na^+ complexation was supported by a straight-line plot for the ratio of absorbance, $A_0/(A_0-A)$, versus $1/[Na^+]$ throughout the titration (insert of Fig. 3), and an association constant of as high as $(2.5\pm0.5)\times10^4\ M^{-1}$ was deduced in CH_3CN.

Drastic changes on the Na^+ fluorescence titration spectra were also observed, in which the 585 nm zwitterion emission decreased with increasing Na^+ concentrations (Fig. 4). The relationship between the measured

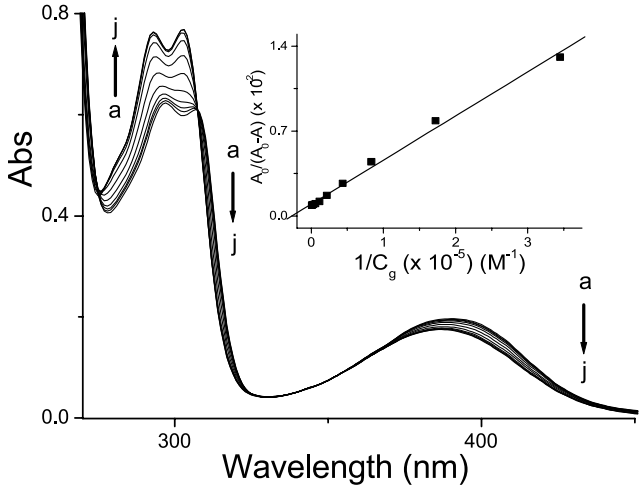


Figure 3. Absorption spectra of **1a** (3.2×10^{-5} M) in CH_3CN by adding $NaClO_4$ concentrations (C_g) of (a) 0, (b) 1, (c) 2, (d) 4, (e) 8, (f) 16, (g) 30, (h) 60, (i) 120, (j) 240 equiv (1 equiv = 2.9×10^{-6} M). Insert: the plot of A_0/A_0-A against $1/C_g$ at 400 nm.

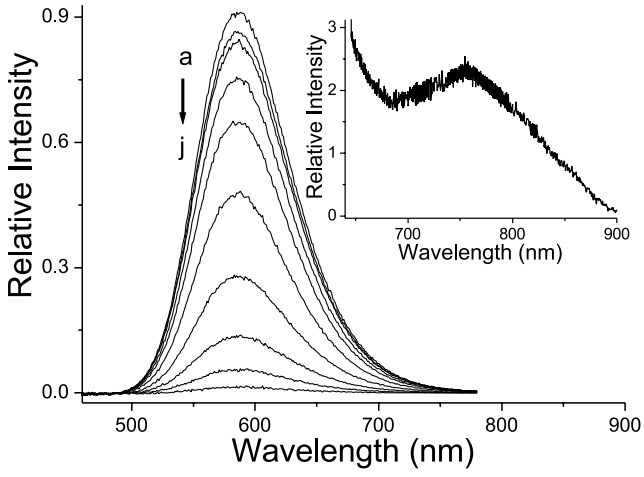


Figure 4. Fluorescence spectra of **1a** (3.2×10^{-5} M) in CH_3CN by adding $NaClO_4$ concentrations (C_g) of (a) 0, (b) 1, (c) 2, (d) 4, (e) 8, (f) 16, (g) 30, (h) 60, (i) 120, (j) 240 equiv (1 equiv = 2.9×10^{-6} M), λ_{ex}: 400 nm. Insert: The spectrum of **1a** at >700 nm by adding 10^{-3} M $NaClO_4$.

Table 1. The photophysical properties of ion-free **1a** and **2a** and the association constants of various **1a**/metal ion and **2a**/metal ion complexes in CH_3CN

	Absorption λ_{max} (nm)	Fluorescence λ_{max} (nm), τ_f	Association constant K_a (M^{-1})	
			Na^+	Ca^{2+}
1a	390	585 (4.7 ns), 730 (520 fs)	2.3×10^4	3.8×10^4
2a	327	355 (4.6 ns), 432 (4.3 ns)	5.5×10^3	1.2×10^4

fluorescence intensity F and C_g in a selected wavelength can be expressed by Eq. 3[12]

$$\frac{F_0}{F-F_0}=\frac{\Phi_M\varepsilon_M}{(\Phi_C\varepsilon_C-\Phi_M\varepsilon_M)}\left(\frac{1}{K_aC_g}+1\right) \quad (3)$$

where F_0 denotes the fluorescence intensity of free **1a**. Φ_M and Φ_C are fluorescence quantum yields of the free **1a** and complex, respectively, which are assumed to be constant throughout the titration. A linear plot for the ratio of fluorescence intensity, $F_0/(F-F_0)$, versus $1/[Na^+]$ for the 585 nm band reconfirmed the 1:1 complex formation, and K_a was deduced to be $(2.3\pm0.3)\times10^4\,M^{-1}$. Upon the addition of $[Na^+]$ of $>10^{-3}$ M, in which >99% of **1a**/Na^+ complex is formed, a weak emission band ($\Phi_f<10^{-4}$) maximized at ~730 nm was observed (see insert of Fig. 4). The mechanism of complexation can thus be rationalized by the rupture of the O–H···N hydrogen bond due to the usage of lone pair electrons on the nitrogen atom upon formation of the **1a**/Na^+ complex, resulting in switching the intramolecular HB sites from O–H···N (conformer **A**) to O–H···O=C (conformer **B**). ESIPT takes place in the Na^+/conformer **B** complex, giving rise to a keto-tautomer 730 nm emission.

In contrast to a unique, zwitterionic emission band in **1a**, **2a** exhibits dual emission maximized at 355 (4.6 ns) and 432 nm (τ_f=4.3 ns) (see Fig. 5). Similar to that assigned for 1-diethylaminomethyl-2-naphthol,[13] the 432 nm emission can be ascribed to a zwitterion emission resulting from ESIPT. Accordingly, the 355 nm band, being a mirror image with respect to the S_0–S_1 ($\pi\pi^*$) absorption of **2a**, can be unambiguously ascribed to the emission associated with the normal form of **2a** in that the intramolecular hydrogen bond is ruptured due to the strong solute-solvent polar–polar interaction in CH_3CN. ESIPT is thus prohibited during the lifespan of the excited conformer **C**. It should be noted that the existence of conformer **C** is negligible in **1a** due to its dual HB sites, that is, conformers **A** and **B**, providing an intact intramolecular HB environment free from solvent perturbation.

Titration of **2a** by $NaClO_4$ revealed a similar hypsochromic absorption shift with that of **1a**, and an association constant of $(5.5\pm0.5)\times10^3\,M^{-1}$ was deduced in CH_3CN (not shown here). During titration the 432 nm emission band decreased, accompanied by the increase of a 355 nm normal emission (τ_f=4.6 ns) with an isoemissive point at 397 nm. The results lead us to conclude the rupture of the O–H···N hydrogen bond on the formation of the **2a**/Na^+ complex so that ESIPT is prohibited, giving rise to a normal Stokes shifted emission. This is quite different from **1a** in that the conformation of **1a** switches from the OH···N to the OH···O=C site upon **1a**/Na^+ complexation, resulting in a weak keto-tautomer emission (vide supra). In comparison to **2a**, the ~4-folds larger K_a value in **1a** can be rationalized by the more stable **1a**/Na^+ complex due to the intramolecular OH···O=C hydrogen bond formation.

Attempts have also been made to titrate DMHN with Na^+. The results revealed negligible spectral differences, verifying the importance of capping Na^+ with 1-aza-15-crown-5 ether in **1a** and **2a**. Furthermore, within the same range of concentrations, absorption and emission titration remained unchanged on adding K^+ to both **1a** and **2a**, and the results can simply be rationalized by the mismatched sizes between K^+ and 1-aza-15-crown-5 ether.

The absorption and emission spectra of **1a** as a function of the divalent metal ions, for example, Ca^{2+}, in CH_3CN are shown in Figure 6. Upon an increase in $[Ca^{2+}]$, a decrease in the 393 nm absorption band was observed, accompanied

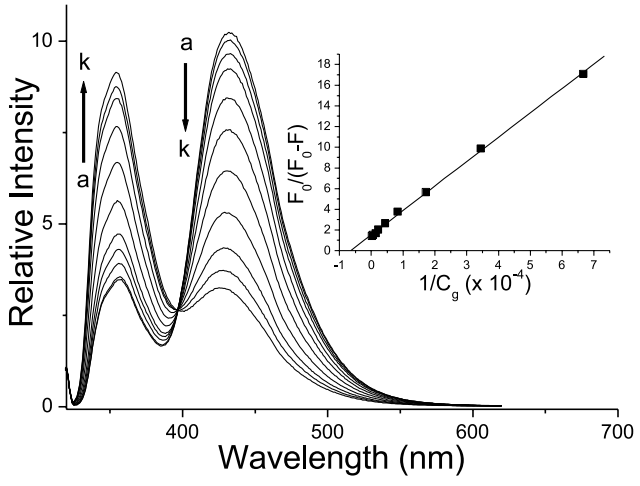


Figure 5. Fluorescence spectra of **2a** (3.2×10^{-5} M) in CH_3CN by adding $NaClO_4$ concentrations (C_g) of (a) 0, (b) 1, (c) 5, (d) 10, (e) 20, (f) 40, (g) 80, (h) 160, (i) 230, (j) 650, (k) 1300 equiv (1 equiv=2.9×10^{-6} M). Insert: the plot of $F_0/F-F_0$ against $1/C_g$, λ_{ex}: 320 nm.

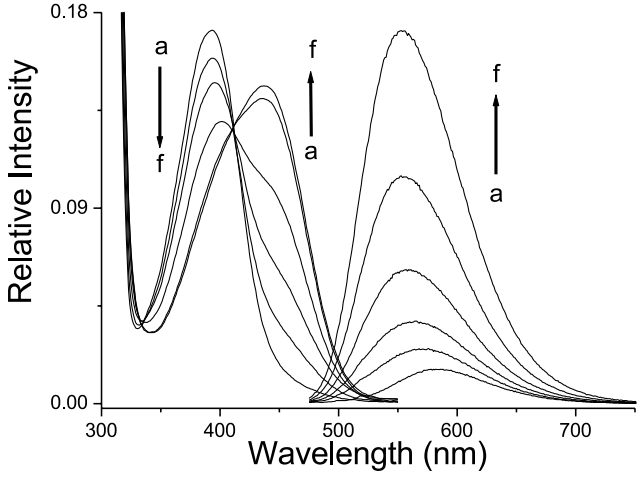


Figure 6. Absorption and emission spectra of **1a** (3.2×10^{-5} M) in CH_3CN by adding Ca^{2+} concentrations (C_g): (a) 0, (b) 1, (c) 2, (d) 4, (e) 6, (f) 8, (g) 18, (h) 23, (i) 28, (j) 33 equiv (1 equiv=2.9×10^{-6} M), λ_{ex}: 450 nm.

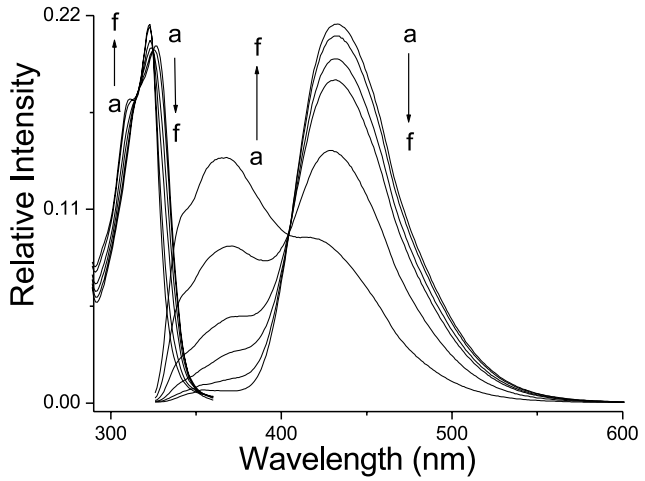


Figure 7. Absorption and emission spectra of **2a** (3.2×10^{-5} M) in CH_3CN by adding Ca^{2+} concentrations (C_g): (a) 0, (b) 2, (c) 4, (d) 6, (e) 10, (f) 15 equiv (1 equiv $=2.9\times10^{-6}$ M). λ_{ex}: 320 nm.

by the gradual increase of a new band maximized at 438 nm and the appearance of an isosbestic point at 412 nm. The straight-line plot of $A_0/(A-A_0)$ versus $1/[Ca^{2+}]$ confirms a 1:1 **1a**/Ca^{2+} complexation, and an association constant of $(3.8\pm0.4)\times10^4\ M^{-1}$ was deduced. Upon 450 nm excitation, the increase of fluorescence intensity as a function of $[Ca^{2+}]$ was observed, and the emission peak wavelengths shifted from 580 to 560 nm (Fig. 6). During titration, the relaxation dynamics of the entire band could be well fitted by biexponential decay kinetics, and lifetimes were resolved to be 4.7 and 7.1 ns, indicating the existence of two distinct species. Due to its spectral similarity with that of the KOH basified **1a** oxide (in MeOH), the 438 nm absorption band can be assigned to a **1a**/Ca^{2+} complex absorption, in which the hydroxyl proton is detached to form oxide, along with the nitrogen atom binding to Ca^{2+}, giving rise to a 560 nm ($\tau_f\sim7.1$ ns) anion emission. In a comparative study, although similar spectral change was observed upon titration of DMHN with Ca^{2+}, the association constant of $(8.0\pm0.3)\times10^3\ M^{-1}$ is smaller than that of the **1a**/Ca^{2+} complex by ~five folds. We thus conclude that in addition to oxide (O^-) and nitrogen atoms, the remaining ether oxygens in azacrown are also incorporated in the **1a**/Ca^{2+} complexation. A similar coordination structure has been reported in a ([Ca(1-aza-15-crown-5 ether)$(CH_3–OH)_2$] BPh_4) single crystal.[14]

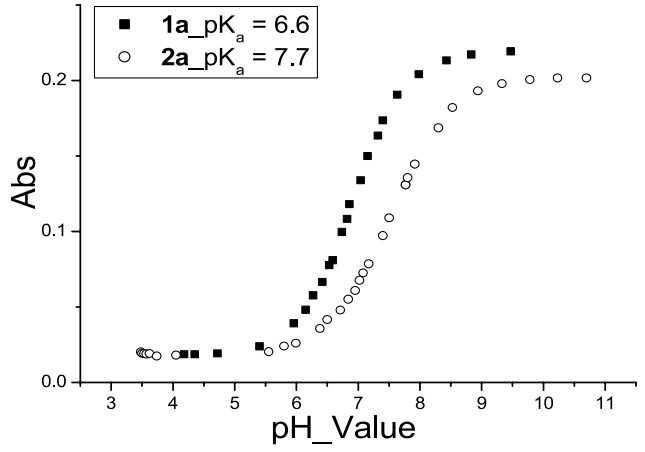


Figure 8. The ground-state pH (NaOH) titration experiment for **1a** (■) and **2a** (●) in water. Data were obtained from the pH dependent absorbance at 450 nm and 350 nm for **1a** and **2a**, respectively.

In contrast to the oxy-anion characteristic for the **1a**/Ca^{2+} complex, drastically different $Ca(ClO_4)_2$ titration spectra for **2a** were observed, in which increasing Ca^{2+} resulted in a hypsochromic spectral shift with an appearance of an isosbestic point at 324 nm (Fig. 7). The lack of oxide absorption indicates that the hydroxyl group remains intact in **2a** during the Ca^{2+} titration. This viewpoint is further supported by a decrease of the 435 nm zwitterion emission during the titration, accompanied by an increase of the 360 nm normal emission with an isoemissive point appearing at 405 nm. The difference in capping Ca^{2+} can be qualitatively rationalized by the stronger acidity of the hydroxyl group in **1a** due to the aldehyde (CHO) electron withdrawing property (p*K*a ~6.6 in **1a** versus ~7.7 in **2a** according to the pH titration shown in Fig. 8). The dissimilar binding property is also manifested by the association strength, in which K_a of $(1.2\pm0.3)\times10^4\ M^{-1}$ for **2a** is smaller than that of **1a** by more than three folds.

4. Conclusion

In conclusion, we have reported the design and synthesis of a new type of metal-cation probes **1a** and **2a**, in which 1-aza-15-crown-5 ether in combination with a hydroxyl group acts as a receptor, while a mechanism of switch or prohibition of ESIPT upon complexation is exploited as the signal transducer. **1a** is superior to **2a** owing to its larger K_a values and metal-ion-selective spectral change. It is thus conceivable to design multiple HB systems capable of sensing bio-analytes based on the ESIPT mechanism. Further work focusing on this issue is currently in progress.

Acknowledgements

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References and notes

1. (a) Kosower, E. M.; Huppert, D. *Ann. Rev. Phys. Chem.* **1986**, *37*, 127–156. (b) Special Issue *Spectroscopy and Dynamics of Elementary Proton Transfer in Polyatomic Systems*; Firth, D., Barbara, P. F., Trommsdorff, H. P., Eds.; *Chem. Phys.* **1989**, *130*, 349–360. (c) Formosinho, S. F.; Arnaut, L. G. *J. Photochem. Photobiol. A Chem.* **1993**, *75*, 21–48. (d) Scheiner, S. *J. Phys. Chem. A* **2000**, *104*, 5898–5909. (e) Waluk, J. Conformational aspects of intra- and intermolecular excited state proton transfer. In *Conformational Analysis of Molecules in Excited States*; Waluk, J., Ed.; Wiley, 2000. (f) Chou, P. T. *J. Chin. Chem. Soc.* **2001**, *48*, 651–682. (g) Elsaesser, T. Ultrafast excited state hydrogen transfer in the condensed phase. In *Ultrafast Hydrogen Bonding Dynamics and Proton*

Transfer Processes in the Condensed Phase; Elsaesser, T., Bakker, H. J., Eds.; Kluwer: Dordecht, 2002.
2. Chou, P. T.; McMorrow, D.; Aartsma, T. J.; Kasha, M. *J. Phys. Chem.* **1984**, *88*, 4596–4599.
3. Acuna, A. V.; Amat, F.; Catalán, J.; Costella, A.; Figuera, J. M.; Munoz, J. M. *Chem. Phys. Lett.* **1986**, *132*, 567–569.
4. Parsapour, F.; Kelley, D. F. *J. Phys. Chem.* **1996**, *100*, 2791–2798.
5. Sytnik, A.; Kasha, M. *Proc. Natl. Acad. Sci.* **1994**, *91*, 8627–8630.
6. Catalán, J.; del Valle, J. C.; Claramunt, R. M.; Sanz, D.; Dotor, J. *J. Lumin.* **1996**, *68*, 165–170.
7. Renschler, C. L.; Harrah, L. A. *Nucl. Instrum. Methods Phys. Rev., A235, Sept., U.S. Patent* **1985**, 635–639.
8. Wu, K. C.; Cheng, Y. M.; Lin, Y. S.; Yeh, Y. S.; Pu, S. C.; Hu, Y. H.; Yu, J. K.; Chou, P. T. *Chem. Phys. Lett.* **2004**, *384*, 203–209.
9. (a) For fluorescent Ca^{2+} metal ion chemosensors, see: Mlyamaki, A.; Llopis, J.; Holm, R.; McCarffery, J. A.; Ikurn, M.; Tsien, R. Y. *Nature* **1997**, *388*, 882–887. (b) Arunkumar, E.; Chithra, P.; Ajayaghosh, A. *J. Am. Chem. Soc.* **2004**, *126*, 6590–6598. (c) Yamniuk, A. P.; Nguyen, L. T.; Hoang, T. T.; Vogel, H. J. *Biochemistry* **2004**, *43*, 2558–2568.
10. Roshal, A. D.; Grigorovich, A. V.; Doroshenko, A. O.; Pivovarenko, V. G. *J. Phys. Chem. A* **1998**, *102*, 5907–5914.
11. Lakowicz, J. R. *Principles of Fluorescence Spectroscopy*; Plenum: New York, 1999; pp 185–192.
12. Chou, P. T.; Wu, G. R.; Wei, C. Y.; Cheng, C. C.; Chang, C. P.; Hung, F. T. *J. Phys. Chem. B* **2000**, *104*, 7818–7829. A_0, F_0, A and F denote respectively the absorbance and fluorescent intensity of free **1a**, and solution after adding metal ions at a selective wavelength.
13. Tolbert, L. M.; Nesselroth, S. M. *J. Phys. Chem.* **1991**, *103*, 10331–10336.
14. Itoh, S.; Kumei, H.; Nagatomo, S.; Kitagawa, T.; Fukuzumi, S. *J. Am. Chem. Soc.* **2001**, *123*, 2165–2175.

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Logistic flexibility in the preparation of isomeric halopyridinecarboxylic acids

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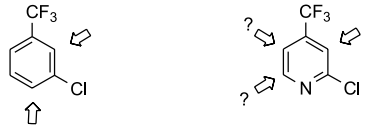
Abstract—Although there are many conceivable ways to funtionalize, and specifically carboxylate, 2-chloro-4-(trifluoromethyl)pyridine optionally at all three vacant positions, it is more straightforward to prepare only the 2-chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (**1**) from this precursor and the other 6-chloro-4-(trifluoromethyl)pyridine-2- and -3-carboxylic acids (**2** and **3**) from a different one, viz. 5-bromo-2-chloro-4-(trifluoromethyl)pyridine. In the same manner, it proved more convenient to convert 5-chloro-2-(trifluoromethyl)pyridine in only two of the corresponding acids (**6** and **7**) and to make the third one (**8**) from 3-bromo-5-chloro-2-(trifluoromethyl)pyridine as an alternative starting material. All model substrates for functionalization were readily accessible from the correspondingly substituted chloroiodopyridine through heavy halogen displacement by in situ generated (trifluoromethyl)copper.

1. Introduction

The principle of regioexhaustive functionalization[1] was successfully applied to several chloro(trifluoromethyl)pyridines and one bromo(trifluoromethyl)pyridine as disclosed in preceding articles.[2,3] Relying on procedures such as reagent-modulated site selective metalation, regiocontrol through protective groups and deprotonation-triggered heavy halogen migrations, metals were optionally introduced into any vacant position of each substrate and the organometallic species thus produced were trapped with a suitable electrophile, typically with carbon dioxide. The present report is a plea to prove pragmatism while pursuing the goal of developing a given model structure into all regioisomerically possible derivatives. Although it looks logistically most attractive to have the same building block as the common precursor to all congeners, it may sometimes be more advantageous to employ two or even three different starting materials. The correctness of this assertion will be illustrated by the synthesis of two 'triplets' of regioisomeric chloro(trifluoromethyl)pyridinecarboxylic acids.

2. Results

2-Chloro-4-(trifluoromethyl)pyridine is a commercial compound, but its catalogue price is prohibitive (about 20,000 €/mol). Therefore, we have made it from the known 2-chloro-4-iodopyridine by heavy halogen displacement with in situ generated (trifluoromethyl)copper.[4] Depending on the choice of the reagent, 1-chloro-3-(trifluoromethyl)-benzene undergoes a permutational hydrogen/metal interconversion ('metalation') either at the 2- or 6-position.[5] Seen against this background, one would expect 2-chloro-4-(trifluoromethyl)pyridine to react with bases preferentially or exclusively at the 3-position. Other sites would be attacked only under exceptional conditions, if at all.



In fact, the metalation of 2-chloro-4-(trifluoromethyl)pyridine proceeded smoothly at the 3-position when accomplished with lithium diisopropylamide in tetrahydrofuran at −75 °C. Reaction with dry ice afforded the 2-chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (**1**) in 82% yield. In contrast, no trace of the isomeric pyridinecarboxylic acids **2** and **3**, respectively, was identified in the product mixture when other metalating reagents, such as Caubère's base, that is, butyllithium in the presence

Keywords: Base-triggered halogen migration; Halogen/metal permutation; Heterocycles; Metalation reactions; Pyridinecarboxylic acids; Regioisomers; (Trifluoromethyl)copper.
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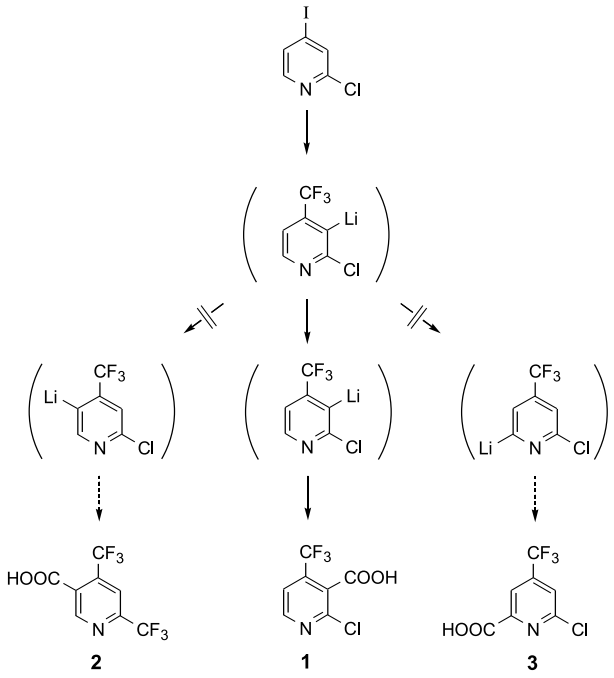
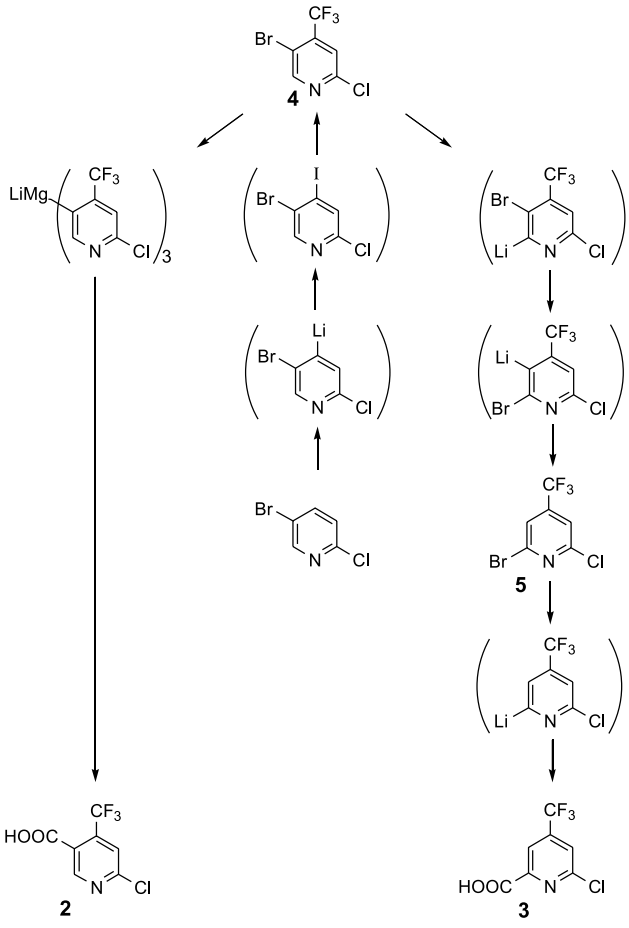


Scheme 1.

of lithium 2-(dimethylamino)ethoxide,[6] were employed (Scheme 1).

Both acids **2** and **3** were found to be readily accessible through 5-bromo-2-chloro-4-(trifluoromethyl)pyridine (**4**). Consecutive treatment of 5-bromo-2-chloropyridine with lithium diisopropylamide and molecular iodine afforded 5-bromo-2-chloro-4-iodopyridine (66%) from which the heaviest halogen was readily displaced by the trifluoromethyl entity. When the resulting bromopyridine **4** (64%) was subjected to a halogen/metal permutation with lithium tributylmagnesate,[7,8] the 2-chloro-4-(trifluoromethyl)pyridine-5-carboxylic acid (**2**; 77%) was obtained after carboxylation. On the other hand, when intermediate **4** was exposed to lithium disopropylamide, a basicity gradient driven heavy halogen migration[9,10] was unleashed which provided 2-bromo-6-chloro-4-(trifluoromethyl)pyridine (**5**; 68%) after neutralization. This time, the halogen/metal permutation was accomplished with butyllithium in toluene at −75 °C. The resulting organometallic species was carboxylated to give the 6-chloro-4-(trifluoromethyl)pyridine-2-carboxylic acid (**3**; 82%) (Scheme 2).

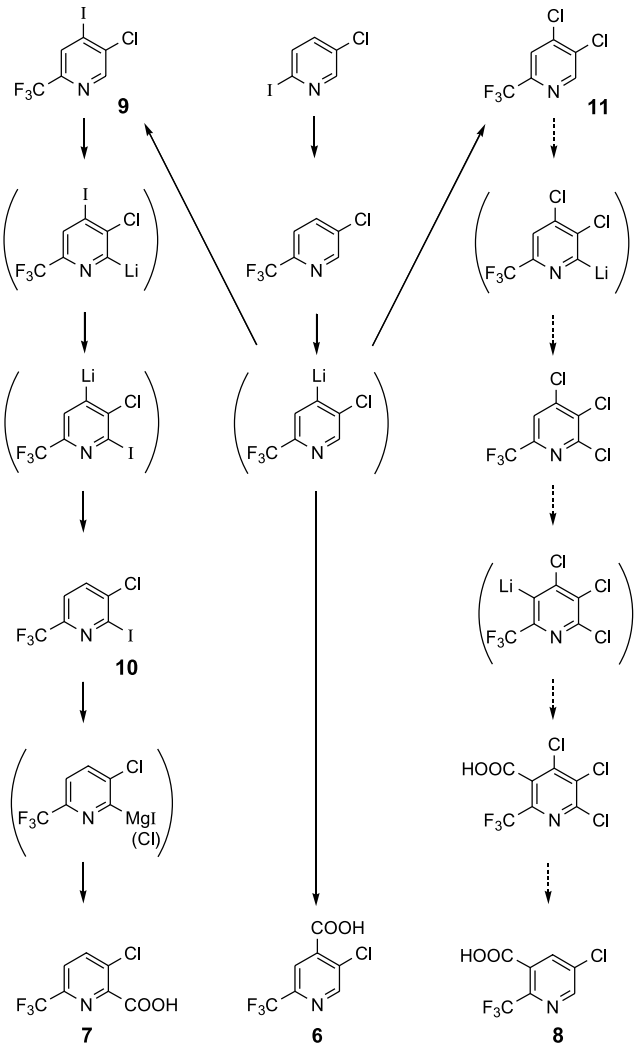


Scheme 2.

1-Chloro-4-(trifluoromethyl)benzene is invariably metalated at the 2-position. This allows us to predict the deprotonation of 5-chloro-2-(trifluoromethyl)pyridine to occur essentially at the 4-position as the intrinsic local acidity in pyridines increases with the distance of the CH bond from the heterocyclic nitrogen atom.[11,12] On the other hand, the coordination-requiring mixture of butyllithium with 2-(dimethylamino)ethoxide might at least this time favor the attack at the 2-position (in analogy with the behavior of 3-chloropyridine[13]).

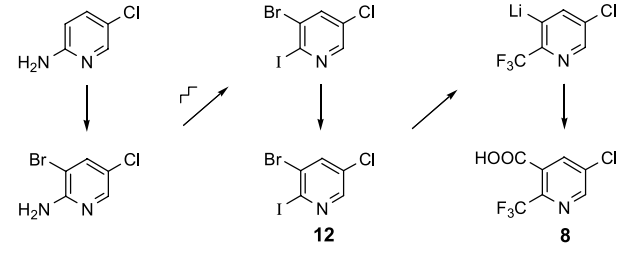
In fact, consecutive treatment of 5-chloro-2-(trifluoromethyl)pyridine with an excess of Caubère's base and dry ice afforded 3-chloro-6-(trifluoromethyl)pyridine-2-carboxylic acid (**7**) in 40% yield. The same acid was prepared in 95% yield from 3-chloro-2-iodo-6-(trifluoromethyl)pyridine (**10**) by consecutive reaction with isopropylmagnesium chloride and dry ice. The iodo compound **10** resulted from the lithium diisopropylamide-triggered isomerization of 5-chloro-4-iodo-2-(trifluoromethyl)pyridine (**9**), which was obtained by the interception of 4-lithiated 5-chloro-2-(trifluoromethyl)pyridine with elemental iodine in 86% yield. Carboxylation of the same intermediate furnished the 5-chloro-2-(trifluoromethyl)pyridine-4-carboxylic acid (**6**; 83%) (Scheme 3).

4,5-Dichloro-2-(trifluoromethyl)pyridine (**11**), prepared by reaction of the 4-lithiated 5-chloro-2-(trifluoromethyl)pyridine with 1,1,2-trichloro-1,2,2-trifluoroethane in 48% yield, and 2,3,4-trichloro-5-(trifluoromethyl)pyridine were the milestones on the initially conceived route to 5-chloro-2-(trifluoromethyl)pyridine-3-carboxylic acid (**8**). To remove the extra chloro substituents at the nucleophilically activated 2- and 4-positions, one could have replaced one after the other of them by a hydrazino unit and eventually carried out oxidative dediazotations.[14,15] Ultimately, this sequence was considered too laborious as it would have comprised at least half a dozen of operational steps. Therefore, we elaborated a short-cut approach starting



Scheme 3.

with the inexpensive 2-amino-5-chloropyridine which was brominated, diazotized, bromodediazotized, subjected to iodine/bromine displacement and converted into 3-bromo-5-chloro-2-(trifluoromethyl)pyridine (**12**) by CF_3I displacement. Halogen/metal permutation using lithium tributylmagnesate and reaction with carbon dioxide completed the preparation of 5-chloro-2-(trifluoromethyl)pyridine-3-carboxylic acid (**8**; 84%) (Scheme 4).



Scheme 4.

The chloro(trifluoromethyl)pyridinecarboxylic acids described above will certainly find their place in the life science arena as attractive building blocks. In addition, their reactivity profile can be profoundly modified by the nucleophilic displacement of the chlorine atom if located at the 2-, 4- or 6-position. Thus, both 2-chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (**1**) and 2-chloro-5-(trifluoromethyl)pyridine-4-carboxylic acid[2] were readily converted under evolution of hydrogen chloride into the bromo analogs 2-bromo-4-(trifluoromethyl)pyridine-3-carboxylic acid (80%) and 2-bromo-5-(trifluoromethyl)pyridine-4-carboxylic acid (84%), respectively, when treated with bromotrimethylsilane at 100 °C.

3. Experimental

3.1. Generalities

Working practices and abbreviations are specified in previous articles from this laboratory.[16–18] ^1H and (^1H decoupled) ^{13}C NMR spectra were recorded of samples dissolved in deuterochloroform at 400 and 101 MHz, respectively, relative to the internal standard tetramethylsilane (chemical shift $\delta=0.00$ ppm). The samples were dissolved in deuterochloroform or, if marked by an asterisk, in hexadeuteroacetone unless stated otherwise.

3.2. Starting materials

5-Bromo-2-chloropyridine was prepared by the diazotation of the commercially available 2-amino-5-bromopyridine essentially as described in the literature[19] but in the absence of cuprous chloride (as this has no effect on the rate of the reaction nor on the yield). 2-Amino-3-bromo-5-chloropyridine[20] could probably be directly converted into the required 3-bromo-5-chloro-2-iodopyridine but existing methods of diazotation seemed either complicated or low yielding.[21,22] Therefore, we have preferred the detour through the 2,3-dibromo-5-chloropyridine (see below).

3.2.1. 5-Bromo-4-iodo-2-chloropyridine. A solution of 5-bromo-2-chloropyridine (38 g, 0.20 mol) in tetrahydrofuran (0.20 L) was added dropwise over 1 h to the solution prepared from diisopropylamine (28 mL, 20 g, 0.20 mol) and butyllithium (0.20 mol) in tetrahydrofuran (0.27 L) and hexanes (0.12 L) kept in a dry ice/methanol bath. Afterwards, the reaction mixture was kept 45 min at −75 °C, before iodine (51 g, 0.20 mol) dissolved in tetrahydrofuran (0.15 L) was added in one shot. At 25 °C, the reaction mixture was filtered through basic alumina (0.10 L) and eluted with diethyl ether (2×0.20 L). After evaporation of the volatiles, the residue crystallized from ethanol as colorless needles; mp 144–145 °C; yield: 42.0 g (66%). ^1H NMR: $\delta=8.47$ (s, 1H), 7.86 (s, 1H). ^{13}C NMR: $\delta=149.8$, 149.6, 134.8, 127.4, 114.1. Anal. Calcd for $C_5H_2BrClIN$ (318.34): C 18.87, H 0.63. Found: C 18.83, H 0.69.

3.2.2. 5-Bromo-2-chloro-4-(trifluoromethyl)pyridine (4). 'Spray dried' potassium fluoride (6.4 g, 0.11 mol) and cuprous iodide (21 g, 0.11 mol) were thoroughly mixed before being heated under vacuum (1 mm Hg) with the flame of a Bunsen burner with gentle shaking until an homogeneous greenish color was obtained. *N*-Methylpyrrolidinone (0.20 L), trimethyl(trifluoromethyl)silane (15 mL, 14 g, 0.10 mol) and, after the slurry had been slowly heated

to 50 °C in the course of 45 min, 5-bromo-2-chloro-4-iodopyridine (32 g, 0.10 mol) were added. After 20 h at 50 °C, the reaction mixture was poured into 12% aqueous ammonia (0.20 L) and extracted with diethyl ether (3× 0.20 L). The combined organic layers were washed with 12% aqueous ammonia (2×0.20 L), 2.0 M hydrochloric acid (0.10 L), a saturated solution (0.10 L) of aqueous sodium hydrogen carbonate and brine (0.10 L). After drying and upon distillation, a colorless oil was collected; bp 80–81 °C/16 mm Hg; mp 11–13 °C; n_D^{20} 1.5084; d_4^{20} 1.813; yield: 18.3 g (64%). ^{1}H NMR: δ=8.68 (s, 1H), 7.62 (s, 1H). ^{13}C NMR: δ=153.9, 151.2, 140.0 (q, J=33 Hz), 122.6 (q, J=5 Hz), 121.0 (q, J=275 Hz), 115.8 (q, J=2 Hz). Anal. Calcd for $C_6H_2BrClF_3N$ (260.44): C 27.67, H 0.77. Found: C 27.75, H 0.56.

3.2.3. 2-Bromo-6-chloro-4-(trifluoromethyl)pyridine (5). 5-Bromo-2-chloro-4-(trifluoromethyl)pyridine (2.9 mL, 5.2 g, 20 mmol) was added to the solution prepared at 0 °C from 2,2,6,6-tetramethylpiperidine (6.8 mL, 5.7 g, 40 mmol) and butyllithium (40 mmol) in diethyl ether (0.10 L) and hexanes (25 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was treated with 1.0 M hydrochloric acid (50 mL). The organic layer was filtered through a pad of basic alumina (50 mL) which was rinsed with diethyl ether (0.10 L). Upon distillation, a colorless oil was obtained; bp 68–70 °C/12 mm Hg; n_D^{20} 1.4966; d_4^{20} 1.770; yield: 3.52 g (68%). ^{1}H NMR: δ=7.66 (s, 1H), 7.53 (s, 1H). ^{13}C NMR: δ=152.4, 142.6 (q, J=33 Hz), 141.7, 122.9 (q, J=4 Hz), 121.2 (q, J=274 Hz), 119.5 (q, J=4 Hz). Anal. Calcd for $C_6H_2BrClF_3N$ (260.44): C 27.67, H 0.77. Found: C 27.75, H 0.75.

3.2.4. 5-Chloro-2-iodopyridine. 2-Bromo-5-chloropyridine[23] (9.6 g, 50 mmol) was heated to reflux in the presence of sodium iodide (22 g, 0.15 mol) and chlorotrimethylsilane (6.4 mL, 5.4 g, 50 mmol) in propionitrile for 6 h. The reaction mixture was poured into 2.0 M aqueous solution of sodium hydroxide and extracted with diethyl ether (2× 50 mL). The combined organic layers were washed with brine (50 mL), dried and evaporated. The residue crystallized from hexanes as colorless platelets; mp 85–87 °C (lit.[23] mp 85–87 °C); yield: 10.4 g (87%; lit.[23] 52% from the 2,5-dichloropyridine).

3.2.5. 5-Chloro-2-(trifluoromethyl)pyridine. Analogously from 5-chloro-2-iodopyridine (24 g, 0.10 mol), a colorless solid was obtained after sublimation of the reaction product; mp 37–39 °C; 13.1 g (72%). ^{1}H NMR: δ=8.69 (d, J=2.3 Hz, 1H), 7.87 (dd, J=8.3, 2.3 Hz, 1H), 7.66 (d, J=8.3 Hz, 1H). ^{13}C NMR: δ=149.0, 146.2 (q, J=35 Hz), 137.0, 135.2, 121.3 (q, J=2 Hz), 121.2 (q, J=274 Hz). Anal. Calcd for $C_6H_3ClF_3N$ (181.54): C 39.70, H 1.67. Found: C 39.66, H 1.60.

3.2.6. 5-Chloro-4-iodo-2-(trifluoromethyl)pyridine (9). 5-Chloro-2-(trifluoromethyl)pyridine (3.6 g, 50 mmol) was added to the solution prepared from butyllithium (20 mmol) and diisopropylamine (2.8 mL, 2.0 g, 20 mmol) in tetrahydrofuran (30 mL) and hexanes (13 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was treated with iodine (5.1 g, 20 mmol) in tetrahydrofuran (20 mL). The solvents were evaporated and the residue partitioned between diethyl ether (20 mL) and a 2.0 M aqueous solution of sodium thiosulfate (20 mL). The phases were separated and the aqueous one extracted with diethyl ether (20 mL). The combined organic layers were washed with 2.0 M hydrochloric acid (20 mL), saturated sodium hydrogen carbonate aqueous solution, dried and evaporated. The residue crystallized from hexanes as yellow needles; 5.35 g (87%); mp 83–85 °C. ^{1}H NMR: δ=8.63 (s, 1H), 8.15 (s, 1H). ^{13}C NMR: δ=148.3, 146.0 (q, J=35 Hz), 140.4, 131.8, 120.2 (q, J=275 Hz). Anal. Calcd for $C_6H_2ClF_3IN$ (307.44): C 23.44, H 0.65. Found: C 23.16, H 0.78.

3.2.7. 2-Iodo-3-chloro-6-(trifluoromethyl)pyridine (10). 5-Chloro-4-iodo-2-(trifluoromethyl)pyridine (1.5 g, 5.0 mmol) was added to the solution prepared from butyllithium (5.0 mmol) and diisopropylamine (0.71 mL, 0.51 g, 5.0 mmol) in tetrahydrofuran (20 mL) and hexanes (3 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was treated with water (2.0 mL) and the solvents were evaporated. The residue was taken up in diethyl ether (30 mL) and was washed with 2.0 M hydrochloric acid (20 mL) and saturated sodium hydrogen carbonate aqueous solution. After evaporation, the residue crystallized from hexanes as yellowish prisms; 1.27 g (83%); mp 62–64 °C. ^{1}H NMR: δ=7.81 (dq, J=8.0, 0.6 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H). ^{13}C NMR: δ=146.5 (q, J=36 Hz), 141.8, 136.9, 121.6, 120.4 (q, J=3 Hz), 120.3 (q, J=275 Hz). Anal. Calcd for $C_6H_2ClF_3IN$ (307.44): C 23.44, H 0.65. Found: C 23.53, H 0.65.

3.2.8. 2,3-Dibromo-5-chloropyridine. At 60 °C, 2-amino-3-bromo-5-chloropyridine[20] (73 g, 0.35 mol) was dissolved in 48% hydrobromic acid (0.20 L, 0.30 kg, 1.8 mol). After cooling to −5 °C, bromine (36 mL, 0.11 kg, 0.70 mol) was added dropwise over 20 min. A solution of sodium nitrite (60 g, 0.90 mol) in water (80 mL) was then added at a rate to keep the temperature of the reaction mixture between −5 and 0 °C. When finished, the temperature was allowed to reach 25 °C. The bromine was reduced with an excess of solid sodium sulfite, and the reaction mixture was extracted with diethyl ether (3×0.20 L). The combined organic layers were filtered through a pad of basic alumina (0.25 L) which was rinsed with diethyl ether (0.40 L). Evaporation of the volatiles afforded pure 2,3-dibromo-5-chloropyridine; mp 38–41 °C (lit.[24] mp 39.5–43.0 °C); yield: 64.9 g (68%).

3.2.9. 3-Bromo-5-chloro-2-iodopyridine. A mixture of 2,3-dibromo-5-chloropyridine (20 g, 75 mmol), sodium iodide (33 g, 0.22 mol) and chlorotrimethylsilane (9.5 mL, 8.1 g, 75 mmol) in propionitrile (75 mL) was heated under reflux for 45 min. The reaction mixture was then poured into a 2.0 M aqueous solution of sodium hydroxide (0.20 L) and extracted with diethyl ether (3×0.20 L). The combined organic layers were washed with brine and evaporated to yield some 20 g of a brownish oil containing 2-iodo-3-bromo-5-chloropyridine (79%) and 3-bromo-5-chloropyridine (21%) as determined by gas chromatography (DB-1, 20 m, 150 °C, pentadecane as an internal standard). Twofold crystallization from methanol afforded pure 3-bromo-5-chloro-2-iodopyridine as tiny colorless needles; mp 58–60 °C; yield: 9.7 g (42%). ^{1}H NMR: δ=8.30 (d, J=2.2 Hz, 1H), 7.83 (d, J=2.2 Hz, 1H). ^{13}C NMR: δ=147.2, 139.1, 131.9, 130.0, 120.7. Anal. Calcd for $C_5H_2BrClIN$ (318.34):

C 18.87, H 0.63. Found: C 18.88, H 0.62. Threefold crystallization of the mother liquors from methanol afforded pure 3-bromo-5-chloropyridine as colorless platelets; mp 74–76 °C; 0.81 g (6%). ^{1}H NMR: δ=8.57 (d, J=1.9 Hz, 1H), 8.51 (d, J=2.2 Hz, 1H), 7.87 (t, J=2.1 Hz, 1H). ^{13}C NMR: δ=148.8, 147.0, 138.3, 132.4, 120.5. Anal. Calcd for C_5H_3BrClN (192.44): C 31.21, H 1.57. Found: C 31.27, H 1.16.

3.2.10. 4,5-Dichloro-2-(trifluoromethyl)pyridine (11). 5-Chloro-2-(trifluoromethyl)pyridine (5.4 g, 30 mmol) was added to the solution prepared from diisopropylamine (4.2 mL, 3.0 g, 30 mmol) and butyllithium (30 mmol) in tetrahydrofuran (45 mL) and hexanes (12 mL) kept in a dry ice/methanol bath. After 45 min at −75 °C, 1,2,2-trichloro-1,2,2-trifluoroethane (3.6 mL, 5.6 g, 30 mmol) was added and the reaction mixture was allowed to reach 25 °C. After dilution with diethyl ether (30 mL), the reaction mixture was washed consecutively with 2.0 M hydrochloric acid (2×20 mL), a saturated aqueous solution (20 mL) of sodium hydrogen carbonate and brine (20 mL). Upon distillation, a slightly yellowish oil was obtained; bp 65–66 °C/19 mm Hg; mp 10–13 °C; n_D^{20} 1.4732; d_4^{20} 1.549; yield: 3.12 g (48%); ^{1}H NMR: δ=8.73 (s, 1H), 7.79 (s, 1H). ^{13}C NMR: δ=150.5, 147.1 (q, J=35 Hz), 143.6, 134.0, 122.5 (q, J=3 Hz), 120.7 (q, J=275 Hz). Anal. Calcd for $C_6H_2Cl_2F_3N$ (215.99): C 33.36, H 0.93. Found: C 33.54, H 1.04.

3.2.11. 3-Bromo-5-chloro-2-(trifluoromethyl)pyridine (12). A similar reaction as the one described above (see preparation of 5-bromo-2-chloro-4-(trifluoromethyl)pyridine; subsection 3.2.2) was performed with 3-bromo-5-chloro-2-iodopyridine (32 g, 0.10 mol); upon distillation, a colorless oil was obtained which solidified; bp 75–76 °C/13 mm Hg; mp 23–25 °C; yield: 18.0 g (69%). ^{1}H NMR: δ=8.58 (d, J=1.9 Hz, 1H), 8.09 (d, J=1.9 Hz, 1H). ^{13}C NMR: δ=146.2, 144.3 (q, J=35 Hz), 142.2, 135.2, 120.9 (q, J=275 Hz), 118.3. Anal. Calcd for $C_6H_2BrClF_3N$ (260.44): C 27.67, H 0.77. Found: C 27.30, H 0.47.

3.3. Carboxylic acids derived from 2-chloro-4-(trifluoromethyl)pyridine

3.3.1. 2-Chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (1). 2-Chloro-4-(trifluoromethyl)pyridine (6.4 mL, 9.1 g, 50 mmol) was added to the solution prepared from diisopropylamine (7.0 mL, 5.1 g, 50 mmol) and butyllithium (50 mmol) in tetrahydrofuran (0.17 L) and hexanes (23 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice covered with tetrahydrofuran (25 mL) before being allowed to reach 25 °C. Upon extraction with 2.0 M aqueous solution of sodium hydroxide (3×50 mL), washing of the combined basic organic layers with diethyl ether (2×50 mL), acidification to pH 1 with concentrated hydrochloric acid, extraction with diethyl ether (3×0.10 mL), drying and evaporation to dryness, a pale brown residue was obtained. Crystallization of the latter from ethyl acetate afforded colorless prisms; mp 150–151 °C; 9.31 g (82%). ^{1}H NMR: δ=8.62 (d, J=5.2 Hz, 1H), 7.54 (d, J=5.2 Hz, 1H). ^{13}C NMR: δ=165.4, 150.5, 148.9, 137.4 (q, J=35 Hz), 124.4, 121.7 (q, J=275 Hz), 118.8 (q, J=4 Hz). Anal. Calcd for $C_6H_3ClF_3NO_2$ (225.55): C 37.28, H 1.34. Found: C 37.21, H 1.32.

3.3.2. 6-Chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (2). At 0 °C, butylmagnesium chloride (6.6 mmol) in tetrahydrofuran (4.2 mL) was added to butyllithium (13 mmol) in hexanes (8.5 mL). After 10 min, the reaction mixture was diluted with tetrahydrofuran (25 mL), cooled to −75 °C. 5-Bromo-2-chloro-4-(trifluoromethyl)pyridine (2.9 mL, 5.2 g, 20 mmol) was added and the reaction mixture was kept 45 min at −75 °C, before being poured onto an excess of freshly crushed dry ice covered with tetrahydrofuran (25 mL). The solvents were evaporated, and the residue partitioned between 6.0 M hydrochloric acid (20 mL) and diethyl ether (70 mL). The organic phase was dried, evaporated and the residue crystallized from heptane as colorless needles; mp 114–116 °C; yield: 3.49 g (77%). ^{1}H NMR: δ=9.13 (s, 1H), 7.77 (s, 1H). ^{13}C NMR: δ=168.1, 156.6, 153.0, 140.2 (q, J=35 Hz), 122.8 (q, J=2 Hz), 122.1 (q, J=6 Hz), 121.1 (q, J=275 Hz). Anal. Calcd for $C_7H_3ClF_3NO_2$ (225.55): C 37.28, H 1.34. Found: C 37.55, H 1.09.

3.3.3. 6-Chloro-4-(trifluoromethyl)pyridine-2-carboxylic acid (3). 2-Bromo-6-chloro-4-(trifluoromethyl)pyridine (1.5 mL, 2.6 g, 10 mmol) was added to a solution of butyllithium (10 mmol) in toluene (50 mL) and hexanes (6.1 mL) kept in a dry ice/methanol bath. After 15 min at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice covered with diethyl ether (25 mL). At 25 °C, the products were partitioned between diethyl ether (20 mL) and 6.0 M hydrochloric acid (20 mL). The organic layer was dried and the volatiles evaporated. Crystallization of the residue from petroleum ether afforded tiny colorless needles; mp 99–101 °C; yield: 1.85 g (82%). ^{1}H NMR: δ=8.38 (s, 1H), 7.85 (s, 1H). ^{13}C NMR: δ=164.1, 152.4, 148.4, 143.1 (q, J=36 Hz), 125.0 (q, J=4 Hz), 121.5 (q, J=274 Hz), 119.6 (q, J=3 Hz). Anal. Calcd for $C_7H_3ClF_3NO_2$ (225.55): C 37.28, H 1.34. Found: C 37.14, H 1.30.

3.4. Carboxylic acids derived from 5-chloro-2-(trifluoromethyl)pyridine

3.4.1. 5-Chloro-2-(trifluoromethyl)pyridine-4-carboxylic acid (6). 5-Chloro-2-(trifluoromethyl)pyridine (1.8 g, 10 mmol) was added to the solution prepared from diisopropylamine (1.4 mL, 1.0 g, 10 mmol) and butyllithium (10 mmol) in tetrahydrofuran (15 mL) and hexanes (5 mL) kept in a dry ice/methanol bath. After 45 min at −75 °C, the mixture was poured on an excess of freshly crushed dry ice. Volatiles were then evaporated and the residue crystallized from a 9:1 (v/v) mixture of 2.0 M aqueous solution of hydrochloric acid and ethanol as colorless needles; mp 206–207 °C (reprod.); 1.88 g (83%). ^{1}H NMR*: δ=8.94 (s, 1H), 8.22 (s, 1H). ^{13}C NMR*: δ=152.7, 147.1 (q, J=35 Hz), 140.3, 134.0, 122.3 (q, J=2 Hz), 122.3 (q, J=273 Hz). Anal. Calcd for $C_7H_3ClF_3NO_2$ (225.55): C 37.27, H 1.34; found C 36.97, H 1.35.

3.4.2. 3-Chloro-6-(trifluoromethyl)pyridine-2-carboxylic acid (7). Isopropylmagnesium chloride (3.0 mmol) was added to 3-chloro-2-iodo-6-(trifluoromethyl)pyridine

(0.92 g, 3.0 mmol) in tetrahydrofuran (6 mL) at −75 °C. After 2 h, carbon dioxide was bubbled through the solution for 20 min, before adding diethyl ether (20 mL) and 6.0 M hydrochloric acid (10 mL). The phases were separated, and the aqueous layer extracted with diethyl ether (10 mL). The combined organic layers were dried and evaporated. Sublimation of the residue afforded a colorless solid; mp 97–99 °C (colorless needles from ethyl acetate/hexanes 1:6); 0.642 g (95%). ^{1}H NMR: δ=8.17 (dq, J=8.6, 0.7 Hz, 1H), 7.90 (d, J=8.6 Hz, 1H). ^{13}C NMR: δ=161.7, 145.1 (q, J=37 Hz), 143.3, 142.7, 136.4, 124.8 (q, J=2 Hz), 120.8 (q, J=275 Hz). Anal. Calcd for $C_6H_3ClF_3NO_2$ (225.55): C 37.27, H 1.34. Found: C 37.46, H 1.24. The same acid was obtained in 40% yield (0.90 g) after treatment of 5-chloro-2-(trifluoromethyl)pyridine (1.8 g, 10 mmol) with butyllithium (30 mmol) in the presence of LIDMAE (30 mmol) at −75 °C in hexanes (50 mL), carboxylation, neutralization and crystallization from cyclohexane.

3.4.3. 5-Chloro-2-(trifluoromethyl)pyridine-3-carboxylic acid (8). A similar reaction as above (see preparation of 6-chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid; subsection 3.3.2) performed with 3-bromo-5-chloro-2-(trifluoromethyl)pyridine (5.2 g, 20 mmol) afforded after crystallization from a 6:1 (v/v) mixture of heptane and ethyl acetate colorless needles; mp 137–139 °C; yield: 3.81 g (84%). ^{1}H NMR*: δ=8.88 (d, J=2.2 Hz, 1H), 8.37 (dq, J=2.2, 0.6 Hz, 1H). ^{13}C NMR*: δ=166.3, 150.6, 143.6 (q, J=35 Hz), 138.8, 135.8, 130.6, 122.1 (q, J=275 Hz). Anal. Calcd for $C_7H_3ClF_3NO_2$ (225.55): C 37.27, H 1.34. Found: C 37.15, H 1.41.

3.5. Chlorine/bromine displacement

3.5.1. 2-Bromo-4-(trifluoromethylpyridine-3-carboxylic acid. 2-Chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (11 g, 50 mmol) and bromotrimethylsilane (20 mL, 23 g, 0.15 mol) were heated slowly (over 2 h) to 100 °C and kept for 4 h at this temperature, while 70 °C warm water was circulated through the spiral of the reflux condenser. Hydrogen chloride and small amounts of chlorotrimethylsilane were allowed to escape through a drying tube filled with calcium chloride. The mixture was then poured into a 2.0 M aqueous solution (0.15 L) of sodium hydroxide. The aqueous phase was washed with diethyl ether (3×0.10 L) before being acidified with hydrochloric acid to pH 1 and extracted with diethyl ether (3×0.10 L). The combined organic layers were dried and evaporated. The residue was recrystallised from a 1:1 (v/v) mixture of ethyl acetate and hexanes; colorless prisms; mp 159–161 °C; 10.8 g (80%). ^{1}H NMR: δ=8.61 (d, J=5.1 Hz, 1H), 7.57 (d, J=5.1 Hz, 1H). ^{13}C NMR: δ=166.0, 1150.7, 139.8, 136.8 (q, J=34 Hz), 131.1, 121.4 (q, J=275 Hz), 119.0 (q, J=4 Hz). Anal. Calcd for $C_7H_3BrF_3NO_2$ (270.00): C 31.14, H 1.12. Found: C 31.09, H 1.12.

3.5.2. 2-Bromo-5-(trifluoromethyl)pyridine-4-carboxylic acid. Analogously from 2-chloro-5-(trifluoromethyl)pyridine-4-carboxylic acid (11 g, 50 mmol); colorless prisms (from ethyl acetate); mp 190–191 °C (decomp.); 11.4 g (84%); ^{1}H NMR: δ=8.88 (s, 1H), 8.08 (s, 1H); ^{13}C NMR: δ=164.8, 149.5 (q, J=6 Hz), 147.4, 142.5, 128.7, 123.9 (q, J=273 Hz), 123.1 (q, J=33 Hz); $C_7H_3BrF_3NO_2$ (270.00): C 31.14, H 1.12. Found: C 31.18, H 1.36.

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References and notes

1. Schlosser, M. The 2×3 toolbox of organometallic methods for regiochemically exhaustive functionalizations. *Angew. Chem.* **2004**, in press.
2. Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 3793–3798.
3. Cottet, F.; Marull, M.; Mongin, F.; Espinosa, D.; Schlosser, M. *Synthesis* **2004**, 1619–1624.
4. Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2000**, 327–330.
5. Mongin, F.; Desponds, O.; Schlosser, M. *Tetrahedron Lett.* **1996**, *37*, 2767–2770.
6. Gros, P.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1685–1689.
7. Iida, T.; Wada, T.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2001**, *42*, 4841–4844.
8. Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333–4339.
9. Mongin, F.; Tognini, A.; Cottet, F.; Schlosser, M. *Tetrahedron Lett.* **1998**, *39*, 1749–1752.
10. Schlosser, M. In *Organometallics in Synthesis*, 2nd ed.; Schlosser, M., Ed.; Wiley: Chichester, 2002; pp 1–352; spec. 262–265.
11. Tupitsyn, I. F.; Zatspina, N. N.; Kirova, A. V.; Kaminskii, Y. L.; Ivanenko, A. G. *Reakts. Sposobnost Org. Soedin* **1973**, *10*, 143–162. *Chem. Abstr.* **1973**, *79*, 114928v.
12. Reutov, O. A.; Beletskaya, I. P.; Butin, K. P. *CH Acids*; Pergamon: Oxford, 1978; pp 111–114.
13. Choppin, S.; Gros, P.; Fort, Y. *Org. Lett.* **2000**, *2*, 803–805.
14. Schlosser, M.; Rausis, T.; Bobbio, C. *Chem. Eur. J.*, in press.
15. Ondi, L.; Lefebvre, O.; Schlosser, M. *Tetrahedron*, in press.
16. Bobbio, C.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 3991–3997.
17. Heiss, C.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 447–451.
18. Schlosser, M.; Marull, M. *Eur. J. Org. Chem.* **2003**, 1569–1575.
19. Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2000**, *58*, 2885–2890.
20. Brignell, P. J.; Jones, P. E.; Katritzky, A. R. *J. Chem. Soc. B* **1970**, 117–121.
21. Daab, J. C.; Bracher, F. *Monatsh. Chem.* **2003**, *134*, 573–583.
22. Case, F. H. *J. Am. Chem. Soc.* **1946**, *68*, 2574–2577.
23. Schlosser, M.; Cottet, F. *Eur. J. Org. Chem.* **2002**, 4181–4184.
24. Quallich, G. J.; Fox, D. E.; Friedmann, R. C.; Murtiashaw, C. W. *J. Org. Chem.* **1992**, *57*, 761–764.

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A new route to pyrazolo[3,4-*c*] and [4,3-*c*]pyridinones via heterocyclization of *vic*-substituted hydroxamic acids of acetylenylpyrazoles

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Abstract—We report in this paper the synthesis of 6-substituted pyrazolo[4,3-*c*]pyridin-4-ones, 6-substituted 5-hydroxypyrazolo[4,3-*c*]pyridin-6-ones, 5-substituted pyrazolo[3,4-*c*]pyridin-7-ones and 5-substituted 6-hydroxypyrazolo[3,4-*c*]pyridin-7-ones by heterocyclization of *vic*-acetylenylpyrazol-hydroxamic acids under the influence of copper(I) salt in dimethylformamide or with organic bases in butanol or methanol.

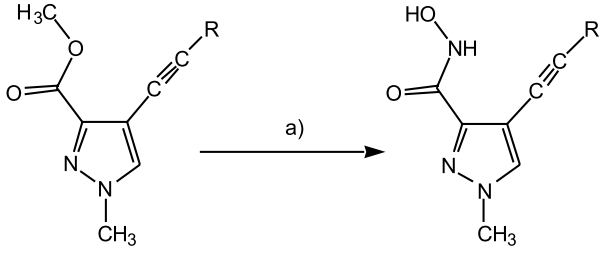
1. Introduction

Pyrazolopyridines, due to their analogy with purines have been the subject of many studies[1,2] particularly in what concerns their pharmacological properties, the five isomers, [3,4-*b*], [3,4-*c*], [4,3-*c*], [4,3-*b*] and [1,5-*a*], displaying high biological activity.[3] We have already published two papers[4,5] and one review[6] on these fused systems, for example, on the more common pyrazolo[3,4-*c*]pyridines[4–6] and on the less frequent pyrazolo[4,3-*c*]pyridines[5] (for a recent report on this last ring system see Ref. 3). In one of them[4] we reported that the heterocyclization of 4-acetylenylpyrazole-5-hydroxamic acids under influence of copper(I) salt in dimethylformamide or with organic bases in butanol or methanol leads to 5-substituted pyrazolo[3,4-*c*]pyridin-7-ones and 5-substituted 6-hydroxy-pyrazolo[3,4-*c*]pyridin-7-ones.

It is known that the electrophilicity of a triple bond and the nucleophilicity of a functional group depend on their position in the pyrazole ring. In fact, we showed earlier that the direction of cycloisomerization of *vic*-functionalized acetylenylpyrazoles depends on the mutual arrangement of acetylenic and the other functional group.[1,7] These facts prompted us to carry out a systematic investigation of the cyclization of *vic*-substituted hydroxamic acids of acetylenylpyrazoles. In the present article we report the study of cyclization of (4-acetylenylpyrazolyl-3)- and (3-acetylenyl-pyrazolyl-4)hydroxamic acids.

2. Results and discussion

Heating the methyl esters of 1-methyl-4-phenylethynyl- (**1a**) and 1-methyl-4-(phenoxymethyl-ethynyl)pyrazole-3 (**1b**) carboxylic acids with an excess of hydroxylamine in boiling methanol leads to the corresponding 4-acetylenic derivatives of pyrazole-3 hydroxamic acids **2a** (95%) and **2b** (87%) (see Scheme 1 and Section 3).



1a,b **2a,b**

R = C_6H_5 (**a**), $CH_2OC_6H_5$ (**b**)

Scheme 1. (a) NH_2OH/MeOH. R = C_6H_5 (**a**), $CH_2OC_6H_5$ (**b**).

Keywords: Pyrazolopyridines; Cross-coupling; Hydroxamic acids; Hetarylacetylenes; Heterocyclization.
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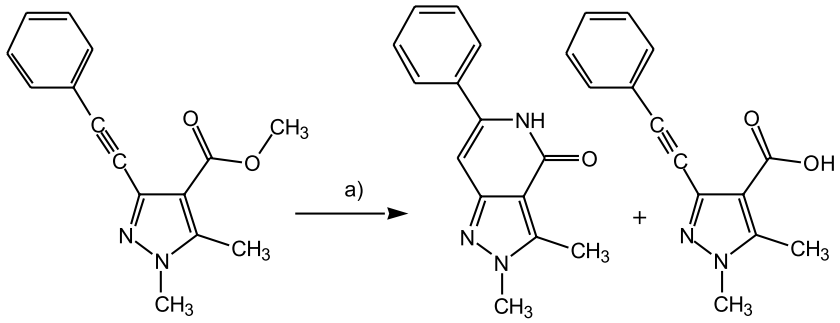
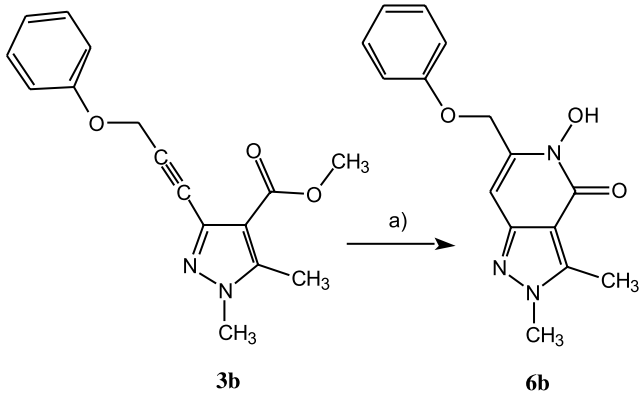


Scheme 2. (a) NH_2OH/MeOH, 12 h.

Isolation of the intermediate hydroxamic acid by interaction of the isomeric methyl esters of 1-methyl-4-(phenoxymethylethynyl)pyrazole-5 carboxylic acids with an excess of hydroxylamine in the same reaction conditions[4] was not possible and only the product of cyclization, namely the *N*-hydroxylactame was obtained. This fact confirms the necessity to study the reactivity of all the isomeric positions of acetylenylpyrazoles.

Another result was obtained in the attempt to prepare hydroxamic acids by interaction of the methyl esters of 1,5-dimethyl-3-phenylethynylpyrazole-4-carboxylic acid (**3a**)[5] with hydroxylamine in boiling methanol (Scheme 2). We observed the formation of the product of cyclization, that is, 6-phenylpyrazolo[4,3-*c*]pyridin-4-one (**4a**, 44%), as well as the product of hydrolysis of the starting ester, i.e. 1,5-dimethyl-3-phenylethynylpyrazole-4 carboxylic acid (**5**, 27%). Physical and spectral data of **5** are in agreement with literature ones.[8]

The phenoxymethylethynyl derivative **3b**[6] leads directly only to 5-hydroxy-2,3-dimethyl-6-phenoxymethyl-2,5-dihydropyrazolo[4,3-*c*]pyridin-4-one (**6b**, 50%, Scheme 3), without isolation of the hydroxamic acid intermediate.



Scheme 3. (a) NH_2OH/MeOH.

The different behavior of 4- and 3-acetylenylpyrazoles (isolation of hydroxamic acids **2a**,**b** and formation of pyrazolo[4,3-*c*]pyridines **4a**, **6b**) is related to the reduced electrophilicity of the ethynyl group in 4 position and the higher nucleophilicity of the 5 position of the pyrazole ring.

Isolation of the hydroxamic acids in the case of **2a** and **2b** allowed us to study the behavior of phenylethynyl (**2a**) and phenoxymethylethynyl (**2b**) derivatives both in neutral and basic conditions of heterocyclization (Scheme 4).

We have showed that heterocyclization of hydroxamic acids could be carried out in the presence of a weaker organic base (Et_3N instead of KOH, as in Schemes 2 and 3). Thus, the cycloisomerization of hydroxamic acids **2a** and **2b** occurs at reflux of **2a** and **2b** in presence of Et_3N in butanol and leads to the formation of the corresponding *N*-hydroxylactames **7a** (12 h) and **7b** (3 h) (76 and 54%) derived from the pyrazolo[3,4-*c*]pyridine skeleton.

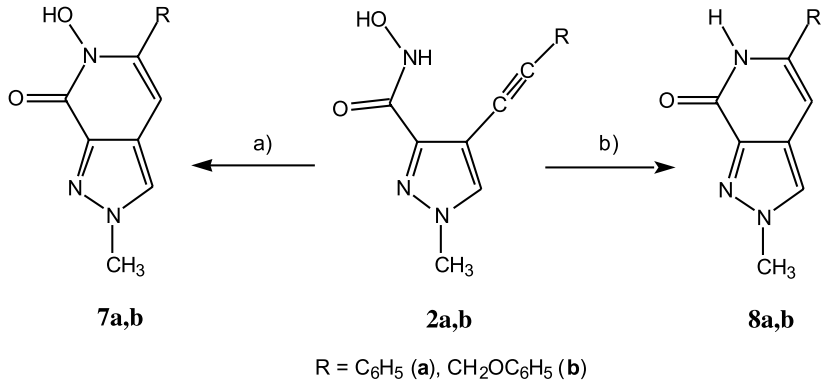
The reaction performed in neutral conditions using CuCl in boiling DMF, as well as in basic conditions, leads to the 6-membered aminolactames **8a** and **8b** (57 and 40%), the *N*-oxygen atom being unexpectedly lost in the final product.

We propose (see Scheme 5) that pyrazolo[3,4-*c*]pyridines **8a** and **8b** are formed via tautomeric equilibrium followed by thermal deoxygenation of tautomer **I**, by analogy to the loss of the oxygen atom that takes place for *N*-oxides of 2-imidazoline derivatives.[9] Thus, as follows from the above data, the cyclization of acetylenic derivatives of pyrazolylhydroxamic acids both in basic and neutral conditions leads to 4-substituted pyrazolo[4,3-*c*]pyridin-6-one and 5-substituted pyrazolo[3,4-*c*]pyridin-3-one.

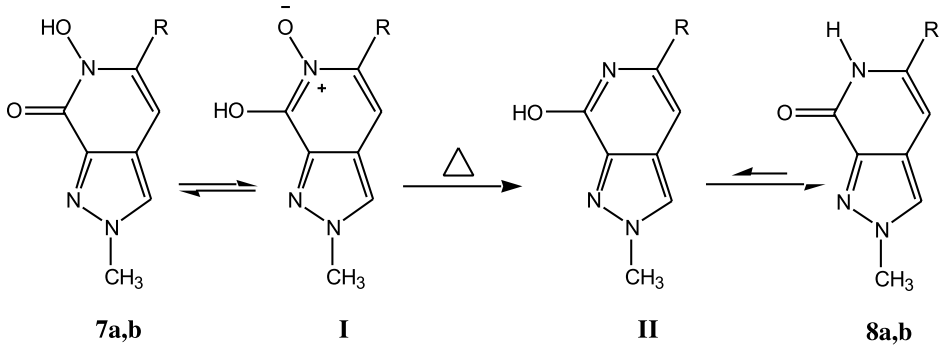
3. Experimental

3.1. General

Melting points were determined with a Kofler apparatus. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh). The R_f values were measured on aluminium backed TLC plates of silica gel Silufol UV-254 with the indicated eluent. NMR spectra were recorded on a 'Bruker Avance 300' spectrometer at 25 °C. ^{1}H NMR chemical shifts (δ in ppm) were given from internal $CHCl_3$ (7.26) or DMSO-d_6 (2.5) standards. Coupling constants (J in Hz) were accurate to ± 0.2 Hz for ^{1}H. Mass spectra (HRMS) at 70 eV using electron impact mode were performed on a Finnigan SSQ-710. The IR-spectra were recorded in KBr pellets on a 'Bruker IFS 66' instrument. Sodium, hydroxylamine hydrochloride, Et_3N, CuCl



Scheme 4. (a) Et_3N/butanol; (b) CuCl/DMF/Argon. R = C_6H_5 (**a**), $CH_2OC_6H_5$ (**b**).



Scheme 5.

('Aldrich') were commercially available reactants. All the organic solvents were of analytical quality.

3.1.1. 1-Methyl-4-(phenylethynyl)pyrazolo-3-hydroxamic acid (2a). 1.21 g (53.0 mmol) of Na was added to 30 mL of absolute methanol and then 1.76 g (24.0 mmol) of hydroxylamine hydrochloride in 20 mL of absolute methanol were added. The sodium chloride precipitate was filtered off. To the prepared solution of free hydroxylamine was added 2.2 g (9.10 mmol) of the methyl ester of ethynylpyrazolecarboxylic acid (**1**). The reaction mixture was refluxed 10 min (TLC control). Methanol was distilled off in vacuum, the residue was dissolved in water and acetic acid added (pH = 5–6). Precipitate **2a** was filtered off and crystallized from water (2.10 g, 95%), mp 133–134 °C; ν/cm^{-1} (KBr): 2223 (C≡C), 3446 (NH), 1663 (C=O), 3368 (OH); δ^1H (DMSO-d_6) 2.15s (1H, OH); 3.93s (3H, NCH_3); 7.58s [1H, H(5)], 7.31–7.53 m (5H, ArH); 8.54s (1H, NH). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 64.72; H, 4.59; N, 17.42. Found: C, 64.79; H, 4.60; N, 17.36.

3.1.2. 1-Methyl-4-(phenoxymethylethynyl)pyrazolo-3-hydroxamic acid (2b). 1.40 g (61.0 mmol) of Na was added to 30 mL of absolute methanol and then 2.10 g (29.0 mmol) of hydroxylamine hydrochloride in 20 mL of absolute methanol were added. The sodium chloride precipitate was filtered off. To the prepared solution of free hydroxylamine was added 2.63 g (9.7 mmol) of the methyl ester of ethynylpyrazolecarboxylic acid **1**. The reaction mixture was boiled 10 min (TLC control). Methanol was distilled off in vacuum, the residue was dissolved in water and acetic acid added (pH = 5–6). Precipitate **2** was filtered off and crystallized from water (2.30 g, 87.5%), mp 99–100 °C; ν/cm^{-1} (KBr): 2244 (C≡C), 3399 (NH), 1657 (C=O), 3364 (OH); δ^1H (DMSO-d_6) 1.52s (1H, OH); 3.89s (3H, NCH_3); 4.94s (2H, CH_2); 7.53s [1H, H(5)], 6.95–7.36 m (5H, ArH); 9.18s (1H, NH). Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.98; H, 4.89; N, 15.49. Found: C, 62.13; H, 4.75; N, 15.25.

3.1.3. 2,3-Dimethyl-6-phenyl-2,5-dihydropyrazolo[4,3-*c*]pyridin-4-one (4a). 1.07 g (46.5 mmol) of Na was added to 20 mL of absolute methanol and then 1.56 g (22.6 mmol) of hydroxylamine hydrochloride in 20 mL of absolute methanol. The sodium chloride precipitate was filtered off. To prepared solution of free hydroxylamine was added 1.95 g (7.60 mmol) of the methyl ester of ethynylpyrazolecarboxylic acid **3a**. The reaction mixture was boiled 12 h (TLC control). Methanol was distilled off in vacuum, the residue was dissolved in water and acetic acid added (pH = 5–6). Precipitate **4a** was filtered off and crystallized from EtOH (0.68 g, 43.9%), mp 252–253 °C; ν/cm^{-1} (KBr): 1651 (C=O), 3432 (NH); δ^1H ($CDCl_3$) 2.64 [s, 3H, CH_3 (3)]; 3.87 (s, 3H, NCH_3); 6.29 [s, 1H, H(7)]; 7.36–7.54 (m, 5H, Ph); 8.3 (s, 1H, NH); MS (70 eV) *m*/*z*: 239 $[M]^+$ (100); 43 (8); 56 (14); 77 (10); 171 (7); 224 (9); 238 (51); 240 (17). M_w: found *m*/*z* 239.10801 $[M]^+$, $C_{14}H_{13}N_3O$; calcd: M = 239.10586.

3.1.4. 5-Hydroxy-2,3-dimethyl-6-phenoxymethyl-2,5-dihydropyrazolo[4,3-*c*]pyridin-4-one (6b). 1.22 g (53.0 mmol) of Na were added to 25 mL of absolute methanol and then 1.76 g (24.0 mmol) of hydroxylamine hydrochloride in 25 mL of absolute methanol. To a prepared

solution of free hydroxylamine was added 2.23 g (7.82 mmol) of the methyl ester of ethynylpyrazolecarboxylic acid (**3b**). The reaction mixture was refluxed 7 h (TLC control). Methanol was distilled off in vacuum, the residue was dissolved in water and acetic acid added (pH = 5–6). Precipitate **6b** was filtered off and crystallized from water (1.32 g, 59.2%), mp 200.5–202 °C; ν/cm^{-1} (KBr): 1665 (C=O), 3434 (OH); δ^1H (DMSO-d_6) 2.64 [s, 3H, CH_3 (3)]; 3.86 (s, 3H, NCH_3); 6.44 [s, 1H, H(7)]; 5.07 (s, 2H, CH_2); 6.98–7.35 (m, 5H, Ph); 2.1 (s, 1H, OH); MS (70 eV) *m/z*: 285 $[M]^+$ (28); 43 (17); 56 (31); 65 (13); 77 (13); 146 (15); 149 (51); 162 (61); 176 (61); 192 (100). $C_{15}H_{15}N_3O_3$, M_w: found *m/z* 285.11146 $[M]^+$; calcd: 285.11133. Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.14; H, 5.29; N, 14.73. Found: C, 62.89; H, 5.21; N, 14.47.

3.1.5. 6-Hydroxy-2-methyl-5-phenyl-2,6-dihydropyrazolo[3,4-*c*]pyridin-7-one (7a). 0.50 g (2.10 mmol) of the hydroxamic acid of acetylenylpyrazole **2a** and 5 mL of triethylamine in 10 mL butanol were refluxed 12 h (TLC control). The solvent was distilled off in vacuum, the product **7a** was recrystallized from ethanol. (0.38 g, 76%), mp 228–230 °C; ν_{max}/cm^{-1} (KBr) 3410 (OH), 1659 (C=O); δ^1H ($CDCl_3$) 2.0s (1H, OH); 4.18s (3H, N-CH_3); 6.47s (1H, 4-H); 7.3–7.5 m (5H, ArH); 7.65s [1H, H(3)]; $\delta^{13}C$ ($CDCl_3$) 40.32 (NCH_3); 94.01 [C(4)]; 116.09 [C(3′)]; 124.03–128.65 ($Ph^{o,m,p}$); 132.68 [C(7)]; 135.80 (Ph^{i}); 143.62 [C(7′)]; 147.77 [C(5)]; 175.47 (CO). Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.44; H, 4.66; N, 17.35.

3.1.6. 6-Hydroxy-2-methyl-5-phenoxymethyl-2,6-dihydropyrazolo[3,4-*c*]pyridin-7-one (7b). 0.5 g (1.90 mmol) of the hydroxamic acid of acetylenylpyrazole (**2b**) and 5 mL of triethylamine in 10 mL butanol were refluxed 3 h (TLC control). The solvent was distilled off in vacuum, the product **7b** was recrystallized. (0.27 g, 54%), mp 201–202 °C [EtOH/H_2O (5:3)]; ν_{max}/cm^{-1} (KBr) 3440 (OH), 1660 (C=O); δ^1H ($CDCl_3$) 2.7s (1H, OH); 4.08s (3H, NCH_3); 5.16s (2H, CH_2); 6.54s (1H, H(4)]; 6.9–7.2 m (5H, ArH); 7.56s [1H, H(3)]. Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.98; H, 4.80; N, 15.49. Found: C, 61.79; H, 4.75; N, 15.33.

3.1.7. 2-Methyl-5-phenyl-2,6-dihydropyrazolo[3,4-*c*]pyridin-7-one (8a). 0.3 g (1.2 mmol) of hydroxamic acid **2a**, 0.13 g (1.30 mmol) CuCl in 4 mL of dimethylformamide were refluxed 3 h under an atmosphere of argon (TLC control). The reaction mixture was cooled and poured into chloroform and then was washed with aqueous ammonia. Chloroform solution was dried with Na_2SO_4 and filtered through alumina (3×1.5 cm^2), the solvent was evaporated under reduced pressure. The product **8a** was recrystallized from ethanol, yield 0.17 g, 57%, mp 313–315 °C (lit.: mp. 314–315 °C[10]).

3.1.8. 2-Methyl-5-phenoxymethyl-2,6-dihydropyrazolo[3,4-*c*]pyridin-7-one (8b). 1.0 g (3.70 mmol) of hydroxamic acid **2c**, 0.20 g (2.00 mmol) CuCl in 12 mL of dimethylformamide were refluxed 30 min in an atmosphere of argon (TLC control). The reaction mixture was cooled and poured into chloroform and then was washed with aqueous ammonia. Chloroform solution was dried with Na_2SO_4 and filtered through alumina (3×1.5 cm^2), the solvent was evaporated under reduced pressure. The product **8b** was recrystallized from ethanol, yield 0.35 g, 40%, mp 236.5–237.5 °C; ν/cm^{-1} (KBr): 3428 (NH), 1647 (C=O); δ^1H ($CDCl_3$) 3.91s (3H, NCH_3); 4.76s (2H, CH_2); 6.43s [1H, H(4)]; 6.9–7.4 m (5H, ArH); 7.49s [1H, H(3)]; 10.1s (1H, NH). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.86; H, 5.13; N, 16.46. Found: C, 66.13; H, 4.96; N, 16.47.

Acknowledgements

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References and notes

1. Greenhill, J. V. In *Pyrazoles with Fused Six-membered Heterocyclic Rings*; Katritzky, A. R., Rees, C. W., Eds.; Comprehensive Heterocyclic Chemistry; Pergamon: Oxford, 1984; Vol. 5, p 305.
2. Townsend, L. B.; Wise, D. S. In *Bicyclic 5–6 Systems: Three Heteroatoms 2:1*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Comprehensive Heterocyclic Chemistry II; Pergamon: Oxford, 1996; Vol. 7, p 283.
3. Commeiras, L.; Woodcock, S. C.; Baldwin, J. E.; Adlington, R. M.; Cowley, A. R.; Wilkinson, P. J. *Tetrahedron* **2004**, *60*, 933.
4. Vasilevsky, S. F.; Mshvidobadze, E. V.; Elguero, J. *Heterocycles* **2002**, *57*, 2255.
5. Vasilevsky, S. F.; Mshvidobadze, E. V.; Elguero, J. *J. Heterocycl. Chem.* **2002**, *39*, 1229.
6. Vasilevsky, S. F.; Tretyakov, E. V.; Elguero, J. *Adv. Heterocycl. Chem.* **2002**, *82*, 1.
7. Tretyakov, E. V.; Knight, D. W.; Vasilevsky, S. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3721.
8. Vasilevsky, S. F. *Doctor Thesis*. Novosibirsk, 1986.
9. Klyatskaya, S. V.; Tretyakov, E. V.; Vasilevsky, S. F. *Izv. Akad. Nauk., Ser. Khim.* **2002**, 122. (*Russ. Chem. Bull. Int. Ed.* **2002**, *51*, 128).
10. Vasilevsky, S. F.; Shvartsberg, M. S. *Izv. Akad. Nauk., Ser. Khim.* **1990**, 2089.

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Novozym 435-catalyzed kinetic resolution of β-allenols. A facile route for the preparation of optically active β-allenols or allenyl acetates

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Abstract—A variety of optically active β-allenols and β-allenyl acetates were synthesized via the Novozym 435-mediated kinetic resolution of racemic β-allenols. A dramatic solvent effect was observed for the stereoselectivity. The scope of the substrates and the effect of the concentration and temperature on the reaction were also investigated.

1. Introduction

Allenes are a class of compounds with two cumulative carbon–carbon double bonds, which demonstrate interesting properties such as unique reactivity and chirality.[1] In the past decades, much attention has been paid to the synthesis and reaction of functionalized allenes.[2] Since the chirality of allenes can be transformed to the products with one or more chiral center, people are interested in the synthesis of optically active allenes.[3] Allenols are a very important class of functionalized allenes, which can be converted to many organic intermediates. For example, 2,3-allenols can be stereoselectively converted into oxiranes,[4] 2,5-dihydrofurans,[5] α-methylenelactones,[6] α or γ-amino alcohols[7] etc. Starting from β-allenols, 3-oxacyclohexanone,[8] 3,6-dihydro-2*H*-pyran,[9] 2,3-dihydrofuran[10] and furans[11] can also easily be obtained. Thus, the synthesis of optically active allenols is of current interest. For optically active 2,3-allenols, some synthetic methods were developed in recent years.[12] However, the methodologies for the synthesis of optically active β-allenols were very limited: the methodologies for the optically active β-allenols reported in the literature are mainly using optically active 3-en-5-yn-2-ols as the starting material, which are not easily available.[13] Biocatalytic methods are now well-established routes to enantiomerically pure or enriched alcohols with the advantages of easy availability of starting materials and the biocatalyst. The kinetic resolution of 2-methylpenta-3,4-dien-1-ol using Lipase AK and Novozym-435 (a form of *candida antarctica lipase B*) as the biocatalyst has been reported.[14] The kinetic resolution of those β-allenols with chiral centers connected with the hydroxyl group using an enzyme or a microorganism as the catalyst has not been reported. Previously, we have reported that Novozym-435 (a form of *candida antarctica lipase B*) is an efficient biocatalyst for the kinetic resolution of a series of racemic 2,3-allenols[15] and terminal aryl-substituted propargylic alcohols that can be converted to the corresponding 2,3-allenols.[16] Here we wish to report our recent results on Novozym-435-catalyzed kinetic resolution of β-allenols.

2. Results and discussion

2.1. Synthesis of starting racemic 2,3-allenols

The required racemic β-allenols can be synthesized according to the known procedure as shown in Scheme 1.[17]

2.2. Kinetic resolution

We started our research with the kinetic resolution of **1a** using the same reaction conditions reported in Ref. 15. Optically active **2a** was obtained in 35% yield with 96% ee

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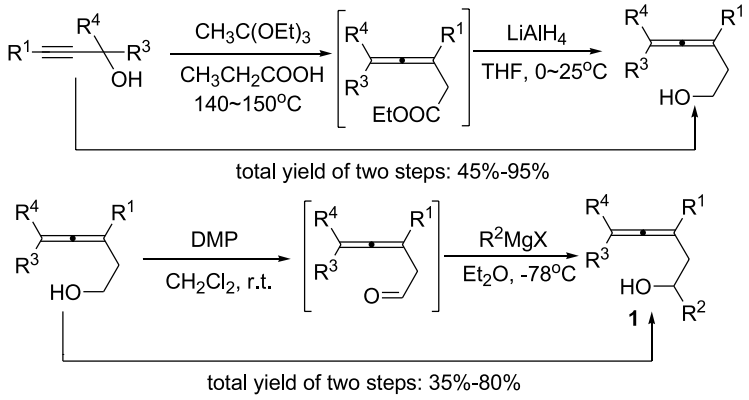


1a $R^1 = n\text{-}C_4H_9$, $R^2 = Et$, $R^3 = R^4 = H$ **1b** $R^1 = n\text{-}C_3H_7$, $R^2 = Et$, $R^3 = R^4 = H$

1c $R^1 = n\text{-}C_6H_{13}$, $R^2 = Et$, $R^3 = R^4 = H$ **1d** $R^1 = n\text{-}C_7H_{15}$, $R^2 = Et$, $R^3 = R^4 = H$

1e R^1 = allyl, $R^2 = Et$, $R^3 = R^4 = H$ **1f** $R^1 = PhCH_2$, $R^2 = Et$, $R^3 = R^4 = H$

1g $R^1 = H$, $R^2 = Et$, $R^3 = R^4 = CH_3$ **1h** $R^1 = n\text{-}C_4H_9$, $R^2 = Et$, $R^3 = R^4 = CH_3$

1i $R^1 = n\text{-}C_4H_9$, $R^2 = Et$, $R^3 = R^4 = (CH_2)_5$ **1j** $R^1 = n\text{-}C_4H_9$, $R^2 = Me$, $R^3 = R^4 = H$

1k $R^1 = n\text{-}C_4H_9$, $R^2 = Me$, $R^3 = R^4 = Me$ **1l** $R^1 = n\text{-}C_4H_9$, R^2 = ethenyl, $R^3 = R^4 = H$

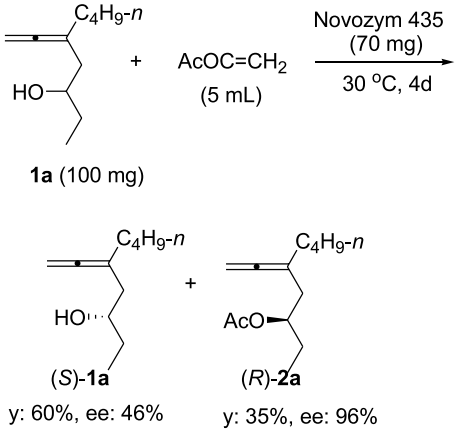
1m $R^1 = n\text{-}C_5H_{11}$, R^2 = ethenyl, $R^3 = R^4 = H$ **1n** $R^1 = n\text{-}C_4H_9$, R^2 = ethynyl, $R^3 = R^4 = H$

1o $R^1 = n\text{-}C_5H_{11}$, R^2 = ethynyl, $R^3 = R^4 = H$ **1p** $R^1 = n\text{-}C_4H_9$, $R^2 = n\text{-}Pr$, $R^3 = R^4 = H$

1q $R^1 = t\text{-}C_4H_9$, $R^2 = Et$, $R^3 = R^4 = H$ **1r** $R^1 = CH_3$, $R^2 = Me$, $R^3 = R^4 = H$

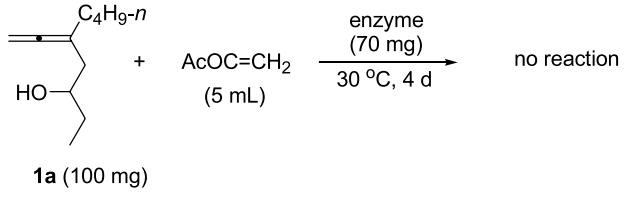
Scheme 1.

while the ee value of unreacted **1a** was not good (Eq. 1).



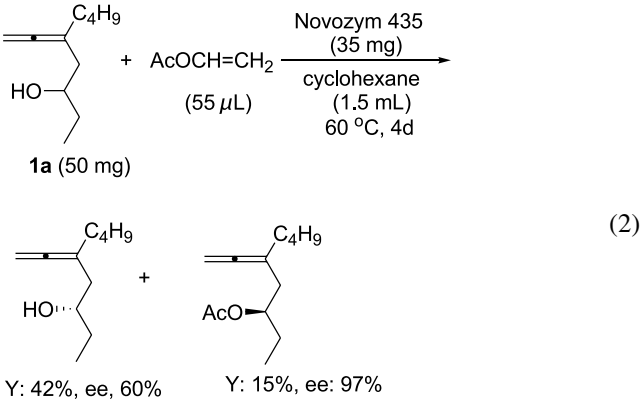
(1)

In order to identify the best enzyme for the present class of compounds, extensive screening experiments were carried out. Using PPL, CRL, Lipase AK, and Lipase Ps 30 as the catalyst, the reaction is extremely slow or does not even occur (Scheme 2).



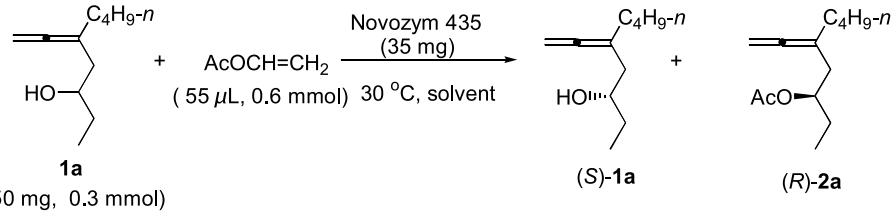
Scheme 2.

It was reported that the solvent may be critical to the enzyme-catalyzed reaction.[18] Some typical results using Novozym 435 as the biocatalyst in different solvent are listed in Table 1. As shown in Table 1, the solvent did affect the reaction dramatically: using 1,4-dioxane as the solvent, the reaction cannot occur (Table 1, entry 1); when the reaction was carried out in vinyl acetate, *E* value of the reaction is 62 (Table 1, entry 2); when using hexane, benzene, acetone, or acetonitrile, the results are better with the *E* values being 144, 148, 156, and 178, respectively (Table 1, entries 3, 4, 5, and 6); while using the cyclohexane as the solvent, optically active (*S*)-**1a** can be obtained in 44% yield and 74% ee and (*R*)-**2a** in 42% yield and 97% ee (Table 1, entry 7). Changing the concentration (Table 2) and reaction temperature (Eq. 2) did not greatly alter the selectivity of the reaction (Eq. 2).



(2)

Table 1. Novozym 435-catalyzed kinetic resolution of **1a** in different solvents[a]

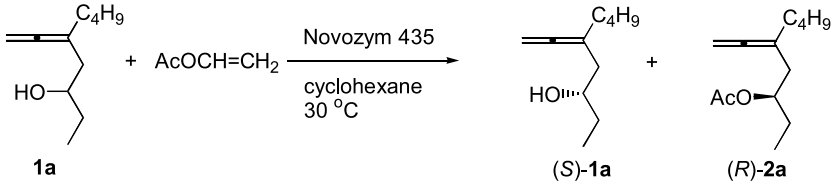


1a (50 mg, 0.3 mmol) (*S*)-**1a** (*R*)-**2a**

Entry	Time (d)	Solvent	Alcohol (**1a**)		Ester (**2a**)		E[b]
			Yield[c] (%)	ee (%)[d]	Yield[c] (%)	ee[e] (%)	
1	4	1,4-Dioxane			NR		
2	4	Vinyl acetate	56	43	29	95	62
3	3	Hexane	58	77	38	97	144
4	4	Benzene	64	67	34	97	148
5	3	Acetone	56	74	43	97	156
6	4	Acetonitrile	64	48	35	98	178
7	4	Cyclohexane	44	74	42	98	192

[a] The reaction was carried out at 30 °C using **1a** (50 mg), vinyl acetate (55 μL), solvent (1.5 mL) and enzyme (35 mg).
[b] $E=\ln[ee_P(1-ee_S)]/(ee_P+ee_S)/\ln[ee_P(1+ee_S)]/(ee_P+ee_S)$.
[c] Isolated yield based on **1a**.
[d] Determined after its conversion into the corresponding acetate.
[e] Enantiomeric excess determined via GC.

Table 2. Novozym 435-catalyzed kinetic resolution of **1a** at different concentrations[a]



1a (*S*)-**1a** (*R*)-**2a**

Entry	Solvent (mL)	(*S*)-**1a**		(*R*)-**2a**		E[b]
		Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]	
1	3.0	68	39	32	98	172
2	2.5	50	58	30	98	199
3	2	48	52	37	98	176
4	1	46	45	29	98	155

[a] The reaction was carried out at 30 °C using **1a** (50 mg), vinyl acetate (55 μL), solvent (1.5 mL) and enzyme (35 mg).
[b] $E=\ln[ee_P(1-ee_S)]/(ee_P+ee_S)/\ln[ee_P(1+ee_S)]/(ee_P+ee_S)$.
[c] Isolated yield based on **1a**.
[d] Enantiomeric excess determined by GC.

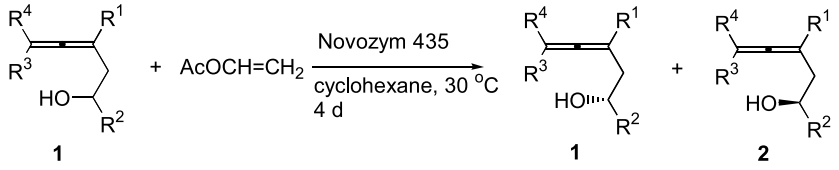
Subsequently, a series of β-allenols were resolved. Some typical results were listed in Table 3. From the results shown in Table 3, it can be clearly seen that this methodology can accommodate a wide range of substrates. In most cases, the reaction went well affording optically active β-allenols or allenyl acetates in good yields and good ees. The substituents have some effect on the stereoselectivity of the reaction. The result with R^2 being ethyl is better than those with R^2 being methyl, ethenyl, and ethynyl (Table 3, entries 1, 10, 12, and 14). When R^2 is beyond two carbon atoms, the reaction is extremely slow or even does not occur at all. Although R^3 and R^4 are far away from the chiral center, they also affect the stereoselectivity of the reaction. The results are different when R^3 and R^4 are H, methyl, and cyclohexylidene (Table 3, entries 1, 8, and 9). When R^1 is *t*-butyl, perhaps due to the stereic hindrance, the reaction did not occur. The absolute configuration of the obtained (+)-4-methylhexa-4,5-dien-2-ol (**1r**) was determined to be *S* by the comparison of the sign of the specific rotation with the known (*R*)-(−)-4-methylhexa-4,5-dien-2-ol (Scheme 3).[13] The absolute configuration of the compounds in Table 3 was tentatively assigned based on this result (Scheme 3).

(+)-**1r** (*R*)-(-)-**1r**

Scheme 3.

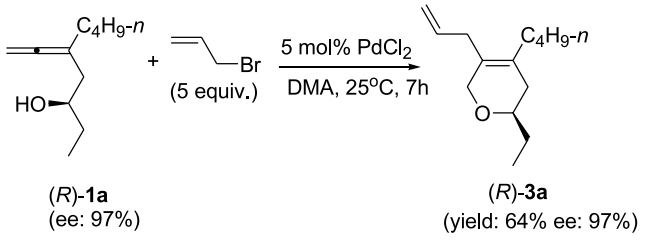
The resulting optically active allenol (**1a**) can easily be converted to the corresponding 3,6-dihydropyran without obvious racemization (Eq. 3).

Table 3. Novozym-435-catalyzed kinetic resolution of β-allenols[a]



Entry	1				1		2		E[b]
	R^1	R^2	R^3	R^4	Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]	
1	n-C_4H_9	Et	H	H (**1a**)	46	83 (*S*-**1a**)	42	97 (*R*-**2a**)	199
2	n-C_3H_7	Et	H	H (**1b**)	39	82 (*S*-**1b**)	36	96 (*R*-**2b**)	143
3	n-C_6H_{13}	Et	H	H (**1c**)	51	58 (*S*-**1c**)	28	98 (*R*-**2c**)	178
4	n-C_7H_{15}	Et	H	H (**1d**)	40	54 (*S*-**1d**)	25	98 (*R*-**2d**)	191
5[e]	Allyl	Et	H	H (**1e**)	48	50 (*S*-**1e**)	28	97 (*R*-**2e**)	111
6[e]	$PhCH_2$	Et	H	H (**1f**)	38	71 (*S*-**1f**)	44	72 (*R*-**2f**)	12
7[f]	H	Et	Me	Me (**1g**)	27	93 (*S*-**1g**)	59	22 (*R*-**2g**)	4
8	n-C_4H_9	Et	Me	Me (**1h**)	46	44 (*S*-**1h**)	26	95 (*R*-**2h**)	66
9	n-C_4H_9	Et	$(CH_2)_5$ (**1i**)		42	96 (*S*-**1i**)	51	82 (*R*-**2i**)	41
10[e]	n-C_4H_9	Me	H	H (**1j**)	37	88 (*S*-**1j**)	35	89 (*R*-**2j**)	52
11	n-C_4H_9	Me	Me	Me (**1k**)	38	91 (*S*-**1k**)	52	42 (*R*-**2k**)	31
12[e]	n-C_4H_9	Ethenyl	H	H (**1l**)	43	93 (*R*-**1l**)	56	75 (*S*-**2l**)	24
13	n-C_5H_{11}	Ethenyl	H	H (**1m**)	44	93 (*R*-**1m**)	40	85 (*S*-**2m**)	108
14	n-C_4H_9	Ethynyl	H	H (**1n**)	38	88 (*R*-**1n**)	56	44[f] (*S*-**2n**)	7
15	n-C_5H_{11}	Ethynyl	H	H (**1o**)	40	90 (*R*-**1o**)	40	60 (*S*-**2o**)	35

[a] The reaction was carried out at 30 °C using **1** (100 mg), vinyl acetate (2 equiv), Novozym 435 (100 mg), and cyclohexane (3.0 mL).
[b] $E=\ln[ee_P(1-ee_S)]/(ee_P+ee_S)/\ln[ee_P(1+ee_S)]/(ee_P+ee_S)$.
[c] Isolated yield based on **1**.
[d] Enantiomeric excess determined via GC or HPLC.
[e] Novozym 435 (70 mg).
[f] Reaction time: 1 day.



(3)

In conclusion, we have developed an efficient and facile method for the preparation of optically active β-allenols or β-allenyl acetates under mild conditions. Due to the easy availability of the catalyst and the synthetic potential of the products, this methodology should be useful in organic chemistry. Further studies on this reaction are being carried out in our laboratory.

3. Experimental

3.1. Synthesis of racemic β-allenols (1a–s)

The racemic β-allenols were synthesized according to the procedure reported in the literature.[17] A typical example was presented as follows:

3.1.1. Synthesis of (±)-5-(*n*-butyl)hepta-5,6-dien-3-ol (1a). To a dried three-neck flask were added hepta-2-yn-1-ol (6.12 g, 54.7 mmol), triethyl orthoacetate (34.8 mL, 189 mmol), and propionic acid (0.68 mL) under nitrogen. Additional 0.5 mL of propionic acid was added after 145 min. The mixture was stirred at 140–150 °C for 5 h as the resulting EtOH was removed by a Dean–Stark trap. After the starting material was completely consumed as monitored by TLC, the mixture was cooled to room temperature, evaporated, and purified by chromatography on silica gel to afford 3-(*n*-butyl)penta-3,4-dienoic acid ethyl ester, which was submitted to the next step without further characterization.

To a suspension of $LiAlH_4$ (2.13 g, 56.1 mmol) in dried THF (72 mL) was added a solution of the obtained 3-(*n*-butyl)penta-3,4-dienoic acid ethyl ester in dried THF (72 mL) dropwise at 0 °C. After stirring at rt for 1 h, the reaction was quenched by the careful addition of water at 0 °C. Filtration, drying over anhydrous Na_2SO_4, and concentration afforded the crude product, which was purified by chromatography on silica gel (eluent: petroleum ether/ethyl ether = 10/1) to afford pure 3-(*n*-butyl)penta-3,4-dien-1-ol (4.65 g, 61% (two steps)).

A solution of 3-(*n*-butyl)penta-3,4-diene-1-ol (1.57 g, 11.2 mmol) in CH_2Cl_2 (5 mL) was added to a suspension of Dess–Martin periodinane (DMP) (6.61 g, 17.6 mmol) in CH_2Cl_2 (15 mL). After 0.5 h, the reaction was diluted with ethyl ether (30 mL), and the resulting suspension was added to a solution of saturated $NaHCO_3$ (50 mL) with sodium thiosulfate (30.00 g, 121 mmol). After the mixture was stirred for 30 min, the ether layer was separated and the aqueous layer was extracted with ethyl ether (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the allenal, which was used without further purification.

To a solution of the obtained allenal in ethyl ether (20 mL) was added EtMgBr (1 M in THF, 20 mL) dropwise at −78 °C under nitrogen. Then, the resulting mixture was stirred for 10 h at −78 °C as monitored by TLC. The reaction was quenched with saturated NH_4Cl at −78 °C. After the temperature rose to rt, the organic layer was separated. The aqueous layer was extracted with ethyl ether (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by chromatography on silica gel (eluent: petroleum ether/ethyl ether = 15/1) to afford racemic 5-(*n*-butyl)hepta-5,6-dien-3-ol (**1a**) (0.90 g, 48%); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80–4.70 (m, 2H), 3.75–3.64 (m, 1H), 2.20–1.90 (m, 5H), 1.58–1.28 (m, 6H), 0.96 (t, J=7.5 Hz, 3H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.7, 100.5, 75.9, 70.9, 39.9, 31.9, 29.5, 29.3, 22.2, 13.8, 9.8; IR (neat): 3388, 1956 cm^{-1}; MS (*m/z*) 168 (M^+, 2.47), 43 (100); HRMS Calcd for $C_{11}H_{20}O$ (M^+): 168.1514. Found 168.1488.

3.2. Kinetic resolution of racemic β-allenols (1a–1o)

3.2.1. Synthesis of (*S*)-5-(*n*-butyl)hepta-5,6-dien-3-ol ((*S*)-1a) and (*R*)-5-(*n*-butyl)hepta-5,6-dien-3-yl acetate ((*R*)-2a). *Typical procedure*. Novozym 435 (100 mg) was added into the mixture of racemic 5-(*n*-butyl)hepta-5,6-dien-3-ol (100 mg), cyclohexane (3 mL) and vinyl acetate (110 μL). After stirring at 30 °C for 96 h, the reaction was stopped by filtration. Evaporation and purification by flash chromatography on silica gel (petroleum ether/ether = 40/1→10/1) afforded (*S*)-**1a** (46 mg, 46%) and (*R*)-**2a** (52 mg, 42%). Compound (*S*)-**1a**: 83% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}$ + 1.2 (*c* 1.10, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80–4.70 (m, 2H), 3.75–3.64 (m, 1H), 2.20–1.90 (m, 5H), 1.58–1.28 (m, 6H), 0.96 (t, J=7.5 Hz, 3H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.7, 100.5, 75.9, 70.9, 39.9, 31.9, 29.5, 29.3, 22.2, 13.8, 9.8; IR (neat): 3388, 1956 cm^{-1}; MS (*m/z*) 168 (M^+, 2.47), 43 (100); HRMS Calcd for $C_{11}H_{20}O$ (M^+): 168.1514. Found 168.1488. Compound (*R*)-**2a**: 97% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 120 °C (10 min), then 1.0 °C to 180 °C (20 min)); $[\alpha]_D^{20}$ + 5.8 (*c* 1.10, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.93–4.85 (m, 1H), 4.65–4.57 (m, 2H), 2.22–2.05 (m, 2H), 2.02 (s, 3H), 1.96–1.87 (m, 2H), 1.64–1.50 (m, 2H), 1.50–1.23 (m, 4H), 0.87 (t, J=7.5 Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.9, 170.5, 99.2, 75.2, 73.7, 36.6, 31.7, 29.5, 26.7, 22.2, 21.1, 13.8, 9.4; IR (neat): 1958, 1740 cm^{-1}; MS (*m/z*) 210 (M^+, 0.55), 43 (100); HRMS Calcd for $C_{13}H_{22}O_2$ (M^+): 210.1620. Found 210.1593.

3.2.2. Synthesis of (*S*)-5-(*n*-propyl)hepta-5,6-dien-3-ol ((*S*)-1b) and (*R*)-5-(*n*-propyl)hepta-5,6-dien-3-yl acetate ((*R*)-2b). The reaction of racemic 5-(*n*-propyl)hepta-5,6-dien-3-ol (100 mg) with Novozym-435 (100 mg) and vinyl acetate (117 μL) afforded (*S*)-**1b** (39 mg, 39%) and (*R*)-**2b** (46 mg, 36%). Compound (*S*)-**1b**: 81% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}$ + 6.8 (*c* 0.75, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80–4.72 (m, 2H), 3.76–3.62 (m, 1H), 2.20–2.00 (m, 2H), 2.00–1.88 (m, 3H), 1.60–1.40 (m, 4H), 0.96 (t, J=7.5 Hz, 3H), 0.91 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.8, 100.4, 76.0, 71.0, 40.0, 34.4, 29.6, 20.6, 13.7, 9.9; IR (neat): 3396, 1956 cm^{-1}; MS (*m/z*) 154 (M^+, 5.39), 43 (100); HRMS Calcd for $C_{10}H_{18}O$ (M^+): 154.1358. Found 154.1345. Compound (*R*)-**2b**: 96% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 105 °C (40 min)); $[\alpha]_D^{20}$ + 19.5 (*c* 1.10, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00–4.84 (m, 1H), 4.66–4.60 (m, 2H), 2.28–2.06 (m, 2H), 2.05 (s, 3H), 2.00–1.82 (m, 2H), 1.74–1.40 (m, 4H), 0.92 (t, J=7.2 Hz, 3H), 0.88 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.5, 170.7, 99.1, 75.2, 73.8, 36.7, 34.2, 26.8, 21.2, 20.6, 13.7, 9.5; IR (neat): 1958, 1740 cm^{-1}; MS (*m/z*) 196 (M^+, 1.64), 43 (100); HRMS Calcd for $C_{12}H_{20}O2$ (M^+): 196.1463. Found 196.1454.

3.2.3. Synthesis of (*S*)-5-(*n*-hexyl)hepta-5,6-dien-3-ol ((*S*)-1c) and (*R*)-5-(*n*-hexyl)hepta-5,6-dien-3-yl acetate ((*R*)-2c). The reaction of racemic 5-(*n*-hexyl)hepta-5,6-diene-3-ol (100 mg) with Novozym-435 (100 mg) and vinyl acetate (94 μL) afforded (*S*)-**1c** (51 mg, 51%) and (*R*)-**2c** (34 mg, 28%). Compound (*S*)-**1c**: 58% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}$ + 1.4 (*c* 1.05, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80–4.68 (m, 2H), 3.75–3.60 (m, 1H), 2.20–1.90 (m, 5H), 1.60–1.20 (m, 10H), 0.96 (t, J=7.5 Hz, 3H), 0.88 (t, J=6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.7, 100.7, 76.1, 71.0, 40.1, 32.4, 31.7, 29.6, 28.9, 27.4, 22.6, 14.1, 10.0; IR (neat): 3398, 1956 cm^{-1}; MS (*m/z*) 196 (M^+, 1.96), 43 (100); HRMS Calcd for $C_{13}H_{24}O$ (M^+): 196.1827. Found 196.1848. Compound (*R*)-**2c**: 98% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 8.0 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 130 °C (80 min), then 1 °C/min to 150 °C (2 min)); $[\alpha]_D^{20}$ + 16.8 (*c* 1.10, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.98–4.85 (m, 1H), 4.66–4.60 (m, 2H), 2.25–2.06 (m, 2H), 2.03 (s, 3H), 1.98–1.87 (m, 2H), 1.70–1.45 (m, 2H), 1.43–1.23 (m, 8H), 0.92–0.80 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.4, 170.7, 99.3, 75.3, 73.8, 36.7, 32.1, 31.7, 28.9, 27.4, 26.8, 22.6, 21.2, 14.1, 9.5; IR (neat): 1958, 1740 cm^{-1}; MS (*m/z*) 238 (M^+, 4.76), 43 (100); HRMS Calcd for $C_{15}H_{26}O_2$ (M^+): 238.1933. Found 238.1916.

3.2.4. Synthesis of (*S*)-5-(*n*-heptyl)hepta-5,6-dien-3-ol ((*S*)-1d) and (*R*)-5-(*n*-heptyl)hepta-5,6-dien-3-yl acetate ((*R*)-2d). The reaction of racemic 5-(*n*-heptyl)hepta-5,6-dien-3-ol (100 mg) with Novozym-435 (100 mg) and vinyl acetate (88 μL) afforded (*S*)-**1d** (40 mg, 40%) and (*R*)-**2d** (30 mg, 25%). Compound (*S*)-**1d**: 54% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}$ − 1.5 (*c* 1.00, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80–4.70 (m, 2H), 3.74–3.62 (m, 1H), 2.20–1.92 (m, 5H), 1.70–1.38 (m, 4H), 1.38–1.20 (m, 8H), 0.96 (t, J=7.5 Hz, 3H), 0.87 (t, J=6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.7, 100.7, 76.1, 71.0, 40.1, 32.4, 31.8, 29.6, 29.2, 29.1, 27.4, 22.6, 14.1, 10.0; IR (neat): 3383, 1956 cm^{-1}; MS (*m/z*) 210 (M^+, 2.08), 43 (100); HRMS Calcd for $C_{14}H_{26}O$ (M^+): 210.1984. Found 210.1965. Compound (*R*)-**2d**: 98% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 8.0 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 130 °C

(80 min), then 1 °C/min to 150 °C (2 min)); $[\alpha]_D^{20}+15.9$ (*c* 0.90, $CHCl_3$); liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 4.94–4.87 (m, 1H), 4.66–4.59 (m, 2H), 2.23–2.04 (m, 2H), 2.02 (s, 3H), 1.95–1.87 (m, 2H), 1.70–1.45 (m, 2H), 1.43–1.19 (m, 10H), 0.91–0.83 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.4, 170.7, 99.3, 75.3, 73.8, 36.7, 32.1, 31.8, 29.2, 29.1, 27.4, 26.8, 22.6, 21.2, 14.1, 9.5; IR (neat): 1958, 1740 cm^{-1}; MS (*m/z*) 252 (M^+, 5.28), 43 (100); HRMS Calcd for $C_{16}H_{28}O_2$ (M^+): 252.2089. Found 252.2097.

3.2.5. Synthesis of (*S*)-5-allylhepta-5,6-dien-3-ol ((*S*)-1e) and (*R*)-5-allylhepta-5,6-dien-3-yl acetate ((*R*)-2e). The reaction of racemic 5-allylhepta-5,6-dien-3-ol (100 mg) with Novozym-435 (70 mg) and vinyl acetate (122 μL) afforded (*S*)-**1e** (48 mg, 48%) and (*R*)-**2e** (36 mg, 28%). Compound (*S*)-**1e**: 50% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}+0.8$ (*c* 2.40, $CHCl_3$); liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 5.86–5.76 (m, 1H), 5.12–5.04 (m, 2H), 4.80–4.70 (m, 2H), 3.73–3.67 (m, 1H), 2.76–2.74 (m, 2H), 2.20–2.03 (m, 2H), 1.92 (d, $J=3.0$ Hz, 1H), 1.60–1.47 (m, 2H), 0.97 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.1, 135.4, 116.3, 99.1, 76.2, 71.0, 39.5, 37.4, 29.6, 10.0; IR (neat): 3414, 1957, 1639 cm^{-1}; MS (*m/z*) 152 (M^+, 0.97), 79 (100); HRMS Calcd for $C_{10}H_{16}O$ (M^+): 152.1201. Found 152.1210. Compound (*R*)-**2e**: 97% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 100 °C (60 min)); $[\alpha]_D^{20}+23.9$ (*c* 0.50, $CHCl_3$); liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 5.84–5.73 (m, 1H), 5.11–5.03 (m, 2H), 4.96–4.91 (m, 1H), 4.69–4.65 (m, 2H), 2.75–2.72 (m, 2H), 2.22–2.15 (m, 2H), 2.30 (s, 3H), 1.68–1.54 (m, 2H), 0.89 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.8, 170.6, 135.4, 116.1, 97.7, 75.4, 73.6, 37.1, 36.0, 26.8, 21.2, 9.5; IR (neat): 1960, 1743, 1639 cm^{-1}; MS (*m/z*) 194 (M^+, 1.28), 43 (100); HRMS Calcd for $C_{12}H_{18}O_2$ (M^+): 194.1307. Found 194.1271.

3.2.6. Synthesis of (*S*)-5-benzylhepta-5,6-dien-3-ol ((*S*)-1f) and (*R*)-5-benzylhepta-5,6-dien-3-yl acetate ((*R*)-2f). The reaction of racemic 5-benzylhepta-5,6-dien-3-ol (100 mg) with Novozym-435 (70 mg) and vinyl acetate (92 μL) afforded (*S*)-**1f** (38 mg, 38%) and (*R*)-**2f** (53 mg, 44%). Compound (*S*)-**1f**: 71% ee (HPLC conditions: Chiralcel OD Column (0.46 cm$\phi\times$25 cm); λ 254 nm; rate: 0.7 mL/min; hexane: *i*-PrOH=100: 1.25); $[\alpha]_D^{20}-4.8$ (*c* 1.10, $CHCl_3$); liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 4.82–4.70 (m, 2H), 3.80–3.60 (m, 1H), 3.35 (t, $J=2.4$ Hz, 2H), 2.20–1.98 (m, 3H), 1.60–1.40 (m, 2H), 0.94 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.7, 139.1, 128.9, 128.3, 126.4, 100.1, 75.9, 71.1, 39.8, 39.1, 29.6, 10.0; IR (neat): 3398, 1957 cm^{-1}; MS (*m/z*) 202 (M^+, 27.45), 91 (100); HRMS Calcd for $C_{14}H_{18}O$ (M^+): 202.1358. Found 202.1371. Compound (*R*)-**2f**: 72% ee (determined after its conversion to the corresponding alcohol); $[\alpha]_D^{20}+54.6$ (*c* 1.10, $CHCl_3$); liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.12 (m, 5H), 5.00–4.80 (m, 1H), 4.67–4.63 (m, 2H), 3.32 (t, $J=2.4$ Hz, 2H), 2.23–2.09 (m, 2H), 2.03 (s, 3H), 1.70–1.52 (m, 2H), 0.94 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.4, 170.6, 139.1, 128.9, 128.2, 126.2, 98.8, 75.1, 73.6, 39.4, 35.6, 26.8, 21.2, 9.4; IR (neat): 1959, 1737 cm^{-1}; MS (*m/z*) 244 (M^+, 3.13), 43 (100); HRMS Calcd for $C_{16}H_{20}O_2$ (M^+): 244.1463. Found 244.1424.

3.2.7. Synthesis of (*S*)-7-methylocta-5,6-dien-3-ol ((*S*)-1g) and (*R*)-7-methylocta-5,6-dien-3-yl acetate ((*R*)-2g). The reaction of racemic 3-methylocta-5,6-dien-3-ol (100 mg) with Novozym-435 (100 mg) and vinyl acetate (132 μL) afforded (*S*)-**1g** (27 mg, 27%) and (*R*)-**2g** (77 mg, 59%). Compound (*S*)-**1g**: 93% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}-2.1$ (*c* 0.50, $CHCl_3$); liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 5.02–4.90 (m, 1H), 3.63–3.51 (m, 1H), 2.23–1.96 (m, 2H), 1.79 (d, $J=3.9$ Hz, 1H), 1.70 (s, 3H), 1.69 (s, 3H), 1.59–1.44 (m, 2H), 0.96 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 203.0, 95.3, 84.9, 72.4, 36.8, 29.3, 20.7, 20.6, 10.0; IR (neat): 3362, 1969 cm^{-1}; MS (*m/z*) 140 (M^+, 100), 125 (M^+-CH_3, 27.90); HRMS Calcd for $C_9H_{16}O$ (M^+): 140.1201. Found 140.1206. Compound (*R*)-**2g**: 22% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 120 °C (20 min)); $[\alpha]_D^{20}+12.2$ (*c* 0.75, $CHCl_3$); liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 4.81–4.74 (m, 2H), 2.20–2.06 (m, 2H), 1.99 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.59–1.42 (m, 2H), 0.82 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 202.9, 170.8, 95.0, 84.0, 74.9, 33.5, 26.3, 21.2, 20.52, 20.46, 9.5; IR (neat): 1970, 1740 cm^{-1}; MS (*m/z*) 182 (M^+, 8.40), 43 (100); HRMS Calcd for $C_{11}H_{18}O_2$ (M^+): 182.1307. Found 182.1292.

3.2.8. Synthesis of (*S*)-7-methyl-5-(*n*-butyl)octa-5,6-dien-3-ol ((*S*)-1h) and (*R*)-7-methyl-5-(*n*-butyl)octa-5,6-dien-3-yl acetate ((*R*)-2h). The reaction of racemic 7-methyl-5-(*n*-butyl)octa-5,6-diene-3-ol (100 mg) with Novozym-435 (100 mg) and vinyl acetate (94 μL) afforded (*S*)-**1h** (46 mg, 46%) and (*R*)-**2h** (31 mg, 26%). Compound (*S*)-**1h**: 44% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}+0.7$ (*c* 1.45, $CHCl_3$); liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 3.68–3.58 (m, 1H), 2.20–2.00 (m, 1H), 2.00–1.80 (m, 4H), 1.69 (s, 6H), 1.58–1.42 (m, 2H), 1.42–1.22 (m, 4H), 0.96 (t, $J=7.5$ Hz, 3H), 0.89 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 198.6, 99.2, 96.5, 71.1, 40.7, 33.0, 29.7, 29.5, 22.3, 21.1, 20.8, 14.0, 10.1; IR (neat): 3373, 1960 cm^{-1}; MS (*m/z*) 196 (M^+, 5.64), 96 (100); HRMS Calcd for $C_{13}H_{24}O$ (M^+): 196.1827. Found 196.1827. Compound (*R*)-**2h**: 95% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 100 °C (60 min), then 2 °C/min to 150 °C (60 min)); $[\alpha]_D^{20}+10.7$ (*c* 1.40, $CHCl_3$); liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 4.92–4.82 (m, 1H), 2.20–2.02 (m, 2H), 2.01 (s, 3H), 1.92–1.80 (m, 2H), 1.67 (s, 3H), 1.66 (s, 3H), 1.60–1.40 (m, 2H), 1.40–1.20 (m, 4H), 0.87 (t, $J=7.2$ Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 199.3, 170.7, 97.8, 95.6, 74.2, 37.1, 32.7, 29.7, 26.8, 22.2, 21.3, 20.74, 20.71, 14.0, 9.5; IR (neat): 1740 cm^{-1}; MS (*m/z*) 238 (M^+, 1.01), 195 (M^+-COCH_3, 3.11), 43 (100); HRMS Calcd for $C_{13}H_{23}O$ (M^+-COCH_3): 195.1749. Found 195.1765.

3.2.9. Synthesis of (*S*)-6-cyclohexylidene-5-(*n*-butyl)hexa-5-en-3-ol ((*S*)-1i) and (*R*)-6-cyclohexylidene-5-(*n*-butyl)-hex-5-en-3-yl acetate ((*R*)-2i). The reaction of racemic

6-cyclohexylidene-5-(*n*-butyl)hexa-5-en-3-ol (100 mg) with Novozym-435 (100 mg) and vinyl acetate (78 μL) afforded (*S*)-**1i** (42 mg, 42%) and (*R*)-**2i** (60 mg, 51%). Compound (*S*)-**1i**: 96% ee (determined after its conversion to the corresponding benzoate (HPLC conditions: Chiralcel OD Column (0.46 cm$\phi\times$25 cm); λ 254 nm; rate: 0.7 mL/min; hexane: *i*-PrOH=100: 0.1)); $[\alpha]_D^{20}+0.5$ (*c* 2.55, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69–3.55 (m, 1H), 2.15–2.03 (m, 6H), 2.01–1.86 (m, 3H), 1.70–1.42 (m, 8H), 1.40–1.21 (m, 4H), 0.95 (t, J=7.2 Hz, 3H), 0.88 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 194.8, 104.3, 99.0, 71.2, 40.9, 33.0, 32.3, 32.0, 29.7, 29.4, 27.7, 26.2, 22.2, 15.3, 14.0, 10.1; IR (neat): 3375, 1959 cm^{-1}; MS (*m*/*z*) 236 (M^+, 8.77), 57 (100); HRMS Calcd for $C_{16}H_{28}O$ (M^+): 236.2140. Found 236.2170. Compound (*R*)-**2i**: 82% ee (determined after its conversion to the corresponding benzoate); $[\alpha]_D^{20}+5.3$ (*c* 1.75, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.92–4.87 (m, 1H), 2.21–2.08 (m, 2H), 2.08–2.00 (m, 7H), 1.92–1.82 (m, 2H), 1.78–1.40 (m, 8H), 1.40–1.20 (m, 4H), 0.88 (t, J=7.5 Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 195.7, 170.7, 103.3, 97.5, 74.2, 37.4, 32.7, 31.89, 31.86, 29.7, 27.7, 27.6, 26.6, 26.2, 22.2, 21.3, 14.0, 9.5; IR (neat): 1961, 1741 cm^{-1}; MS (*m*/*z*) 278 (M^+, 0.77), 147 (100); HRMS Calcd for $C_{18}H_{30}O_2$ (M^+): 278.2246. Found 278.2247.

3.2.10. Synthesis of (*S*)-4-(*n*-butyl)hexa-4,5-dien-2-ol ((*S*)-1j) and (*R*)-4-(*n*-butyl)hexa-4,5-dien-2-yl acetate ((*R*)-2j). The reaction of racemic 4-(*n*-butyl)hexa-4,5-dien-2-ol (100 mg) with Novozym-435 (70 mg) and vinyl acetate (120 μL) afforded (*S*)-**1j** (37 mg, 37%) and (*R*)-**2j** (45 mg, 35%). Compound (*S*)-**1j**: 88% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}+7.7$ (*c* 1.85, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.69–4.74 (m, 2H), 4.00–3.80 (m, 1H), 2.10–2.00 (m, 3H), 2.00–1.88 (m, 2H), 1.43–1.26 (m, 4H), 1.20 (d, J=6.0 Hz, 3H), 0.88 (t, J=7.5 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.7, 100.6, 76.1, 65.9, 42.2, 32.0, 29.5, 22.7, 22.3, 13.9; IR (neat): 3355, 1957 cm^{-1}; MS (*m*/*z*) 154 (M^+, 2.01), 43 (100); HRMS Calcd for $C_{10}H_{18}O$ (M^+): 154.1358. Found 154.1353. Compound (*R*)-**2j**: 89.3% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 110 °C (5 min), then 1 °C/min to 120 °C (20 min)); liquid; $[\alpha]_D^{20}+2.3$ (*c* 1.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08–4.94 (m, 1H), 4.64 (m, 2H), 2.32–2.18 (m, 1H), 2.10–2.02 (m, 1H), 2.01 (s, 3H), 2.00–1.92 (m, 2H), 1.50–1.26 (m, 4H), 1.23 (d, J=6.0 Hz, 3H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.3, 170.5, 99.3, 75.5, 69.5, 38.7, 31.9, 29.5, 22.3, 21.3, 19.9, 13.9; IR (neat): 1958, 1741 cm^{-1}; MS (*m*/*z*) 196 (M^+, 7.23), 43 (100); HRMS Calcd for $C_{12}H_{20}O_2$ (M^+): 196.1463. Found 196.1455.

3.2.11. Synthesis of (*S*)-6-methyl-4-(*n*-butyl)hepta-4,5-dien-2-ol ((*S*)-1k) and (*R*)-6-methyl-4-(*n*-butyl)hepta-4,5-dien-2-yl acetate ((*R*)-2k). The reaction of racemic 6-methyl-4-(*n*-butyl)hepta-4,5-diene-2-ol (100 mg) with Novozym-435 (100 mg) and vinyl acetate (102 μL) afforded (*S*)-**1k** (38 mg, 38%) and (*R*)-**2k** (64 mg, 52%). Compound (*S*)-**1k**: 91% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}+6.0$ (*c* 1.45, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93–3.85 (m, 1H), 2.11–1.88 (m, 5H), 1.70 (s, 3H), 1.69 (s, 3H), 1.40–1.25 (m, 4H), 1.20 (d, J=6.6 Hz, 3H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 198.6, 99.2, 96.4, 66.1, 42.8, 33.0, 29.7, 22.4, 22.2, 21.0, 20.8, 14.0; IR (neat): 3362, 1961 cm^{-1}; MS (*m*/*z*) 182 (M^+, 7.68), 45 (100); HRMS Calcd for $C_{12}H_{22}O$ (M^+): 182.1671. Found 182.1693. Compound (*R*)-**2k**: 42% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 95 °C (120 min)); $[\alpha]_D^{20}-1.6$ (*c* 1.30, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00–4.92 (m, 1H), 2.24–2.15 (m, 1H), 2.06–1.98 (m, 1H), 2.00 (s, 3H), 1.88 (t, J=6.9 Hz, 2H), 1.64 (s, 3H), 1.63 (s, 3H), 1.38–1.27 (m, 4H), 1.21 (d, J=6.6 Hz, 3H), 0.88 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 199.2, 170.6, 97.8, 95.8, 69.9, 39.3, 32.8, 29.7, 22.2, 21.4, 20.8, 20.7, 19.9, 14.0; IR (neat): 1961, 1740 cm^{-1}; MS (*m*/*z*) 182 (M^++1−$COCH_3$, 15.04), 181 (M^+−$COCH_3$, 33.90), 107 (100); HRMS Calcd for $C_{14}H_{24}O_2$ (M^+): 224.1776. Found 224.1778.

3.2.12. Synthesis of (*R*)-5-(*n*-butyl)hepta-1,5,6-trien-3-ol ((*R*)-1l) and (*S*)-5-(*n*-butyl)hepta-1,5,6-trien-3-yl acetate ((*S*)-2l). The reaction of racemic 5-(*n*-butyl)hepta-1,5,6-trien-3-ol (100 mg) with Novozym-435 (70 mg) and vinyl acetate (111 μL) afforded (*R*)-**1l** (43 mg, 43%) and (*S*)-**2l** (70 mg, 56%). Compound (*R*)-**1l**: 93% ee liquid; (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}-2.4$ (*c* 1.40, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96–5.84 (m, 1H), 5.29 (dt, J=22.4, 1.5 Hz, 1H), 5.12 (dt, J=10.5, 1.5 Hz, 1H), 4.80–4.68 (m, 2H), 4.36–4.20 (m, 1H), 2.22–2.08 (m, 2H), 2.05–1.84 (m, 3H), 1.50–1.30 (m, 4H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.0, 140.2, 114.6, 99.9, 76.2, 70.7, 40.3, 31.9, 29.5, 22.3, 13.9; IR (neat): 3377, 1957, 1645 cm^{-1}; MS (*m*/*z*) 166 (M^+, 3.65), 107 (100); HRMS Calcd for $C_{11}H_{18}O$ (M^+): 166.1358. Found 166.1310. Compound (*S*)-**2l**: 75% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 120 °C (40 min)); $[\alpha]_D^{20}+1.8$ (*c* 1.80, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88–5.78 (m, 1H), 5.40–5.32 (m, 1H), 5.27 (dt, J=17.1, 1.5 Hz, 1H), 5.16 (dt, J=10.5, 1.5 Hz, 1H), 4.70–4.60 (m, 2H), 2.40–2.06 (m, 2H), 2.05 (s, 3H), 2.00–1.82 (m, 2H), 1.42–1.24 (m, 4H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.5, 170.2, 136.2, 116.6, 98.9, 75.8, 72.9, 37.2, 31.9, 29.5, 22.3, 21.2, 13.9; IR (neat): 1958, 1743, 1646 cm^{-1}; MS (*m*/*z*) 208 (M^+, 0.09), 166 (M^++1−$COCH_3$, 18.30), 165 (M^+−$COCH_3$, 4.74), 43 (100); HRMS Calcd for $C_{11}H_{17}O$ (M^+−$COCH_3$): 165.1280. Found 165.1318.

3.2.13. Synthesis of (*R*)-5-(*n*-pentyl)hepta-1,5,6-trien-3-ol ((*R*)-1m) and (*S*)-5-(*n*-pentyl)hepta-1,5,6-trien-3-yl acetate ((*S*)-2m). The reaction of racemic 5-(*n*-pentyl)hepta-1,5,6-trien-3-ol (100 mg) with Novozym-435 (100 mg) and vinyl acetate (103 μL) afforded (*R*)-**1m** (44 mg, 44%) and (*S*)-**2m** (49 mg, 40%). Compound (*R*)-**1m**: 93% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}-1.3$ (*c*1.55, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96–5.82 (m, 1H), 5.29 (dt, J=17.1, 1.5 Hz, 1H), 5.12 (dt, J=10.5, 1.5 Hz, 1H), 4.79–4.70 (m, 2H), 4.31–4.25 (m, 1H), 2.25–2.07 (m, 2H), 2.01–1.90 (m, 3H),

1.49–1.20 (m, 6H), 0.88 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 200.0, 140.2, 114.6, 100.0, 76.2, 70.7, 40.3, 32.2, 31.4, 27.0, 22.5, 14.0; IR (neat): 3384, 1957, 1644 cm^{-1}; MS (*m/z*) 180 (M^+, 0.40), 67 (100); HRMS Calcd for $C_{12}H_{20}O$ (M^+): 180.1514. Found 180.1481. Compound (*S*)-**2m**: 85% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 120 °C (60 min)); $[\alpha]_D^{20}+1.1$ (*c* 1.10, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87–5.74 (m, 1H), 5.39–5.10 (m, 3H), 4.69–4.60 (m, 2H), 2.35–2.10 (m, 2H), 2.03 (s, 3H), 1.96–1.86 (m, 2H), 1.44–1.20 (m, 6H), 0.86 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.5, 170.1, 136.2, 116.5, 98.9, 75.8, 72.9, 37.2, 32.1, 31.4, 27.0, 22.5, 21.2, 14.0; IR (neat): 1958, 1744, 1648 cm^{-1}; MS (*m/z*) 180 ($M^+ +1-COCH_3$, 1.07), 179 ($M^+ -COCH_3$, 1.21), 43 (100); HRMS Calcd for $C_{12}H_{19}O$ ($M^+ -COCH_3$): 179.1436. Found 179.1425.

3.2.14. Synthesis of (*R*)-5-(*n*-butyl)hepta-5,6-dien-1-yn-3-ol ((*R*)-1n) and (*S*)-5-(*n*-butyl)hepta-5,6-dien-1-yn-3-yl acetate ((*S*)-2n). The reaction of racemic 5-(*n*-butyl)hepta-5,6-dien-1-yn-3-ol (100 mg) with Novozym-435 (100 mg) and vinyl acetate (113 μL) afforded (*R*)-**1n** (38 mg, 38%) and (*S*)-**2n** (71 mg, 56%). Compound (*R*)-**1n**: 88% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}+5.6$ (*c* 1.90, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80–4.72 (m, 2H), 4.60–4.42 (m, 1H), 2.46 (d, $J=2.4$ Hz, 1H), 2.42–2.38 (m, 2H), 2.16 (bs, 1H), 2.08–1.96 (m, 2H), 1.50–1.22 (m, 4H), 0.90 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.9, 99.1, 84.5, 76.8, 72.7, 60.7, 40.4, 31.9, 29.4, 22.2, 13.9; IR (neat): 3310, 1957 cm^{-1}; MS (*m/z*) 164 (M^+, 0.50), 55 (100); HRMS Calcd for $C_{11}H_{16}O$ (M^+): 164.1201. Found 164.1179. Compound (*S*)-**2n**: 44% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 8.0 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 120 °C (10 min), then 1 °C/min to 140 °C (30 min)); $[\alpha]_D^{20}-15.9$ (*c* 0.85, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.50–5.40 (m, 1H), 4.75–4.66 (m, 2H), 2.57–2.38 (m, 3H), 2.08 (s, 3H), 2.02–1.92 (m, 2H), 1.44–1.28 (m, 4H), 0.90 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.2, 169.8, 98.3, 81.2, 76.5, 73.4, 62.3, 37.4, 31.8, 29.5, 22.3, 20.9, 13.9; IR (neat): 2125, 1959, 1746 cm^{-1}; MS (*m/z*) 164 ($M^+ +1-COCH_3$, 7.73), 163 ($M^+ -COCH_3$, 6.92), 43 (100); HRMS Calcd for $C_{11}H_{15}O$ ($M^+ -COCH_3$): 163.1123. Found 163.1103.

3.2.15. Synthesis of (*R*)-5-(*n*-pentyl)hepta-5,6-dien-1-yn-3-ol ((*R*)-1o) and (*S*)-5-(*n*-pentyl)hepta-5,6-dien-1-yn-3-yl acetate ((*S*)-2o). The reaction of racemic 5-(*n*-pentyl)-hepta-5,6-dien-1-yn-3-ol (100 mg) with Novozym-435 (100 mg) and vinyl acetate (103 μL) afforded (*R*)-**1o** (40 mg, 40%) and (*S*)-**2o** (50 mg, 40%). Compound (*R*)-**1o**: 90% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}+7.1$ (*c* 1.10, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.81–4.74 (m, 2H), 4.55–4.48 (m, 1H), 2.46 (d, $J=1.5$ Hz, 1H), 2.45–2.35 (m, 2H), 2.19–2.16 (m, 1H), 2.02–1.92 (m, 2H), 1.48–1.23 (m, 6H), 0.88 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.9, 99.2, 84.4, 76.8, 72.8, 60.7, 40.4, 32.2, 31.4, 27.0, 22.4, 14.0; IR (neat): 3385, 2249, 1957 cm^{-1}; MS (*m/z*) 178 (M^+, 0.31), 55 (100); HRMS Calcd for $C_{12}H_{18}O$ (M^+): 178.1358. Found: 178.1360. Compound (*S*)-**2o**: 60% ee (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 130 °C (50 min)); $[\alpha]_D^{20}-23.2$ (*c* 1.30, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.48–5.37 (m, 1H), 4.74–4.66 (m, 2H), 2.52–2.30 (m, 3H), 2.07 (s, 3H), 2.00–1.90 (m, 2H), 1.49–1.36 (m, 2H), 1.34–1.20 (m, 4H), 0.88 (t, $J=6.6$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.2, 169.8, 98.3, 81.2, 76.6, 73.4, 62.3, 37.4, 32.1, 31.4, 27.0, 22.5, 20.9, 14.0; IR (neat): 2257, 1959, 1746 cm^{-1}; MS (*m/z*) 220 (M^+, 0.31), 178 ($M^+ +1-COCH_3$, 4.43), 177 ($M^+ -COCH_3$, 2.83), 43 (100); HRMS Calcd for $C_{12}H_{17}O$ ($M^+ -COCH_3$): 177.1280. Found 177.1266.

3.2.16. Pd^{II}-catalyzed coupling cyclization of (*R*)-1a with allylic bromide: synthesis of (*R*)-(−)-6-ethyl-3-allyl-4-(*n*-butyl)-5,6-dihydro-2H-pyran ((*R*)-3a). A mixture of (*R*)-**1a** (52 mg, 0.3 mmol, 97% ee obtained from hydrolysis of (*R*)-**2a**), allylic bromide (0.13 mL, 1.5 mmol), and $PdCl_2$ (0.003 g, 5 mol%) was stirred in *N*,*N*-dimethylacetamide (1.8 mL) at room temperature. When the reaction was complete as monitored by TLC, diethyl ether (50 mL) was added. The resulting mixture was washed with brine (three times) and dried over anhydrous sodium sulfate. The product was purified by column chromatography on silica gel (petroleum ether/ethyl ether = 80/1) to afford (*R*)-(−)-6-ethyl-3-allyl-4-(*n*-butyl)-5,6-dihydro-2H-pyran ((*R*)-**3a**) (41 mg, 64%) with 97% ee; (GC condition: Column: RT-βDEXcst (30 m, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250 °C; Detector (FID, H_2, 0.218 MPa): 250 °C; Oven temperature: 135 °C (30 min)); $[\alpha]_D^{20}-118.7$ (*c* 1.05, $CHCl_3$); liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86–5.59 (m, 1H), 5.10–4.85 (m, 2H), 4.02 (s, 2H), 3.39–3.32 (m, 1H), 2.78 (dd, $J=6.3$, 14.0 Hz, 1H), 2.60 (dd, $J=6.9$, 14.0 Hz, 1H), 2.10–1.89 (m, 4H), 1.65–1.40 (m, 2H), 1.39–1.21 (m, 4H), 0.95 (t, $J=7.8$ Hz, 3H), 0.88 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 135.9, 129.7, 126.3, 115.2, 75.6, 68.3, 34.0, 33.0, 32.1, 30.2, 28.7, 22.8, 14.0, 9.9; IR (neat): 1637, 1465, 1150 cm^{-1}; MS (*m/z*) 208 (M^+, 5.85), 167 (100); HRMS Calcd for $C_{14}H_{24}O$ (M^+): 208.1827. Found 208.1859.

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References and notes

1. (a) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, 1984. (b) Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds, Part 1*; Wiley: New York, 1980.
2. For the reaction of functionalized allenes, see: (a) Zimmer, R.;

Dinesh, U.; Nanolanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067–3125. (b) Ma, S.; Li, L. *Synlett* **2001**, *8*, 1206–1216. (c) Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387–6389. (d) Ma, S.; Zhao, S. *Org. Lett.* **2000**, *16*, 2495–2497.

3. (a) Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F. *J. Org. Chem.* **1991**, *56*, 1083–1088. (b) Mashall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854–5855. (c) Schultz-Fademrecht, C.; Wibbeling, B.; Frohlic, R.; Hoppe, D. *Org. Lett.* **2001**, *3*, 1221–1224. (d) Ma, S.; Wu, S. *Chem. Commun.* **2001**, 441–442. (e) Ramaswamy, S.; Hui, R.; Jones, J. B. *J. Chem. Soc. Chem. Commun.* **1986**, 1545–1546. (f) Ogadawara, M.; Ileda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089–2090.
4. (a) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943–7944. (b) Kang, S.-K.; Yamaguchi, T.; Pyum, S.-J.; Lee, Y.-T.; Baik, T.-G. *Tetrahedron Lett.* **1998**, *39*, 2127–2130.
5. (a) Olsson, L.-I.; Claesson, A. *Synthesis* **1979**, 743–745. (b) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180–7184. (c) Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550–5555. (d) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1990**, *55*, 2995–2998. (e) Nikam, S. S.; Chu, K. H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 745–747. (f) Krause, N.; Hoffmann-Röder, A. *Org. Lett.* **2001**, *3*, 2537–2538. (g) Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, *41*, 8933–8936. (h) Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104–6112.
6. Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Org. Lett.* **2000**, *2*, 441–443.
7. Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **2001**, *123*, 5578–5579.
8. Crandall, J. K.; Batal, D. J.; Lin, F.; Reix, T.; Nadol, G. S.; Ng, R. A. *Tetrahedron* **1992**, *48*, 1427–1448.
9. (a) Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104–6112. (b) Grimaldi, J.; Commons, A. *Tetrahedron Lett.* **1987**, *28*, 3487–3488.
10. Ma, S.; Gao, W. *Synlett* **2002**, 65–68.
11. Mashall, J. A.; Dubag, W. J. *J. Org. Chem.* **1993**, *58*, 3435–3443.
12. (a) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878–879. (b) Brown, H. C.; Khire, U. R.; Narla, G. *J. Org. Chem.* **1995**, *60*, 8130–8131. (c) Kulkarni, S. V.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 4125–4128. (d) Yu, C.-M.; Yoon, S.-K.; Baek, K.; Lee, K. J.-Y. *Angew. Chem.* **1998**, *110*, 2504–2506. (e) *Angew. Chem. Int. Ed.* **1998**, *37*, 2392–2394. (f) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129–6139.
13. Santelli, M.; Bertrand, M. *Tetrahedron* **1974**, *30*, 235–241.
14. Konegawa, T.; Ohtsuka, Y.; Ikeda, H.; Sugai, T.; Ohta, H. *Synlett* **1997**, *11*, 1297–1299.
15. (a) Xu, D.; Li, Z.; Ma, S. *Chem. Eur. J.* **2002**, *21*, 5012–5019. (b) Xu, D.; Li, Z.; Ma, S. *Tetrahedron: Asymmetry* **2003**, *14*, 3657–3666.
16. Xu, D.; Li, Z.; Ma, S. *Tetrahedron Lett.* **2003**, *44*, 6343–6346.
17. Maynard, D. F.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 1763–1771.
18. Kitaguchi, H.; Fitzpatrick, P.; Huber, J. E.; Klibanov, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 3094–3095.

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3-[2-(8-Quinolinyl)benzoxazol-5-yl]alanine derivative—a specific fluorophore for transition and rare-earth metal ion detection

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Abstract—A novel aromatic amino acid, 3-[2-(8-quinolinyl)benzoxazol-5-yl]alanine derivative was synthesized as a potential Zn(II) and rare-earth metal, Eu(III) and Tb(III), ion chemosensor. The fluorophore was obtained using lead tetraacetate in DMSO to oxidize the Schiff base obtained from *N*-Boc-3-amino-tyrosine methyl ester and quinoline-8-carboxaldehyde. Preliminary photophysical properties of this ligand show that it possesses the properties necessary to be an effective chemosensor for Zn^{2+}, Tb^{3+} and Eu^{3+} ions.

1. Introduction

Considerable attention has been recently focused on the development of compounds capable to respond selectively, via changes in UV–vis absorption and fluorescence spectra, to the presence of specific ions.[1–8] Among numerous analytical methods of cation detection, those based on fluorescence sensors offer several distinct advantages in terms of sensitivity, selectivity, response time and local observation.[1,5–8] The oldest class of fluorescence sensor molecules are fluorescence ligands which are mostly heteroaromatic ring systems often substituted by potentially metal ion chelating functional groups which acts as both the recognition and signaling site.[4] Well known group of ligands for heavy and transition metal ions consists of 8-amino or 8-hydroxyquinoline and its derivatives.[9,10] Its selectivity/sensitivity can be modified by appending to diaza-18-crown-6.[11,12] Depending on the 8-quinoline derivative used, this chemosensor is selective to Zn^{2+} or Cd^{2+} ions.[9–12] In spite of the presence of numerous fluorescence sensors,[4–8] there is still a need for new ones—more selective and sensitive. In this paper we describe a new chemosensor containing an 8-quinoline moiety appended to position 2 of 3-(benzoxazol-5-yl)-alanine (Bx(8-Q)) (Fig. 1). This compound has been synthesized according to the procedure developed previously in our laboratory[13,14] and it is a representative of a group of new fluorescent aromatic amino acids the spectral and photophysical properties of which depend on the substituent in position 2.[15]

Keywords: Chemosensor; Benzoxazolyl-alanine; Fluorophore; 8-Quinoline.

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2. Results and discussion

A new fluorophore, *N*-Boc-3-[2-(8-quinolinyl)benzoxazol-5-yl]alanine methyl ester (Bx(8-Q)) (**5**), was synthesized adapting the procedure published previously (Fig. 1).[13,14] *N*-Boc-3-nitrotyrosine methyl ester (**1**) was reduced to *N*-Boc-3-aminotyrosine methyl ester (**2**) by means of catalytic hydrogenation in methanol (H_2/Pd/C). The intermediate Schiff base (**4**) was prepared in absolute ethanol from **2** and quinoline-8-carboxaldehyde (**3**), obtained from 8-methylquinoline using selenium dioxide. Cyclization of the Schiff base to the benzoxazole structure was performed using lead tetraacetate in DMSO giving the product (**5**) in 10% yield.

The interaction of Bx(8-Q) with the following ions: Li^+, Na^+, K^+, Mg^{2+}, Ca^{+2}, Ba^{2+}, Sr^{2+}, Ag^+, Co^{2+}, Cd^{2+}, Cu^{2+}, Zn^{2+}, Tb^{3+}, Eu^{3+} was studied by means of absorption and steady-state fluorescence spectroscopy. The studied ions can be divided into three groups. The first contains alkaline and alkaline earth metal ions which do not cause changes in the absorption spectrum of the ligand. The exceptions are lithium and magnesium ions the interaction of which with the ligand causes a small increase of absorbance of the long-wave part of the absorption spectrum, but these changes do not allow calculation of an equilibrium constant. All ions from this group caused a relatively small increase of the fluorescence quantum yield without changing the shape or position of the emission band of the ligand (Table 1).

Transition metal ions, belonging to the second group, cause substantial changes of absorption and fluorescence spectra.

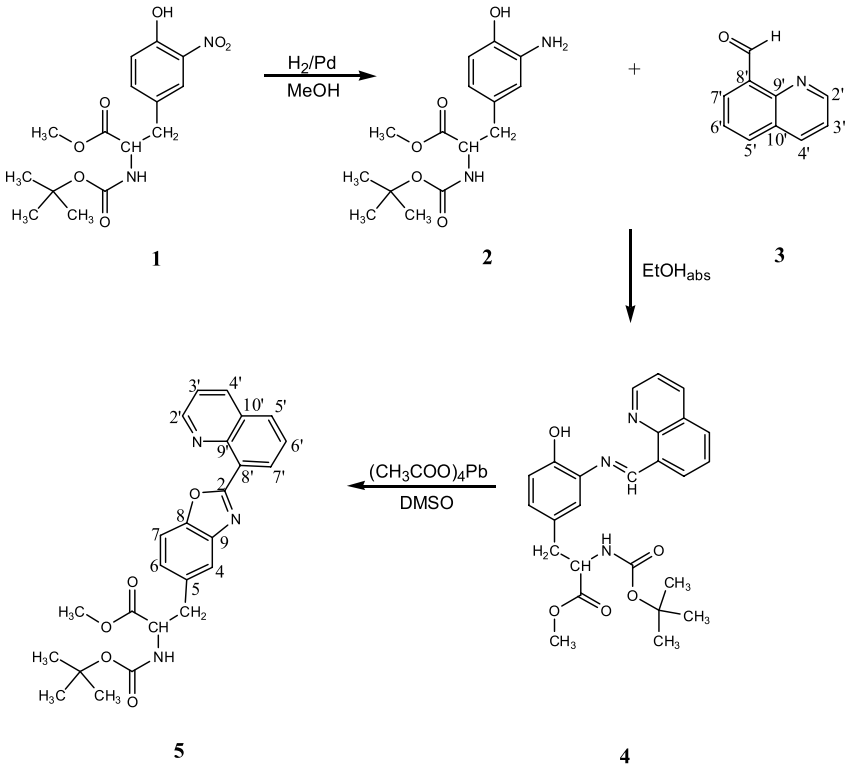

Figure 1. Scheme of synthesis and structure of ligand (Bx(8-Q)).

A spectrophotometric and spectrofluorimetric titrations of the ligand using Zn^{2+} ion are shown in Figure 2.

An increase of metal ion concentration, up to a ligand/metal ion ratio equal to one, causes an increase of absorbance of the long-wave absorption band (at about 350, 275 and 240 nm) and a decrease at about 300 nm, moreover, sharp isosbestic points can be detected. A further increase of the ion concentration causes a blue shift of the absorption spectrum with simultaneous broadening of isosbestic points and the formation of a new peak at the long-wavelength band of the spectrum. Such behaviour indicates on the formation of a new type of the complex with different stoichiometry to the previous one present in the solution, which is additionally confirmed by the absorbance–absorbance (A–A) diagram (Fig. 3).

The A–A diagram composes of two linear segments intersecting at ligand:metal ratio about 1:1, indicating that the system involves two titration steps.[16] However, the contribution of the second complex to the absorption spectra is insufficient for the calculation of stability constants of each complex formed, thus the overall stability constant ($\log \beta = 11.7$) is presented in Table 1. A relatively high standard error of the calculated overall binding constant is a result of the fact that the formation of a higher order complex, the presence of which is visible in the A–A diagram, has not been considered in calculations. Similar

Table 1. Absorption and fluorescence data for ligand and its metal ion complexes in acetonitrile

	Absorption			Fluorescence		
	ε_{350} (M^{-1} cm^{-1})	% of ligand ε_{350} (M^{-1} cm^{-1})	$\log \beta$	Q.Y.	% of ligand Q.Y.	τ (ns)
L	2550	—		0.024	—	
Li	4430	74	nd	0.093	387	
Na	2550	0		0.032	133	
K	2550	0		0.04	167	
Mg	6250	145	nd	0.223	930	
Ca	2550	0		0.026	108	
Ba	2550	0		0.037	154	
Sr	2550	0		0.046	192	
LCd	15,690	485	5.14 ± 0.15	1	4167	4.98
L_2Co	14,920	485	10.96 ± 0.50	0.004	17	
L_2Ni	15,400	505	11.47 ± 0.45	0.003	12	
L_2Cu	22,040	764	8.12 ± 1.98	0.005	21	
L_2Zn	16,570	550	11.70 ± 3.12	0.955	3980	5.68
LEu	10,590	315	7.57 ± 0.78	0.12	500	4.38
LTb	10,270	303	4.33 ± 0.26	0.11	458	4.39
Ag	2550	0	—	0.116	480	

nd, not determined.

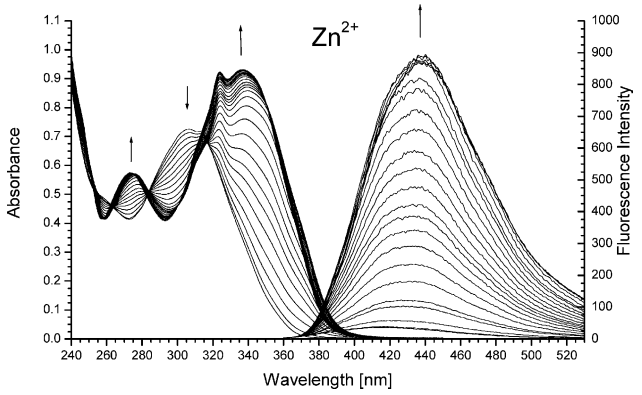

Figure 2. Absorption and fluorescence titrations of the ligand with Zn^{2+} ion in acetonitrile.

behaviour was also observed for the complexes of the ligand with Co^{2+}, Cu^{2+} and Ni^{2+} ions, whereas for Cd^{2+}, the A–A diagram reveals the presence of only one type of complex (ML) with the logarithm of stability constant equal to about 5 (Table 1) (data not shown). The calculated stoichiometry reveals that all ions mentioned in this group form ML_2 complexes with relatively high overall stability constants (log β about 11, except Cu^{2+} for which log β is about 8, Table 1). As in the case of Zn^{2+}, it was impossible to calculate the individual stability constant for the other ML complexes.

A common property of the transition metal ions studied is the almost invariable position of the fluorescence spectrum of the ligand. For Zn^{2+} and Cd^{2+} ions, the fluorescence band of the ML_2 complex was shifted bathochromically by about 15 nm compared to the emission spectrum of the pure ligand (Fig. 2). The property which differentiates the studied ions is the fluorescence quantum yield of a given complex measured at high metal-to-ligand ratio (M:L$>$20). The divalent paramagnetic ions (Cu^{2+}, Ni^{2+}, Co^{2+}) quench almost totally the ligand fluorescence, whereas diamagnetic ions (Zn^{2+} and Cd^{2+}) enhance the fluorescence intensity, resulting in a fluorescence quantum yield equal to 1.0 for Cd^{2+} ion and 0.95 for Zn^{2+} (close to 1.0 at M:L$=$1:1) (Table 1). Such behaviour is typical for this type of ligand and ions.[4] In Figure 4 the changes of normalized absorbance (measured at 350 nm) and fluorescence intensity (measured

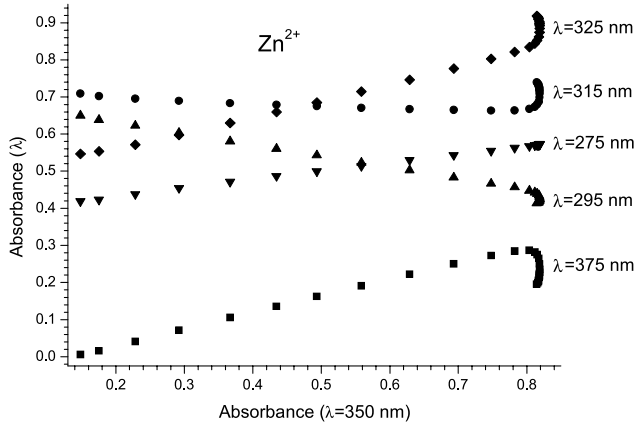

Figure 3. Absorbance–absorbance (A–A) diagram for titration of Bx(8-Q) with Zn^{2+} ion.

at 435 nm) versus a metal/ligand molar ratio are presented. The absorbance and fluorescence intensity curves versus metal/ligand ratio differ substantially, especially for the Cd^{2+} ion. Lower values of normalized fluorescence intensity compared to the normalized absorbance (less pronounced for Zn^{2+} ion) clearly indicate lower stability of the complex in the excited state compared to the ground state. In both cases, up to the M:L ratio of about 0.25, an invariant fluorescence intensity can be observed indicating dissociation of the excited complex. Because of that, the stability constants of the complexes in the excited state cannot be determined. Additionally, an increase of Zn^{2+} ion concentration above the 1:2 M:L ratio causes the quenching of complex fluorescence because of the formation of a new 1:1 ligand:Zn^{2+} complex, confirmed by the intensity–intensity (I–I) diagram (Fig. 5).

Not only are stoichiometry and ground state stability constant different for the Zn^{2+} and Cd^{2+} complexes, but also the fluorescence lifetimes are different. For the Cd^{2+} complex (for M:L ratio about 16) the fluorescence lifetime is 4.98 ns ($\lambda_{em}=430$ nm, $\chi^2_R=1.18$) whereas for the Zn^{2+} complex the fluorescence lifetime is 5.68 ns ($\lambda_{em}=430$ nm, $\chi^2_R=1.10$).

The third class of ions consists of the luminescent rare-earth metal ions, Eu^{3+} and Tb^{3+}. Spectrophotometric and spectrofluorimetric titrations are presented in Figure 6. As for the transition metal ions, the addition of Eu^{3+} or Tb^{3+} to the ligand solution in acetonitrile causes a formation of a new absorption band with a maximum at about 370 nm and simultaneously an increase of the absorbance at about 250 nm and decrease in the range of 300–350 nm.

The A–A diagrams for Eu^{3+} and Tb^{3+} ions are straight lines, indicating on the formation of only one type of the complex. The calculation reveals that the stoichiometry of these complexes are ML with binding constants about two times higher for Eu^{3+} than Tb^{3+} ion (Table 1).

In contrast to the transition metal ions, increasing the Eu^{3+} or Tb^{3+} ion concentration causes a decrease of the ligand

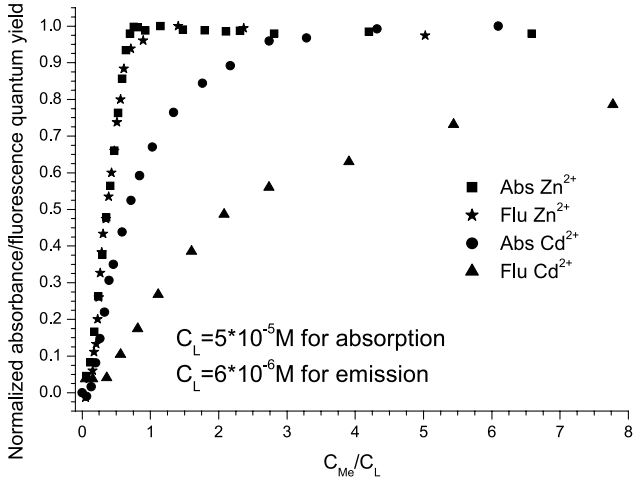

Figure 4. Changes in the normalized absorbance and fluorescence quantum yield upon addition of $Zn(ClO_4)_2$ or $Cd(ClO_4)_2$ to the solution of Bx(8-Q) in acetonitrile.

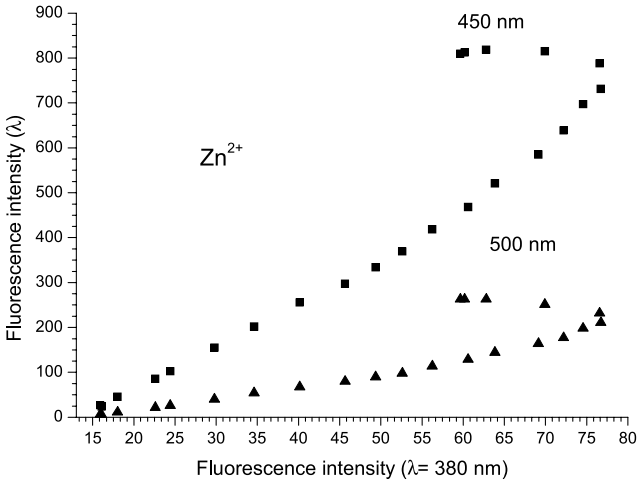

Figure 5. Intensity–intensity (I–I) diagram for titration of Bx(8-Q) with Zn^{2+} ion.

emission band and simultaneously an increase of a new emission band centered at about 530 nm. In Figure 7 the dependencies of the changes of the normalized absorption measured at 365 nm and emission intensities of the ligand (at 425 nm) and complex intensity (at 525 nm) versus the molar ratio of metal to ligand are depicted.

As in the case of the Zn^{2+} and Cd^{2+} complexes, the curves displaying the complex fluorescence increase are situated lower than the corresponding absorption curves, indicating a lower constant binding in the excited state compared to the ground state. On the initial part of these curves a flat region is clearly seen confirming the differences in stability constants in the ground and excited state. The difference in the ground state stability constant as well as the different shape of the curves illustrating the absorption or emission changes with the increase of metal ion concentration between the Eu^{3+} and Tb^{3+} ions, having very similar ion radii and electron configurations, is probably due to the influence of the anion on the complex formation because europium perchlorate and terbium chloride were used for the titration. However, the fluorescence quantum yield (0.12) and the fluorescence lifetime (4.38 ns), (Eu:L ratio = 5, Tb:L ratio = 16) of both complexes are very similar (Table 1).

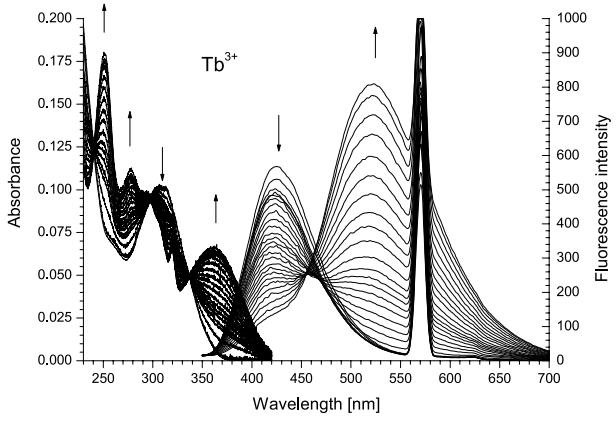

Figure 6. Absorption and fluorescence titrations of the ligand with Tb^{3+} ion in acetonitrile.

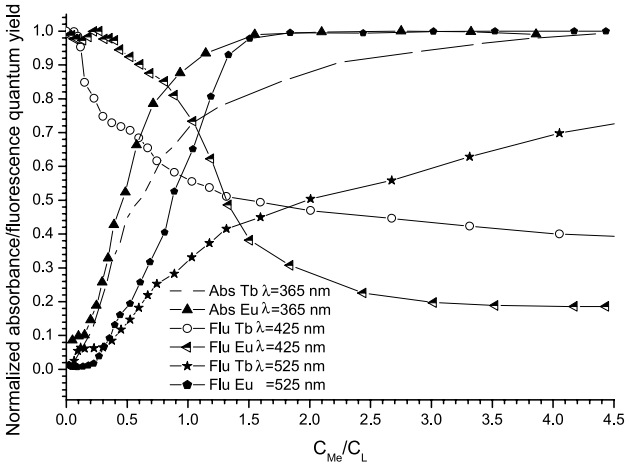

Figure 7. Changes in the normalized absorbance and fluorescence quantum yield upon addition of $Eu(ClO_4)_3$ or $TbCl_3$ to the solution of Bx(8-Q) in acetonitrile.

A different behaviour, compared to above mentioned ions, was observed during a titration with Ag^+ ion. With the increase of Ag^+ ion concentration there was no change in the absorption spectrum of the ligand, as in the case of large alkaline and alkaline earth metal ions (Na^+, K^+, Ca^{2+}, Ba^{2+}, Sr^{2+}), whereas in the excited state this ion interacted with the ligand similarly to the Eu^{3+} and Tb^{3+}, causing an increase of the long-wave fluorescence band with the maximum at 530 nm up to the M:L ratio higher than 20.

The different interactions of ions studied with the ligand cannot be explained taking into account ionic radii only. The change of the absorption spectrum of the ligand caused by small ions, Li^+ and Mg^{2+}, and the lack of such changes in the case of alkaline or alkaline earth metal ions as well as Ag^+ having ionic radii greater than 1 Å and simultaneous changes in absorption spectrum caused by transition metal ions or luminescent rare-earth metal ions having ionic radii similar to Ca^{2+} or Na^+ indicates that not only ionic radius but also the polarizability and/or second ionization potential should be considered.[17] While the quenching of ligand fluorescence is predominantly connected with the nature of metal ion, the ligand fluorescence enhancement can result from changes of geometry in the excited state or be induced by the ion. The fact that all ions studied alter the fluorescence properties of the ligand suggests chelation-induced changes of the relatively close lying ligand centered $n\pi^*$ and $\pi\pi^*$ states. The lower binding affinity in the excited state is probably caused by the lower, compared to the ground state, charge density on the benzoxazolyl nitrogen atom and the increase of the dihedral angle between the benzoxazolyl and quinolinyl moiety (for about 20°) as results from the theoretical calculations using a semi-empirical molecular-orbital PM3 method[18] with semi-conductor-like screening model for solvation (COSMO)[19] implementated in the MOPAC 2002 package.[20] The increase of the ligand flexibility in the excited state, caused by a decrease of interaction between two aromatic moieties, probably facilitates adjusting the ligand chelation cavity to an ion and simultaneously suppresses the radiationless deactivation via torsional motions. The above discussion does not fully explain all observed phenomena and

additional work are currently ongoing in our laboratory and will be published in due course.

3. Conclusions

The formation of highly fluorescent complexes of Bx(8-Q) ligand with the transition metal ions Cd^{2+} and Zn^{2+} as well as with rare-earth metal ion and substantial changes in the absorption spectra and fluorescence lifetime cause that this ligand can be used as a chemosensor for these ions. Moreover, much higher constant binding determined for Zn^{2+} ion over other ions studied indicate that Bx(8-Q) is preferred as a chemosensor for this particular ion. However, the described ligand possesses a remarkable advantage over other chemosensors for Zn^{2+} ion presented in the literature. It has an amino acid moiety allowing it to be incorporated into a peptide chain and/or used for the synthesis of a fluorescent cell-permeable compound for the study of intracellular zinc chemistry.

4. Experimental

4.1. General

8-Methylquinoline, selenium dioxide and lead tetraacetate were purchased from Lancaster whereas 3-nitro-L-tyrosine was purchased from Fluka. The following compounds were prepared according to literature procedures: 3-nitro-L-tyrosine methyl ester[23] and *N*-Boc-3-nitro-L-tyrosine methyl ester.[24] Quinoline-8-carboxaldehyde was synthesized according to a modified literature procedure.[25] *N*-Boc-3-[2-(8-quinolinyl)benzoxazol-5-yl]alanine methyl ester was synthesized adapting the procedure published previously.[13,14] TLC was carried out on Merck silica gel plates (Kieselgel 60 F_{254}). The spots were revealed using a UV lamp (254 nm, 366 nm). All solvent ratios are in volume parts. The purification was carried out by means of column chromatography (Merck, Silica gel 60, 0.040–0.063 mm). The purity of the obtained compounds was checked by means of analytical RP-HPLC (Kromasil column, C-8, 5 μm, 250 mm long, ID=4.5 mm) with detection at 223 nm. The mobile phase was a gradient running from 0 to 100% of B (A=water with addition of 0.01% trifluoroacetic acid, B=80% of an aqueous solution of acetonitrile with addition of 0.08% trifluoroacetic acid) over 60 min. Melting points (mp) were determined in capillary tubes using Gallenkamp Griffin MPA-350.MB2.5 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian, Mercury-400 BB spectrometer (400 MHz) in $CDCl_3$. Infrared spectra were recorded on a Bruker IFS-66 instrument. Mass spectra were recorded on a MASSLAB TRIO-3 instrument (FAB) or Bruker Biflex III (MALDI-TOF). Elemental analysis was achieved on a Carlo Erba CNSO Eager 200 instrument. Absorption spectra were measured on a Perkin–Elmer Lambda 40P spectrophotometer. Fluorescence spectra were measured on a Perkin–Elmer LS-50B spectrofluorimeter. MeCN used in our studies was HPLC grade. Quantum yields (QY) were calculated using as a reference quinine sulphate in 0.5 M H_2SO_4 (QY=0.53±0.02[21]). The fluorescence lifetimes were measured with a time-correlated single-photon counting apparatus Edinburgh CD-900. The excitation source was a NanoLed 03 (UV led 370 nm) from IBH. The half-width of the response function of apparatus measured using a Ludox solution as a scatter was about 1.0 ns. The excitation wavelength was isolated using an interference filter (λ_{ma}=372 nm, spectral band-width about 7 nm) whereas emission wavelengths were isolated using a monochromator (about 12 nm spectral band-width). Fluorescence decay data were fitted by the iterative convolution to the sum of exponents

$$I(t) = \sum_i \alpha_i \exp(-t/\tau_i), \quad (1)$$

where α_i is the pre-exponential factor obtained from the fluorescence intensity decay analysis and τ_i is the decay time of the *i*th component. The adequacy of the exponential decay fitting was judged by visual inspection of the plots of weighted residuals and by the statistical parameter χ^2_R and shape of the autocorrelation function of the weighted residuals and serial variance ratio (SVR).

4.2. Synthesis

4.2.1. Quinoline-8-carboxaldehyde (3). 8-Methylquinoline (10 g, 70 mmol) was heated to 100 °C. Selenium dioxide (7.91 g, 71 mmol) was added in small portions with stirring during 2 h. Then the reaction mixture was cooled to the room temperature and extracted with boiling methanol. After solvent evaporation, the residue was crystallized from MeOH/diethyl ether. The obtained yellow solid was purified by means of column chromatography using as an eluent AcOEt/petroleum ether (1:5). Recrystallization from AcOEt/petroleum ether gave the title compound (0.80 g, 5.08 mmol, 7%) as a white solid (R_f=0.49, AcOEt/petroleum ether (1:3); t_R=12.8 min).

Mp 96–97 °C; (Found: C, 75.98; N, 8.82; H, 4.42. $C_{10}H_7NO$ requires C, 76.42; N, 8.91; H, 4.49%); ν_{max} (KBr) 3347.4 (w), 2868.5 (m), 2711.4 (w), 1681.5 (s), 1572.6 (s), 1498.4 (s), 1403.2 (s), 1320.2 (s), 1248.0 (s), 1164.9 (m), 1131.1 (m), 1035.9 (m), 873.1 (s), 828.8 (s), 787.1 (s), 766.4 (s), 642.5 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 11.5 (1H, s, CHO), 9.06 (1H, dd, J=1.6, 4.0 Hz, $C^{2'}$H), 8.34 (1H, dd, J=1.6, 7.4 Hz, $C^{7'}$H), 8.25 (1H, dd, J=1.2, 8.2 Hz, $C^{4'}$H), 8.11 (1H, dd, J=1.6, 8.2 Hz, $C^{5'}$H), 7.68 (1H, t, J=7.8 Hz, $C^{6'}$H), 7.52 (1H, dd, J=4.0, 8.4 Hz, $C^{3'}$H); δ_C (100 MHz, $CDCl_3$) 192.58 (CHO), 151.55 ($C^{2'}$), 147.84 ($C^{9'}$), 140.00 ($C^{7'}$), 136.53 ($C^{4'}$), 134.43 ($C^{5'}$), 131.95 ($C^{8'}$), 129.55 ($C^{10'}$), 126.46 ($C^{6'}$), 122.03 ($C^{3'}$); *m/z* (FAB) 158 (80, MH^+), 131 (100%).

4.2.2. *N*-(*tert*-Butyloxycarbonyl)-3-[2-(8-quinolinyl)benzoxazol-5-yl]-L-alanine methyl ester (5). A mixture of *N*-Boc-3-nitro-L-tyrosine methyl ester (1.38 g, 4.08 mmol) and 5% palladium on active carbon in MeOH (30 mL) was stirred under a hydrogen atmosphere at room temperature for 90 min (TLC monitoring (CH_2Cl_2/MeOH/AcOH 100:10:1), R_f=0.72). The catalyst was filtered off and the solvent evaporated in vacuo to give the brownish, oily product which was dissolved in absolute EtOH (5 mL) and mixed with the solution of quinoline-8-carboxaldehyde (0.59 g, 3.76 mmol) in absolute EtOH (7 mL). The mixture was stirred at rt overnight (TLC monitoring

(AcOEt/petroleum ether 2:5), $R_f=0.67$), giving the Schiff base as a yellow solid (1.6 g, 3.56 mmol, 87%). The obtained Schiff base was filtered off and dissolved in DMSO (10 mL) and lead tetraacetate (2.78 g, 6.27 mmol) was added. The mixture was stirred at rt for about an hour (TLC monitoring (AcOEt/petroleum ether 1:1), $R_f=0.32$) and then dissolved in ethyl acetate (AcOEt) and washed in turns with a saturated aqueous solution of NaCl ($\times 1$), a 5% solution of $NaHCO_3$ ($\times 2$), a saturated aqueous solution of NaCl ($\times 3$) and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo and the product was isolated by means of column chromatography using as an eluent AcOEt/petroleum ether (1:1). The crude product was recrystallized from AcOEt/petroleum ether, giving the title compound (0.17 g, 0.39 mmol, 10%) as a white solid ($t_R=36.2$ min).

Mp 106–107 °C; (Found: C, 67.40; N, 9.32; H, 5.71. $C_{25}H_{25}N_3O_5$ requires C, 67.10; N, 9.39; H, 5.63%); ν_{max} (KBr) 3358.5 (m), 2969.0 (w), 1751.6 (s), 1736.4 (s), 1686.0 (s), 1525.5 (s), 1439.4 (m), 1351.5 (m), 1297.9 (m), 1259.0 (s), 1210.9 (m), 1166.4 (s), 1056.4 (w), 791.6 (m) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.18 (1H, dd, $J=2.0$, 4.2 Hz, $C^{2'}H$), 8.54 (1H, dd, $J=1.2$, 7.4 Hz, $C^{5'}H$), 8.27 (1H, dd, $J=2.0$, 8.4 Hz, $C^{4'}H$), 8.03 (1H, dd, $J=1.2$, 8.2 Hz, $C^{7'}H$), 7.71 (1H, d, $J=7.2$ Hz, $C^{6'}H$), 7.68 (1H, s, C^4H), 7.60 (1H, d, $J=8.0$ Hz, C^7H), 7.53 (1H, dd, $J=4.4$, 8.2 Hz, $C^{3'}H$), 7.16 (1H, dd, $J=1.6$, 8.2 Hz, C^6H), 5.03 (1H, d, $J=8.0$ Hz, NH), 4.64 (1H, dd, $J=5.6$, 13.6 Hz, $C^{\alpha}H$), 3.74 (3H, s, OCH_3), 3.23–3.28 (2H, m, $C^{\beta}H_2$), 1.40 (9H, s, $(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 172.36 (CO), 157.00 (C^2), 152.08 ($C^{2'}$), 152.00 (HNCO), 146.09 ($C^{9'}$), 146.00 (C^8), 136.85 (C^9), 132.91 ($C^{8'}$), 132.57 (C^5), 131.97 ($C^{4'}$), 128.99 ($C^{10'}$), 126.71 ($C^{5'}$), 126.48 (C^6), 126.20 ($C^{6'}$), 121.94 ($C^{3'}$), 121.15 (C^4), 110.90 (C^7), 80.12 ($C(CH_3)_3$), 54.84 (C^{α}), 52.54 (OCH_3), 38.47 (C^{β}), 28.53 ($(CH_3)_3$); *m/z* (MALDI-TOF) 448 (MH^+).

4.3. UV–vis and fluorescence titration experiments

A solution of ligand (concentration about 5×10^{-5} M for absorption and 5×10^{-6} M for emission) in acetonitrile was treated with increasing amounts of a solution of perchlorate salts of the cation of interest, except for terbium ions where the chloride salt was used, (concentration about 5×10^{-4} M) containing a ligand at the same concentration as in the cuvette at room temperature. After each addition of aliquots using Hamilton microsyringe with micrometer screw, the UV–vis or fluorescence spectrum was recorded. When the titration was complete the spectra were implemented into the STOICHIO software for binding constant calculations.[22]

Acknowledgements

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References and notes

1. de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515–1566.
2. Bargossi, C.; Fiorini, M. C.; Montalti, M.; Prodi, L.; Zaccheroni, N. *Coord. Chem. Rev.* **2000**, *208*, 17–32.
3. Warmke, H.; Wiczk, W.; Ossowski, T. *Talanta* **2000**, *52*, 449–456.
4. Rurack, K. *Spectrochim. Acta, Part A* **2001**, *57*, 2161–2195.
5. *Topics in Fluorescence Spectroscopy*; Lakowicz, J. R., Ed.; Probe Design and Chemical Sensing; Plenum: New York, 1994; Vol. 4.
6. Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3–40.
7. *Fluorescent Chemosensors for Ion and Molecular Recognition*; Czarnik, A., Ed.; American Chemical Society: Washington, DC, 1993.
8. *Handbook of Fluorescent Probes and Research Products*; Haugland, R. P., Ed.; Molecular Probes: Eugene, 2002.
9. Xue, G.; Bradshaw, J. S.; Dalley, N. K.; Savage, P. B.; Izatt, R. M.; Prodi, L.; Montalti, M.; Zaccheroni, N. *Tetrahedron* **2002**, *58*, 4809–4815.
10. Kimber, M. C.; Mahadevan, B. M.; Lincoln, S. F.; Ward, A. D.; Tiekink, E. R. T. J. *Org. Chem.* **2000**, *65*, 8204–8209.
11. Prodi, L.; Montalti, M.; Zaccheroni, N.; Bradshaw, J. S.; Izatt, R. M.; Savage, P. B. *Tetrahedron Lett.* **2001**, *42*, 2941–2944.
12. Xue, G.; Bradshaw, J. S.; Dalley, N. K.; Savage, P. B.; Krakowiak, K. E.; Izatt, R. M.; Prodi, L.; Montalti, M.; Zaccheroni, N. *Tetrahedron* **2001**, *57*, 7623–7628.
13. Guzow, K.; Szabelski, M.; Malicka, J.; Wiczk, W. *Helv. Chim. Acta* **2001**, *84*, 1086–1092.
14. Guzow, K.; Szabelski, M.; Malicka, J.; Karolczak, J.; Wiczk, W. *Tetrahedron* **2002**, *58*, 2201–2209.
15. Guzow, K.; Mazurkiewicz, K.; Szabelski, M.; Ganzynkowicz, R.; Karolczak, J.; Wiczk, W. *Chem. Phys.* **2003**, *295*, 119–130.
16. Polster, J.; Lachmann, H. *Spectrometric Titrations. Analysis of Chemical Equilibria*; VCH: New York, 1989.
17. Irving, H.; Wiliams, R. J. P. *Nature (London)* **1948**, *162*, 746–747.
18. Steward, J. J. P. *J. Comput. Chem.* **1986**, *10*, 221–264.
19. Klamt, A.; Schürmann, G. I. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799–805.
20. Steward, J. J. P. *MOPAC 2002*, Fujitsu Limited, **2001**.
21. Lakowicz, J. R. *Principles of Fluorescence Spectroscopy*, 2nd ed.; Kluwer Academic/Plenum: New York, 1999.
22. Kostrowicki, J.; Liwo, A. *Comput. Chem.* **1987**, *11*, 195–210.
23. Wünsch, E. In Mhller, E., Ed.; Synthese von Peptiden; Houben-Weyl, Methoden der organischen Chemie; Georg Thieme Verlag: Stuttgart, 1974; Vol. 15, p 317.
24. Stewart, J. M.; Young, J. D. *Solid Phase Peptide Synthesis*; Chemical Company: Rockford, IL, 1984; p 63.
25. Teague, C. E. Jr.; Roe, A. *J. Am. Chem. Soc.* **1951**, *73*, 688–689.

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Brønsted acid-mediated ring-opening reactions of methylenecyclopropanes: a dramatic counter ion effect

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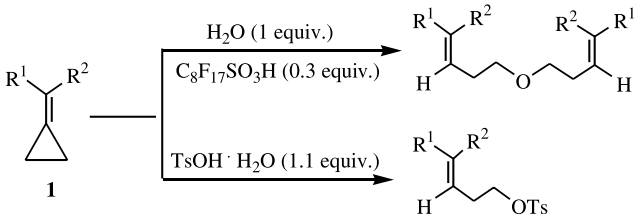
Abstract—We report herein two different ring-opening patterns of methylenecyclopropanes (MCPs) in the presence of two Brønsted acids heptadecafluorooctane-1-sulfonic acid ($C_8F_{17}SO_3H$) and toluene *p*-sulfonic acid (TsOH) under mild conditions: (a) the ring-opening of MCPs by H_2O and subsequent etherification give the corresponding homoallylic ethers in the presence of heptadecafluorooctane-1-sulfonic acid; (b) the direct ring-opening of MCPs by the Brønsted acid gives the corresponding homoallylic alcohol derivatives in the presence of toluene *p*-sulfonic acid.

1. Introduction

Transition metal-catalyzed reactions of methylenecyclopropanes (MCPs) **1** have been widely explored in this area of study over the past decades.[1] The attractive feature of these compounds is their surprising stability along with a high level of strain.[2–4] Strangely, less attention has been paid for the Lewis acid or Brønsted acid-mediated reactions of MCPs.[5] In the continuum of Lewis acid or Brønsted acid-mediated transformations of MCPs **1**, we have found that MCPs **1** can react with various reagents such as alcohols, amines, and imines in a different ring-opening pattern.[6] These progresses stimulate us to investigate further the Lewis acid or Brønsted acid-mediated ring-opening reactions of MCPs **1**. Recently, Yamamoto and co-workers reported that the cyclopropyl ring of MCPs can be opened by water to give the homoallylic alcohol under severe reaction conditions, such as the use of a sealed pressure vial under an inert gas atmosphere and at higher temperature (80 °C) without organic solvent.[7] In the recent program of Brønsted acid-mediated transformations of MCPs **1**, we found that the corresponding anion (counter ion) of the employed Brønsted acid played a significant role in the ring-opening reactions under milder conditions: a) the cyclopropyl ring of MCPs **1** can be opened by H_2O and subsequent etherification to give the homoallylic ethers in the presence of heptadecafluorooctane-1-sulfonic acid ($C_8F_{17}SO_3H$) in which the corresponding anion $C_8F_{17}SO_3^-$ is a weak nucleophile; (b) the cyclopropyl ring of MCPs **1** can be opened directly by the Brønsted acid toluene *p*-sulfonic acid (TsOH) to give the homoallylic alcohol derivatives (sulfonated homoallylic alcohols) in which the corresponding anion TsO^- is a strong nucleophile. In this paper we wish to report the full details of these interesting results (Scheme 1).



Scheme 1. Ring-opening reactions of MCPs **1** in the presence of $C_8F_{17}SO_3H/H_2O$ and $TsOH{\cdot}H_2O$.

2. Results and discussion

At the outset of our investigation, the reaction of MCP **1a** with H_2O (1 equiv) was chosen as a model reaction and carried out under various reaction conditions to confirm the optimum reaction conditions. Table 1 shows the representative results. After several trials and errors, we were pleased to find out that the reaction of MCP **1a** with H_2O in the presence of $C_8F_{17}SO_3H$ (0.1 equiv) gave the homoallylic ether **2a** in 63% yield along with the homoallylic

Keywords: Methylenecyclopropanes (MCPs); Brønsted acid; Ring-opening reaction; Toluene *p*-sulfonic acid (TsOH); Heptadecafluorooctane-1-sulfonic acid ($C_8F_{17}SO_3H$).
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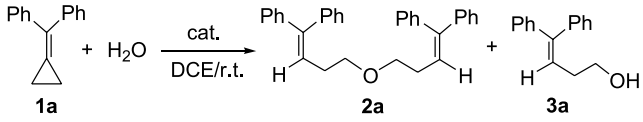
Table 1. The screening of the catalysts of the ring-opening of MCPs by H_2O and subsequent etherification



1a 2a 3a

Entry[a]	Catalyst	Time/(h)	Yield/(%)[b]	
			2a	**3a**
1	$Zn(OTf)_2$	72	—	—
2	$Cu(OTf)_2$	72	Trace	Trace
3	$Eu(OTf)_3$	72	—	—
4	$Sc(OTf)_3$	72	Trace	—
5	$Yb(OTf)_3$	72	Trace	—
6	BF_3OEt_2	72	Trace	11
7	CF_3SO_3H	72	49	5
8	$Zr(OTf)_4$	72	21	Trace
9	$C_8F_{17}SO_3H$	72	63	8
10[c]	$Zr(OTf)_4$	48	48	Trace
11[c]	$C_8F_{17}SO_3H$	24	71	—
12[d]	$C_8F_{17}SO_3H$	24	67	Trace
13[c,e]	$C_8F_{17}SO_3H$	24	11	25
14[c,f]	$C_8F_{17}SO_3H$	24	36	18

[a] Otherwise specified, 0.1 equiv of catalysts were used.
[b] Isolated yields.
[c] 0.3 equiv of catalysts were used.
[d] 1.0 equiv of catalyst was used.
[e] CH_3CN as the solvent.
[f] *n*-Hexane as the solvent.

alcohol **3a** in 8% yield within 72 h (Table 1, entry 9). The product **2a** was also obtained in somewhat lower yields, either in the catalysis of CF_3SO_3H (0.1 equiv) or $Zr(OTf)_4$ (0.1 equiv) (Table 1, entries 7 and 8). Investigation into other catalysts showed that $Zn(OTf)_2$, $Cu(OTf)_2$, $Eu(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$ and $BF_3{\cdot}OEt_2$ were not effective promoters for this reaction (Table 1, entries 1–6). Further screening showed that this reaction can complete within 24 h to give **2a** as a sole product in 71% yield when 0.3 equiv of $C_8F_{17}SO_3H$ was used (Table 1, entry 11) and increasing the amount of $C_8F_{17}SO_3H$ to 1.0 equiv gave **2a** in comparable yield also as a sole product (Table 1, entry 12). In addition, product **2a** was obtained in somewhat lower yields along with **3a** when CH_3CN and *n*-hexane were used as the solvents (Table 1, entries 13 and 14). Of the solvents screened, 1,2-dichloroethane (DCE) proved to be a suitable solvent, giving the best results.

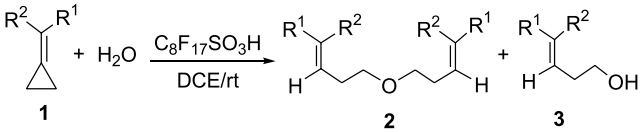
The equivalents of H_2O were investigated for this ring-opening reaction of MCPs. The results are summarized in Table 2. As can be seen from Table 2, the best result was obtained when 1.0 equiv H_2O was used (Table 2, entry 1). Increasing the amount of H_2O to 2.0–4.0 equiv gave product **2a** in somewhat lower yields along with the formation of

Table 2. The effects of the amount of water used

Entry[a]	H_2O (equiv)	Yield (%)[b]	
		2a	**3a**
1	1.0	71	—
2	2.0	62	4
3	3.0	46	14
4	4.0	28	9
5	5.0	Trace	Trace
6	90.0	—	—

[a] All reactions were carried out for 24 h.
[b] Isolated yields.

Table 3. Reaction of MCPs **1** with H_2O (1.0 equiv) under the catalysis of $C_8F_{17}SO_3H$ (0.3 equiv) in DCE



1 2 3

Entry	R^1/R^2	Time/h	Yield (%)[a]	
			2	**3**
1	**1b**, *p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$	1	**2b**, 52	—
2	**1c**, *p*-$MeOC_6H_4$/C_6H_5	2	**2c**, 60	Trace
3	**1d**, *p*-MeC_6H_4/*p*-MeC_6H_4	4	**2d**, 56	—
4	**1e**, *o*-ClC_6H_4/C_6H_5	24	**2e**, 63	**3e**, 9
5	**1f**, *p*-ClC_6H_4/*p*-ClC_6H_4	24	**2f**, 42	—
6	**1g**, *p*-FC_6H_4/*p*-FC_6H_4	24	**2g**, 94	**3g**, 6

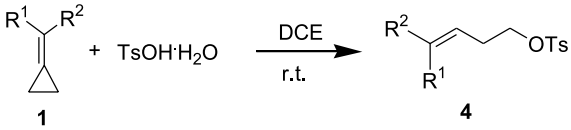
[a] Isolated yields.

homoallylic alcohol **3a** (Table 2, entries 2–4). Traces of **2a** and **3a** were obtained when 5.0 equiv of H_2O was used and no reaction took place when 90.0 equiv of H_2O was used (Table 2, entries 5, 6). Thus, these optimized reaction conditions were 1.0 equiv of H_2O as the reagent, 0.3 equiv of $C_8F_{17}SO_3H$ as the catalyst and DCE as the solvent.

In the following series of reactions, we examined the reactivity of a variety of MCPs **1** under these optimized conditions to surrey the generality of this reaction. The results are shown in Table 3. We were delighted to find out that the reactions proceeded smoothly to give the corresponding homoallylic ether **2** as a sole product in good to excellent yields in most cases except for MCP **1e** and **1g** in which less than 10% of the homoallylic alcohol were obtained (Table 3, entries 4 and 6). For MCPs **1b**, **1c** and **1d**, in which electron-donating groups on the phenyl ring, the reaction time was dramatically reduced (Table 3, entries 1–3). For the unsymmetric MCPs **1c** and **1e**, only one isomer of the product **2** were obtained and we cannot explain these phenomena at present stage (Table 3, entries 2 and 4) (see their ^1H and ^{13}C NMR spectra in Supporting Information).

Interestingly, we found that the ring of MCPs **1** can be opened by the corresponding anion when toluene *p*-sulfonic acid monohydrate ($TsOH{\cdot}H_2O$) was used as the Brønsted acid reagent in 1,2-dichloroethane (DCE). The results are shown in Table 4. As can be seen from Table 4, all reactions

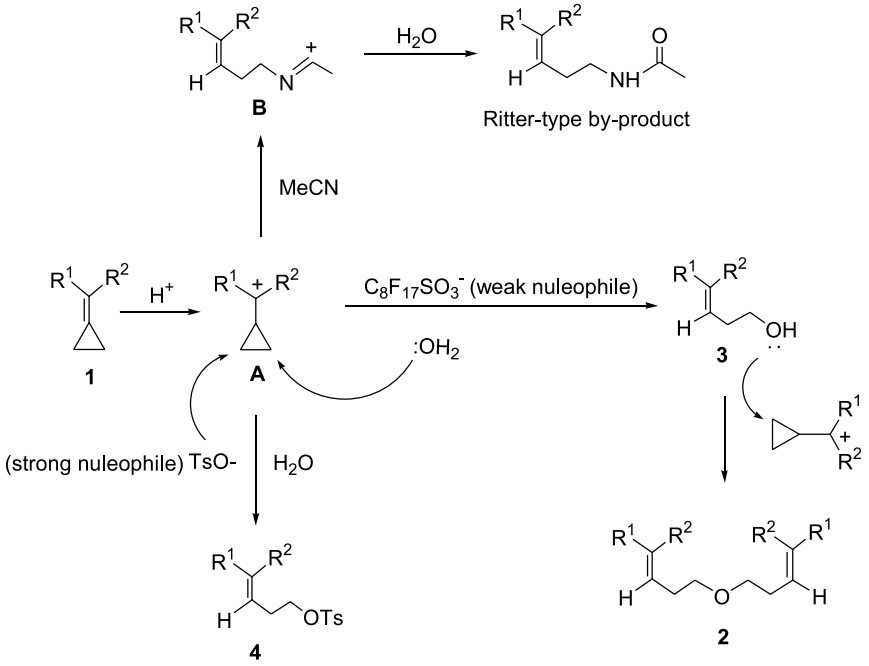
Table 4. The reaction of toluene-4-sulfonic acid with various MCPs **1**



1 4

Entry	R^1/R^2	Time/min	Yield/%[a], **4** (*E*/*Z*)
1	**1a**, C_6H_5/C_6H_5	4	98
2	**1b**, *p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$	5	96
3[b]	**1c**, *p*-$MeOC_6H_4/C_6H_5$	5	99 (1:1)
4	**1d**, *p*-MeC_6H_4/*p*-MeC_6H_4	5	77
5[b]	**1e**, *o*-ClC_6H_4/C_6H_5	25	93 (7.8:1)
6	**1f**, *p*-ClC_6H_4/*p*-ClC_6H_4	20	92
7	**1g**, *p*-FC_6H_4/*p*-FC_6H_4	30	96
8[b]	**1h**, *p*-$EtOC_6H_4$/Me	5	97 (2.5:1)

[a] Isolated yields.
[b] Mixtures of (*Z*)- and (*E*)-isomers.



Scheme 2. Plausible reaction mechanism.

proceeded smoothly to give the homoallylic alcohol derivatives **4** in excellent yields within 30 min. In this case, the ambient H_2O did not participate in the ring-opening reaction. For the unsymmetric MCPs **1b**, **1e** and **1h**, the products **4b**, **4e** and **4h** were obtained as mixtures of *Z*- and *E*-isomers (Table 4, entries 3, 5 and 8). Using MeCN as the solvent, a Ritter reaction product was obtained as the by-product (Scheme 2).[8]

The structures of products **2**, **3** and **4** were determined by ^{1}H NMR and ^{13}C NMR spectroscopic data, microanalysis and HRMS.

A plausible mechanism for these two different ring-opening reactions of MCPs **1** is shown in Scheme 2. The initial protonation of MCPs **1** with Brønsted acid gives the intermediate **A**. The cyclopropylmethyl cation intermediate **A** is further stabilized by two substituents on the double bond.[9] The intermediate **A** is attacked by H_2O if the corresponding anion of the Brønsted acid is a weak nucleophile (in the case of $C_8F_{17}SO_3^-$) to give product **3**. Subsequent ring-opening nucleophilic attack of **3** to another cation intermediate **A** gives product **2**. The intermediate A can also be attacked by the corresponding anion of the Brønsted acid if it is a strong nucleophile (in the case of TsO^-) to furnish product **4**. In the case of MeCN as the solvent, the cation intermediate **A** will be attacked by the solvent (MeCN) to give the cation intermediate **B** which is quenched by H_2O to give the Ritter-type by-product (Scheme 2).

3. Conclusion

In conclusion, we have found two different ring-opening patterns of MCPs **1** in different Brønsted acid-mediated systems. The nucleophilicity of the anion of the employed Brønsted acid has dramatic effect on the ring-opening modes of MCPs **1**: the cyclopropyl ring of MCPs **1** can be opened by water when the corresponding anion is a weak nucleophile such as heptadecafluorooctane-1-sulfonic acid ($C_8F_{17}SO_3H$) as the Brønsted acid mediator; and the cyclopropyl ring of MCPs **1** also can be opened by the corresponding anion when it is a strong nucleophile such as toluene *p*-sulfonic acid (TsOH) as the Brønsted acid mediator. Other Brønsted acids will be investigated in this ring-opening system in the near future. In addition, efforts are underway to elucidate the mechanistic details and subsequent transformation thereof. Work along these lines is currently in progress.

4. Experimental

4.1. General remarks

^{1}H NMR spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ using tetramethylsilane as the internal standard. Infrared spectra were measured on a PERKIN-ELMER 983 spectrometer. Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by a Finnigan MA^+ mass spectrometer. Satisfactory CHN microanalyses were obtained with a Carlo-Erba 1106 analyzer. Melting points are uncorrected. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash Column Chromatography was carried out using 300–400 mesh silica gel.

4.2. General procedure for the ring-opening of MCPs by H_2O and subsequent etherification in the catalysis of heptadecafluorooctane-1-sulfonic acid ($C_8F_{17}SO_3H$)

Under an argon atmosphere, MCPs **1** (0.30 mmol), H_2O (0.30 mmol) and $C_8F_{17}SO_3H$ (0.1 mmol), were added into a

flame-dried Schlenk tube with freshly distilled 1,2-dichloroethane (DCE) (1.0 mL). The obtained white solid suspended reaction mixture was stirred at room temperature. The solvent was removed under reduced pressure and then the residue was purified by a flash column chromatography.

4.2.1. Di(4,4-diphenyl-but-3-en-1-yl) ether (2a). A white solid, Mp: 103–106 °C; IR (neat): ν 3078, 3054, 3023, 2856, 2778, 1945, 1889, 1734, 1597, 1494, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.43 (dt, $J=6.3$, 7.2 Hz, 4H), 3.51 (t, $J=6.3$ Hz, 4H), 6.61 (t, $J=7.2$ Hz, 2H), 7.20–7.39 (m, 20H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ 30.4, 70.4, 126.0, 126.90, 126.93, 127.2, 128.0, 128.2, 129.9, 139.9, 142.5, 143.1. MS (%) *m/z* 430 (M^+, 0.25), 237 (50.68), 206 (75.71), 91 (100). HRMS Calcd. for $C_{32}H_{30}ONa^+$ (Maldi)[10]: 453.2201, Found: 453.2189 ($M+Na^+$).

4.2.2. 4,4-diphenyl-but-3-en-1-ol (3a). A colorless liquid; IR (neat): ν 3344, 3055, 2926, 1493, 1443, 1047, 1031 cm^{-1}. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.40 (dt, $J=6.6$, 7.5 Hz, 2H), 3.72 (t, $J=6.6$ Hz, 2H), 6.11 (t, $J=7.5$ Hz, 1H), 7.17–7.40 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ 33.3, 62.6, 125.2, 127.07, 127.09, 127.2, 128.1, 128.2, 129.8, 139.8, 142.4, 144.2. MS (%) *m/z* 224 (M^+), 193, 178, 165, 115. HRMS Calcd. for $C_{16}H_{16}O$ (EI): 224.1201, Found: 224.1215.

4.2.3. Di[4,4-bis(4-methoxyphenyl)-but-3-en-1-yl] ether (2b). A colorless liquid, IR (CH_2Cl_2): ν 3002, 2956, 2933, 2907, 2836, 2052, 1730, 1645, 1604, 1510, 1462, 1248 cm^{-1}. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.39 (dt, $J=6.6$, 6.9 Hz, 4H), 3.48 (t, $J=6.6$ Hz, 4H), 3.78 (s, 3H, CH_3O), 3.81 (s, 3H, CH_3O), 5.99 (t, $J=6.9$ Hz, 2H), 6.77 (d, $J=$ 8.7 Hz, 4H, Ar), 6.87 (d, $J=8.7$ Hz, 4H, Ar), 7.10 (d, $J=$ 8.7 Hz, 4H, Ar), 7.14 (d, $J=8.7$ Hz, 4H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ 30.4, 55.17, 55.21, 70.5, 113.3, 113.4, 113.5, 124.0, 128.38, 131.0, 132.2, 142.0, 158.4, 162.8. MS (%) *m/z* 550 (M^+, 0.55), 266 (66.78), 236 (100). HRMS Calcd. for $C_{32}H_{30}ONa^+$ (Maldi): 573.2615, Found: 573.2612 ($M+Na^+$).

4.2.4. Di{4,4-[1-phenyl-1-(4-methoxyphenyl)]-but-3-en-1-yl} ether (2c). A colorless liquid, IR (CH_2Cl_2): ν 3054, 3030, 3003, 2955, 2935, 2904, 2859, 2837, 2793, 2548, 2311, 2059, 1893, 1719, 1654, 1606, 1575, 1510, 1493 cm^{-1}. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.31 (dt, $J=6.6$, 7.5 Hz, 4H), 3.36–3.44 (m, 4H), 3.69 (s, 3H, CH_3O), 3.72 (s, 3H, CH_3O), 5.96 (t, $J=7.5$ Hz, 1H), 6.00 (t, $J=7.5$ Hz, 1H), 6.68 (d, $J=9.0$ Hz, 2H, Ar), 6.80 (d, $J=8.4$ Hz, 2H, Ar), 7.16–7.40 (m, 14H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ 30.4, 30.5, 55.16, 55.19, 70.46, 70.49, 113.4, 113.5, 124.2, 125.7, 126.8, 126.9, 127.3, 128.0, 128.1, 128.3, 129.8, 131.0, 132.2, 135.3, 140.2, 142.5, 142.7, 143.0, 158.5, 158.7. MS (%) *m/z* 490 (M^+, 0.50), 267 (20.58), 236 (100). HRMS Calcd. for $C_{34}H_{34}O_3Na^+$ (Maldi): 513.2429, Found: 513.2400 ($M+Na^+$).

4.2.5. Di[4,4-bis-(4-methylphenyl)-but-3-en-1-yl] ether (2d). A colorless liquid, IR (CH_2Cl_2): ν 3023, 2946, 2920, 2865, 2733, 1900, 1719, 1656, 1608, 1511, 1449, 1278 cm^{-1}. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.30–2.46 (m, 16H), 3.51 (t, $J=6.9$ Hz, 4H), 6.61 (t, $J=7.2$ Hz, 2H), 7.04–7.20 (m, 16H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ 21.1, 21.2, 30.4, 70.5, 124.9, 125.7, 127.2, 128.7, 128.8, 129.8, 136.5, 137.1, 140.0, 142.8. MS (%) *m/z* 486 (M^+, 1.5), 265 (28.11), 234 (100). HRMS Calcd. for $C_{36}H_{38}ONa^+$ (Maldi): 509.2817, Found: 509.2815 ($M+Na^+$).

4.2.6. Di{4,4-[1-phenyl-1-(2-chlorophenyl)]-but-3-en-1-yl} ether (2e). A yellow liquid, IR (CH_2Cl_2): ν 3080, 3055, 3024, 2947, 2858, 2791, 1937, 1800, 1730, 1597, 1494, 1473, 1445, 1434, 1360 cm^{-1}. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.14 (dt, $J=6.9$, 7.5 Hz, 4H), 3.39 (t, $J=6.9$ Hz, 4H), 6.23 (t, $J=7.5$ Hz, 2H), 7.09–7.21 (m, 16H, Ar), 7.33–7.36 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ 30.4, 69.9, 126.1, 126.7, 127.0, 127.1, 128.2, 128.6, 129.7, 131.7, 133.8, 138.5, 140.1, 140.3. MS (%) *m/z* 498 (M^+, 0.20), 271 (83.66), 201 (100). HRMS Calcd. for $C_{32}H_{28}Cl_2ONa^+$ (Maldi): 521.1416, Found: 521.1409 ($M+Na^+$).

4.2.7. 1-Phenyl-1-(2-chlorophenyl)-but-3-en-1-ol (3e). A yellow liquid, IR (CH_2Cl_2): ν 3321, 3056, 3024, 2928, 2881, 1945, 1712, 1594, 1560, 1494, 1473, 1445, 1434 cm^{-1}. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.19 (dt, $J=6.6$, 7.2 Hz, 2H), 3.65 (t, $J=6.6$ Hz, 2H), 6.23 (t, $J=7.2$ Hz, 1H), 7.12–7.25 (m, 8H, Ar), 7.37–7.40 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ 33.4, 62.1, 126.17, 126.24, 126.5, 126.8, 127.3, 128.3, 128.8, 129.7, 131.6, 133.7, 138.4, 140.0. MS (%) *m/z* 258 (M^+, 46.87), 227 (100). HRMS Calcd. for $C_{16}H_{15}ClONa^+$ (Maldi): 281.0733, Found: 281.0704 ($M+Na^+$).

4.2.8. Di[4,4-bis(4-chlorophenyl)-but-3-en-1-yl] ether (2f). A bright yellow liquid, IR (CH_2Cl_2): ν 3044, 2857, 2785, 1893, 1778, 1586, 1491, 1405 cm^{-1}. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.38 (dt, $J=6.6$, 7.5 Hz, 4H), 3.49 (t, $J=6.6$ Hz, 4H), 6.12 (t, $J=7.5$ Hz, 2H), 7.095 (d, $J=7.8$ Hz, 4H, Ar), 7.103 (d, $J=7.8$ Hz, 4H, Ar), 7.21 (d, $J=7.8$ Hz, 4H, Ar), 7.31 (d, $J=7.8$ Hz, 4H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ 30.4, 70.2, 127.2, 128.3, 128.4, 128.5, 131.2, 133.0, 133.1, 137.8, 140.6, 141.0. MS (%) *m/z* 566 (M^+, 0.20), 305 (41.37), 275 (10.83), 125 (100). HRMS Calcd. for $C_{32}H_{27}Cl_4O^+$ (Maldi): 567.0815, Found: 567.0811 ($M+H^+$).

4.2.9. Di[4,4-bis(4-fluorophenyl)-but-3-en-1-yl] ether (2g). A colorless liquid, IR (CH_2Cl_2): ν 3045, 2955, 2863, 2778, 2030, 1893, 1782, 1715, 1656, 1601, 1508, 1401, 1225 cm^{-1}. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.39 (dt, $J=6.0$, 6.9 Hz, 4H), 3.51 (t, $J=6.9$ Hz, 4H), 6.07 (t, $J=$ 6.0 Hz, 2H), 6.92 (d, $J=6.9$ Hz, 4H, Ar), 6.97 (d, $J=$ 6.9 Hz, 4H, Ar), 7.03 (d, $J=6.9$ Hz, 4H, Ar), 7.07–7.18 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ 30.4, 70.3, 115.0 (d, $J_{C-F}=21.60$ Hz), 115.2 (d, $J_{C-F}=20.25$ Hz), 126.3, 127.4 (d, $J_{C-F}=7.28$ Hz), 128.7 (d, $J_{C-F}=7.58$ Hz), 131.4 (d, $J_{C-F}=7.28$ Hz), 135.6 (d, $J_{C-F}=3.68$ Hz), 138.6 (d, $J_{C-F}=3.08$ Hz), 141.2, 161.9 (d, $J_{C-F}=246.68$ Hz), 162.1 (d, $J_{C-F}=244.65$ Hz). MS (%) *m/z* 502 (M^+, 0.15), 273 (27.26), 242 (60.00), 109 (100). HRMS Calcd. for $C_{32}H_{26}F_4ONa^+$ (Maldi): 525.1805, Found: 525.1812 ($M+Na^+$).

4.2.10. Di[4,4-bis(fluorophenyl)-but-3-en-1-ol (3g). A yellow liquid, IR (CH_2Cl_2): ν 3341, 3045, 2928, 2881,

1893, 1719, 1602, 1508, 1409, 1225 cm^{-1}. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.31 (dt, $J=6.3$, 7.2 Hz, 2H), 3.66 (t, $J=6.3$ Hz, 2H), 5.98 (t, $J=7.2$ Hz, 1H), 6.85–7.13 (m, 8H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ 33.2, 62.5, 115.0 (d, $J_{C-F}=21.15$ Hz), 115.3 (d, $J_{C-F}=42.9$ Hz), 125.6, 128.8 (d, $J_{C-F}=7.88$ Hz), 131.4 (d, $J_{C-F}=8.03$ Hz), 135.4 (d, $J_{C-F}=3.75$ Hz), 142.2, 162.0 (d, $J_{C-F}=244.95$ Hz), 162.1 (d, $J_{C-F}=244.80$ Hz). MS (%) *m/z* 260 (M^+, 29.31), 229 (100). HRMS Calcd. for $C_{16}H_{14}F_2O$ (EI): 260.1013, Found: 260.0989.

4.3. The direct ring-opening of MCPs by toluene *p*-sulfonic acid (TsOH)

Under an argon atmosphere, MCPs **1** (0.50 mmol) and toluene *p*-sulfonic acid ($TsOH\cdot H_2O$) (0.55 mmol) were added into a Schlenk tube with 1,2-dichloroethane (DCE) (2.0 mL). After gentle heating to make TsOH soluble in DCE, the reaction mixture was stirred at room temperature. The solvent was removed under reduced pressure and then the residue was purified by a flash column chromatography.

4.3.1. Toluene-4-sulfonic acid 4,4-diphenyl-but-3-en-1-yl ester (4a). A white solid, Mp: 84–86 °C; IR (thin film): ν 3027, 1958, 1494, 1444, 1360, 1189, 1176, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.42–2.47 (m, 5H), 4.08 (t, $J=6.6$ Hz, 2H), 5.90 (t, $J=7.2$ Hz, 1H), 7.07–7.15 (m, 4H, Ar), 7.23–7.35 (m, 8H, Ar), 7.76 (d, $J=8.1$ Hz, 2H. Ar); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 21.6, 29.4, 69.8, 122.7, 127.17, 127.23, 127.8, 128.1, 128.3, 129.6, 129.8, 133.0, 139.2, 141.8, 142.2, 144.7, 144.9; MS (%) *m/z* 377 (M^+-1, 0.84), 206 (100), 191 (25.36); Anal. Calcd. for $C_{23}H_{22}O_3S$ requires C, 72.99; H, 5.86; Found: C, 72.91; H, 5.86%.

4.3.2. Toluene-4-sulfonic acid 4,4-bis(4-methoxyphenyl) but-3-en-1-yl ester (4b). A colorless oil, IR (thin film): ν 2956, 2837, 1606, 1575, 1541, 1463, 1359, 1290, 1247, 1176, 1079, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.40–2.47 (m, 5H), 3.79 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 4.06 (t, $J=6.6$ Hz, 2H), 5.75 (t, $J=7.5$ Hz, 1H), 6.78 (d, $J=8.7$ Hz, 2H, Ar), 6.87 (d, $J=8.7$ Hz, 2H, Ar), 6.99 (d, $J=9.0$ Hz, 2H, Ar), 7.06 (d, $J=9.0$ Hz, 2H, Ar), 7.28 (d, $J=8.4$ Hz, 2H, Ar), 7.76 (d, $J=8.4$ Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 21.6, 29.4, 55.21, 55.25, 70.0, 113.4, 113.6, 120.6, 127.9, 128.4, 129.8, 130.7, 131.7, 133.0, 135.0, 144.0, 144.6, 158.7, 158.9; MS (%) *m/z* 438 (M^+, 14.83), 266 (100), 253 (49.35), 235 (92.98); HRMS Calcd. for $C_{25}H_{27}O_5S^+$ (Maldi): 439.1572, Found: 439.1574 ($M+H^+$).

4.3.3. Toluene-4-sulfonic acid 4-(4-methoxyphenyl)-4-phenylbut-3-en-1-yl ester (4c). A yellow oil, IR (thin film): ν 2957, 2837, 1606, 1510, 1360, 1291, 1248, 1176, 1097, 1033 cm^{-1}; (*Z*- or *E*-isomer) ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.39–2.48 (m, 5H), 3.78 (s, 3H, CH_3O), 4.06 (t, $J=6.9$ Hz, 2H), 5.81 (t, $J=6.9$ Hz, 1H), 6.78 (d, $J=8.7$ Hz, 2H, Ar), 6.99–7.15 (m, 4H, Ar), 7.23–7.36 (m, 5H, Ar), 7.75 (d, $J=8.1$ Hz, 2H, Ar); (*E*- or *Z*-isomer) ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.39–2.48 (m, 5H), 3.83 (s, 3H, CH_3O), 4.08 (t, $J=6.6$ Hz, 2H), 5.83 (t, $J=6.9$ Hz, 1H), 6.87 (d, $J=8.7$ Hz, 2H, Ar), 6.99–7.15 (m, 4H, Ar), 7.23–7.36 (m, 5H, Ar), 7.76 (d, $J=8.1$ Hz, 2H, Ar); (*Z*- or *E*-isomer) ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 21.5, 29.2, 55.0, 69.8, 113.3, 120.7, 127.0, 127.7, 128.1, 129.4, 130.6, 132.8, 139.4, 144.2, 144.6, 158.6. (*E*- or *Z*-isomer) ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 21.5, 29.3, 55.0, 69.9, 113.5, 122.4, 127.1, 127.9, 128.1, 129.7, 131.3, 134.4, 142.2, 144.4, 144.6, 158.8. MS (%) *m/z* 408 (M^+, 4.59), 236 (72.85), 91 (100); HRMS Calcd. for $C_{24}H_{25}O_4S^+$ (Maldi): 409.1488, Found: 409.1468 ($M+H^+$).

4.3.4. Toluene-4-sulfonic acid 4,4-di-p-tolyl-but-3-en-1-yl ester (4d). A white solid, Mp: 93–95 °C; IR (thin film): ν 2957, 2930, 1606, 1510, 1494, 1444, 1360, 1291, 1247, 1176, 1097, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.43 (td, $J=6.6$, 7.2 Hz, 2H), 4.06 (t, $J=6.6$ Hz, 2H), 5.82 (t, $J=7.2$ Hz, 1H), 6.96 (d, $J=8.1$ Hz, 2H, Ar), 7.01–7.07 (m, 4H, Ar), 7.14 (d, $J=7.5$ Hz, 2H, Ar), 7.28 (d, $J=8.1$ Hz, 2H, Ar), 7.76 (d, $J=8.1$ Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 21.0, 21.1, 21.5, 29.3, 69.9, 121.5, 127.0, 127.8, 128.7, 128.9, 129.4, 129.7, 130.1, 132.8, 136.3, 136.7, 136.9, 139.2, 144.6; MS (%) *m/z*: 406 (M^+, 1), 346 (3.72), 234 (38.64), 219 (50.67), 59 (100); Anal. Calcd. for $C_{25}H_{26}O_3S$ requires C, 73.86; H, 6.45; Found: C, 73.79; H, 6.46%.

4.3.5. Toluene-4-sulfonic acid 4-(2-chlorophenyl)-4-phenylbut-3-en-1-yl ester (4e). A white solid, Mp: 101–103 °C; IR (thin film): ν 2924, 1598, 1494, 1468, 1444, 1360, 1177, 1189, 1097, 1056, 1035 cm^{-1}; (*Z*-isomer) ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.27 (dt, $J=6.3$, 7.2 Hz, 2H), 2.38 (s, 3H, CH_3), 4.06 (t, $J=6.3$ Hz, 2H), 6.07 (t, $J=7.2$ Hz, 1H), 7.06–7.13 (m, 3H, Ar), 7.17–7.27 (m, 8H, Ar), 7.38–7.41 (m, 1H, Ar), 7.75 (d, $J=8.1$ Hz, 2H, ArH); (*Z*-isomer) ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 21.5, 29.3, 69.3, 123.9, 126.1, 126.8, 127.1, 127.3, 127.72, 128.1, 128.8, 129.7, 131.26, 132.7, 137.7, 139.5, 141.7, 144.7; (*E*-isomer) ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.61 (dt, $J=6.3$, 7.2 Hz, 2H), 2.38 (s, 3H, CH_3), 4.11 (t, $J=6.3$ Hz, 2H), 5.60 (t, $J=7.2$ Hz, 1H), 7.06–7.13 (m, 3H, Ar), 7.17–7.27 (m, 8H, Ar), 7.38–7.41 (m, 1H, Ar), 7.75 (d, $J=8.1$ Hz, 2H, Ar); (*E*-isomer) ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 22.1, 28.8, 69.5, 126.4, 126.7, 127.70, 127.9, 128.5, 129.0, 129.58, 129.61, 131.34, 132.9, 133.3, 138.4, 139.5, 141.8, 142.6. MS (%) *m/z* 240 (M^+–TsOH) (100), 205 (89.98); Anal. Calcd. for $C_{23}H_{21}ClO_3S$ requires C, 66.90; H, 5.13; Found: C, 66.80; H, 5.11%.

4.3.6. Toluene-4-sulfonic acid 4,4-bis-(4-chlorophenyl)-but-3-en-1-yl ester (4f). A white solid, Mp: 83–85 °C; IR (thin film): ν 2919, 2850, 1596, 1491, 1464, 1401, 1360, 1188, 1175, 1091, 1014 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.40–2.45 (m, 5H) 4.10 (t, $J=6.6$ Hz, 2H), 5.92 (t, $J=7.8$ Hz, 1H), 7.01–7.08 (m, 4H, Ar), 7.21–7.36 (m, 6H, Ar), 7.75 (d, $J=8.4$ Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 21.6, 29.4, 69.4, 124.0, 127.8, 128.3, 128.4, 128.7, 129.8, 130.9, 132.9, 133.37, 133.43, 137.2, 139.9, 142.7, 144.8; MS (%) *m/z* 274 (M^+–TsOH) (31.72), 239 (100); Anal. Calcd. for $C_{23}H_{20}Cl_2S$ requires C, 61.75; H, 4.51; Found: C, 61.60; H, 4.67%.

4.3.7. Toluene-4-sulfonic acid 4,4-bis-(4-fluorophenyl) but-3-en-1-yl ester (4g). A yellow oil, IR (thin film): ν 2926, 1601, 1508, 1361, 1223, 1189, 1177, 1096 cm^{-1}; ^1H

NMR ($CDCl_3$, TMS, 300 MHz): δ 2.38–2.45 (m, 5H), 4.08 (t, J=6.6 Hz, 2H), 5.85 (t, J=7.2 Hz, 1H), 6.94 (dd, J=9.0, J_{HF}=9.0 Hz, 2H, Ar), 7.03–7.11 (m, 6H, Ar), 7.29 (d, J=8.1 Hz, 2H, Ar), 7.76 (d, J=8.1 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 21.6, 29.3, 69.6, 115.0 (d, J_{C-F}=21.5 Hz), 115.4 (d, J_{C-F}=21.5 Hz), 123.1, 127.8, 128.8 (d, J_{C-F}=7.9 Hz), 129.8, 131.2, 133.0, 134.9 (d, J_{C-F}=36.9 Hz), 137.9 (d, J_{C-F}=36.9 Hz), 143.0, 144.8, 163.1 (d, J_{C-F}=245.8 Hz), 162.3 (d, J_{C-F}=245.8 Hz); MS (%) m/z 242 (M^+–TsOH) (100), 227 (19.43), 133 (30.78), 109 (59.91); HRMS Calcd. for $C_{23}H_{20}F_2O_3SNa^+$ (Maldi): 437.1008, Found: 437.0993 ($M+Na^+$).

4.3.8. Toluene-4-sulfonic acid 4-(4-ethoxyphenyl)pent-3-en-1-yl ester (4h). A colorless oil, IR (thin film): ν 2978, 2928, 1607, 1511, 1478, 1360, 1245, 1188, 1177, 1117, 1097 cm^{-1}; (Z- or E-isomer) ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ 1.37–1.44 (m, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.44–2.60 (m, 2H), 3.98–4.11 (m, 4H), 5.45–5.53 (m, 1H), 6.80–6.86 (m, 2H, Ar), 7.20–7.31 (m, 4H, Ar), 7.66–7.82 (m, 2H, Ar); (E- or Z-isomer) ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ 1.37–1.44 (m, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.44–2.60 (m, 2H), 3.98–4.11 (m, 4H), 5.45–5.53 (m, 1H), 6.80–6.86 (m, 2H, Ar), 7.20–7.31 (m, 4H, Ar), 7.66–7.82 (m, 2H, Ar); (Z- or E-isomer) ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 21.6, 28.4, 63.25, 63.33, 69.7, 113.8, 114.0, 125.7, 127.7, 127.8, 129.69, 129.74, 135.3, 144.6, 157.3. (E- or Z-isomer) ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 21.6, 29.6, 63.3, 67.4, 70.1, 114.0, 119.3, 126.5, 127.8, 128.7, 129.7, 132.9, 137.6, 144.6, 158.0. MS (%) m/z 360 (M^+, 12.45), 188 (72.15), 173 (100); HRMS Calcd. for $C_{20}H_{26}O_4S^+$ (Maldi): 361.1504, Found: 361.1468 ($M+H^+$).

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Supplementary data

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References and notes

1. Binger, P.; Schuchardt, U. *Chem. Ber.* **1981**, *114*, 3313–3324.
2. For the synthesis of MCPs (a) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589–635. (b) *Carbocyclic Three-membered Ring Compounds*; de Meijere, A., Ed.; Houben-Weyl; Thieme: Stuttgart, 1996; Vol. E17a-c.
3. For recent reviews, please see: (a) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111–129. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213–1269.
4. For some more recent related papers, please see: (a) de Meijere, A.; Leonov, A.; Heiner, T.; Noltemeyer, M.; Bes, M. T. *Eur. J. Org. Chem.* **2003**, 472–478. (b) Belov, V. N.; Savchenko, A. I.; Sokolov, V. V.; Straub, A.; de Meijere, A. *Eur. J. Org. Chem.* **2003**, 551–561. (c) de Meijere, A.; Kuchuk, I. D.; Sokolov, V. V.; Labahn, T.; Rauch, K.; Es-Sayed, M.; Krämer, T. *Eur. J. Org. Chem.* **2003**, 985–997. (d) Huang, X.; Zhou, H.-W.; Chen, W.-L. *J. Org. Chem.* **2004**, *69*, 839–842. (e) Zhou, H.-W.; Huang, X.; Chen, W.-L. *Synlett* **2003**, 2080–2082. (f) Huang, Z.; Zhou, H.-W. *Org. Lett.* **2002**, *4*, 4419–4422. (g) Zhou, H-W. ; Huang, X.; Chen, W.-L. *J. Org. Chem.* **2004**, *69*, 5471–5472. (h) Huang, X.; Chen, W.-L.; Zhou, H.-W. *Synlett* **2004**, 329–331. (i) Siriwardana, A. I.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 3202–3204. (j) Oh, B. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Heterocycles* **2003**, *61*, 247–257.
5. For some related Lewis acid or Brønsted acid-mediated reactions of MCPs, please see: (a) Peron, G. L. N.; Kitteringham, J.; Kilburn, J. D. *Tetrahedron Lett.* **1999**, *40*, 3045–3048. (b) Miura, K.; Takasumi, M.; Hondo, T.; Saito, H.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 4587–4590. (c) Peron, G. L. N.; Kitteringham, J.; Kilburn, J. D. *Tetrahedron Lett.* **2000**, *41*, 1615–1618. (d) Patient, L.; Berry, M. B.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 1015–1017. (e) Peron, G.; Norton, D.; Kitteringham, J.; Kilburn, J. D. *Tetrahedron Lett.* **2001**, *42*, 347–349. (f) Nakamura, I.; Kamada, M.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 2903–2906. (g) Patient, L.; Berry, M. B.; Coles, S. J.; Hursthouse, M. B.; Kilburn, J. D. *Chem. Commun.* **2003**, 2552–2553.
6. For some of the Lewis acid or Brønsted acid-mediated transformations of MCPs in our laboratory, please see: (a) Shi, M.; Xu, B. *Org. Lett.* **2002**, *4*, 2145–2148. (b) Huang, J.-W.; Shi, M. *Tetrahedron* **2004**, *60*, 2057–2062. (c) Shao, L.-X.; Shi, M. *Eur. J. Org. Chem.* **2004**, 426–430. (d) Chen, Y.; Shi, M. *J. Org. Chem.* **2004**, *69*, 426–431. (e) Shao, L.-X.; Shi, M. *Adv. Synth. Catal.* **2003**, *345*, 963–966. (f) Shi, M.; Chen, Y. *J. Fluoro. Chem.* **2003**, *122*, 219–227. (g) Huang, J.-W.; Shi, M. *Tetrahedron Lett.* **2003**, *44*, 9343–9347. (h) Shi, M.; Chen, Y.; Xu, B.; Tang, J. *Green Chem.* **2003**, *5*, 85–88. (i) Shi, M.; Xu, B. *Tetrahedron Lett.* **2003**, *44*, 3839–3842. (j) Xu, B.; Shi, M. *Org. Lett.* **2003**, *5*, 1415–1418. (k) Shi, M.; Shao, L.-X.; Xu, B. *Org. Lett.* **2003**, *5*, 579–582. (l) Shi, M.; Chen, Y.; Xu, B.; Tang, J. *Tetrahedron Lett.* **2002**, *43*, 8019–8024. (m) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175–1178.
7. Siriwardana, A. I.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 4547–4550.
8. Ritter-type reaction product was obtained as a byproduct if the reaction was carried out in CH_3CN (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045–4048. (b) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc.* **1948**, *70*, 4048–4050. (c) Reddy, K. L. *Tetrahedron Lett.* **2003**, *44*, 1453–1455. (d) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213–325. (e) Nair, V.; Rajan, R.; Rath, N. P. *Org. Lett.* **2002**, *4*, 1575–1577.
9. The rearrangement of cyclopropylmethyl cation has already been studied extensively. It is reasonable that the substituents on the double further stabilize the cation. Please seeCarey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 5th ed.; Plenum: New York, 1998; pp 221 and 419.

10. Matrix-assisted laser desorption/ionization (MALDI) is a more soft and sensitive ionization technique than others. Among the chemical and physical ionization pathways suggested for MALDI are gas-phase photoionization, ion-molecule reactions, etc. The most widely accepted ion formation mechanism involves gas-phase proton transfer or alkali metal transfer in the expanding plume with photoionized matrix molecules. The matrix will serve to minimize sample damage from the laser pulse and inhibit the appearance of molecular ionsde Hoffmann, E.; Stroobant, V. *Mass Spectrometry: Principles and Applications*, 2nd ed.; Wiley: Chichester, 2001; pp 28–32.

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Recyclable organotungsten Lewis acid and microwave assisted Diels–Alder reactions in water and in ionic liquids

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Abstract—The water-soluble, organotungsten Lewis acid, $[O{=}P(2\text{-py})_3W(CO)(NO)_2](BF_4)_2$ (**1**), was synthesized and characterized. A series of **1**-catalyzed Diels–Alder reactions were investigated under conventional heating or microwave heating conditions. The cycloaddition reactions were efficiently conducted in either water or in an ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate. The ionic liquid acts as a powerful medium not only for rate- and selectivity enhancements but also for facilitating catalyst recycling. Dramatic rate acceleration via microwave flash heating as compared to thermal heating was observed.

1. Introduction

The Diels–Alder reaction is one of the most powerful synthetic tools for the construction of six-membered ring systems. Remarkable success in the rate acceleration and selectivity enhancement for various Diels–Alder reactions has been accomplished in the past two decades by the application of catalyst, high pressure, sonication, and solvent manipulation, etc.[1] Among these the effects provided by Lewis acid catalysts have been most widely studied. Special solvent effects of water which are almost equivalent to catalysis leading to dramatic enhancements of rate and stereoselectivity have also been demonstrated.[2,3] Due to the limited miscibility of water with most organic substrates, the possibility of using ionic liquids as a solvent substitutes for water and also as Lewis acid catalysts on Diels–Alder reactions has been explored.[4] A very recent trend in the development of environmentally benign processes is to use water[5] or room temperature ionic liquids[6] as solvent media for Diels–Alder catalysis. In the meantime, microwave technology is now a powerful and innovative tool for improving organic synthesis, because it is economical, efficient and provides better selectivity, higher reaction rates, milder reaction conditions, formation of cleaner products with higher yields and minor wastes. The successful application of microwave in chemistry dated since 1975.[7] Numerous organic reactions such as acylation and alkylation reactions, aromatic and nucleophilic substitutions, condensations, cycloadditions, protection and deprotection reactions, esterifications and transesterifications, heterocyclizations, rearrangements, organometallic reactions, oxidations and reductions assisted by microwave heating have been performed and reviewed in articles[8,9] or books.[10] In addition, ionic liquids have been demonstrated to couple very effectively with microwaves through an ionic conduction mechanism.[11b] Also, small amounts of an ionic liquid can be used as additives to increase the dielectric constant of a molecular solvent.[11b] Several recent studies in this area used ionic liquids, or mixtures of ionic liquids and molecular solvents, as reaction media in a number of important microwave-heated transformations,[11] including Diels–Alder reactions.[12]

We report herein the synthesis of a novel organotungsten Lewis acid **1** and a series of **1**-catalyzed Diels–Alder reactions with particular emphasis on the combined effects of this Lewis acid catalyst, the water or ionic liquid solvent system, and microwave radiation on the reaction rates and selectivity. The structures of dienes **2**–**7** and dienophiles **a**–**f** investigated in the current study are illustrated in Figure 1.

2. Results and discussion

The complex $[O{=}P(2\text{-py})_3W(CO)(NO)_2](BF_4)_2$ (**1**) was easily synthesized in two steps within 30 min from the commercially available $W(CO)_6$ (Scheme 1). The precursor $O{=}P(2\text{-py})_3W(CO)_3$ obtained in the first step can be prepared either through conventional heating or under

Keywords: Organotungsten Lewis acid; Diels–Alder; Microwave; Water; Ionic liquid.
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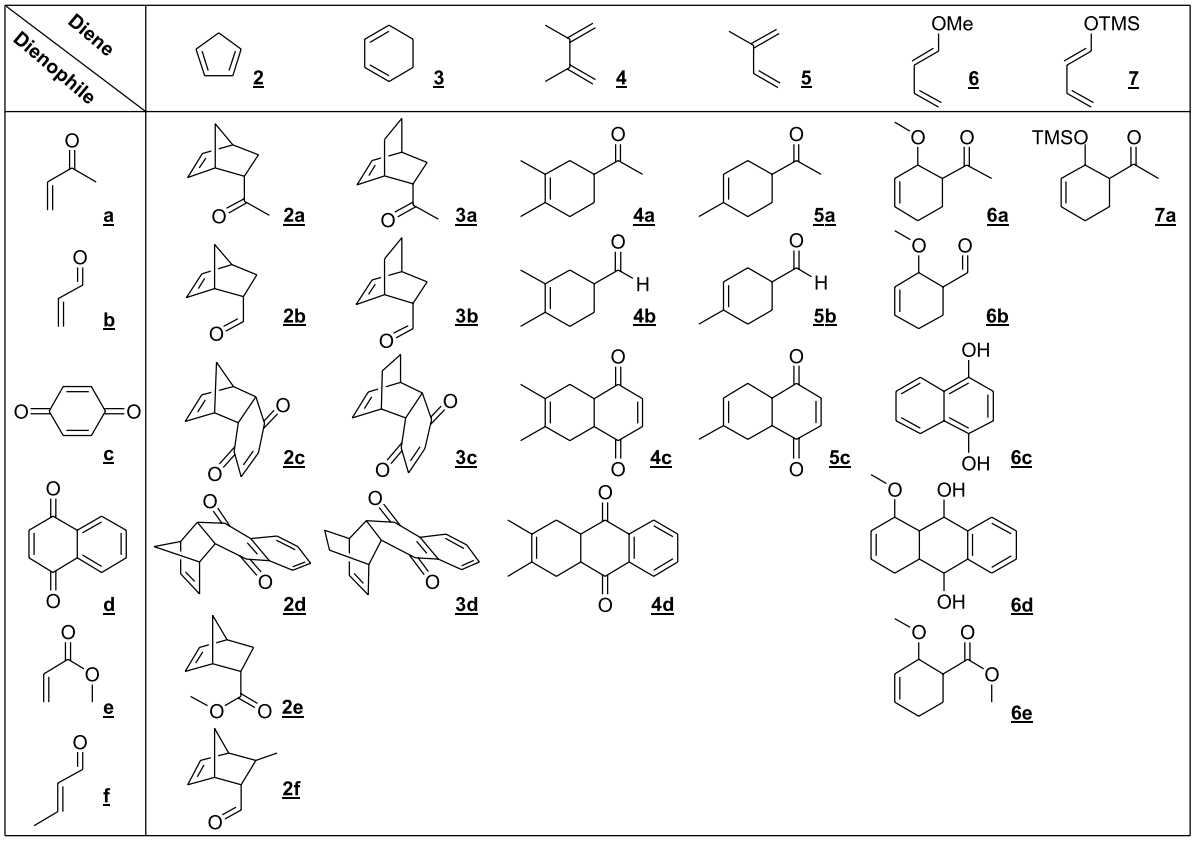
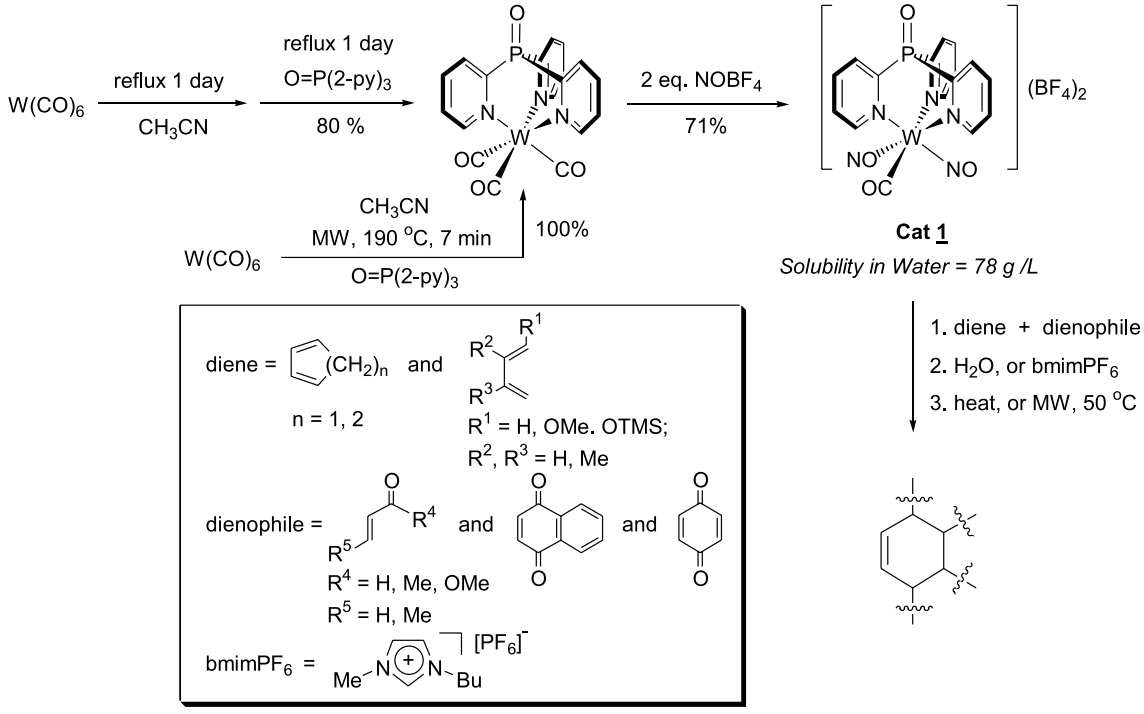


Figure 1. The numbering scheme for the dienes, dienopliles and the Diels–Alder adducts.

microwave irradiation conditions. The first method took more than 48 h and gave 80% yield of product after work-up procedures, while the second method gave 100% yield of high purity product in just 7 min. The direct reaction of $O{=}P(2\text{-py})_3W(CO)_3$ and 2 equiv of $NOBF_4$ afforded **1** which can be stored as a crystalline solid in air for months without significant decomposition. In addition, **1** is very water-soluble (78 g/L H_2O) and possesses strong Lewis acidity upon loss of the CO ligand. The relative Lewis acid strength of **1** was found to be comparable to that of $AlCl_3$.[13]



Scheme 1.

Because of its high solubility and stability in water, we therefore decided to study the effects of using Lewis acid **1** in water on Diels–Alder reactions.

The results of **1**-catalyzed Diels–Alder reactions of dienes **2**, **6** and **7** with dienophiles **a**–**c** and **e** in water are summarized in Table 1. As shown in the table, the reactions at both room temperature and at 50 °C afforded the corresponding cycloadducts in good to excellent yields and selectivities. The reaction at room temperature in entry 1 completed in 2 h with a 95:5 of *endo*-to-*exo* ratio, while the controlled reaction in CH_3NO_2 under similar conditions completed in 5 h with a 97% *endo*-selectivity (entry 10). In addition, two other controlled reactions were performed without the presence of catalyst **1** to give 80% complete in 50 h in CH_3NO_2, and totally complete in 8 h in water (entries 11–12). This clearly demonstrated that both water and **1** can be applied independently to the reaction system to provide rate enhancement, and further acceleration can be made by combining the two in the same system. In addition, a 100% *endo*-selectivity was obtained in entries 3, 5, 6, 8 and 9. In particular, the reaction of 1-methoxybutadiene **6** and methyl vinyl ketone **a** in entry 5, as far as we know, has never been reported previously. It should be noted that the Diels–Alder adduct of **6** and quinone **c** was unstable, the aromatized product **6c** was obtained by loss of the methoxy substituent at C(1) position through elimination.[14] Thus, the present catalytic process provides a potential route to the preparation of substituted dihydroxynaphthalene. The OTMS functionality of the Diels–Alder adduct **7a** in entry 9 was deprotected by the BF_4^- anion of **1** during catalysis. Reprotection of OTMS can be performed by treating the Diels–Alder mixture with TMSCl in the presence of $NaHCO_3$. The diene polymerization became competitive for the reaction between **6** and methyl acrylate **e** under catalytic conditions in water (entry 8). The use of isoprene **5** as the diene source in the Diels–Alder systems, however, resulted in the diene polymerization only.

Due to the usually low substrate solubility and the possibility of promoting the competing diene polymerization, the potential applications of water in the current **1**-catalyzed Diels–Alder systems are limited. We therefore chose the air-stable room-temperature ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF_6),[15,16] as a solvent alternative. The bmimPF_6 is in the same polarity region as the lower alcohols, such as methanol, ethanol and 1-butanol,[17] but it provides miscibility with a much broader range of organic substrates. Also, due to its neutral and weakly coordinating nature,[18] the bmimPF_6 does not interfere with the behavior of the Lewis acid catalyst employed. Table 2 shows the results of the **1**-catalyzed Diels–Alder reactions in bmimPF_6. As shown in the table, a much more variety of substrates can now be applied, and excellent yields and selectivities are obtained in all cases. It is also found that the enhancement in both the reaction rates and stereoselectivities in bmimPF_6 are not significantly different from those in water (Table 2, entries 1–3, 5, and 18–21). In contrast to the system in water, the **1**-in-bmimPF_6 system allowed the reactions of isoprene **5** and dienophiles **a**–**c** to undertake the Diels–Alder path with 78–91% isolated yields of the cycloaddition adducts (Table 2, entries 15–17). Similarly, the reaction of diene **6** and dienophile **e** in bmimPF_6 afforded a 1:1 mixture of products from both Diels–Alder and the competing diene polymerization pathways. On the contrary, the polymerization became dominant when the reaction of **6** and **e** was conducted in water (Table 2, entry 22 and Table 1, entry 8). Since the OTMS functionality of 1-methoxybutadiene **7** would be deproctected by the PF_6^- anion of the ionic liquid to give crotonaldehyde, diene **7** was not applied in the **1**-in-bmimPF_6 system. The cycloadduct from the reaction of **6** and naphthoquinone **d** was transformed to the more stable derivative **6d** with $LiAlH_4$ in Et_2O.

Finally, catalyst recycling can be readily accomplished in the **1**-in-bmimPF_6 system. The ionic liquid phase containing

Table 1. $[O{=}P(2\text{-py})_3W(CO)(NO)_2](BF_4)_2$-catalyzed Diels–Alder reactions in H_2O[a]

Entry	Diene	Dienophile	Diels–Alder adduct	Room temperature/50 °C		
				Time (h)[b]	Yield (%)[c]	*endo*/*exo*[d]
1	**2**	**a**	**2a**	2/0.58	93/90	95:5/10:1
2	**2**	**b**	**2b**	2/0.67	94/92	10:1/19:2
3	**2**	**c**	**2c**	2/0.6	87/82	*endo* only
4	**2**	**e**	**2e**	8/3.5	99/96	4:1/3.7:1
5	**6**	**a**	**6a**	2/0.5	89/80	*endo-syn* only
6	**6**	**b**	**6b**	1/0.35	91/85	*endo-syn* only
7[e]	**6**	**c**	**6c**	1.5/0.42	85/77	
8[f]	**6**	**e**	**6e**	3/1	15/100	*endo-syn* only/polymer
9[g]	**7**	**a**	**7a**	1/0.35	75/69	*endo-syn* only
10[h]	**2**	**a**	**2a**	5	98	97:3
11[i]	**2**	**a**	**2a**	50	80	95:5
12[j]	**2**	**a**	**2a**	8	92	95:5

[a] Reaction conditions: catalyst loading = 3 mol% at both room temperature and 50 °C, [substrate] = 0.1 M for entries 1–4 and 10–12; [substrate] = 0.2 M for entries 5–9.
[b] Time was set for >99% conversion.
[c] Isolated yield.
[d] *endo*/*exo* ratios were estimated by ^1H NMR spectroscopy.
[e] Compound **6c** was the aromatized product after DA reaction.
[f] Diene polymerization was the only observable reaction path at 50 °C.
[g] The overall yields after OTMS-reprotection.
[h] The catalysis was carried out in CH_3NO_2 at room temperature.
[i] The reaction was carried out in CH_3NO_2 at room temperature without catalyst.
[j] The reaction was carried out in water at room temperature without catalyst.

Table 2. $[O{=}P(2\text{-py})_3W(CO)(NO)_2](BF_4)_2$-catalyzed Diels–Alder reactions in $bmimPF_6$[a]

Entry	Diene	Dienophile	Diels–Alder adduct	Room temperature/50 °C		
				Time (h)[b]	Yield (%)[c]	*endo*:*exo*[d]
1	**2**	**a**	**2a**	0.75/0.35	97/90	10:1/10:1
2	**2**	**b**	**2b**	0.75/0.42	91/88	10:1/8:1
3	**2**	**c**	**2c**	2/0.5	87/80	*endo* only
4	**2**	**d**	**2d**	2/0.5	87/83	*endo* only
5	**2**	**e**	**2e**	8/3.5	99/97	4:1/4:1
6[e]	**2**	**f**	**2f**	8/4	40/28	4:1/3.5:1
7	**3**	**a**	**3a**	1.25/0.58	92/90	6:1/11:2
8	**3**	**b**	**3b**	1.25/0.58	80/76	6:1/5:1
9	**3**	**c**	**3c**	8/0.66	81/78	*endo* only
10	**3**	**d**	**3d**	8/0.66	93/85	*endo* only
11	**4**	**a**	**4a**	4/1.1	81/80	
12	**4**	**b**	**4b**	4/1.1	92/87	
13	**4**	**c**	**4c**	2/0.58	83/78	
14	**4**	**d**	**4d**	2/0.58	91/85	
15	**5**	**a**	**5a**	5/1.7	80/78	
16	**5**	**b**	**5b**	5/1.7	91/85	
17	**5**	**c**	**5c**	6/2.5	78/70	
18	**6**	**a**	**6a**	1/0.35	78/72	*endo-syn* only
19	**6**	**b**	**6b**	0.5/0.25	79/72	*endo-syn* only
20[f]	**6**	**c**	**6c**	1/0.35	77/73	
21[g]	**6**	**d**	**6d**	1/0.42	71/65	*endo-syn* only
22[h]	**6**	**e**	**6e**	48/3	40/100	4:1/polymers

[a] Reaction conditions: catalyst loading = 3 mol% at both room temperature and 50 °C, [substrate] = 1.0 M for entries 11–17; [substrate] = 0.67 M for other entries.
[b] Time was set for >99% conversion.
[c] Isolated yield.
[d] *endo*/*exo* ratios were estimated by ^1H NMR spectroscopy.
[e] Diene polymerization dominated over DA reactions.
[f] The yields for the aromatized product **6c**.
[g] Compound **6d** was the derivatized product.
[h] Diene polymerization was the only observable reaction at 50 °C.

$bmimPF_6$ and catalyst **1** was quantitatively recovered after the removal of the etherated extract of products. Figure 2 showed the results of catalyst recycling experiments. The recovered **1**-in-$bmimPF_6$ can be reused many times without significant loss of activity even after the tenth application, while the recovered **1**-in-water showed a 20% of decay in catalytic activity after being recycled six times.[19]

Microwave radiation is an alternative to conventional heating for transforming electromagnetic energy into heat. There are some documented examples involving the use of ionic liquids as additives for microwave heated Diels–Alder reactions in molecular solvents.[9b,c] However, to our knowledge, there has been no report on the microwave-assisted

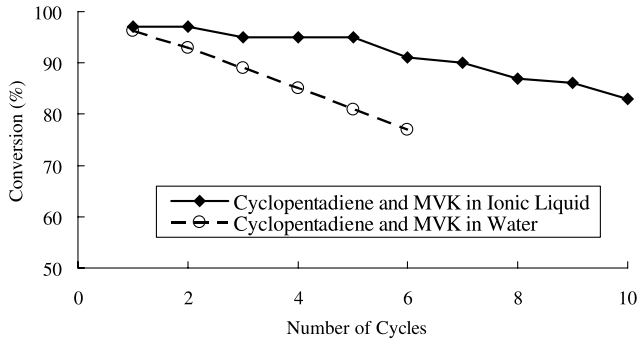


Figure 2. Catalyst systems recycling in $bmimPF_6$ (♦, upper curve) and in H_2O (○, lower curve). Experiments were conducted in a sealed process vial containing 1.5 mL of $bmimPF_6$ or 5 mL of H_2O. Reaction conditions: 3.4 mmol of **2**, 3.4 mmol of **a**, 3 mol% of **1**, 5 mL of $bmimPF_6$ for 45 min or 34 mL of water for 2 h at room temperature.

Diels–Alder reaction with the employment of catalysts in water or in ionic liquids. We next considered applying the Lewis acid **1** in water or in $bmimPF_6$ solvent with microwave heating on a series of Diels–Alder reactions. Table 3 shows the results of microwave heated **1**-catalyzed Diels–Alder reactions in water. As shown in the table, the system provided significant rate acceleration as compared to the data obtained from the system without microwave heating shown in Table 1. In all cases the reactions were complete within 1 min with similar selectivity to those obtained for the thermal reactions in the **1**-in-water system. Table 4 shows the results of microwave heated **1**-catalyzed Diels–Alder reactions in $bmimPF_6$. Interestingly, the **1**-in-$bmimPF_6$ system under microwave irradiation brought about even more acceleration. As shown in Table 4, most of the reactions were complete within 30 s (entries 1–4, 6–13 and 17–20), and even the reaction with a less reactive dienophile methylacrylate **e** took only one minute to complete (entry 5). These results suggested that while water is an excellent medium for microwave irradiation, the ionic liquid $bmimPF_6$ coupled with microwave even more effectively. To compare the efficiency in microwave conductance between the media water and $bmimPF_6$ the following experiments were carried out. A maximum temperature of 50 °C and a maximum power of 20% of 300 W were preselected to afford heating profiles and power supply curves for both solvents shown in Figure 3. As seen in the figure, the $bmimPF_6$ reached 50 °C after being heated for 30 s under sealed vessel conditions, while the water took 48 s to get to 50 °C under the same conditions. Meanwhile, the preset maximum power of 60 W was inputted to both

Table 3. $[O{=}P(2\text{-py})_3W(CO)(NO)_2](BF_4)_2$-catalyzed Diels–Alder reactions in H_2O under microwave irradiation[a]

Entry	Diene	Dienophile	Diels–Alder adduct	Time (s)	Conversion[b] (%)	Yield[c] (%)	*endo*/*exo*[d]
1	**2**	**a**	**2a**	50	94	90	93:4
2	**2**	**b**	**2b**	50	92	87	8:1
3	**2**	**c**	**2c**	50	92	84	*endo* only
4	**2**	**e**	**2e**	60	>99	97	7:2
5	**6**	**a**	**6a**	50	94	86	*endo-syn* only
6	**6**	**b**	**6b**	50	94	88	*endo-syn* only
7	**6**	**c**	**6c**	50	92	83	

[a] Reaction conditions: catalyst loading=3 mol%, [reactant]=0.1 M for entries 1–4; [reactant]=0.2 M for entries 5–7.
[b] Determined by ^{1}H NMR.
[c] Isolated yield.
[d] *endo*/*exo* selectivities were estimated by ^{1}H NMR spectroscopy.

systems in the first 6 s, and the power was found to decrease gradually to zero at 30 s in $bmimPF_6$ and at 48 s in water to prevent the temperature from rising over 50 °C. This is consistent with the results obtained from both Tables 3 and 4.

In conclusion, we have synthesized a water-soluble organotungsten Lewis acid catalyst, $[O{=}P(2\text{-py})_3W(CO)(NO)_2](BF_4)_2$ and have demonstrated a highly effective methodology for the construction of 6-membered ring systems via the combined effects of the Lewis acid catalyst in water or in $bmimPF_6$ under controlled microwave irradiation. The ionic liquid $bmimPF_6$ acts as a powerful reaction media not only for rate acceleration and chemoselectivity enhancement but also for facilitating catalyst recycling in the $[O{=}P(2\text{-py})_3W(CO)(NO)_2](BF_4)_2$-catalyzed Diels–Alder reaction systems. Therefore, this novel methodology involving the use of catalysts, ionic liquids, and microwave radiation is expected to have significant impact in organic synthesis via Diels–Alder reactions that relied on conventional homogeneous catalysts. Further applications of this methodology to other catalytic reactions are under investigations.

3. Experimental

3.1. General method

$O{=}P(2\text{-py})_3$ were synthesized by the oxidation of $P(2\text{-py})_3$[20] with 30% H_2O_2 in acetone. 1-Butyl-3-methylimidazolium hexafluorophosphate ($bmimPF_6$) was synthesized by modification of a reported procedure.[16] All cycloaddition products have previously been characterized, and the data obtained corresponded satisfactorily with the reported NMR data, and comparison with authentic samples.

3.1.1. Synthesis of $O{=}P(2\text{-py})_3W(CO)_3$ via microwave process. To a solution of 25 mL CH_3CN in Teflon container, $W(CO)_6$ (300 mg, 0.85 mmol) and $O{=}P(2\text{-py})_3$ (239 mg, 0.85 mmol) were added. The container was sealed in the acid digestion vessel and placed into microwave (a CEM MARS 5™). The microwave was programmed to give a maximum internal temperature of 190 °C, the reaction mixture was irradiated at 100% of 300 W power for 7 min. All volatiles were removed at room temperature and the crude was dried in vacuo to afford $O{=}P(2\text{-py})_3W(CO)_3$ (468 mg, 100% yield).

Table 4. $[O{=}P(2\text{-py})_3W(CO)(NO)_2](BF_4)_2$-catalyzed Diels–Alder reactions in $bmimPF_6$ under microwave irradiation[a]

Entry	Diene	Dienophile	Diels–Alder adduct	Time (s)	Conversion[b] (%)	Yield[c] (%)	*endo*/*exo*[d]
1	**2**	**a**	**2a**	25	95	92	8:1
2	**2**	**b**	**2b**	25	89	85	8:1
3	**2**	**c**	**2c**	30	95	81	*endo* only
4	**2**	**d**	**2d**	30	92	90	*endo* only
5	**2**	**e**	**2e**	60	>99	96	4:1
6	**3**	**a**	**3a**	25	95	90	6:1
7	**3**	**b**	**3b**	25	82	77	6:1
8	**3**	**c**	**3c**	30	95	80	*endo* only
9	**3**	**d**	**3d**	30	93	90	*endo* only
10	**4**	**a**	**4a**	30	81	80	
11	**4**	**b**	**4b**	30	93	88	
12	**4**	**c**	**4c**	30	92	80	
13	**4**	**d**	**4d**	30	91	86	
14	**5**	**a**	**5a**	35	86	83	
15	**5**	**b**	**5b**	35	90	88	
16	**5**	**c**	**5c**	40	84	75	
17	**6**	**a**	**6a**	25	82	75	*endo-syn* only
18	**6**	**b**	**6b**	25	82	78	*endo-syn* only
19[e]	**6**	**c**	**6c**	25	81	78	
20[f]	**6**	**d**	**6d**	25	81	71	*endo-syn* only

[a] Reaction conditions: catalyst loading=3 mol%, [reactant]=1.0 M for entries 10–16; [reactant]=0.67 M for other entries.
[b] Determined by ^{1}H NMR.
[c] Isolated yield.
[d] *endo*/*exo* selectivities were estimated by ^{1}H NMR spectroscopy.
[e] The yields for the aromatized product **6c**.
[f] Compound **6d** was the derivatized product.

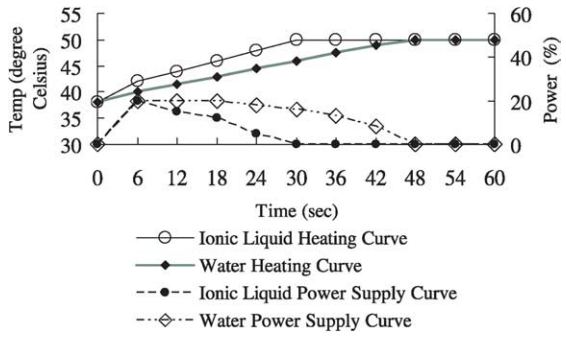


Figure 3. Upper curves: heating profiles for microwave-heated (○) $bmimPF_6$ and (♦) H_2O. Lower curves: power supply profiles for (●) $bmimPF_6$ and (◇) H_2O. Experiments were conducted in a sealed process vial containing 1.5 mL of $bmimPF_6$ or 5 mL of H_2O.

3.1.2. Synthesis of $[O{=}P(2\text{-py})_3W(CO)(NO)_2](BF_4)_2$ (1). A CH_3NO_2 suspension of $NOBF_4$ (43 mg, 0.36 mmol in 3 mL) was cooled to 0 °C before adding $O{=}P(2\text{-py})_3$ $W(CO)_3$ (100 mg, 0.18 mmol). The mixture was stirred at 0 °C for 20 min before filtration. 20 mL of CH_2Cl_2 was transferred into the filtrate, and the mixture was allowed to sit at 0 °C for 0.5 h to give green crystalline solids. The crude was washed with CH_2Cl_2 (3×5 mL) and dried in vacuo (94 mg, 71% yield). ^{1}H NMR (400 MHz, CD_3NO_2): $\delta=9.41$ (3H, m), 8.78 (3H, m), 8.63 (3H, m), 8.09 (3H, m). ^{13}C NMR (100 MHz, CD_3NO_2): $\delta=190.5$ (CO). ^{31}P NMR (160 MHz, CD_3NO_2): $\delta=7.2$. IR (CaF_2): $\nu_{CO}=2156$, $\nu_{NO}=1852$, 1763 cm^{-1}. Anal. Calcd for $C_{16}H_{12}B_2F_8N_5O_4PW$: C, 26.44; H, 1.66; N, 9.64. Found: C, 26.74; H, 1.70; N, 9.85%.

3.1.3. Representative procedure for the 1-catalyzed Diels–Alder reaction in water. Cat. **1** (22 mg, 0.03 mmol) was dissolved in water (5 mL). A mixture of **6** (100 μL, 1.0 mmol) and **a** (80 μL, 1.0 mmol) was transferred into the solution. The solution was stirred at room temperature and monitored by ^{1}H NMR. When the ^{1}H NMR data showed the reaction to be completed (a total disappearance of reactants' signals), the mixture was extracted with ether (3×15 mL). $MgSO_4$ was added to the extract for dehydration. The crude was purified by flash chromatography on SiO_2 using hexane/ether (10:1) as eluent to give **6a** (139 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.99$ (2H, m), 4.05 (1H, m), 3.30 (3H, s), 2.46 (1H, m), 2.22 (1H, m), 2.18 (3H, s), 1.91 (1H, m), 1.83 (2H, m), ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=208.96$, 132.97, 124.27, 72.59, 56.30, 52.27, 28.01, 25.15, 18.35.; MS (EI) *m/e*: 154, 153, 139, 122, 107, 84, 79, 78, 43, 42; M^+/e calcd: 154.0994, found: 154.0992. IR (CaF_2): 3206, 2934, 1713, 1650 cm^{-1}.

3.1.4. Representative procedure for the 1-catalyzed Diels–Alder reaction in $bmimPF_6$. Cat. **1** (22 mg, 0.03 mmol) was dissolved in $bmimPF_6$ (1.5 mL). A mixture of **6** (100 μL, 1.0 mmol) and **a** (80 μL, 1.0 mmol) was transferred into this ionic solution. The mixture was stirred at room temperature and monitored by ^{1}H NMR. The resulting mixture was extracted with ether (3×10 mL). $MgSO_4$ was added to the extract, and the mixture was stirred and allowed to sit for 30 min. Trace amount of ionic solids containing $bmim^+$, SO_4^{2-}, Mg^{2+}, and PF_6^- were filtered off, and the filtrate was dried and purified by flash chromatography on SiO_2 using hexane/ether (10:1) as eluent to give **6a** (128 mg, 78% yield).

3.1.5. Representative procedure for the 1-catalyzed Diels–Alder reaction in water under controlled microwave irradiation. A 10 mL sealed microwave process vial containing an aqueous solution of **1** (22 mg, 0.03 mmol, in 5 mL of H_2O) was added compounds **6** (100 μL, 1.0 mmol) and **a** (80 μL, 1.0 mmol). The mixture was subjected for microwave heating (20% of 300 W maximum power, 50 °C preselected maximum temperature). The process was monitored by ^{1}H NMR. When the reaction showed >90% completion, the mixture was extracted with ether (3× 10 mL). $MgSO_4$ was added to the extract for dehydration. The crude was purified by flash chromatography on SiO_2 using hexane/ether (10:1) as eluent to give **6a** (132 mg, 86% yield).

3.1.6. Representative procedure for the 1-catalyzed Diels–Alder reaction in $bmimPF_6$ under controlled microwave irradiation. A 5 mL sealed microwave process vial containing $bmimPF_6$ solution of **1** (22 mg, 0.03 mmol, in 1.5 mL of $bmimPF_6$) was added compounds **6** (100 μL, 1.0 mmol) and **a** (80 μL, 1.0 mmol). The mixture was subjected for microwave heating (20% of 300 W maximum power, 50 °C preselected maximum temperature). The process was monitored by ^{1}H NMR. When the reaction showed >90% completion, the mixture was extracted with ether (3×10 mL), and $MgSO_4$ was added to the extract. The mixture was stirred and allowed to sit for 30 min. The ionic solids containing $bmim^+$, SO_4^{2-}, Mg^{2+}, and PF_6^- were filtered off. The filtrate was purified by flash chromatography on SiO_2 using hexane/ether (10:1) to give **6a** (116 mg, 75% yield).

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References and notes

1. For recent reviews, see: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (c) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (d) Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996**, *25*, 209. (e) Mehta, G.; Uma, R. *Acc. Chem. Res.* **2000**, *33*, 278. (f) Kumar, A. *Chem. Rev.* **2001**, *101*, 1.
2. (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Breslow, R.; Maitra, U.; Rideout, D. C. *Tetrahedron Lett.* **1983**, *24*, 1901. (c) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239. (d) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5613. (e) Breslow, R.; Rizzo, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4340. (f) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (g) Breslow, R.; Zhu, Z. N. *J. Am. Chem. Soc.* **1995**, *117*, 9923. (h) Breslow, R. In *Water as Solvent for Chemical Reactions*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: Oxford, 1998.
3. (a) Grieco, P. A. *Organic Synthesis in Water*; Blackie: London, 1998, and references therein. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (c)

Garner, P. P. *Diels–Alder Reactions in Aqueous Media*, Chapter 1, in Ref. 4b.

4. (a) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785. (b) Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097. (c) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793. (d) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, *1*, 23. (e) Lee, C. W. *Tetrahedron Lett.* **1999**, *40*, 2461. (f) Welton, T. *Chem. Rev.* **1999**, *99*, 2071.
5. (a) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, *113*, 4241. (b) Blokzijl, W.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1992**, *114*, 5440. (c) Blokzijl, W.; Engberts, J. B. F. N. In *Structure and Reactivity in Aqueous Solution*; Cremer, C. J., Truhlar, D. G., Eds.; ACS Symposium Series No. 568; American Chemical Society: Washington, DC, 1994; Chapter 21, pp 303–317. (d) Otto, S.; Blokzijl, W.; Engberts, J. B. F. N. *J. Org. Chem.* **1994**, *59*, 5372. (e) Engberts, J. B. F. N. *Pure Appl. Chem.* **1995**, *67*, 823. (f) Loh, T.-P.; Pei, J.; Lin, M. *Chem. Commun.* **1996**, 2315. (g) Otto, S.; Bertoncin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1996**, *118*, 7702. (h) Wijnen, J. W.; Zavarise, S.; Engberts, J. B. F. N.; Charton, M. *J. Org. Chem.* **2001**, *1996*, 61. (i) Otto, S.; Boccaletti, G.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238. (j) Otto, S.; Engberts, J. B. F. N.; Kwak, J. C. T. *J. Am. Chem. Soc.* **1998**, *120*, 9517. (k) van Mersbergen, D.; Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8801. (l) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 6798. (m) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365–1372. (n) Rispens, T.; Engberts, J. B. F. N. *Org. Lett.* **2001**, *3*, 941.
6. (a) Ludley, P.; Karodia, N. *Tetrahedron Lett.* **2001**, *42*, 2011. (b) Song, C. E.; Shim, W. H.; Roh, E. J.; Lee, S.; Choi, J. H. *Chem. Commun.* **2001**, 1122. (c) Dzyuba, S. V.; Bartsch, R. A. *Tetrahedron Lett.* **2002**, *43*, 4657. (d) Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Green Chem.* **2002**, *4*, 24. (e) Aggarwal, A.; Lancaster, N. L.; Sethi, A. R.; Welton, T. *Green Chem.* **2002**, *4*, 517.
7. Mingos, D. M. P.; Whittaker, A. G. Microwave dielectric heating effects in chemical synthesis. In *Chemistry under Extreme or non Classical Conditions*; van Eldik, R., Hubbard, C. D., Eds.; Wiley: New York, 1997; pp 479–545.
8. (a) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213. (b) Gedye, R. N.; Wei, J. B. *Can. J. Chem.* **1998**, *76*, 525. (c) Langa, F.; de la Cruz, P.; de la Hoz, A.; Dìaz-Ortiz, A.; Dìez-Barra, E. *Contemp. Org. Synth.* **1997**, *4*, 373. (d) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213. (e) Strauss, C. R. *Aust. J. Chem.* **1999**, *52*, 83. (f) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (g) Varma, R. S. *Green Chem.* **1999**, 43. (h) Varma, R. S. *Clean Prod. Process.* **1999**, *1*, 132. (i) Abramovic, R. A. *Org. Prep. Proc. Int.* **1991**, *23*, 685. (j) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1. (k) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665. (l) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (m) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717. (n) Corsaro, A.; Chiacchio, U.; Venerando Pistarà1, V.; Romeo, G. *Curr. Org. Chem.* **2004**, *8*, 511.
9. For microwave assisted Diels–Alder reactions, see: (a) Dell, C. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873. (b) Tietze, L. F.; Kettschau, G. Hetero Diels–Alder Reactions in Organic Chemistry In *Topics in Current Chemistry*, *Vol. 190,* 1998; pp 1–121. (c) de la Hoz, A.; Díaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659.
10. For microwave in organic synthesis, see: (a) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2003. (b) *Microwave-Enhanced Chemistry: Fundamental, Sample Preparation, and Applications*; Kingston, H. M., Haswell, S. J., Eds.; American Chemical Society: Washington, DC, 1997.
11. (a) Varma, R. S.; Namboodiri, V. V. *Chem. Commun.* **2001**, 643. (b) Leadbeater, N. E.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145. (c) Mayo, K. G.; Nearhoof, E. H.; Kiddle, J. J. *Org. Lett.* **2002**, *4*, 1567. (d) Vallin, K. S. A.; Emilsson, P.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6243.
12. (a) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Jiménez, J. L.; Palacios, J. C.; Sánchez, J. B. *J. Org. Chem.* **1999**, *64*, 6297. (b) Van der Eycken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dallinger, D.; Kappe, C. O. *J. Org. Chem.* **2002**, *67*, 7904. (c) Kaval, N.; Van der Eycken, J.; Caroen, J.; Wim Dehaen, W.; Strohmeier, G. A.; Kappe, C. O.; Van der Eycken, E. *J. Comb. Chem.* **2003**, *5*, 560.
13. The complexation of crotonaldehyde to a Lewis acid provides a downfield shift of the H atom at C-3 position in the ^{1}H NMR spectrum and this correlation has been used to compare the relative acid strength of various Lewis acids. For details, see: (a) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801. (b) Bonnesen, P. V.; Puckett, C. L.; Honeychuck, R. V.; Hersh, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 6070.
14. For similar aromatization reaction, see: Potman, R. P.; van Kleef, F. J.; Scheeren, H. W. *J. Org. Chem.* **1985**, *50*, 1955.
15. The instability of hexafluorophosphate containing ionic liquids towards hydrolysis in contact with moisture at high temperature has been noted in a number of papers. For details, see: (a) Van Wazer, J. R. In *Phosphorous and its Compounds*, Wiley: New York, 1958; Vol. 1. (b) Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Griffin, S. T.; Rogers, R. D. *Ind. Eng. Chem. Res.* **2000**, *39*, 3596. (c) Lall, S. I.; Mancheno, D.; Castro, S.; Behaj, V.; Cohen, J. I.; Engel, R. *Chem. Commun.* **2000**, 2413. (d) Huddleston, J. G.; Visser, A. E.; Reichert, W. M.; Willauer, H. D.; Broker, G. A.; Rogers, R. D. *Green Chem.* **2001**, *3*, 156. (e) Gubicza, L.; Nemestóthy, N.; Fráter, T.; Bélafi-Bakó, J. *Green Chem.* **2003**, *5*, 236. (f) Swatloski, R. P.; Holbrey, J. D.; Rogers, R. D. *Green Chem.* **2003**, *5*, 361.
16. (a) Bonhote, P.; Dias, A.-P.; Papageorgio, N.; Kalyanasundaram, K.; Gratzel, M. *Inorg. Chem.* **1996**, *35*, 1168. (b) Seddon, K. R.; Gordon, M. C.; Holbrey, J. D.; Kennedy, A. R. *J. Mater. Chem.* **1998**, *8*, 2627. (c) Headley, A. D.; Jackson, N. M. *J. Phys. Org. Chem.* **2002**, *15*, 52.
17. Carmichael, A. J.; Seddon, K. R. *J. Phys. Org. Chem.* **2000**, *13*, 591.
18. (a) Chauvin, Y.; Olivier-Bourbigou, H. *CHEMTECH* **1995**, *25*, 26. (b) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772.
19. The conversions for 1–10 run in the recycling experiments in bmimPF_6 were 97, 97, 95, 95, 95, 91, 90, 87, 86, and 83%. The conversions for 1–6 run in water were 96, 93, 89, 85, 81, and 77%.
20. (a) Davies, W. C.; Mann, F. G. *J. Chem. Soc.* **1944**, 276. (b) Mann, F. G.; Watson, J. *J. Org. Chem.* **1948**, *13*, 502. (c) Kurtev, K.; Ribola, D.; Jones, R. A.; Cole-Hamilton, D. J.; Wilkinson, G. *J. Chem. Soc. Dalton. Trans.* **1980**, 55.

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Design and synthesis of an aminobenzo-15-crown-5-labeled estradiol tethered with disulfide linkage

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Abstract—A novel measuring method (electroimmunoassay) of 17β-estradiol (E_2) in urine or blood was proposed on the basis of a competition between E_2 and a labeled E_2 against an immobilizing antibody. To evaluate the principle, 3-{4-[17β-hydroxy-1,3,5(10)-estratrien-3-yloxy]butyldisulfanyl}-*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclopentadecen-2-yl) succinamic acid (**1**) was designed and synthesized as a novel aminobenzo-15-crown-5-containing E_2 tethered with disulfide linkage. Two thiol-intermediates **5b** and **19c** were efficiently synthesized from mercaptosuccinic acid **7** and 4,4′-dithiodibutyric acid **12**, respectively. Formations of disulfide linkages from less reactive thiols were examined and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) could be employed for the formation of an unsymmetrical disulfide **20c** from **5b** and **19c**. Then, removal of TMS- and allyl-protecting groups in **20c** successfully afforded the crown ether-containing E_2 **1**.

1. Introduction

Estrogens are the hormones mainly responsible for the growth of girls into sexually-mature women, in which 17β-estradiol (E_2) is the most abundant and potent.[1,2] In menopausal women, a decline in estrogen production results in discomforts (e.g., hot flashes), changes in the metabolic pathways of several organs, and the loss of essential bone minerals leading to osteoporosis.[3] Estrogen also plays an important role in the maintenance of healthy blood-vessels and blood-lipid profiles.[4]

The E_2 level varies throughout the menstrual cycle and on a day-to-day basis.[5] After about 2 weeks from the first day of menses, the E_2 level eventually reaches a peak and a sudden surge in the production of luteinizing hormone (LH surge) occurs, both of which trigger ovulation.[6]

Nowadays, women with problems related to pregnancy and abortion constitute a major number of gynecological patients.[7] Therefore, it is very important that the woman herself knows her menstrual cycles, menstruation days and ovulation days. Estrogen tests may be also done to aid in the diagnosis of many metabolic conditions. If a compact and personal E_2 sensor, by which the E_2 level can be easily and accurately monitored in the blood and urine, can be developed, it would be helpful for many women to maintain the health or to detect of medical problems in the early stage.

We are now engaged in developing a novel measuring method of E_2 in urine or blood (termed as electro-immunoassay) in collaboration with a certain electric company. The principle of the assay and an equipment of the E_2 sensor are shown in Figure 1. The assay is a solid phase-electroimmunoassay, based on competition between E_2 and a labeled E_2 against an immobilizing antibody. The principle of the assay is assumed as follows [the following headings (1)–(6) correspond to those of Figure 1]: (1) anti-E_2 antibody is coated to a solid phase (agarose bead, etc.) to form an immobilizing antibody (**a**), (2) next, labeled E_2 molecule (**b**) is bound to **a**, giving a complex **X**, (3) then, an electrode (**c**) is inserted into the complex **X** filled in a pipe of the equipment [**Y**], and a working electrode (**d**) covered with hydrophobic molecular film (insulating film) is placed close to the counter-electrode (**c**), (4) when the tip of the pipe is dipped in urine, a cross reaction occurs between urinary E_2 and the labeled E_2 (**b**), (5) the liberated **b** is absorbed to the hydrophobic film on the surface of the working electrode **d**, and electric conduction is simultaneously caused between the two electrodes, (6) the concentration of E_2 in the urine is measured by an alternating current (AC) resistance.

4′-Aminobenzo-15-crown-5 (**2**)[8] may be first adopted as a

Keywords: 17β-Estradiol; Labeled estradiol; 4′-Aminobenzo-15-crown-5; Unsymmetrical disulfides; 4-Phenyl-1,2,4-triazoline-3,5-dione.
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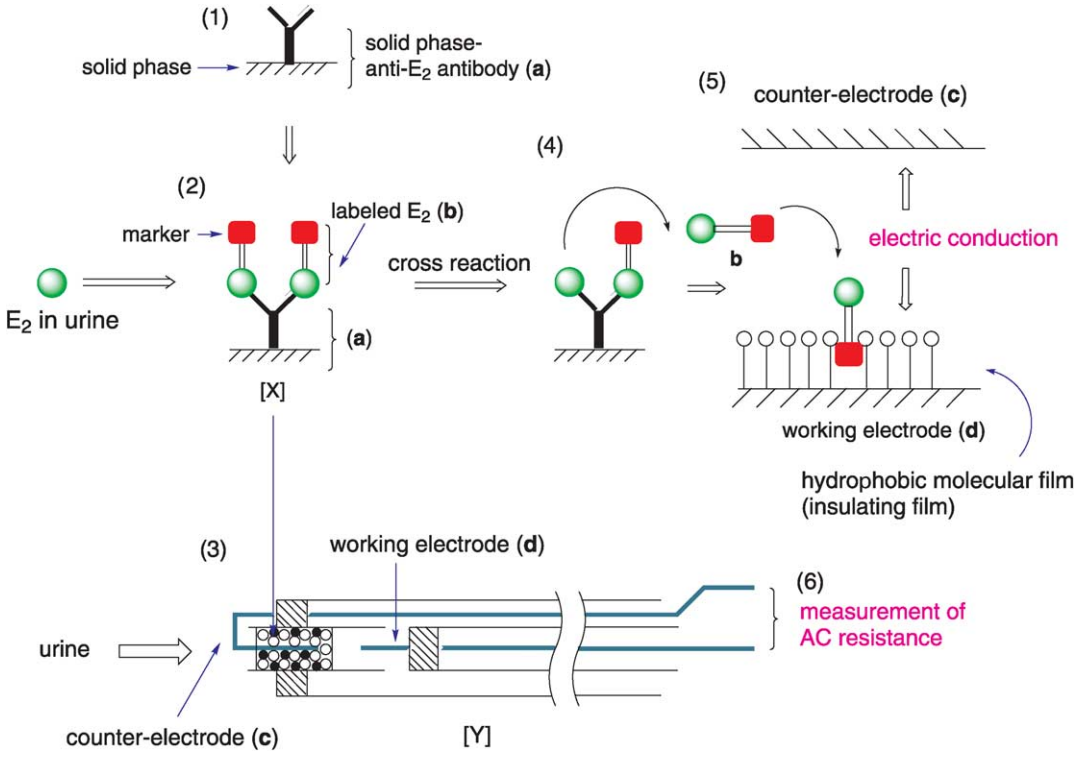


Figure 1. Principle of the electroimmunoassay.

marker in Figure 1. As the relationship between the concentration of **2** and electrode-response could be formulated, the concentration of **2** could be quantitatively calculated from the numerical value arising from the electrode-response.[9] Anti-E_2-glucuronide antibody (FKA-238™)[10] can be employed in this assay. Data of the cross reactivity of FKA-238 with many steroids apparently show that the sugar moiety of the E_2-glucuronide is not required as the antigen-recognition sites of FKA-238, as shown in Figure 2, while the phenolic moiety and steroid D ring containing secondary-OH are necessary.[11] Therefore, affinity of free E_2 having phenolic-OH against the antibody may be approximately equivalent to that of the E_2-glucuronide.

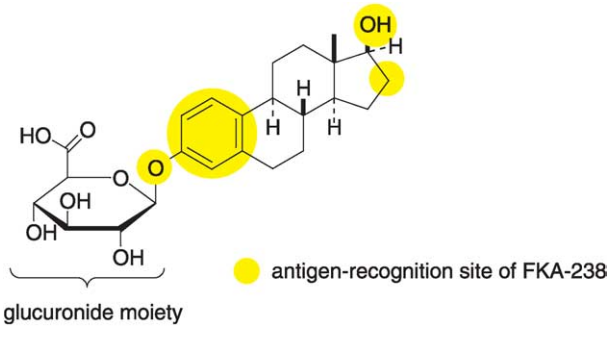


Figure 2. Antigen-recognition site of anti-E_2-glucuronide (FKA-238).

We thus needed a labeled antigen **b** to evaluate the principle in Figure 1. On the basis of the structural requirements described above, we designed a candidate in which the aromatic-NH_2 of **2** was attached through a spacer group to the phenolic-OH of E_2 (Fig. 3). Introduction of sodium carboxylate into the spacer might make the molecule water-soluble. Further, the solubility in water would be increased by trapping of the sodium cation into the benzo-15-crown-5 (BC) residue. Herein, we describe the synthesis of a crown ether-containing E_2 **1** tethered with a disulfide linkage, which may be formed by oxidative coupling of two thiol units. In this synthetic study, we found that 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) can employed for formation of unsymmetrical disulfides from two less reactive thiols.

2. Results and discussion

2.1. Synthesis of unsymmetrical disulfides

We first aimed at a synthesis of carboxylic acid **4**, in which the phenolic-OH was linked to an ester bond in the bridged structure (Fig. 4). A crucial disulfide bond formation was investigated in this synthetic study. Thiols **5** containing a crown ether were synthesized from mercaptosuccinic acid **7**[8], as shown in Scheme 1. Oxidation of **7** with alkaline hydrogen peroxide followed by treatment of Ac_2O[12] afforded 2,2′-dithiodisuccinic anhydride **9** as a viscous brown oil. Reaction of the crude **9** with 4′-amino BC ether **2**[8] resulted in a disuccinamic acid **10** with a disulfide linkage.[13] Treatment of **10** with trimethylsilyldiazomethane[14] gave a dimethyl disuccinamate **11a** in 81% overall yield from the starting **7**. The following reduction of **11a** did not proceed under mild reducing conditions such as H_2/Pd-black/MeOH,[15] Ph_3P/H_2O–dioxane,[16] Mg/THF–MeOH,[17] or Zn/AcOH,[18] while the use of activated zinc in a mixture of THF and saturated aqueous ammonium chloride[19] under reflux successfully afforded a thiol-intermediate **5a** in 76% yield. Further, diallyl disuccinamate

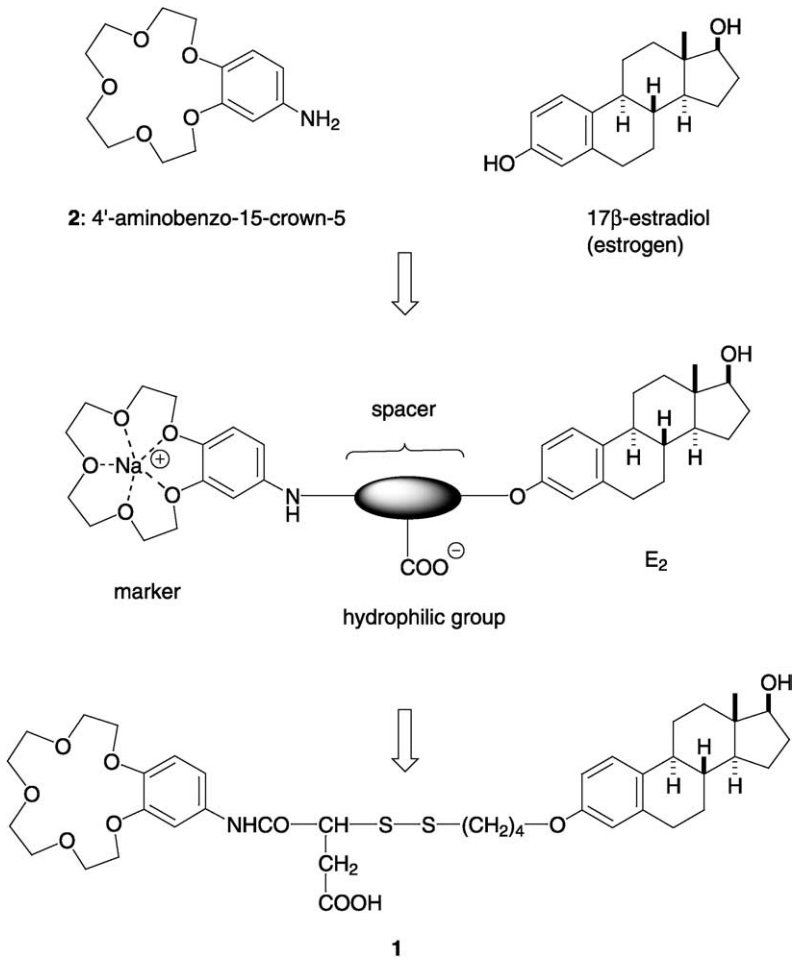


Figure 3. Design of a crown ether-labeled estradiol soluble in water.

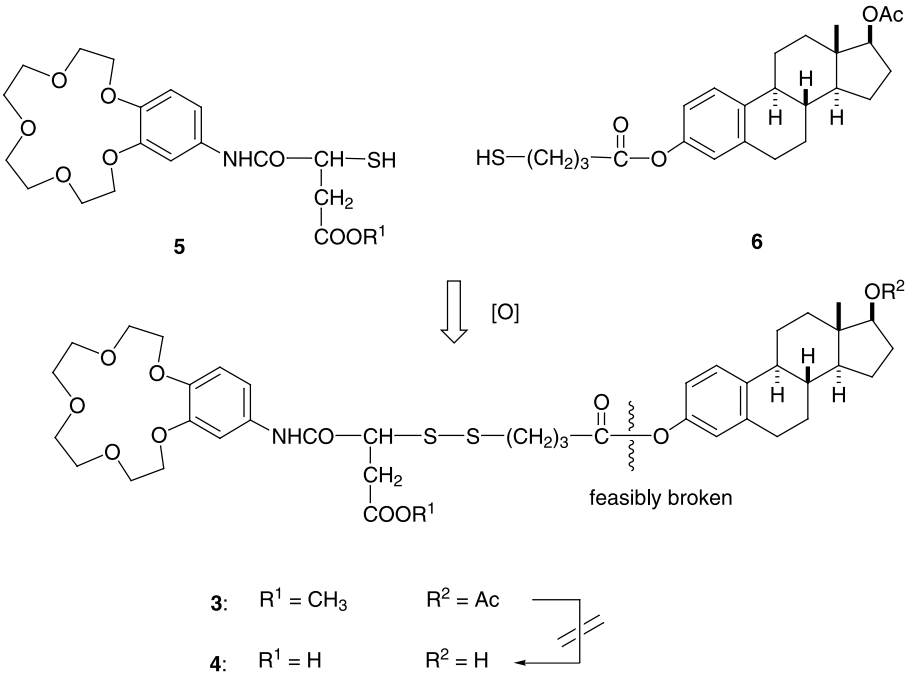
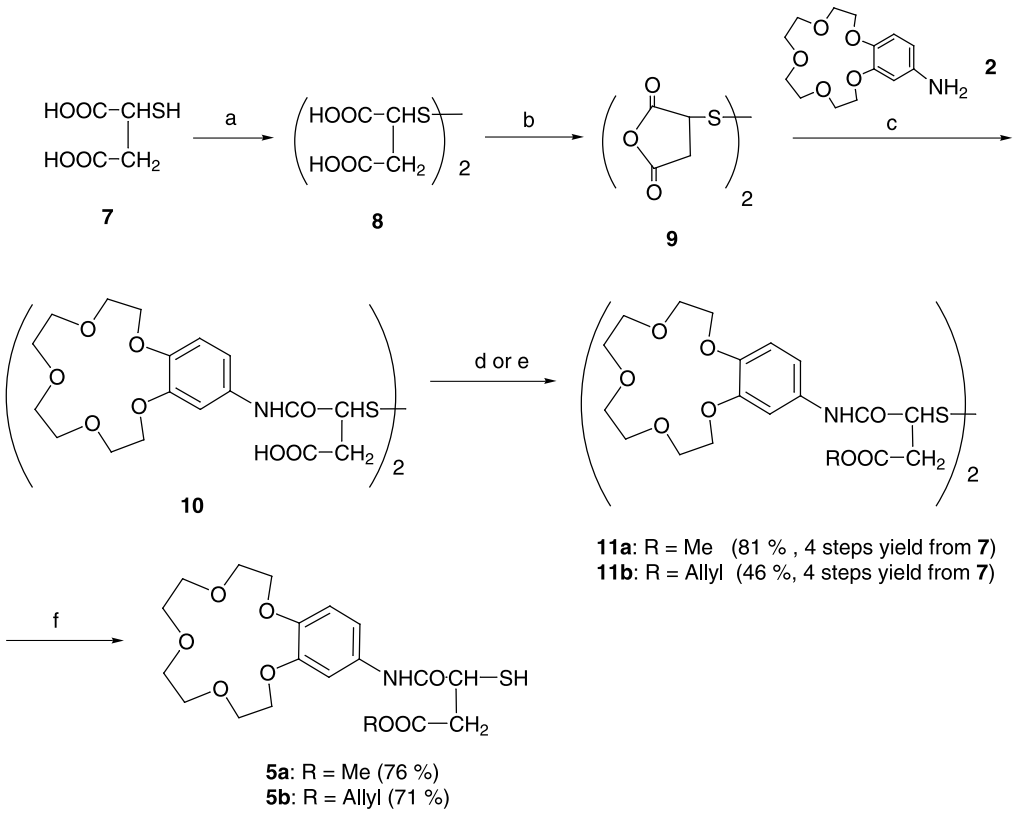


Figure 4. Retrosynthesis of carboxylic acid **4** tethered with an ester bond.

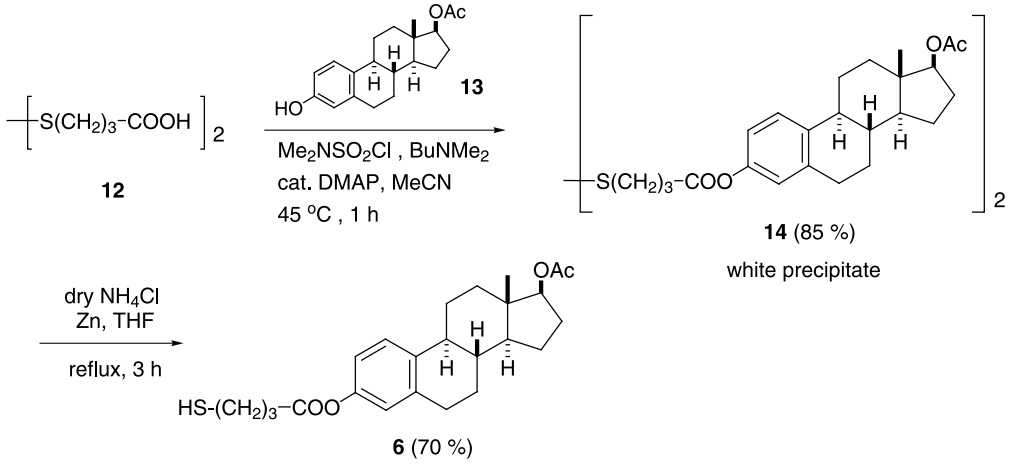


Scheme 1. Reagents and conditions: (a) 8 N NaOH, 30%H_2O_2, rt, 2 h; (b) Ac_2O, 60 °C, 3 h; (c) **2**, MeCN, 50 °C, 2 h; (d) for **11a**: $TMSCHN_2$, THF, MeOH, rt, 10 min; (e) for **11b**: allyl alcohol, WSC, DMAP, THF, rt, 3 h; (f) satd aqueous NH_4Cl, Zn, THF, reflux, 16 h (for **5a**), 24 h (for **5b**).

11b, mentioned in the next section was synthesized by esterification of **10** with allyl alcohol in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC)/cat. DMAP in 46% overall yield from **7**.[20] Disulfide **11b** was similarly converted into a thiol **5b** (71%).

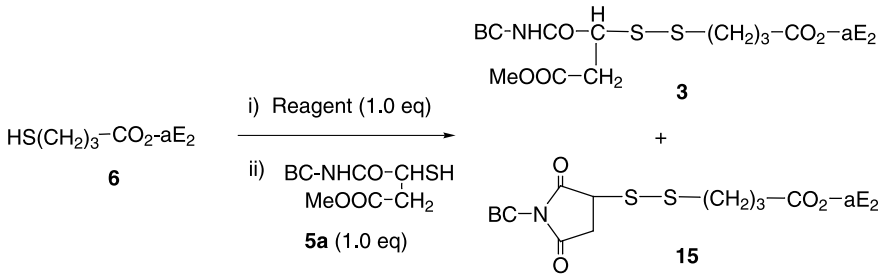
Another steroidal thiol **6** was synthesized from 4,4′-dithiodibutyric acid **12**[8] (Scheme 2). Treatment of a mixture of **12** and β-estradiol-17 acetate **13**[8] with DCC afforded only a small amount of 4-dithiodibutanoate **14**. Since Tanabe et al. recently reported use of dimethylsulfamoyl chloride and N,N-dimethylamine for esterification and amidation,[21] we applied it to the synthesis of **14**. The new reagent system gave **14** in 85% yield. The reduction of **14** was carried out by the previous zinc-aqueous ammmonium chloride, but afforded thiol **6** in only 46% yield with recovery of estadiolacetate **13**. On the other hand, use of dried ammonium chloride increased the yield of **6** to 70%.

Unsymmetrical disulfides can be prepared by the reaction of sulfenyl derivatives with thiols.[22a,b] In the case of the Mukaiyama method,[22c] reaction of a thiol RSH with diethyl azodicarboxylate (DEAD) gives an N-alkanesulfenyl-hydrazodicarboxylate, to which another thiol R'SH is then added, producing the disulfide RSSR'. Oxidative coupling of the two different thiols **5a** and **6** using DEAD afforded an



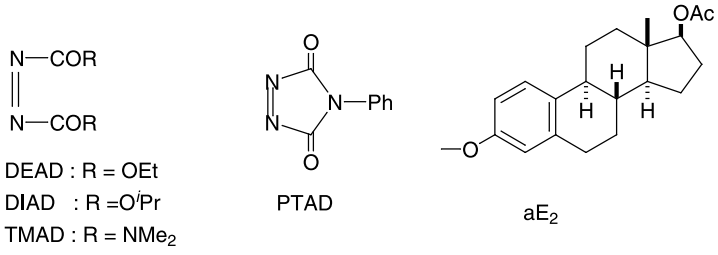
Scheme 2.

Table 1. Synthesis of unsymmetrical disulfide **3**



Entry	Reaction conditions (h)		Product (%)	
	(i)	(ii)	**3**	**15**
1	DEAD, MeCN, rt, 1	Reflux, 5	15	—
2	DIAD, MeCN, rt, 1	Reflux, 17	10	—
3	TMAD, CH_2Cl_2, reflux, 1[a]	—	—	—
4	PTAD, MeCN, rt, 0.3	rt, 4	40	10

[a] TLC indicated no reaction



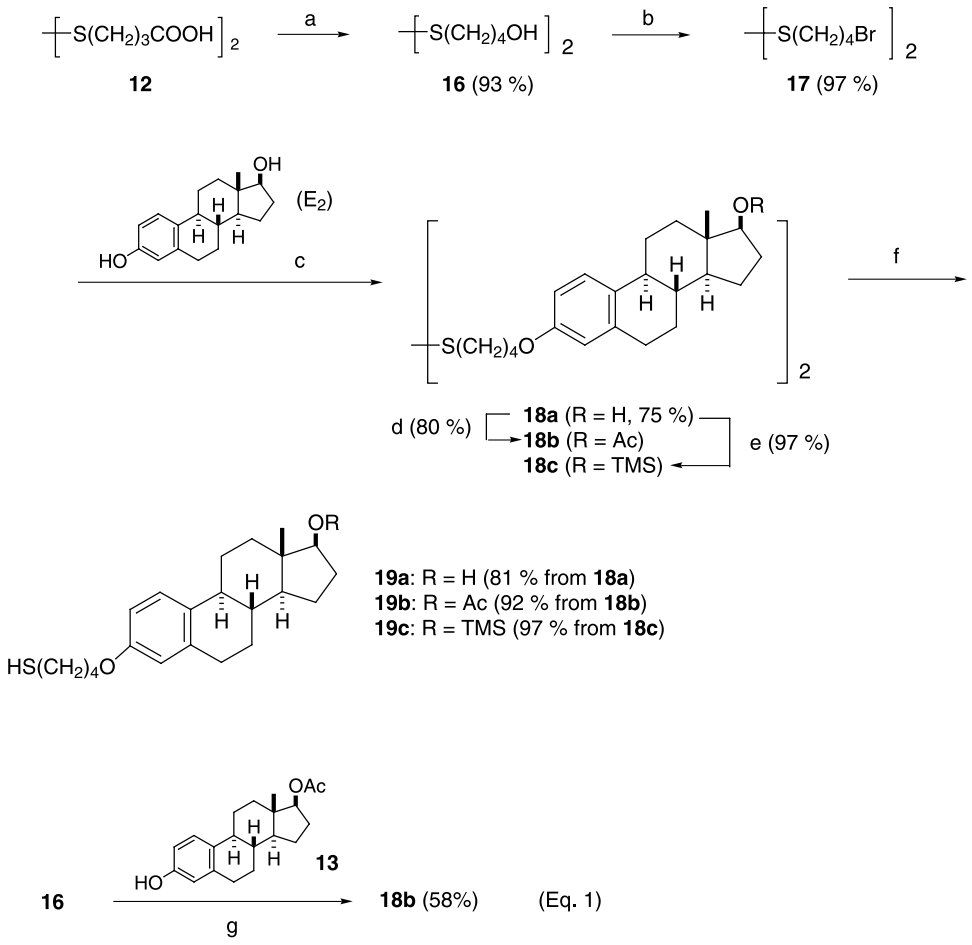
expected mixed-disulfide **3** in only 15% yield (Table 1, entry 1). Other similar oxidizing agents, diisopropyl azodicarboxylate (DIAD) or tetramethylazodicarboxamide (TMAD)[23] did not improve the reaction (entries 2 and 3). Evidently, the low yield is due to the lower reactivity of **5a** and **6**, because of small occupying of SH groups in the large molecules. These results suggested to us that 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD),[8,24] which is a powerful dienophile of Diels–Alder reaction,[25] might be able to effect the dehydrogenation of two structurally different thiols to disulfides. When thiol **6** was added to a characteristic red solution of PTAD (1.0 equiv) in dichloromethane at rt, the color faded to pale yellow (in ca 20 min), indicating the formation of an N-alkanesulfenyl 4-phenylurazole intermediate. Then, the secondary thiol **5a** (1.0 equiv) was added to the resulting solution and the whole was stirred at rt for 4 h. The expected disulfide **3** was obtained in an acceptable yield (40%), along with a succinimide **15** (10%) cyclized by internal elimination of methanol (entry 4). When the more nucleophilic primary thiol **6** was reversely added to an adduct formed from **5a** and PTAD, the yield of **3** was only 10%. While Pilipenko et al. only used PTAD as an oxidant for conversions of 2-mercaptopyridines into 2,2′-dipyridyl disulfides,[26] PTAD has not been done for the synthesis of unsymmetrical disulfides. This preliminary use of PTAD was further extended in the preparation of unsymmerical disulfides **20**, as described in the next section.

It was, however, found that the CO–O bond of the phenolic ester in **3** thus obtained was feasibly cleaved at the further removal steps of two protecting groups: an acetyl group at the steroid C-17 and a methyl group of the ester moiety (Fig. 4). Treatment of disulfide **3** with standard hydrolysis-conditions (aqueous methanolic 1 N NaOH or LiOH) easily led to the original E_2-17-acetate **13**. Therefore, we modified the target compound to carboxylic acid **1** connected to phenolic-OH of E_2 with a stable ether-bonding (Fig. 3).

2.2. Synthesis of an amino BC containing-E_2

The right-halves **19a–c** of **1** were synthesized, as shown in Scheme 3. Diborane-reduction[27] of **12**[8] (93%) followed by bromination[28] (97%) afforded a dibromide **17**. Williamson reaction of **17** with E_2 in the presence of K_2CO_3 resulted in a symmetrical disulfide **18a** (75%),[29] which was subsequently reduced to a mercaptoestratrien-17-ol **19a** (81%) by Zn-NH_4Cl. Alternatively, the C-17 hydroxy groups of **18a** were subjected to acetylation or trimethylsilylation to give acetate **18b** (80%) or TMS-ether **18c** (97%). Their zinc reductions also provided protected estradienylacetates **19b** (92%) and **19c** (97%), respectively. Although diacetate **18b** could be also obtained by Mitsunobu reaction[30] of diol **16** with E_2-acetate **13** in the presence of DEAD and Ph_3P in 58% yield (Scheme 3, Eq. 1), separation of **18b** from **13** remaining in the reaction mixture was tedious.

Oxidative couplings between the right-half thiols **19** with thiols **5** having a BC ether were performed using PTAD (Table 2). The coupling of **19a** (R^1=H) having a free hydroxy group with left-half thiol **5a** (R^2=Me) did not proceed, while the reaction of protected thiols **19b** (R^1=Ac) or **19c** (R^1=TMS) with **5a** supplied disulfides **20a** or **20b** in 50 or 62% yield, respectively (Table 2, entries 2 and 3). The formation of **20a** from **19b** was accompanied with a small amount of succinimide **21** as a byproduct (Scheme 4). The reaction of **19c** with allyl ester **5b** afforded disulfide **20c** in 41% yield.

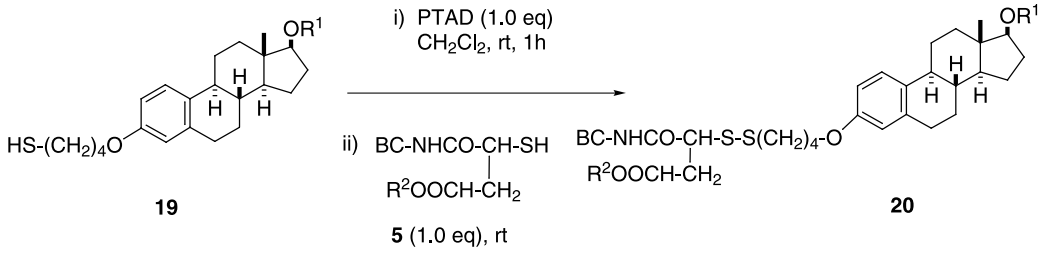


Scheme 3. (a) $BH_3 \cdot SMe_2$, THF, 0 °C, 0.5 h, then rt, 2.5 h; (b) CBr_4, Ph_3P, CH_2Cl_2, rt, 1 h; (c) E_2, K_2CO_3, acetone, reflux, 24 h; (d) Ac_2O, py, 100 °C, 1 h; (e) TMSCl, Et_3N, THF, rt, 16 h; (f) dry NH_4Cl, Zn, THF, reflux, 3.5 h (for **18a** and **18c**), 6 h (for **18b**); (g) **13**, DEAD, Ph_3P, CH_2Cl_2, 40 °C,16 h.

During this synthetic study, Arisawa and Yamaguchi[31a] reported an interesting formation of unsymmetrical disulfides using a novel exchange reaction of symmetrical disulfides catalyzed by a rhodium complex.[31a,b] However, the desired disulfides **20c** could not be obtained by the disulfide exchange reaction from the corresponding disulfides **11b** and **18c**.[31c]

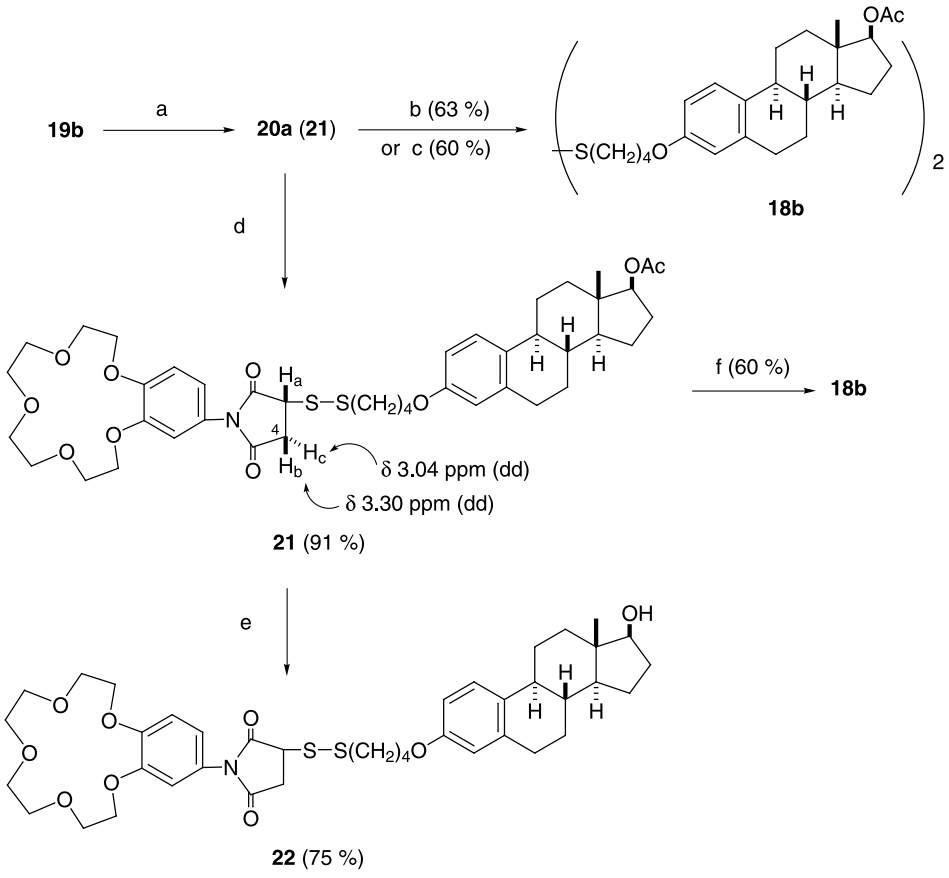
Next, removal of the protecting groups of disulfides **20a** (R^1=Ac and R^2=Me) was investigated. Hydrolysis of **20a** with aqueous 1 N LiOH–MeOH or aqueous 1 N $KHCO_3$–MeOH led to a symmetrical disulfide **18b** (Scheme 4), the formation of which indicated an easy cleavage of the S–S bond under alkaline conditions. Treatment of **20a** in the presence of cat. TsOH using a water separator afforded

Table 2. Synthesis of unsymmetrical disulfides **20**



Entry	19	R^1	5	R^2	Time (h)[a]	20	Yield (%)
1	**19a**	H	**5a**	Me	4	—	—[b]
2	**19b**	Ac	**5a**	Me	4	**20a**	50[c]
3	**19c**	TMS	**5a**	Me	20	**20b**	62
4	**19c**	TMS	**5b**	allyl	4	**20c**	41

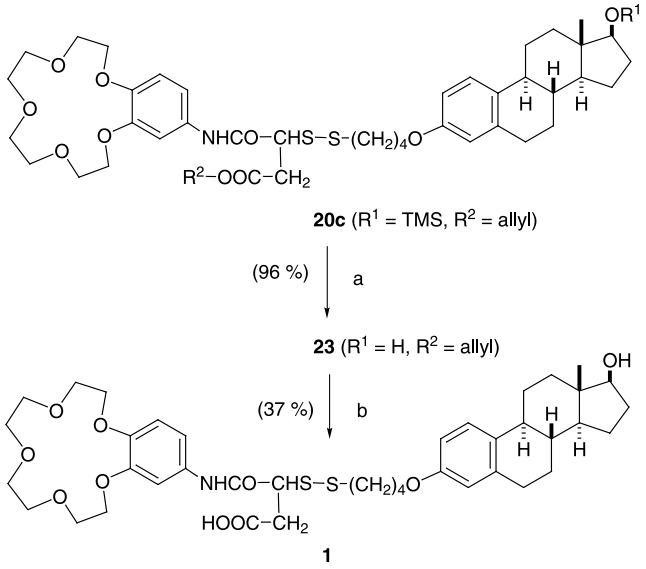
[a] Time of step (ii).
[b] The used thiols were recovered.
[c] Succinimide **21** was accompanied as byproduct.



Scheme 4. Reagent and conditions: (a) Table 2, entry 2; (b) 1 N $KHCO_3$, MeOH, rt; (c) 1 N LiOH, MeOH, rt; (d) cat. *p*-TsOH, benzene, reflux, 6 h, Dean–Stark water separator; (e) 1 N HCl, THF, reflux, 24 h; (f) 1 N NaOH, THF, rt.

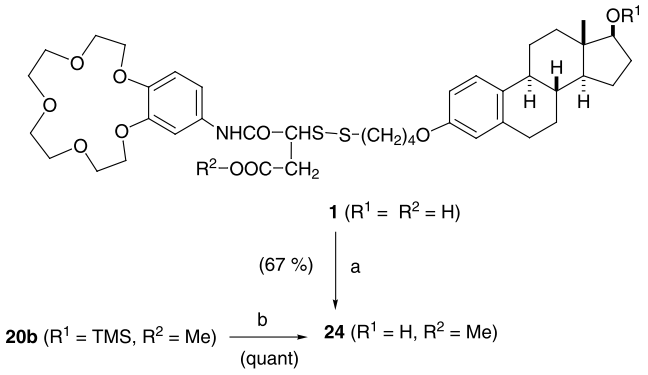
succinimide **21** (91%) which was identical with the compound contaminated during the formation of **20a** from **19b** (Table 2, entry 2). The ^{1}H NMR spectra of **21** exhibited characteristic C_4-methylene peaks (H_b, H_c) at 3.04 (dd) and 3.30 (dd) ppm, respectively, showing their coupling constants $^2J_{b-c}$ (18.8 Hz), $^3J_{b-a}$ (9.4 Hz), and $^3J_{c-a}$ (4.0 Hz), as shown in Scheme 4. Alkaline hydrolysis of **21** also brought about the formation of **18b**, while reflux of succinimide **21** in aqueous 1 N HCl produced only **22** with a free hydroxy group at steroid C-17, the succinimide ring and disulfide bond remaining intact.

From these results, we selected **20c** (Table 2, run 4) with TMS and allyl groups as suitable protecting groups which might enable removal of the protecting groups under neutral or acidic conditions (Scheme 5).[32] It is known that the cleavage of the allyl group is accomplished by palladium-catalyzed reaction with an allyl scavenger that attacks the allyl group, forming a π allyl palladium complex. Further, Nagakura et al.[33] recently reported that sulfinic acid or its salt in the presence of a catalytic amount of $Pd(PPh_3)_4$ was highly effective for facilitating the carbon–oxygen bond cleavage of allyl esters. After TMS removal of **20c** in methanolic citric acid (96%),[32] the final deallylation of the resulting allylic ester **23** provided a crude carboxylic acid **1** by treatment of **23** with sodium *p*-toluenesulfinate in the presence of catalytic amounts of $Pd(PPh_3)_4$ and PPh_3.[33] Purification of the crude product was not easy, but further efforts clarified that the succinamic acid **1** could be isolated by silica gel chromatography with a solvent system (H_2O:MeOH:$CHCl_3$ = 0.5:25:65) as a mixture of diastereomers (1:3, ^{13}C NMR analysis[34]) in 37% yield. When succinamic acid **1** thus obtained was added in saturated aqueous sodium bicarbonate, it dissolved with visual bubbling.[35] The structure of **1** was further confirmed by



Scheme 5. Reagents and conditinos: (a) citric acid, CH_2Cl_2, MeOH, rt, 1 h; (b) (i) $(Ph_3P)_4Pd$, Ph_3P, $TolSO_2Na$, THF, MeOH, rt, 16 h; (ii) SiO_2 chromatography, H_2O:MeOH:$CHCl_3$ (0.5:25:65).

conversion into a methyl ester **24** (67%), which was correlated to the previous disulfide **20b**, since desilylation of **20b** afforded **24** (Scheme 6).



Scheme 6. Reagents and conditions: (a) $TMSCHN_2$, THF, MeOH, rt, 0.5 h; (b) citric acid, CH_2Cl_2, MeOH, rt, 0.5 h.

3. Conclusion

In conclusion, we have described the design and synthesis of a novel BC-containing antigen **1** for the newly proposed measuring system of E_2 in urine and blood, as shown in Figure 1. The synthetic approach was briefly outlined in Figure 5, in which PTAD was effective for the formation of the unsymmetrical disulfide **20c** from less reactive thiols **5b** and **19c**, and TMS and allyl groups were selected as the protecting groups of **20c**. Further work on use of **1** in the electroimmunoassay is under way and will be published in due course.

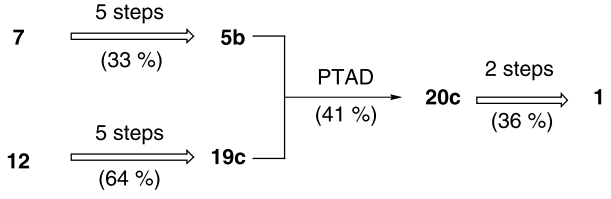


Figure 5. The outline of the present synthetic study.

4. Experimental

4.1. General methods

The melting points were determined on a hot-stage apparatus and were uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrometer. ^1H and ^{13}C NMR spectra were taken with tetramethylsilane as an internal standard on a Varian Gemini-200, Varian Mercury-300 and Varian UNITY INOVA-500 spectrometers. Reactions with air- and moisture-sensitive compounds were carried out under an argon atmosphere. Unless otherwise noted, all extracts were dried over Na_2SO_4, and the solvent was removed in a rotary evaporator under reduced pressure. Unless otherwise stated, Fuji Silysia FL-60D silica gel, Fuji Silysia BW-127ZH silica gel, and Merck $60F_{254}$ were used for flash column chromatography, column chromatography and thin-layer chromatography (TLC), respectively.

4.1.1. 2,2′-Dithiodisuccinic acid (8). To 8 N aqueous NaOH (18 ml) was added gradually mercaptosuccinic acid **7**[8] (10 g, 67 mmol) at 0 °C to avoid an exothermic reaction and then 30% H_2O_2 (5.2 ml) was added slowly to the solution at rt. The reaction mixture was stirred at rt for 2 h and subsequently acidified to pH 1 by addition of 20% aqueous H_2SO_4 (19 ml). The whole was extracted with Et_2O (×3) by salting-out techniques. The extract was dried and evaporated to give **8** (10 g, quant) as pale brown powders; ^1H NMR (DMSO-d_6) δ 2.69 (dd, J=11.6, 3.2 Hz, 2H), 2.83 (ddd, J=11.6, 6.4, 1.1 Hz, 2H), 3.75 (dt, J=6.4, 3.2 Hz, 2H), 12.4–13.0 (br, 1H); HRMS (SIMS) calcd for $C_8H_{11}O_8S_2$ [$(M+1)^+$] 298.9894, found 298.9891.

4.1.2. 2,2′-Dithiodisuccinic anhydride (9). Acetic anhydride (5 ml) was added to **8** (900 mg, 3.0 mmol), and the mixture was stirred at 60 °C for 3 h. Then, the acetic anhydride was evaporated using an aspirator in a hood, and the resulting residue was dissolved with EtOAc. The EtOAc solution was washed with H_2O, brine, dried, and evaporated to give a black oil **9** (791 mg, quant); IR (nujol) 1860, 1780, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.16 (ddd, J=19.8, 6.4, 2.1 Hz, 2H), 3.48 (dq, J=19.8, 4.9 Hz, 2H), 4.28–4.40 (m, 2H); HRMS (SIMS) calcd for $C_8H_7O_6S_2$ [$(M+1)^+$] 262.9683, found 262.9687.

4.1.3. 3,3′-Dithiobis[*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxa-benzocyclopentadecen-2-yl)] disuccinamic acid (10). To a solution of **9** (791 mg, 3.0 mmol) in acetonitrile (20 ml) was added slowly **2**[8] (1700 mg, 6.0 mmol) at 50 °C. The mixture was stirred at the same temperature for 2 h, and the solvent was evaporated to give a residue. The residue was washed twice with hot benzene (20 ml) by decantation. The collected benzene solutions were evaporated to give **10** (2490 mg, quant) as pale brown amorphous product; ^1H NMR (DMSO-d_6) δ 2.69–3.08 (m, 2H), 3.49–3.68 (m, 16H), 3.68–3.88 (m, 8H), 3.88–4.16 (m, 10H), 6.80–7.31 (m, 6H), 12.1–12.8 (br, 2H); HRMS (SIMS) calcd for $C_{36}H_{49}N_2O_{16}S_2$ [$(M+1)^+$] 829.2520, found 829.2529.

4.1.4. Dimethyl 3,3′-dithiobis[*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclopentadecen-2-yl)] disuccinamate (11a). To a solution of the disuccinamic acid (**10**, 300 mg, 0.36 mmol) in MeOH–THF (1:1, 4 ml) was added slowly 2.0 N hexane solution of $TMSCHN_2$ (0.36 ml, 0.72 mmol). After 10 min at rt, the solvent was evaporated to give a residue which was subsequently purified by column chromatography (MeOH:$CHCl_3$=1:20) to give **11a** (252 mg, 81%) as pale brown amorphous product; ^1H NMR ($CDCl_3$) δ 2.72–2.98 (m, 2H), 2.98–3.29 (m, 2H), 3.64–3.81 (m, 22H), 3.81–3.98 (m, 8H), 3.98–4.16 (m, 10H), 6.66–7.02 (m, 6H); HRMS (SIMS) calcd for $C_{38}H_{53}N_2O_{16}S_2$ [$(M+1)^+$] 857.2833, found 857.2836.

4.1.5. Diallyl 3,3′-dithiobis[*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclopentadecen-2-yl)] disuccinamate (11b). To a solution of **10** (300 mg, 0.36 mmol), DMAP (4 mg, 0.04 mmol) and allyl alcohol (0.49 ml, 7.25 mmol) in THF (6 ml) was added WSC (174 mg, 0.91 mmol). The mixture was stirred for 3 h at rt and evaporated to give a residue which was subsequently

dissolved with $CHCl_3$. The organic layer was washed with 2 N HCl, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography (MeOH:$CHCl_3$ = 3:97) to give **11b** (150 mg, 46%) as yellow amorphous product; ^{1}H NMR ($CDCl_3$) δ 2.76–2.99 (m, 2H), 2.99–3.34 (m, 2H), 3.68–3.79 (m, 16H), 3.79–3.94 (m, 8H), 4.01–4.18 (m, 10H), 4.52–4.77 (m, 4H), 5.15–5.44 (m, 4H), 5.76–6.02 (m, 2H), 6.66–7.09 (m, 6H); HRMS (SIMS) calcd for $C_{42}H_{57}N_2O_{16}S_2$ [$(M+1)^+$] 909.3146, found 909.3151.

4.1.6. Methyl 3-mercapto-*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclopentadecen-2-yl) succinamate (5a). To a solution of **11a** (300 mg, 0.35 mmol) in THF (6 ml) was added activated zinc (68 mg, 1.00 mmol) and saturated aqueous ammonium chloride solution (0.5 ml). The mixture was refluxed for 16 h to produce green precipitates. The supernatant liquid of the mixture was separated and the remaining precipitate was stirred in $CHCl_3$–MeOH (1:1) to form a suspension. The suspension was combined with the previous precipitate, and the whole was filtered through a Celite pad. The filtrate was washed with H_2O, dried ($MgSO_4$), and evaporated to give a residue. It was purified by SiO_2 column chromatography (Mallincrodt 6447) using MeOH–$CHCl_3$ (1:9) to give **5a** (228 mg, 76%) as a pale yellow amorphous product; ^{1}H NMR ($CDCl_3$) δ 2.58–3.42 (m, 2H), 3.60–3.81 (m, 11H), 3.81–4.00 (m, 4H), 4.00–4.22 (m, 5H), 6.70–6.95 (m, 3H); HRMS (SIMS) calcd for $C_{19}H_{28}NO_8S$ [$(M+1)^+$] 430.1534, found 430.1540.

4.1.7. Allyl 3-mercapto-*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclopentadecen-2-yl) succinamate (5b). By the same as for the preparation of **5a**, a mixture of **11b** (546 mg, 0.60 mmol), activated zinc (195 mg, 3.0 mmol), and saturated aqueous ammonium chloride solution (1.0 ml) was reluxed for 24 h followed by column chromatography (Mallincrodt 6447) to yield **5b** (387 mg, 71%) as a pale yellow amorphous product; ^{1}H NMR ($CDCl_3$) δ 2.60–3.32 (m, 2H), 3.60–3.80 (m, 8H), 3.80–4.00 (m, 4H), 4.00–4.22 (m, 5H), 4.52–4.76 (m, 2H), 5.16–5.43 (m, 2H), 5.76–6.00 (m, 1H), 6.68–7.01 (m, 3H); HRMS (EIMS) calcd for $C_{21}H_{29}NO_8S$ [$(M+1)^+$] 455.1612, found 455.1613.

4.1.8. Bis[17-acetoxy-1,3,5(10)-estratrien-3-yl] 4,4′-dithiodibutanoate (14). To a suspension of 4,4′-dithiodibutyric acid **12**[8] (723 mg, 3.0 mmol) in acetonitrile (21 ml) were added β-estradiol-17 acetate **13**[8] (1900 mg, 6.1 mmol), $BuNMe_2$ (2.2 ml, 18.2 mmol), DMAP (75 mg, 0.61 mmol), Me_2NSO_2Cl (1.3 ml, 12.2 mmol) in that order. The mixture was stirred at 45 °C for 1 h to produce white precipitate. The precipitate was filtered and washed with cold acetonitrile to give **14** (2150 mg, 85%) as a white powder; mp 167–170 °C (colorless small needles from 5% benzene in acetonitrile); ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 6H), 1.20–1.62 (m, 14H), 1.68–1.80 (m, 2H), 1.82–1.94 (m, 4H), 2.06 (s, 6H), 2.15 (quint, J=6.9 Hz, 4H), 2.09–2.34 (m, 6H), 2.69 (t, J=6.9 Hz, 4H), 2.81 (t, J=6.9 Hz, 4H), 2.75–2.90 (m, 4H), 4.68 (t, J=8.3 Hz, 2H), 6.77 (d, J=2.4 Hz, 2H), 6.83 (dd, J=8.3, 2.4 Hz, 2H), 7.26 (d, J=8.3 Hz, 2H); HRMS (SIMS) calcd for $C_{48}H_{63}O_8S_2$ [$(M+1)^+$] 831.3961, found 831.3963; Anal. Calcd for $C_{48}H_{62}O_8S_2$: C, 69.37; H, 7.52; S, 7.72. Found: C, 69.15; H, 7.39; S, 7.84.

4.1.9. 17-Acetoxy-1,3,5(10)-estratrien-3-yl 4-mercaptobutanoate (6). By the same as for the preparation of **5a**, a mixture of **14** (415 mg, 0.5 mmol), activated zinc (98 mg, 1.5 mmol), and dried ammonium chloride (80 mg, 1.5 mmol) in THF (8 ml) was refluxed for 3 h followed by column chromatography (Mallincrodt 6447) to yield **6** (292 mg, 70%) as a white powder (which was susceptible to oxidation into disulfide **14** in storage); mp 72–73 °C (colorless needles from 5% benzene in acetonitrile; ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3H), 1.24–1.59 (m, 8H), 1.70–1.78 (m, 1H), 1.85–1.92 (m, 2H), 2.06 (s, 3H), 2.05 (quint, J=7.0 Hz, 2H), 2.17–2.32 (m, 3H), 2.66 (dt, J=8.5, 7.0 Hz, 2H), 2.69 (t, J=7.0 Hz, 2H), 2.84–2.89 (m, 2H), 4.69 (dd, J=9.0, 8.0 Hz, 1H), 6.78 (d, J=2.5 Hz, 1H), 6.83 (dd, J=8.6, 2.5 Hz, 1H), 7.27 (d, J=8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.0, 21.1, 23.2, 23.9, 26.0, 27.0, 27.5, 28.9, 29.5, 32.7, 36.8, 38.2, 42.8, 43.9, 49.8, 82.6, 118.5, 121.4, 126.4, 137.9, 138.1, 148.3, 171.2, 171.8.

4.1.10. Methyl 3-{3-[17-acetoxy-1,3,5(10)-estratrien-3-yloxycarbonyl]propyl-disulfanyl}-*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclo-pentadecen-2-yl) succinamate (3). To a solution of **6** (75 mg, 0.18 mmol) in acetonitrile (2 ml) was added PTAD (32 mg, 0.18 mmol). The resulting red solution changed to a pale yellow solution by a stirring at rt for 20 min. Then, a solution of **5a** (84 mg, 0.20 mmol) in acetonitrile (1 ml) was added to the mixture which was further stirred at rt for 4 h. The solvent was evaporated to give a residue, which was purified by flash chromatography with $CHCl_3$ to give **3** (62 mg, 40%) and **15** (13 mg, 10%). **3**: a pale yellow amorphous product; ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3H), 1.22–1.59 (m, 7H), 1.70–1.78 (m, 1H), 1.84–1.92 (m, 2H), 2.06 (s, 3H), 2.08–2.16 (m, 2H), 2.17–2.32 (m, 3H), 2.60–2.72 (m, 2H), 2.79–2.89 (m, 4H), 3.10–3.39 (m, 2H), 3.71 (s, 3H), 3.73–3.77 (m, 8H), 3.84–3.98 (m, 5H), 4.07–4.12 (m, 4H), 4.69 (t, J=8.4 Hz, 1H), 6.75–6.86 (m, 5H), 7.24–7.28 (m, 1H); HRMS (SIMS) calcd for $C_{43}H_{58}NO_8S_2$ [$(M+1)^+$] 844.3397, found 844.3393. **15**: oil; ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3H), 1.23–1.78 (m, 8H), 1.85–1.91 (m, 2H), 2.06 (s, 3H), 2.10–2.32 (m, 5H), 2.66 (t, J=9.1 Hz, 2H), 2.80–2.92 (m, 4H), 3.03 (dd, J=18.7, 4.2 Hz, 1H), 3.32 (dd, J=18.7, 9.3 Hz, 1H), 3.76 (m, 8H), 3.88 (m, 4H), 3.96 (dd, J=9.3, 4.2 Hz, 1H), 4.11 (m, 4H), 4.69 (t, J=5.4 Hz, 1H), 6.77–6.86 (m, 4H), 7.24–7.28 (m, 2H).

4.1.11. 4,4′-Dithiodibutan-1-ol (16). To a suspension of **12**[8] (2.00 g, 8.4 mmol) in THF (30 ml) was added slowly 2 M THF solution of $BH_3 \cdot SMe_2$ (12.0 ml, 24.0 mmol) over 30 min at 0 °C to give a pale brown precipitate. After the resulting mixture was stirred at the same temperature for 30 min and further at rt for 2.5 h, methanol was added to dissolve the precipitate. The solvent was evaporated to give a residue, which was subsequently diluted with EtOAc. The solution was washed with saturated aqueous sodium bicarbonate, brine, and dried, and evaporated to give a crude oil, which was subjected to a flash chromatography. Elution with MeOH–$CHCl_3$ (3:17) afforded **16** (1.63 g, 93%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.62–1.86 (m, 8H), 2.73 (t, J=6.3 Hz, 4H), 3.67 (t, J=6.3 Hz, 4H); HRMS (EIMS) calcd for $C_8H_{18}O_2S_2$ (M^+) 210.0747, found 210.0741.

4.1.12. 4,4′-Dithiodibutyl bromide (17). To a solution of **16** (250 mg, 1.19 mmol) in CH_2Cl_2 (8 ml) was added CBr_4 (1250 mg, 3.81 mmol) and PPh_3 (749 mg, 2.86 mmol) at 0 °C. The mixture was stirred at rt for 1 h and a small amount of silica gel was added to the solution. The solvent was evaporated to give a coated silica gel, which was subsequently placed in a column (Mallincrodt 6447). Chromatography using EtOAc–hexane (1:9) gave **17** (387 mg, 97%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.78–2.06 (m, 8H), 2.72 (t, J=7.2 Hz, 4H), 3.43 (t, J=7.2 Hz, 4H); HRMS (EIMS) calcd for $C_8H_{16}O_2Br_2$ [(M+1)$^+$] 333.9060, found 333.9054.

4.1.13. Bis{4-[17-hydroxy-1,3,5(10)-estratrien-3-yloxy]-butyl} disulfide (18a). A suspension of **17** (85 mg, 0.25 mmol), E_2 (345 mg, 1.27 mmol), and potassium carbonate (263 mg, 1.91 mmol) in acetone (10 ml) was refluxed for 24 h and then diluted with EtOAc. The resulting mixture was washed with H_2O, brine, dried, and evaporated to give a residue. The residue was dissolved with EtOAc and a small amount of silica gel was added to the solution. The solvent was evaporated to give a coated silica gel, which was subsequently placed in a column. Flash chromatography using EtOAc–hexane (3:7) gave **18a** (137 mg, 75%) as white amorphous product; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 6H), 1.12–1.62 (m, 16H), 1.64–1.76 (m, 2H), 1.80–1.98 (m, 12H), 2.02–2.24 (m, 4H), 2.24–2.36 (m, 2H), 2.70–2.80 (m, 4H), 2.80–2.88 (m, 4H), 3.68–3.78 (m, 2H), 3.90–3.98 (m, 4H), 6.61 (d, J=2.4 Hz, 2H), 6.68 (dd, J=8.7, 2.4 Hz, 2H), 7.18 (d, J=8.7 Hz, 2H); HRMS (EIMS) calcd for $C_{44}H_{62}O_4S_2$ (M$^+$) 718.4086, found 718.4089.

4.1.14. Bis{4-[17-acetoxy-1,3,5(10)-estratrien-3-yloxy]-butyl} disulfide (18b). A solution of **18a** (200 mg, 0.28 mmol) in acetic anhydride (5 ml) and pyridine (0.5 ml) was stirred at 100 °C for 1 h. Ice was added to the mixture, and the resulting mixture was diluted with EtOAc. The organic layer was washed with 2 N HCl, saturated aqueous sodium bicarbonate, H_2O, brine, dried and evaporated. The residue was dissolved in EtOAc and a small amount of silica gel was added to the solution. The solvent was evaporated to give a coated silica gel, which was subsequently placed in a column. Flash chromatography using EtOAc–hexane (1:9) gave **18b** (179 mg, 80%) as a white powder; ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 6H), 1.16–2.00 (m, 20H), 1.86 (m, 8H), 2.06 (s, 6H), 2.10–2.36 (m, 6H), 2.68–2.70 (m, 8H), 3.94 (m, 6H), 4.68 (t, J=8.5 Hz, 2H), 6.61 (d, J=3.0 Hz, 2H), 6.68 (dd, J=8.7, 3.0 Hz, 2H), 7.17 (d, J=8.7 Hz, 2H); HRMS (EIMS) calcd for $C_{48}H_{66}O_6S_2$ (M$^+$) 802.4297, found 802.4299.

4.1.15. Bis{4-[17-trimethylsilyloxy-1,3,5(10)-estratrien-3-yloxy]butyl} disulfide (18c). To a solution of **18a** (1.05 g, 1.47 mmol) in THF (40 ml) were added chlorotrimethylsilane (1.87 ml, 1.47 mmol) and triethylamine (2.00 ml, 14.7 mmol). The resulting mixture was stirred at rt for 16 h and evaporated to give a residue, which was subsequently dissolved in hexane. The solution was washed with saturated aqueous sodium bicarbonate, dried, and evaporated to give **18c** (1.22 g, 97%) as amorphous product; R_f=0.48 on silica gel TLC (EtOAc–hexane=1:9, v/v); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 18H), 0.73 (s, 6H), 1.08–1.72 (m, 16H), 1.78–2.00 (m, 14H), 2.10–2.22 (m, 2H), 2.22–2.34 (m, 2H), 2.70–2.90 (m, 8H), 3.63 (t, J=8.4 Hz, 2H), 3.90–4.00 (m, 4H), 6.60 (d, J=2.6 Hz, 2H), 6.67 (dd, J=8.6, 2.6 Hz, 2H), 7.18 (d, J=8.6 Hz, 2H); HRMS (EIMS) calcd for $C_{50}H_{78}O_4S_2Si_2$ (M$^+$) 862.4876, found 862.4881.

4.1.16. 3-(4-Mercaptobutoxy)-1,3,5(10)-estratrien-17-ol (19a). By the same procedure as for the preparation of **5a**, a mixture of **18a** (93 mg, 0.13 mmol), activated zinc (43 mg, 0.65 mmol), and dried ammonium chloride (35 mg, 0.65 mmol) in THF (5 ml) was refluxed for 3.5 h. Filtration of the resulting mixture through a Celite pad, evaporation, and column chromatography gave **19a** (76 mg, 81%) as a white powder; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3H), 1.12–1.60 (m, 9H), 1.64–2.00 (m, 7H), 2.04–2.24 (m, 2H), 2.26–2.36 (m, 1H), 2.60 (q, J=7.0 Hz, 2H), 2.80–2.88 (m, 2H), 3.72 (t, J=8.1 Hz, 1H), 3.94 (t, J=6.2 Hz, 2H), 6.61 (d, J=2.7 Hz, 1H), 6.68 (dd, J=8.4, 2.7 Hz, 1H), 7.18 (d, J=8.4 Hz, 1H); HRMS (EIMS) calcd for $C_{22}H_{32}O_2S$ (M$^+$) 360.2121, found 360.2128.

4.1.17. 3-(4-Mercaptobutoxy)-1,3,5(10)-estratrien-17-yl acetate (19b). A mixture of **18b** (240 mg, 0.3 mmol), activated zinc (104 mg, 1.5 mmol), and dried ammonium chloride (80 mg, 1.5 mmol) in THF (6 ml) was refluxed for 6 h to give **19b** (222 mg, 92%) as a white powder; ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3H), 1.20–1.62 (m, 8H), 1.68–1.96 (m, 7H), 2.06 (s, 3H), 2.14–2.34 (m, 3H), 2.60 (q, J=7.7 Hz, 2H), 2.80–2.90 (m, 2H), 3.94 (t, J=6.9 Hz, 2H), 4.68 (t, J=8.3 Hz, 1H), 6.61 (d, J=2.7 Hz, 1H), 6.68 (dd, J=8.6, 2.7 Hz, 1H), 7.17 (d, J=8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.5, 21.6, 23.6, 24.8, 26.6, 27.9, 28.4, 30.1, 37.1, 38.8, 43.1, 44.0, 50.0, 67.2, 82.6, 111.7, 114.1, 125.9, 132.1, 137.4, 156.2, 170.5; HRMS (EIMS) calcd for $C_{24}H_{34}O_3S$ (M$^+$) 402.2227, found 402.2225.

4.1.18. 4-[17-Trimethylsilyloxy-1,3,5(10)-estratrien-3-yloxy]butanethiol (19c). A mixture of **18c** (424 mg, 0.49 mmol), activated zinc (96 mg, 1.50 mmol), and dried ammonium chloride (78 mg, 1.47 mmol) in THF (10 ml) was refluxed for 3.5 h. The mixture was evaporated to give a residue, which was dissolved with hexane. Filtration of the solution through a Celite pad and evaporation gave **19c** (413 mg, 97%) as a white amorphous product; R_f=0.54 on silica gel TLC (EtOAc–hexane=1:9); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9H), 0.74 (s, 3H), 1.08–1.72 (m, 9H), 2.08–2.36 (m, 2H), 2.60 (q, J=7.4 Hz, 2H), 2.79–2.87 (m, 2H), 3.63 (t, J=8.3 Hz, 1H), 3.94 (t, J=6.1 Hz, 2H), 6.60 (d, J=2.6 Hz, 1H), 6.68 (dd, J=8.4, 2.6 Hz, 1H), 7.18 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$)δ 0.8, 11.8, 23.6, 24.8, 26.8, 27.7, 28.4, 30.2, 31.0, 31.2, 37.3, 39.1, 43.6, 44.3, 49.9, 67.2, 81.7, 111.7, 114.1, 126.0, 132.4, 137.6, 156.1, HRMS (EIMS) calcd for $C_{25}H_{40}O_2SSi$ (M$^+$) 432.2516, found 432.2519.

4.1.19. Methyl 3-{4-[17-acetoxy-1,3,5(10)-estratrien-3-yloxy]butyl-disulfanyl}-*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclo-pentadecen-2-yl) succinamate (20a). To a solution of **19b** (60 mg, 0.15 mmol) in CH_2Cl_2 (1 ml) was added PTAD (26 mg, 0.15 mmol). The solution was stirred at rt for 1 h. Then, a solution of **5a** (65 mg, 0.15 mmol) in CH_2Cl_2 (1 ml) was added to the mixture which was stirred at rt for 4 h to give **20a** (62 mg, 50%) as a pale yellow amorphous product; ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3H), 1.18–1.97 (m, 15H), 2.06 (s,

3H), 2.11–2.35 (m, 4H), 2.72–2.90 (m, 4H), 3.71 (s, 3H), 3.68–3.82 (m, 8H), 3.82–4.01 (m, 7H), 4.06–4.18 (m, 4H), 4.68 (t, J=7.8 Hz, 1H), 6.60 (d, J=2.8 Hz, 1H), 6.67 (dd, J=8.4, 2.8 Hz, 1H), 6.73–6.95 (m, 3H), 7.18 (d, J=8.4 Hz, 1H); HRMS (SIMS) calcd for $C_{43}H_{59}NO_{11}S_2$ [$(M+1)^+$] 829.3526, found 829.3530.

4.1.20. Methyl 3-{4-[17-trimethylsilyloxy-1,3,5(10)-estratrien-3-yloxy]butyldisulfanyl}-*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclo-pentadecen-2-yl) succinamate (20b). A pale yellow amorphous product; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9H), 0.74 (s, 3H), 1.06–1.58 (m, 7H), 1.58–2.02 (m, 8H), 2.08–2.36 (m, 2H), 2.72–2.92 (m, 4H), 3.16–3.40 (m, 2H), 3.63 (t, J=8.3 Hz, 1H), 3.71 (s, 3H), 3.60–3.82 (m, 8H), 3.82–4.04 (m, 7H), 4.02–4.22 (m, 4H), 6.60 (d, J=2.5 Hz, 1H), 6.67 (dd, J=8.0, 2.5 Hz, 1H), 6.74–6.96 (m, 3H), 7.18 (d, J=8.0 Hz, 1H); HRMS (SIMS) calcd for $C_{44}H_{66}NO_{10}S_2Si$ [$(M+1)^+$] 860.3893, found 860.3902.

4.1.21. Allyl 3-{4-[17-trimethylsilyloxy-1,3,5(10)-estratrien-3-yloxy]butyldisulfanyl}-*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclo-pentadecen-2-yl) succinamate (20c). To a solution of **19c** (139 mg, 0.32 mmol) in CH_2Cl_2 (8 ml) was added PTAD (68 mg, 0.39 mmol). The resulting red solution was changed to a pale yellow solution by a stirring at rt for 1 h. Then, a solution of **5b** (147 mg, 0.32 mmol) in CH_2Cl_2 (4 ml) was added to the mixture which was stirred at rt for 4 h. The solvent was evaporated to give a residue, which was purified by column chromatography (Mallinckrodt 6447) with MeOH–$CHCl_3$ (1:99) to give **20c** (116 mg, 41%) as a pale yellow amorphous product; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9H), 0.73 (s, 3H), 1.08–1.73 (m, 8H), 1.73–2.02 (m, 7H), 2.08–2.36 (m, 2H), 2.72–2.92 (m, 4H), 2.98–3.42 (m, 2H), 3.63 (t, J=8.0 Hz, 2H), 3.67–3.82 (m, 8H), 3.82–4.00 (m, 7H), 4.02–4.20 (m, 4H), 4.53–4.72 (m, 2H), 5.13–5.40 (m, 2H), 5.79–5.98 (m, 1H), 6.60 (d, J=2.8 Hz, 1H), 6.67 (dd, J=8.4, 2.8 Hz, 1H), 6.74–6.95 (m, 3H), 7.18 (d, J=8.4 Hz, 1H); HRMS (SIMS) calcd for $C_{46}H_{68}NO_{10}S_2Si$ [$(M+1)^+$] 886.405, found 886.4038.

4.1.22. 1-{4-[17-Acetoxy-1,3,5(10)-estratrien-3-yloxy]}-butyl-2-{*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclopentadecen-2-yl)-2,5-dioxo-pyrrolidin-3-yl} disulfide (21). A solution of **20a** (11 mg, 0.01 mmol) in benzene (15 ml) was refluxed with *p*-TsOH (1 mg) for 6 h using a Dean–Stark water separator. The solvent was evaporated to give a residue, which was dissolved with CH_2Cl_2. The solution was washed with H_2O, dried ($MgSO_4$), and evaporated to give a crude oil that was purified by column chromatography with MeOH–$CHCl_3$ (3:97) to give **21** (10 mg, 91%) as an amorphous product; ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3H), 1.20–1.98 (m, 15H), 2.05 (s, 3H), 2.12–2.34 (m, 4H), 2.72–2.94 (m, 4H), 3.04 (dd, J=18.8, 4.0 Hz, 1H), 3.30 (dd, J=18.8, 9.4 Hz, 1H), 3.69–3.83 (m, 8H), 3.83–4.02 (m, 7H), 4.05–4.22 (m, 4H), 4.68 (t, J=8.0 Hz, 1H), 6.59 (d, J=2.4 Hz, 1H), 6.66 (dd, J=8.7, 2.4 Hz, 1H), 6.78 (d, J=1.7 Hz, 1H), 6.83 (dd, J=8.7, 1.7 Hz, 1H), 6.90 (d, J=8.7 Hz, 1H), 7.16 (d, J=8.7 Hz, 1H); HRMS (SIMS) calcd for $C_{42}H_{55}NO_{10}S_2$ (M^+) 797.3264, found 797.3257.

4.1.23. 1-{4-[17-Hydroxy-1,3,5(10)-estratrien-3-yloxy]-butyl-2-{*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclopentadecen-2-yl)-2,5-dioxopyrrolidin-3-yl} disulfide (22). A solution of **21** (8 mg, 0.01 mmol) in THF (2 ml) was refluxed with 1 N HCl for 24 h to give **22** (6 mg, 75%) as a pale yellow amorphous product; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3H), 1.12–2.03 (m, 15H), 2.03–2.36 (m, 4H), 2.71–2.94 (m, 4H), 3.04 (dd, J=18.8, 3.8 Hz, 1H), 3.30 (dd, J=18.8, 9.0 Hz, 1H), 3.62–3.81 (m, 9H), 3.81–4.02 (m, 7H), 4.02–4.20 (m, 4H), 6.60 (d, J=2.3 Hz, 1H), 6.66 (dd, J=8.9, 2.3 Hz, 1H), 6.78 (d, J=1.5 Hz, 1H), 6.83 (dd, J=8.9, 1.5 Hz, 1H), 6.90 (d, J=8.9 Hz, 1H), 7.16 (d, J=8.9 Hz, 1H); MS of **22** could not be measured owing its thermal instability.

4.1.24. Allyl 3-{4-[17-hydroxy-1,3,5(10)-estratrien-3-yloxy]butyldisulfanyl}-*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclo-pentadecen-2-yl) succinamate (23). To a solution of **20c** (340 mg, 0.38 mmol) in CH_2Cl_2–MeOH (1:1, 10 ml) was added citric acid (37 mg, 0.19 mmol). The mixture was stirred at rt for 1 h. The solvent was evaporated to give a residue, which was diluted with CH_2Cl_2. The resulting insoluble material was filtered off through a Celite pad to give a filtrate. Evaporation of the filtrate gave **23** (296 mg, 96%) as a pale yellow amorphous product; ^{1}H NMR ($CDCl_3$) δ 0.77 (s, 3H), 1.12–2.02 (m, 15H), 2.02–2.36 (m, 2H), 2.70–2.94 (m, 4H), 2.98–3.36 (m, 2H), 3.68–3.83 (m, 9H), 3.83–4.02 (m, 7H), 4.05–4.18 (m, 4H), 4.57–4.68 (m, 2H), 5.20–5.40 (m, 2H), 5.81–5.99 (m, 1H), 6.61 (d, J=2.8 Hz, 1H), 6.68 (dd, J=8.4, 2.8 Hz, 1H), 6.73–6.98 (m, 3H), 7.18 (d, J=8.4 Hz, 1H); HRMS (SIMS) calcd for $C_{43}H_{60}NO_{10}S_2$ [$(M+1)^+$] 814.3655, found 814.3651.

4.1.25. 3-{4-[17-Hydroxy-1,3,5(10)-estratrien-3-yloxy]-butyldisulfanyl}-*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclo-pentadecen-2-yl) succinamic acid (1). To a THF–MeOH (4:3, 7 ml) solution of **23** (208 mg, 0.26 mmol) in a flask, which was blinded by aluminum foil, were added $Pd(PPh_3)_4$ (15 mg, 0.01 mmol), PPh_3 (7 mg, 0.03 mmol), and sodium *p*-toluenesulfinate (46 mg, 0.26 mmol). The mixture was stirred at rt for 16 h and acidified with 2 N hydrochloric acid (0.15 ml). The solvent was evaporated to give a residue, which was chromatographed [BW-127ZH, H_2O–MeOH–$CHCl_3$ (0.5:25:65)] to give **1** (73 mg, 37%) as a pale yellow amorphous product. It was dissolved with visual bubbling in saturated aqueous sodium bicarbonate[35]; R_f=0.4, 0.5 [a mixture of diastereomers (1:3)[34], H_2O–MeOH–$CHCl_3$ (4:25:65)]; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3H), 1.08–2.50 (m, 17H), 2.62–2.94 (m, 4H), 3.03–3.20 (m, 2H), 3.56–3.75 (m, 9H), 3.75–3.99 (m, 7H), 3.99–4.20 (m, 4H), 6.50–6.70 (m, 2H), 6.81–7.18 (m, 3H), 7.19–7.36 (m, 1H); HRMS (SIMS) calcd for $C_{40}H_{56}NO_{10}S_2$ [$(M+1)^+$] 774.3342, found 774.3337.

4.1.26. Methyl 3-{4-[17-hydroxy-1,3,5(10)-estratrien-3-yloxy]butyldisulfanyl}-*N*-(6,7,9,10,12,13,15,16-octahydro-5,8,11,14,17-pentaoxabenzocyclo-pentadecen-2-yl) succinamate (24). To a MeOH–THF (1:1, 1 ml) solution of **1** (9 mg, 0.01 mmol) was added slowly 2.0 N hexane solution of $TMSCHN_2$ (0.007 ml, 0.01 mmol). After 30 min at rt, the solvent was evaporated to give a residue which was

subsequently purified by silica gel chromatography with MeOH–$CHCl_3$ (1:20) to give **24** (6 mg, 67%) as a brown amorphous product; IR ($CHCl_3$, cm^{-1}) 1720, 1670; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3H), 1.11–2.02 (m, 15H), 2.02–2.36 (m, 2H), 2.68–2.90 (m, 4H), 3.14–3.42 (m, 2H), 3.70 (s, 3H), 3.63 (m, 9H), 3.81–4.01 (m, 7H), 4.01–4.20 (m, 4H), 6.60 (d, $J=2.8$ Hz, 1H), 6.67 (dd, $J=8.6$, 2.8 Hz, 1H), 6.73–6.95 (m, 3H), 7.17 (d, $J=8.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 11.0, 23, 25.7, 26.1, 26.3, 27.3, 28.0, 29.8, 30.6, 35.7, 38.7, 38.9, 43.3, 44.0, 50.0, 52.2, 58.6, 67.1, 68.8, 69.4, 69.7, 70.6, 71.0, 76.5, 76.5, 76.8, 77.0, 77.3, 81.9, 106.7, 112.0, 114.5, 118.7, 126.3, 132.8, 138.0, 156.7, 171.4, 171.8; HRMS (SIMS) calcd for $C_{41}H_{58}NO_{10}S_2$ $[(M+1)^+]$ 788.3498, found 788.3502.

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References and notes

1. Sakamoto, S.; Mizuno, M.; Taketani, F. *Principles of Obstetrics and Gynecology 2*, 2nd ed.; MEDICAL VIEW: Tokyo, 2001.
2. (a) Speroff, L.; Glass, R. H.; Kase, N. G. *Clinical Gynecologic Endocrinology and Infertility*, 2nd ed.; Williams and Wilkins: Baltimore, 1978; pp 65–70. (b) Marshall, W. A.; Tanner, J. M. *Arch. Dis. Child.* **1969**, *44*, 291–298.
3. (a) Grant, N. F.; Cunningham, F. G. *Basic Gynecology and Obstetrics*, 1st ed.; Appleton & Lange: East Norwalk, 1993. (b) Riggs, L. B.; Melton III, J. L. *N. Eng. J. Med.* **1992**, *327*, 620–627.
4. (a) Barrett-Connor, E. *Circulation* **1997**, *95*, 252–264. (b) Mendelsohn, M. E.; Karas, R. H. *N. Eng. J. Med.* **1999**, *340*, 1801–1811.
5. Brown, J. B.; Gronow, M. Endocrinology of ovulation prediction. In *Clinical Reproductive Endocrinology*; Shearman, R. P., Ed.; Churchill Livingstone: Edinburgh, 1985; pp 165–184.
6. Moore, K. L. *The Developing Human: Clinically Oriented Embryology*, 4th ed.; Saunders: Philadelphia, 1988.
7. (a) *United Nations: Demographic Yearbook*; United Nations-Statistical Office, Ed.; 1999. Table 14. (b) Statistics and Information Department, Minister's Secretariat, Ed.; Patient Survey 2002 (All Japan); Ministry of Health, Labor and Welfare (Japanese Government), 2002.
8. This was purchased from Aldrich Chemical Company.
9. Unpublished Data: in the low concentration, the relationship between the concentration of **2** and electrode-response was well approximated to a Langmuir's adsorption isotherm: $\Delta G=K_1/(1+K_2/C)+K_3\cdot C$.
10. FKA 238 (COSMO FKA 238) was available from COSMO BIO Co., Ltd.
11. Cross reactivities of FKA 238 with steroids is shown in the data sheet of FKA 238.
12. Cason, J. *Org. Synth. Coll.*, *4*, 630–633.
13. Disuccinamic acid **10** could not be reduced to a thiol **5** (R=H) by zinc-saturated aqueous ammonium chloride.
14. Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475–1478.
15. Zervas, B. L.; Theodoropoulos, D. M. *J. Am. Chem. Soc.* **1956**, *78*, 1359–1363.
16. Overman, L. E.; Smoot, J.; Overman, J. D. *Synthesis* **1974**, 59–60.
17. Sridhar, M.; Vadivel, S. K.; Bhalerao, U. T. *Synth. Commun.* **1997**, *27*, 1347–1350.
18. Allen, C. F. H.; MacKay, D. D. *Org. Synth. Coll.*, *2*, 580–583.
19. Holton, R. A.; Crouse, D. J.; Williams, A. D.; Kennedy, R. M. *J. Org. Chem.* **1987**, *52*, 2317–2318.
20. Yamazaki, S.; Sakamoto, M.; Suzuri, M.; Doi, M.; Nakazawa, T.; Kobayashi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1870–1875.
21. Wakasugi, K.; Nakamura, A.; Tanabe, Y. *Tetrahedron Lett.* **2001**, *42*, 7427–7430.
22. (a) Smith, M. B.; March, J. *March's Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, 5th ed.; Wiley Inter-Science: New York, 2001; pp 1543–1544. (b) Bao, M.; Shimizu, M. *Tetrahedron* **2003**, *59*, 9655–9659 and references cited therein. (c) Mukaiyama, T.; Takahashi, K. *Tetrahedron Lett.*, 5907–5908.
23. Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539–542.
24. Cookson, R. C.; Gilani, S. S. H.; Stevens, I. D. R. *Tetrahedron Lett.* **1962**, 615–618.
25. Barton, D. H. R.; Shioiri, T.; Widdowson, D. A. *Chem. Commun.* **1970**, 939–940.
26. Pilipenko, V. S.; Shusherina, N. P. *Zh. Org. Khim.* **1980**, *16*, 2444.
27. Kende, A. S.; Fludzinski, P. *Org. Synth. Coll.*, *7*, 221–222.
28. Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1972**, *37*, 2289–2299.
29. Allen, C. F. H.; Gates, J. W. Jr. *Org. Synth. Coll.*, *3*, 140–141.
30. Hughes, D. L. In Paquatte, L. A., Ed.; Organic Reactions; Wiley: New York, 1992; Vol. 42, pp 335–669.
31. (a) Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2003**, *125*, 6624–6625. (b) Tanaka, K.; Ajiki, K. *Tetrahedron Lett.* **2004**, *45*, 5677–5679. (c) Disulfides **11b** (0.2 mmol) and **18c** (0.2 mmol) were treated in the presence of $RhH(PPh_3)_4$ (3 mol%), tris(*p*-tolyl)phosphine (12 mol%), and trifluoromethanesulfonic acid (6 mol%) according the procedure of Ref. 31a, but the reaction was inactive with recovery of disulfides **11b** and **18a**, the latter of which was lacking TMS group of used **18c**.
32. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 116–121, pp 409–411, and references cited therein.
33. Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932–8936.
34. The ratio of diastereomers was determined from ^{13}C NMR analysis of **24**.
35. The sodium salt of **1** showed solubility in water, while its triethylammonium carboxylate was an insoluble salt in water. From these observations, the metal cation of the sodium salt is assumed to be trapped by the BC ether in **1**.

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Synthesis and conformational properties of model dipeptides containing novel axially chiral α,β-didehydroamino acids at the (*i*+1) position of a β-turn conformation

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Abstract—A series of model dipeptides containing some novel axially chiral α,β-didehydroamino acids at the (*i*+1) position has been synthesised by reaction of the corresponding 4-(4-alkylcyclohexylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one with (*S*)-phenylalanine cyclohexylamide. The conformations of two dipeptides in the crystal state have been studied by X-ray diffraction crystallographic analysis. The backbone torsion angles suggest that both peptides adopt similar type-II′ β-turn conformations. NMR spectroscopy has revealed that relatively rigid β-turn structures also persist in solution and that the absolute configurations of the axially chiral α,β-didehydroamino acids do not significantly influence the conformation of the peptide chain. Both heterochiral and homochiral dipeptides are found to accommodate the same βII′-turn conformation. Axially chiral α,β-didehydroamino acids (R_a)- and (S_a)-4-methyl-, 4-phenyl- and (4-*tert*-butylcyclohexylidene)glycine can be considered as elongated structural analogues of alanine, phenylglycine and *tert*-leucine of *R* and *S* configuration since, in these chiral α,β-didehydroamino acids, the methyl, phenyl and *tert*-butyl groups are located about 4.3 Å away from the peptide backbone in which they are incorporated.

1. Introduction

Non-coded α-amino acids with unusual side chains can exhibit peculiar properties once introduced into peptides. Such systems now represent some of the most important areas of research in the fields of organic chemistry, medicinal chemistry, and protein engineering.[1] Among non-proteinogenic α-amino acids, the α,β-didehydroamino acids have recently received a great deal of attention.[2] These compounds are present in many naturally occurring peptides that show important biological activities.[3] For example, didehydroalanine, the most widely observed natural α,β-unsaturated amino acid, has been identified as a constituent of a substantial number of cyclic peptides produced by microorganisms, including the antibiotics nisin, mersacidin, subtilin[4] and phytotoxic AM-toxins.[5] This compound has also been found in some enzymes, for example, phenylalanine ammonia lyase from plants,[6] which are formed by post-translational dehydration of serine residues.

One of the major goals in modern amino acid chemistry is to develop conformationally restricted amino acids that, after incorporation into peptides, may give rise to enhanced biological activity by decreasing the degree of freedom of the peptide. Whereas extensive efforts have been devoted to the design of peptides with well defined backbone conformations,[7] the geometry of the side chain in amino acid moieties has received considerable less attention despite side chains are directly involved in the molecular recognition processes which depend on their adequate spatial disposition.[8]

Structurally, α,β-didehydroamino acid residues are distinguished by forming, upon incorporation into a peptide chain, a system involving three rigid groups located on the C^{α} atom: the α,β-double bond flanked by two adjacent amide bonds. Consequently, these amino acids have a powerful rigidifying effect on the peptide backbone and effectively restrict the orientation of the side chain. The orientation of the β-substituents is fixed by the stereochemistry of the double bond which offers the possibility to

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evaluate accurately the influence of the side chain three-dimensional arrangement. For this reason these amino acids have been used for the modification of bioactive peptide sequences in order to obtain highly active agonist or antagonist analogues and indeed this modification has become one of the most promising ways to establish structure–bioactivity relationships.[9] Another feature of didehydropeptides is the increased stability to degradative enzymes, which has led to synthetic enzyme inhibitors that act as non-hydrolyzable substrate mimics.[10] These features have been the driving force for the increased interest in the design of didehydropeptide-based therapeutic agents.

As pointed out above, the presence of the sp^2 hybridised α-carbon atom, the extended conjugation on account of the π system, the restriction of the peptide backbone and the specific orientation of the side chain due to the double bond are some of the special features that make didehydropeptides attractive targets for conformational studies.[11] Most such studies have been limited to model synthetic peptides containing α,β-didehydroamino acids derived from standard (proteinogenic) saturated residues, mainly didehydrophenylalanine (ΔPhe). X-ray diffraction analyses, conformational energy calculations, NMR, and CD have largely been used to confirm the presence of ordered structures in such peptides both in the crystal state and in solution.[12] The available data, most concerning systems with the α,β-didehydroamino acid located at the $(i+2)$ position, indicate that β-turns[13] are often stabilised in short sequences, whereas helix formation may be promoted in longer peptides. For example, it has been clearly established that a didehydrophenylalanine residue at this position gives rise to a type-II β-turn conformation.

On the other hand, the number of available structures with a α,β-didehydroamino acid at the $(i+1)$ position remains very small. Thus, a clear picture has not yet emerged in terms of preferred conformations and more sequences with the α,β-didehydroamino acid at the $(i+1)$ position need to be analysed.

2. Results and discussion

A preliminary account of the results described here has been published[14] and dealt with the synthesis, isolation and characterisation of dipeptides PhCO-(R_a)-(CH_3Cy)Gly-(*S*)-Phe-NHCy and PhCO-(S_a)-(CH_3Cy)Gly-(*S*)-Phe-NHCy [(R_a,*S*)- and (S_a,*S*)-**4a**], where (CH_3Cy)Gly stands for (4-methylcyclohexylidene)glycine. Both of these systems contain an axially chiral dehydroamino acid at the $(i+1)$ position. To the best of our knowledge, that preliminary communication described the first examples of chiral α,β-didehydroamino acids as structural features of α,β-didehydroamino acids preclude the existence of a stereogenic centre. In the present paper, we report in detail the preparation of the two aforementioned model dipeptides and four structural analogues: PhCO-(R_a)-(PhCy)Gly-(*S*)-Phe-NHCy [(R_a,*S*)-**4b**], PhCO-(S_a)-(PhCy)Gly-(*S*)-Phe-NHCy [(S_a,*S*)-**4b**], PhCO-(R_a)-(^{t}BuCy)Gly-(*S*)-Phe-NHCy [(R_a,*S*)-**4c**], and PhCO-(S_a)-(^{t}BuCy)Gly-(*S*)-Phe-NHCy [(S_a,*S*)-**4c**], where (PhCy)Gly and (^{t}BuCy)Gly represent α,β-didehydroamino acids (4-phenylcyclohexylidene)glycine and (4-*tert*-butylcyclohexylidene)glycine, respectively.

Bearing in mind that model dipeptides RCO-X_{aa}-Y_{aa}-NHR′ are the most simple molecules that are compatible with β-turn folding, compounds (R_a,*S*)-**4a–c** and (S_a,*S*)-**4a–c** would be expected to allow the study of the conformational preferences induced by this kind of α,β-didehydroamino acid when incorporated at the $(i+1)$ position of a model dipeptide and enable analysis of how the absolute configuration of axially chiral residues affects the folding mode of the compound.

Conformational analyses of the six model dipeptides in solution were performed by ^{1}H NMR spectroscopy. The isolation of crystalline samples of compounds PhCO-(R_a)-(CH_3Cy)Gly-(*S*)-Phe-NHCy [(R_a,*S*)-**4a**] and PhCO-(R_a)-(^{t}BuCy)Gly-(*S*)-Phe-NHCy [(R_a,*S*)-**4c**] allowed their analysis in the crystal state by X-ray diffraction.

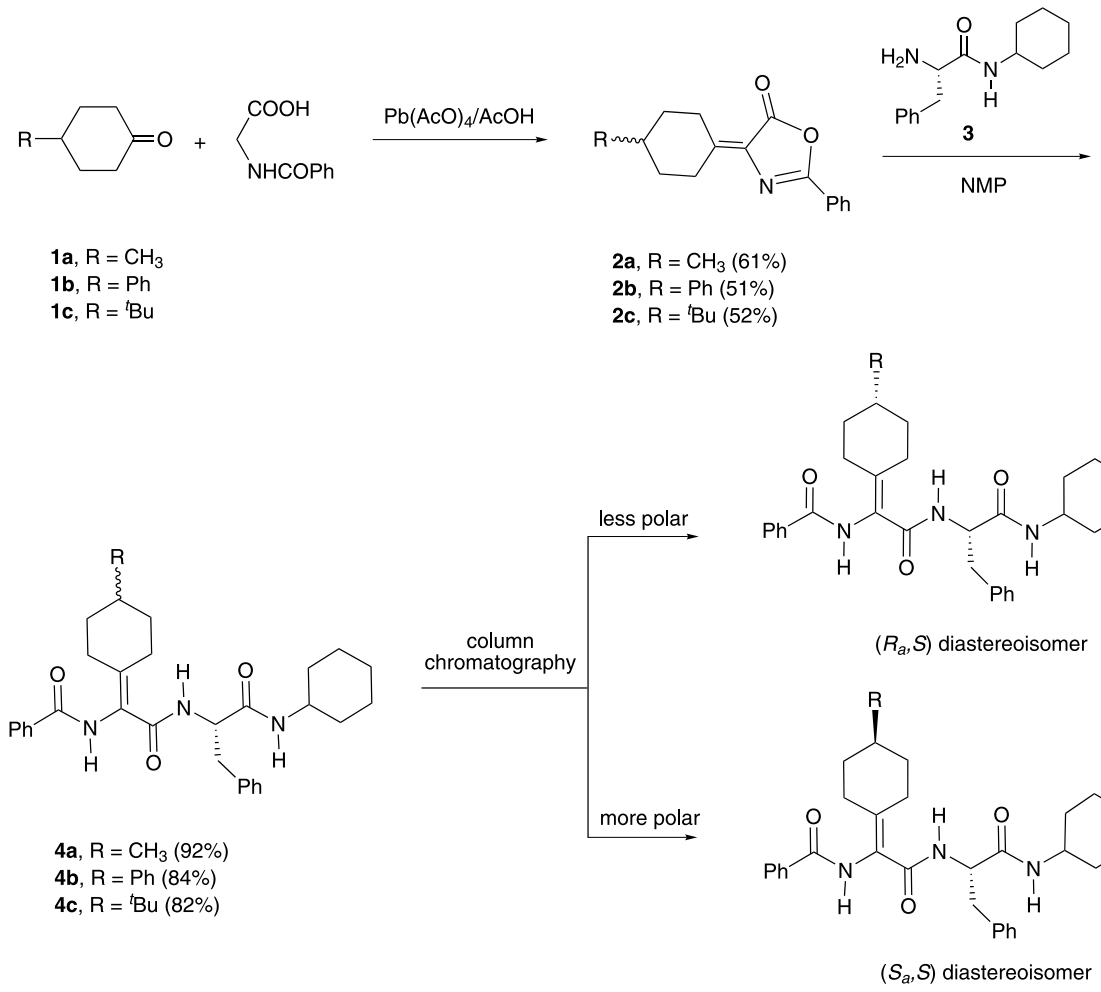
2.1. Synthesis of compounds (R_a,*S*)-4a–c and (S_a,*S*)-4a–c

Compounds (R_a,*S*)-**4a–c** and (S_a,*S*)-**4a–c** were synthesised by the 'oxazolone method' outlined in Scheme 1. This strategy was developed by Obrecht et al.[15] to prepare enantiomerically pure C^{α}-tetrasubstituted amino acids using (*S*)-phenylalanine cyclohexylamide as a chiral resolving agent. In our case, the synthesis started with the condensation of three different 4-alkylcyclohexanones (**1a–c**) with hippuric acid under typical Erlenmeyer conditions to give the required 4-(4-alkylcyclohexylidene)-2-phenyl-1,3-oxazol-5(4*H*)-ones (**2a–c**) as racemic mixtures in moderate yields (50–60%). Coupling of these compounds with (*S*)-phenylalanine cyclohexylamide (**3**) at 90 °C using *N*-methylpyrrolidin-2-one (NMP) as solvent cleanly afforded the corresponding peptides **4a–c** as equimolecular mixtures of diastereoisomers in high yields. Careful column chromatography on silica gel, using methylene chloride/ethyl acetate (3/1) as the eluent, gave analytically pure samples of both (R_a,*S*) and (S_a,*S*) diastereoisomers from each mixture of compounds.

The configuration of the less polar diastereoisomer of compounds **4a** and **4c** was unambiguously assigned by single crystal X-ray diffraction analysis based on the known (*S*)-configuration of phenylalanine. This analysis established the absolute configuration of the corresponding chiral α,β-didehydroamino acid residues as R_a in both compounds. The assignment of the S_a configuration for the more strongly retained diastereoisomers of compounds **4a** and **4c** was deduced by exclusion. Unfortunately, all efforts to crystallise the two diastereoisomers of dipeptide **4b** were unsuccessful. Thus, the absolute configurations (R_a,*S*) and (S_a,*S*) were assumed for the less polar diastereoisomer and the more polar one, respectively. This assumption is supported by the similarity in the spectroscopic behaviour of these compounds and those of peptides (R_a,*S*)-**4a** and **4c** and (S_a,*S*)-**4a** and **4c**, whose absolute configurations were known.

2.2. Crystal structures

Dipeptides (R_a,*S*)-**4a** and (R_a,*S*)-**4c** gave suitable crystals for



Scheme 1. Synthesis of compounds (R_a,*S*)-**4a**–**c** and (S_a,*S*)-**4a**–**c** according to the 'oxazolone method'.

analysis by X-ray diffraction. The peptide (R_a,*S*)-**4a** crystallised with two independent molecules, A and B, in the asymmetric unit. These two independent molecules differ slightly in their conformation. The molecular structures of the two compounds, along with the atomic numbering schemes, are illustrated in Figures 1 and 2, respectively. Relevant backbone and side-chain torsion angles[16] are given in Table 1. Table 2 contains the intra- and intermolecular H-bond parameters.

With the exception of the α,β-didehydroamino acid residues, bond lengths and angles in (R_a,*S*)-**4a** and

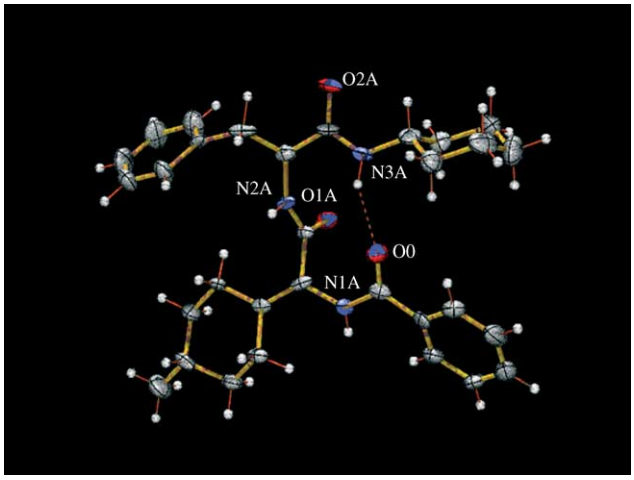


Figure 1. X-ray diffraction structure of compound (R_a,*S*)-**4a** (independent molecule A). Ellipsoids are shown at the 50% probability level. The intramolecular H-bond is represented by dashed lines.

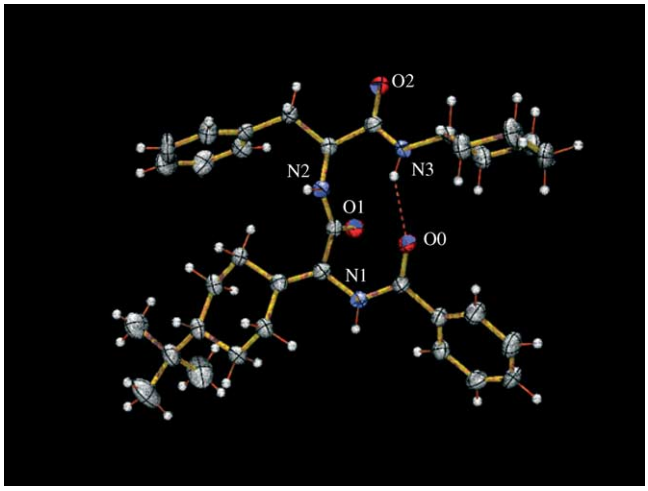


Figure 2. X-ray diffraction structure of compound (R_a,*S*)-**4c**. Ellipsoids are shown at the 50% probability level. The intramolecular H-bond is represented by a dashed line.

Table 1. Selected torsion angles (deg) for the dipeptides (R_a,*S*)-**4a** and (R_a,*S*)-**4c**

Torsion angle	(R_a,*S*)-**4a** (mol A/mol B)	(R_a,*S*)-**4c**
ω_0	171.5(9)/174.1(9)	−171.3(4)
ϕ_1	51.2(13)/48.0(13)	38.7(6)
ψ_1	−122.5(9)/−124.7(9)	−126.1(4)
ω_1	−179.1(9)/−178.3(9)	−176.7(4)
ϕ_2	−87.5(12)/−83.8(12)	−89.9(5)
ψ_2	6.5(15)/4.7(14)	9.4(6)
ω_2	170.1(10)/171.6(9)	175.0(4)
$\chi_1^{1,1}$	−170.6(9)/−171.1(10)	−166.5(4)
$\chi_1^{1,2}$	8.9(15)/7.0(17)	5.0(7)
χ_2^1	−73.1(12)/−76.2(12)	−59.0(6)

(R_a,*S*)-**4c** are in good agreement with those found in usual peptides.[17] The average C^{α}=C^{β} bond length in (CH_3-Cy)Gly and (^{t}BuCy)Gly residues from crystal structure data is 1.35 Å, which is slightly larger than the value found in other unsaturated residues.[11b] The C^{α}–C bond length (1.50 Å) is somewhat shorter (by 0.03 Å) than that in saturated amino acid residues (1.53 Å).[17] The N–C^{α} bond distance is 1.43 Å, again also slightly less than the corresponding distance of 1.45 Å in saturated amino acid residues. The values of the N–C^{α}–C and $C^{\gamma 1}$–C^{β}–$C^{\gamma 2}$ bond angles of 114.1 and 113.2°, respectively, are less than the standard value, 120°, from an sp^2 hybridised carbon atom, whereas the values of N–C^{α}=C^{β}, C–C^{α}=C^{β}, $C^{\gamma 1}$–C^{β}=C^{α} and $C^{\gamma 2}$–C^{β}=C^{α} are larger (between 123.8 and 122.4°).

Both model dipeptides exhibit interesting aspects of peptide folding. The similarity of the conformations is clearly shown by the torsion angles of the dipeptide backbone (Table 1). All amide bonds have the *trans*-conformation ($\omega = \pm 170$–179) and the ϕ/ψ-combinations for amino acids $i+1$ and $i+2$ are close to the ideal values for type II′ β-turn conformations (60/−120, −80/0). In (R_a,*S*)-**4a** the mean deviation from these values is ±6.3°, with the highest deviation being −12° for the torsion angle ϕ_1 in molecule B. In the case of (R_a,*S*)-**4c**, which contains the bulkier *tert*-butyl substituent in the cyclohexane ring, all backbone torsion angles show larger deviations from ideal values, with the mean deviation being ±11.7°. In each compound, the molecular conformation is stabilised by an intramolecular C=O···H–N hydrogen bond that links two termini of the backbone chain to form a 10-membered ring (Table 2), which is typical for a β-turn conformation.

The side-chain torsion angles indicate that both structures have the benzyl side chain of the (*S*)-phenylalanine residue in a (−)-*syn*-clinal disposition that allows the central amide group to be engaged in intermolecular hydrogen bonds. The torsion angles $\chi_1^{1,1}$ and $\chi_1^{1,2}$ are centered around 0° but deviations from this value are considerable, even rising to 13.5°. This information indicates that three side-chain atoms (C^{β}, $C^{\gamma 1}$ and $C^{\gamma 2}$) and three backbone atoms (N, C^{α}, C′) of the α,β-didehydroamino acid residues are not coplanar. Methyl and *tert*-butyl substituents at the 4-position of the cyclohexane ring are found in the equatorial position. Cyclohexylidene moieties adopt a distorted chair conformation.

Considering the relative spatial dispositions of the side chains in both crystalline compounds, it is found that 4-alkylcyclohexylidene and benzyl side chains are situated in nearly orthogonally planes. The N-terminal benzoyl and the C-terminal cyclohexylamino moieties extend in the opposite direction and are also situated in nearly orthogonally planes. With this arrangement of the hydrophobic groups, the molecules can pack in two dimensional layers parallel to the *z*-axis and expose tightly packed arrays of phenyl, benzyl, 4-alkylcyclohexylidene and cyclohexyl groups on either side, thus forming relatively smooth hydrophobic contact surfaces between adjacent layers. The hydrophobic surfaces of the layers are devoid of marked cavities that could provide possibilities for tight side-chain interlocking. Within each layer, there are two orthogonal H-bond networks with all amide units H-bonded (Table 2). The first network is established by intermolecular H-bonds between the central and C-terminal peptide units. The second one is formed by above-mentioned intramolecular H-bonds and intermolecular H-bonds between the N-terminal and central peptides units, in crystal packing of dipeptide (R_a,*S*)-**4a**, or between the N-terminal peptide unit, a molecule of solvent (methanol) and the central peptide unit, in crystal packing of dipeptide (R_a,*S*)-**4c**. In the second case, the presence of a solvent molecule in the asymmetric unit provides the opportunity for the formation of additional intermolecular H-bonds. N1–H1 donates an H-bond to the CH_3OH molecule, which in turn acts as a donor for another H-bond to O1. Thus, the CH_3OH molecule is H-bonded to two dipeptide molecules.

2.3. Structures in solution

Information about the three dimensional structures of compounds (R_a,*S*)-**4a–c** and (S_a,*S*)-**4a–c** can be obtained from NMR measurements. In these structures, intramolecular hydrogen bonding may provide the principal

Table 2. Intra- and intermolecular H-bond parameters for the dipeptides (R_a,*S*)-**4a** and (R_a,*S*)-**4c**

Dipeptide	Donor (D–H)	Acceptor (A)	Symmetry operation	Distance D…A (Å)	Distance H…A (Å)	Angle D–H…A (deg)
(R_a,*S*)-**4a**	N1A–H1A	O1A	$1-x, 1/2+y, -1-z$	3.166(11)	2.30	168.3
	N2A–H2A	O2A	$2-x, 1/2+y, -1-z$	3.068(11)	2.20	169.4
	N3A–H3A	O0A	x, y, z	2.866(12)	2.05	153.9
	N1B–H1B	O1B	$2-x, -1/2+y, -2-z$	3.187(11)	2.31	170.9
	N2B–H2B	O2B	$1-x, -1/2+y, -2-z$	3.008(12)	2.14	167.6
	N3B–H3B	O0B	x, y, z	2.851(11)	2.04	152.8
(R_a,*S*)-**4c**	N1–H1	OM	$-x, -1/2+y, 1-z$	2.965(5)	2.10	166.2
	N2–H2	O2	$1-x, -1/2+y, 1-z$	2.929(5)	2.07	166.8
	N3–H3	O0	x, y, z	2.865(5)	2.06	151.4
	OM–HOM	O1	x, y, z	2.766(5)	1.94	169.3

Table 3. Most significant NMR parameters for compounds (R_a,*S*) and (S_a,*S*)-**4a–c** in $CDCl_3$ solution

NMR parameter	(R_a,*S*)-**4a**	(S_a,*S*)-**4a**	(R_a,*S*)-**4b**	(S_a,*S*)-**4b**	(R_a,*S*)-**4c**	(S_a,*S*)-**4c**
δ-NHCy[a]	7.27	7.58	7.23	7.65	7.25	7.60
δ-NHPhe[a]	6.05	6.04	6.13	6.11	6.03	6.02
δ-NHBz[a]	8.26	8.91	7.91	9.20	8.00	8.89
$^3J^{\alpha}_{NH-CH}$(Phe)[b]	8.50	8.90	8.70	8.90	8.60	8.70

[a] ppm.
[b] Hz.

driving force for turn conformation. For this reason, experimental investigations were carried out in a relatively non-polar solvent ($CDCl_3$), which does not offer strong hydrogen-bonding competition in 10 mM solutions.

Well-resolved 300 MHz ^{1}H NMR spectra were obtained for all compounds examined in this work. These spectra allowed completely unambiguous assignment of most CH proton resonances and all NH proton resonances. In $CDCl_3$ solution the benzoylamino group NH proton resonances appeared as downfield singlets (8–9 ppm), a situation that allowed their straightforward assignment because amide proton resonances in conjugation with the double bond system in α,β-didehydroamino acid derivatives have often been observed downfield with respect to other NH resonances. The cyclohexylamide NH and phenylalanine NH protons appeared as doublets and were unambiguously assigned by two-dimensional correlated spectroscopy (COSY), which showed that the phenylalanine NH proton resonance always appears at a higher field than the cyclohexylamide NH proton resonance. Table 3 contains the chemical shifts of the amido NH protons in 10 mM solutions in $CDCl_3$ for all compounds at 293 K.

Insights into the nature of hydrogen bonding can be gained from NMR data in relation to different criteria: chemical shifts of the amide NH protons, concentration dependence of the ^{1}H NMR chemical shifts of amide protons, amide proton–deuterium exchange rate, solvent perturbation of the amide proton signal upon addition of an H-bonding acceptor solvent (DMSO-d_6), paramagnetic radical induced line broadening of NH proton resonances caused by the addition of the free radical TEMPO, and temperature dependence of the ^{1}H NMR chemical shifts of amide protons.[18] In the following discussion we considered the chemical shifts of the amide NH protons, and the effect of the addition of increasing amounts of the H-bonding acceptor solvent (DMSO-d_6) to a 10 mM solution of the corresponding dipeptide in $CDCl_3$ over the range from 0 to 10%. Figure 3 shows the effects of the added perturbing agent on the NH proton resonances in compounds (R_a,*S*)- and (S_a,*S*)-**4a–c** in $CDCl_3$ solution.

In 10 mM $CDCl_3$ solution, the benzoylamino NH proton resonances of compounds (R_a,*S*)- and (S_a,*S*)-**4a–c** appeared downfield ($\delta > 8.5$ ppm) and an appreciable downfield shift is observed upon the addition of increasing amounts of the H-bonding acceptor solvent (DMSO-d_6) to a 10 mM of the corresponding dipeptide in $CDCl_3$. These data suggest that benzamido protons are not involved in intramolecularly hydrogen-bonded states.

In all model dipeptides the following ^{1}H NMR parameters were observed for the NH proton of the cyclohexylamide group. A chemical shift of about 7.5 ppm, which is downfield by about 0.5 ppm relative to the corresponding amide proton in the cyclohexylamide unit of phenylalanine, and a reduced solvent perturbation upon addition of increasing amounts of DMSO-d_6 [δ(NH) 0.1–0.25 ppm] were observed. This behaviour is consistent with the presence of a significant population of molecules in which these protons are involved in the formation of a stable intramolecular hydrogen bond.

The resonance of the NH proton signal of phenylalanine appears at about 6 ppm, a chemical shift characteristic of a peptide backbone proton that is not involved in hydrogen bonding. In all model dipeptides the addition of increasing

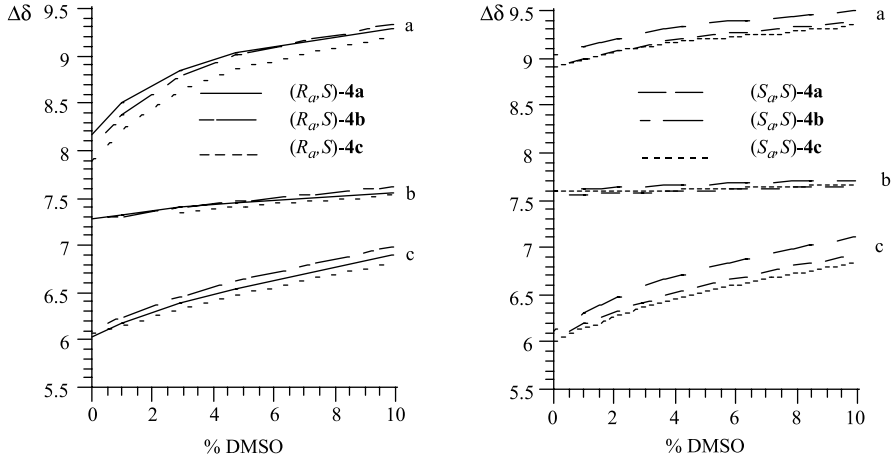


Figure 3. Plot of NH proton chemical shifts in the ^{1}H NMR spectra as a function of increasing % of DMSO added to the $CDCl_3$ solution for (a) NHCOPh, (b) NHCOCy and (c) NHPhe protons.

Table 4. Most significant results observed for compounds (R_a,*S*)- and (S_a,*S*)-**4a–c** in conventional 1D-difference NOE experiments carried out in 10 mM $CDCl_3$ solutions at 293 K

Spin *i* identity	Spin *j* identity	$\eta i(j)$ [$\eta j(i)$]×100					
		(R_a,*S*)-**4a**	(S_a,*S*)-**4a**	(R_a,*S*)-**4b**	(S_a,*S*)-**4b**	(R_a,*S*)-**4c**	(S_a,*S*)-**4c**
NHCOPh	$H^{\gamma'}$[(RCy)Gly]	7.5(10.9)	11.0(12.1)	6.2(n.d.)	3.2(2.2)	8.9(14.6)	9.9(14.2)
NHPhe	H^{γ}[(RCy)Gly]	3.4(6.5)	4.8(7.1)	2.3(4.2)	1.4(4.5)	3.9(6.9)	3.2(8.0)
NHPhe	H^{α}(Phe)	6.4(2.5)	6.1(1.9)	3.5(2.4)	3.1(1.8)	6.1(2.4)	6.7(2.0)
NHPhe	$H^{\beta h}$(Phe)	3.5(4.7)	3.0(3.7)	−(2.1)	1.3(2.9)	n.r.[a]	3.0(6.1)
H^{α}(Phe)	NHCy	7.3	7.2	n.r.[a]	2.5	n.r.[a]	6.8
H^{α}(Phe)	$H^{\beta l}$(Phe)	5.4(16.5)	4.3(17.5)	1.8(7.7)	2.8(8.1)	n.r.[a]	4.0(25.9)

h and l superscripts indicate β proton to higher or lower field, respectively.
[a] Signals due to this proton were not resolved to allow presaturation.

amounts of the H-bonding acceptor solvent (DMSO-d_6) to a 10 mM solution of the corresponding dipeptide in $CDCl_3$ resulted in appreciable downfield shifts of the phenylalanine NH ($\Delta\delta$ 0.8–1 ppm) resonances. These observations are characteristic of a peptide backbone proton that is not involved in hydrogen bonding.

It is worth mentioning that in homochiral compounds (S_a,*S*)-**4a–c** the benzoylamino NH proton signal is shifted to a lesser extent upon addition of DMSO-d_6 than the same signal in heterochiral compounds (R_a,*S*)-**4a–c**. This situation could be indicative of a relative shielding effect from the solvent in homochiral compounds due to the position of this NH within the β-turn. On the other hand in $CDCl_3$ solution the benzoylamino NH proton signal in heterochiral compounds (R_a,*S*)-**4a–c** is more shielded than the same signal in homochiral compounds (S_a,*S*)-**4a–c**.

All the above data are consistent with the occurrence of a significant population of β-turn conformers stabilised by an intramolecular hydrogen bond of the $i \leftarrow i+3$ type residues for compounds (R_a,*S*)- and (S_a,*S*)-**4a–c** in solution.

Of all the NMR parameters, coupling constants can be fruitfully used in determining spatial orientations of the interacting nuclei. For the phenylalanine residue, the vicinal ^1H–^1H coupling constant for groupings H–N–C–H^{α} (J^{α}_{NH-CH}) and H^{α}–C–C–H^{β} ($J_{\alpha\beta}$) could be elucidated by analysing the NH, H^{α} and H^{β} signals simultaneously.

The vicinal coupling constants J^{α}_{NH-CH} can be related to the torsion angle around the NH–CH^{α} Φ by a Karplus-type equation and, among the different sets of coefficients described in the literature for this type of equation, we chose that proposed by Cung et al.[19]

$$J^{\alpha}_{NH-CH} = 8.6\cos^2(\Phi \pm 60) - 2.9\cos(\Phi \pm 60)$$

[(+) for D and *R* configurations and (−) for L and *S* configurations, respectively]

According to this equation a J^{α}_{NH-CH} value of 8.50–8.90 H is indicative of a dihedral angle Φ, defined as recommended by the IUPAC-IUB commission,[16] of about −90°, as one would expect for the residue $i+2$ of a type II′ or a type I β-turn.

The best means of obtaining direct evidence for the predominance of a particular β-turn conformation in solution is from NOE experiments. This is because the observation of a direct $^1H\{^1H\}$NOE between a pair of protons is evidence for a significant population of conformers in which the protons are close, typically within 3–3.5 Å for flexible small peptides in solution.[20] Difference NOE experiments were carried out by irradiation of various X–H protons in compounds (R_a,*S*)-**4a–c** and (S_a,*S*)-**4a–c** in 10 mM $CDCl_3$ solutions at 293 K. A summary of the results obtained upon irradiation of these signals is shown in Table 4

A small but reproducible NOE was observed between the $H^{\gamma}_{(i+1)}$ [(RCy)Gly] and the phenylalanine NH protons for compounds (R_a,*S*)-**4a–c** and (S_a,*S*)-**4a–c** (see Table 4), which suggests short distances (<3.5 Å) between these nuclei. The interatomic distances between H^{γ} on the residue $i+1$ and the phenylalanine NH protons mainly depend on the absolute configuration of the chiral axis (R_a or S_a) and the ϕ and ψ torsion angles of the central residues, that is, on the type of turn adopted by the main chain. Molecular mechanics calculations were performed to ascertain the interatomic distances[21] between both *axial* and *equatorial* protons occupying this position and the phenylalanine NH proton in energy-minimised structures. Ideal β-turn conformations of types I and II′ were adopted and these show that this condition is only fulfilled if the studied compounds adopt a type II′ β-turn. In this case the existence of NOE between the $H^{\gamma}_{(i+1)}$ [(RCy)Gly] and the phenylalanine NH protons for compounds (R_a,*S*)-**4a–c** and (S_a,*S*)-**4a–c** proves that these compounds adopt a type II′ β-turn conformation in $CDCl_3$ solution. The calculated values for ideal β-turn conformations for compounds (R_a,*S*)-**4c** and (S_a,*S*)-**4c** are given in Table 5.

Table 5. Interatomic distances[a] (MM) between the $H^{\gamma}_{(i+1)}$ [(RCy)Gly] and the Phe($i+1$) NH proton calculated for ideal β-turn conformations of compounds (R_a,*S*)-**4c** and (S_a,*S*)-**4c**

	βI	βII′
H^{γ}_{eq}···NHPhe [(R_a,*S*)-**4c**]	4.39	2.63
H^{γ}_{ax}···NHPhe [(R_a,*S*)-**4c**]	5.21	2.68
NHBz···NHPhe [(R_a,*S*)-**4c**]	2.94	4.29
H^{γ}_{eq}···NHPhe [(S_a,*S*)-**4c**]	4.40	2.74
H^{γ}_{ax}···NHPhe [(S_a,*S*)-**4c**]	5.17	4.27
NHBz···NHPhe [(S_a,*S*)-**4c**]	2.98	4.36

[a] Distances are in Å.

Finally, we focused our attention on the side chain of these new axially chiral α,β-didehydroamino acids. Indeed, (R_a)- and (S_a)-4-methyl-, 4-phenyl- and (4-*tert*-butylcyclohexylidene)glycines can be regarded as alanine, phenylglycine

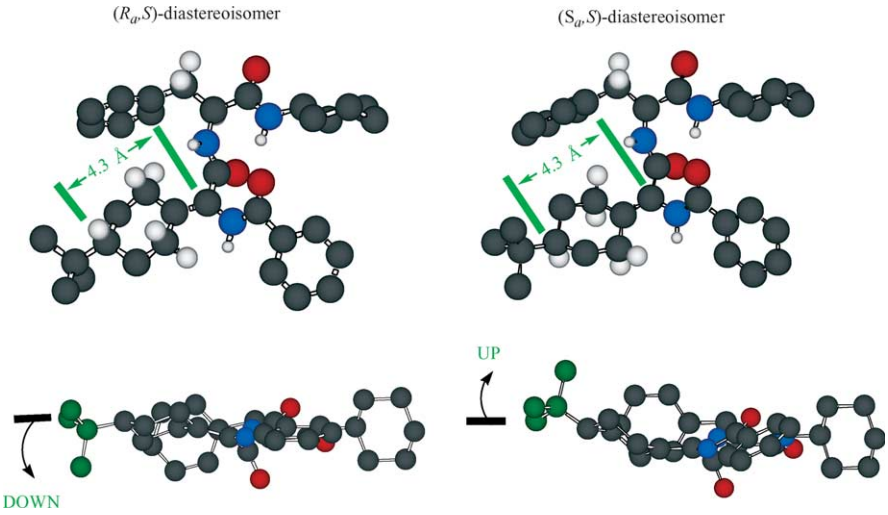


Figure 4. Spatial disposition of the side chain of (R_a)- and (S_a)-(4-*tert*-butylcyclohexylidene)glycine in compounds (R_a,S)-**4c** and (S_a,S)-**4c**.

and *tert*-leucine analogues of *R* and *S* configuration that contain conformationally locked spacers between the side chain of the amino acid and the backbone. In the model dipeptides (R_a,S)-**4a–c** and (S_a,S)-**4a–c**, which incorporate these axially chiral amino acids, the methyl, phenyl and *tert*-butyl groups are located 4.3 Å away from the peptide backbone and directed either down, (R_a,S) diastereoisomer, or up, (S_a,S) diastereoisomer, with respect to the middle plane of the β-turn. (Fig. 4).

3. Conclusions

Diastereomerically pure model dipeptides containing axially chiral α,β-didehydroamino acids at the ($i+1$) position can be conveniently obtained by applying the 'oxazolone method' developed by Obrecht et al.[15]

X-ray diffraction analyses of monocrystalline samples of compounds (R_a,S)-**4a** and (R_a,S)-**4c** revealed that in the crystal both compounds adopt a type II′ β-turn conformation with the two amino acids in the β-turn positions and a transannular hydrogen bond between the benzoyl C═O group and the cyclohexylamide NH group. NMR studies clearly indicate that this structure prevails in solution and reveals a similar behaviour for all synthesised compounds. It can therefore be concluded that axially chiral α,β-didehydroamino acids can accommodate in the ($i+1$) position of a β-turn in the heterochiral as well as in the homochiral dipeptides studied.

The introduction of axially chiral amino acids in model dipeptides allows the synthesis of conformationally restricted analogues in which the side chain of the amino acid is pulled out from the backbone peptide.

The development of synthetic methodologies to gain access to peptides that incorporate new axially chiral amino acids in different positions of the main chain is currently underway. In this context, the Wittig–Horner olefination has proven to be synthetically useful to obtain model dipeptides containing chiral α,β-didehydroamino acid moieties in the ($i+2$) position as diastereomeric mixtures.[22] Development of diastereoselective syntheses is underway and will be published in due course.

4. Experimental

4.1. General

All reagents were of analytical grade and were used as obtained from commercial sources. Most reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were visualised using UV light (254 nm) and anisaldehyde/sulfuric acid/ethanol (2:1:100). Column chromatography was performed using silica gel (Kiesegel 60, 230–400 mesh). (*S*)-Phenylalanine cyclohexylamide (**3**) was prepared according to the previously described procedure.[15]

Melting points were determined in open capillaries and are uncorrected. FTIR spectra of liquids were recorded as thin films on NaCl plates and FTIR spectra of solids were recorded as nujol dispersions on NaCl plates, ν_{max} expressed in cm^{-1} is given for the main absorption bands and prominent peaks. Optical rotations were measured in a cell with a 10 cm path length at 25 °C, concentrations are given in g/100 mL. Elemental analyses were performed using a C, H, N, S elemental analyser. ^1H NMR and ^{13}C NMR spectra were acquired at 25 °C in $CDCl_3$ at 300 and 75 MHz, respectively. The chemical shifts (δ) are reported in parts per million and the coupling constants (J) in Hertz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad signal; bd, broad doublet; dd, doublet of doublets, ddd, doublet of doublet of doublets. The concentration of samples amounted to 10 mM for ^1H NMR, COSY spectra, and ^1H NOE experiments. No special precautions, such as degassing of the samples, were taken. In the NOE experiments Bruker standard microprogram NOEMULT was used and scans were recorded on applying 70 dB decoupling power, 8 s total irradiation time and 1 s relaxation delay. All two dimensional correlated spectroscopy (COSY) data consisted of 256 t_1 increments with a relaxation delay of 1 s. Shifted squared sine functions were applied to the data before transformation.

4.2. X-ray diffraction

The X-ray diffraction data were collected at room temperature on a four circle Siemens P4 diffractometer, using graphite-monochromated Mo Kα radiation (λ= 0.71073 Å). Structures were solved by direct methods using SIR92[23] and refinement was performed using SHELXL 97[24] by the full-matrix least-squares technique with anisotropic thermal factors for heavy atoms. Hydrogen atoms were calculated at idealised positions, and during refinement they were allowed to ride on their carrying atom with an isotropic thermal factor fixed to 1.2 times the U_{eq} value of the carrier atom (1.5 for the methyl protons).

Crystallographic data for the structures of compounds (R_a,*S*)-**4a** and (R_a,*S*)-**4c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-210790 and 210789, respectively. Copies of the data can be obtained, free of charge, via http://www.ccdc.cam.uk/conts/retrieving.html or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ. UK [fax: +44 9 1223 336033 or e-mail deposit@ccdc.cam.ac.uk].

4.3. General procedure for the synthesis of 4-(4-substituted-cyclohexylidene)-2-phenyl-1,3-oxazol-5(4*H*)ones (2a–c)

Ac_4Pb (2.22 g, 5 mmol) was added at room temperature to a mixture of the corresponding 4-substituted-cyclohexanone **1a–c** (30 mmol), hippuric acid (1.74 g, 10 mmol) and Ac_2O (3.06 g, 30 mmol). The reaction mixture was stirred for 5 h under reflux and then cooled to 0 °C, treated with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (eluting with diethyl ether/hexane 1/4) afforded the corresponding product **2a–c**.

4.3.1. 4-(4-Methylcyclohexylidene)-2-phenyl-1,3-oxazol-5(4*H*)one (2a). The above general procedure, starting from 4-methylcyclohexanone (**1a**) (3.36 g, 30 mmol), gave compound **2a** (1.56 g, 61%) as a white solid after column chromatography. Mp = 86 °C; IR absorption (nujol) 1782, 1744, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, J=6.5 Hz, 3H), 1.12–1.27 (m, 2H), 1.68–1.75 (m, 1H), 1.93–2.02 (m, 2H), 2.13–2.29 (m, 2H), 3.45 (bd, J= 12.6 Hz, 1H), 3.85 (bd, J=13.8 Hz, 1H), 7.44–7.52 (m, 3H), 8.00–8.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 28.2, 31.4, 31.9, 35.8, 36.0, 126.1, 127.6, 128.7, 129.0, 132.3, 159.2, 161.1, 165.7. Elemental analysis calcd (%) for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49; found: C, 75.56; H, 6.63; N, 5.57.

4.3.2. 4-(4-Phenylcyclohexylidene)-2-phenyl-1,3-oxazol-5(4*H*)one (2b). The above general procedure, starting from 4-phenylcyclohexanone (**1b**) (5.22 g, 30 mmol), gave compound **2b** (1.62 g, 51%) as a white solid after column chromatography. Mp = 128 °C; IR absorption (nujol) 1791, 1755, 1664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.69–1.79 (m, 2H), 2.20–2.40 (m, 4H), 2.85–2.93 (m, 1H), 3.70 (bd, J=13.8 Hz, 1H), 4.10 (bd, J=13.6 Hz, 1H), 7.18–7.31 (m, 5H), 7.44–7.55 (m, 3H), 8.04–8.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 31.7, 34.9, 35.0, 43.7, 126.0, 126.4, 126.7, 127.6, 128.5, 128.8, 129.5, 132.5, 145.4, 159.3, 159.6, 165.5. Elemental analysis calcd (%) for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41; found: C, 79.52; H, 6.09; N, 4.35.

4.3.3. 4-(4-*tert*-Butylcyclohexylidene)-2-phenyl-1,3-oxazol-5(4*H*)one (2c). The above general procedure, starting from 4-*tert*-butylcyclohexanone (**1c**) (4.62 g, 30 mmol), gave compound **2c** (1.54 g, 52%) as a white solid after column chromatography. Mp = 125 °C; IR absorption (nujol) 1784, 1755, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 9H), 1.18–1.42 (m, 3H), 2.00–2.22 (m, 4H), 3.55 (bd, J=13.2 Hz, 1H), 3.98 (bd, J=14.1 Hz, 1H), 7.40–7.48 (m, 3H), 7.98–8.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5, 28.8, 28.9, 28.9, 32.0, 32.5, 47.5, 126.2, 127.6, 128.7, 128.8, 132.3, 159.3, 161.5, 165.7. Elemental analysis calcd (%) for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71; found: C, 77.68; H, 7.71; N, 4.67.

4.4. General procedure for the synthesis of N^2-[(R_a)-N^1-benzoyl-(4-substituted-cyclohexylidene)glycyl]-(*S*)-phenylalanine cyclohexylamide [(R_a,*S*)-4a–c] and N^2-[(S_a)-N^1-benzoyl-(4-substituted-cyclohexylidene)glycyl]-(*S*)-phenylalanine cyclohexylamide [(S_a,*S*)-4a–c]

A mixture of the corresponding 5(4*H*)-oxazolone **2a–c** (1.5 mmol) and (*S*)-phenylalanine cyclohexylamide (**3**) (492 mg, 2 mmol) in *N*-methylpyrrolidin-2-one (8 mL) was stirred under argon for 24 h at 70 °C. The reaction mixture was cooled to room temperature and poured onto a mixture of ice (10 g), 1 N HCl (15 mL) and EtOAc (40 mL). The organic layer was washed with water and the combined aqueous layers extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography, eluting first with Et_2O and then with EtOAc, afforded the corresponding peptide **4a–c** as an equimolecular mixture of diastereoisomers. Careful column chromatography, eluting with CH_2Cl_2/EtOAc 1/4, afforded analytically pure samples of the two diastereoisomers of compounds **4a–c**.

4.4.1. N^2-[(R_a)-N^1-Benzoyl-(4-methylcyclohexylidene) glycyl]-(*S*)-phenylalanine cyclohexylamide [(R_a,*S*)-4a]. The above general procedure, starting from 5(4*H*)-oxazolone **2a** (382 mg, 1.5 mmol), gave compound **4a** (691 mg, 92%) as an equimolecular mixture of diastereoisomers. Compound (R_a,*S*)-**4a** was eluted first upon additional column chromatography and isolated as a white solid. Mp = 195 °C (dec); $[\alpha]_D^{25} = -74.4$ (c 0.5, MeOH); IR absorption (nujol) 3292, 1650, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J=6.5 Hz, 3H), 1.00–1.94 (m, 17H), 2.09 (bd, J=14.4 Hz, 1H), 2.52 (bd, J=14.4 Hz, 1H), 3.09 (dd, J=14.3, 8.9 Hz, 1H), 3.39 (dd, J=14.3, 4.9 Hz, 1H), 3.69–3.82 (m, 1H), 4.82 (ddd, J=8.9, 8.5, 4.9 Hz, 1H), 6.05 (d, J=8.5 Hz, 1H), 7.17–7.22 (m, 6H), 7.28–7.36 (m, 2H), 7.40–7.48 (m, 1H), 7.66–7.71 (m, 2H), 8.26 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 25.2, 25.3, 25.7, 28.8, 29.1, 31.7, 32.6, 32.8, 34.5, 35.6, 37.5, 48.7, 54.6, 123.0, 126.9, 127.4, 128.3, 128.7, 129.1, 131.7, 132.3, 137.1, 139.7, 166.8, 167.2, 169.5. Elemental analysis

calcd (%) for $C_{31}H_{39}N_3O_3$: C, 74.22; H, 7.84; N, 8.38; found: C, 74.16; H, 7.79; N, 8.45.

4.4.2. N^2-[(S_a)-N^1-Benzoyl-(4-methylcyclohexylidene)-glycyl]-(*S*)-phenylalanine cyclohexylamide [(S_a,*S*)-4a]. Compound (S_a,*S*)-**4a** was eluted second upon additional column chromatography and isolated as a white solid. Mp = 245 °C (dec); $[\alpha]_D^{25} = -84.2$ (*c* 0.5, MeOH); IR absorption (nujol) 3303, 1656, 1631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.5 Hz, 3H), 1.00–1.97 (m, 17H), 2.09 (bd, *J* = 14.0 Hz, 1H), 2.49 (bd, *J* = 13.6 Hz, 1H), 3.12 (dd, *J* = 14.7, 8.9 Hz, 1H), 3.41 (dd, *J* = 14.7, 4.6 Hz, 1H), 3.70–3.85 (m, 1H), 4.89 (ddd, *J* = 8.9, 8.9, 4.6 Hz, 1H), 6.04 (d, *J* = 8.9 Hz, 1H), 7.17–7.28 (m, 7H), 7.33–7.41 (m, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.64–7.72 (m, 2H), 8.91 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 25.3, 25.4, 25.7, 29.1, 29.3, 32.4, 32.6, 32.9, 35.0, 36.0, 37.3, 48.7, 54.6, 123.1, 127.0, 127.4, 128.1, 128.7, 129.0, 131.7, 132.1, 137.2, 138.3, 166.7, 167.8, 169.3. Elemental analysis calcd (%) for $C_{31}H_{39}N_3O_3$: C, 74.22; H, 7.84; N, 8.38; found: C, 74.21; H, 7.92; N, 8.42.

4.4.3. N^2-[(R_a)-N^1-Benzoyl-(4-phenylcyclohexylidene)-glycyl]-(*S*)-phenylalanine cyclohexylamide [(R_a,*S*)-4b]. The above general procedure, starting from 5(4*H*)-oxazolone **2b** (475 mg, 1.5 mmol), gave compound **4b** (709 mg, 84%) as an equimolecular mixture of diastereoisomers. Compound (R_a,*S*)-**4b** was eluted first upon additional column chromatography and isolated as a white solid. Mp = 201 °C (dec); $[\alpha]_D^{25} = -103.0$ (*c* 0.5, MeOH); IR absorption (nujol) 3297, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00–2.04 (m, 17H), 2.32 (bd, *J* = 14.4 Hz, 1H), 2.60 (bd, *J* = 12.2 Hz, 1H), 3.11 (dd, *J* = 14.3, 8.6 Hz, 1H), 3.36 (dd, *J* = 14.3, 5.3 Hz, 1H), 3.72–3.84 (m, 1H), 4.82 (ddd, *J* = 8.7, 8.6, 5.3 Hz, 1H), 6.13 (d, *J* = 8.7 Hz, 1H), 7.09–7.32 (m, 11H), 7.36–7.44 (m, 2H), 7.46–7.54 (m, 1H), 7.73–7.76 (m, 2H), 7.91 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 25.3, 25.7, 29.5, 29.7, 32.7, 32.8, 33.9, 34.5, 37.4, 43.5, 48.7, 54.4, 123.5, 126.3, 126.6, 127.0, 127.4, 128.4, 128.5, 128.7, 129.2, 131.9, 132.3, 136.9, 138.9, 145.6, 166.9, 167.0, 169.4. Elemental analysis calcd (%) for $C_{36}H_{41}N_3O_3$: C, 76.70; H, 7.33; N, 7.45; found: C, 76.83; H, 7.25; N, 7.38.

4.4.4. N^2-[(S_a)-N^1-Benzoyl-(4-phenylcyclohexylidene)-glycyl]-(*S*)-phenylalanine cyclohexylamide [(S_a,*S*)-4b]. Compound (S_a,*S*)-**4b** was eluted second upon additional column chromatography and isolated as a white solid. Mp = 130 °C (dec); $[\alpha]_D^{25} = -98.8$ (*c* 0.5, MeOH); IR absorption (nujol) 3315, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–2.00 (m, 16H), 2.27 (bd, *J* = 14.3 Hz, 1H), 2.57 (dt, *J* = 11.8, 2.9 Hz, 1H), 2.67 (bd, *J* = 14.4 Hz, 1H), 3.15 (dd, *J* = 14.7, 8.7 Hz, 1H), 3.43 (dd, *J* = 14.7, 4.9 Hz, 1H), 3.75–3.90 (m, 1H), 4.95 (ddd, *J* = 8.9, 8.7, 4.9 Hz, 1H), 6.11 (d, *J* = 8.9 Hz, 1H), 7.12–7.28 (m, 12H), 7.28–7.39 (m, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.68–7.72 (m, 2H), 9.20 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 25.4, 25.7, 29.5, 29.7, 32.7, 32.9, 34.3, 35.0, 37.3, 44.3, 48.7, 54.7, 123.7, 126.5, 126.7, 127.0, 127.5, 128.1, 128.6, 128.8, 129.1, 131.7, 131.9, 137.1, 137.3, 166.8, 167.9, 169.2. Elemental analysis calcd (%) for $C_{36}H_{41}N_3O_3$: C, 76.70; H, 7.33; N, 7.45; found: C, 76.81; H, 7.39; N, 7.51.

4.4.5. N^2-[(R_a)-N^1-Benzoyl-(4-*tert*-butylcyclohexylidene)-glycyl]-(*S*)-phenylalanine cyclohexylamide [(R_a,*S*)-4c]. The above general procedure, starting from 5(4*H*)-oxazolone **2c** (445 mg, 1.5 mmol), gave compound **4c** (688 mg, 82%) as an equimolecular mixture of diastereoisomers. Compound (R_a,*S*)-**4c** was eluted first upon additional column chromatography and isolated as a white solid. Mp = 158 °C (dec); $[\alpha]_D^{25} = -72.4$ (*c* 0.5, MeOH); IR absorption (nujol) 3319, 1661, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 9H), 0.98–1.98 (m, 17H), 2.37 (bd, *J* = 13.3 Hz, 1H), 2.62 (bd, *J* = 14.0 Hz, 1H), 3.24 (d, *J* = 6.7 Hz, 2H), 3.66–3.84 (m, 1H), 4.80 (ddd, *J* = 8.7, 6.7, 6.7 Hz, 1H), 6.03 (d, *J* = 8.7 Hz, 1H), 7.15–7.27 (m, 6H), 7.31–7.39 (m, 2H), 7.42–7.50 (m, 1H), 7.67–7.73 (m, 2H), 8.00 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 25.2, 25.7, 27.4, 27.5, 28.6, 29.7, 30.1, 32.4, 32.6, 32.7, 37.3, 47.4, 48.7, 54.3, 122.7, 127.0, 127.2, 128.4, 128.8, 129.4, 131.8, 132.4, 136.7, 140.5, 166.6, 166.8, 169.4. Elemental analysis calcd (%) for $C_{34}H_{45}N_3O_3$: C, 75.10; H, 8.34; N, 7.73; found: C, 75.22; H, 8.25; N, 7.83.

4.4.6. N^2-[(S_a)-N^1-Benzoyl-(4-*tert*-butylcyclohexylidene)-glycyl]-(*S*)-phenylalanine cyclohexylamide [(S_a,*S*)-4c]. Compound (S_a,*S*)-**4c** was eluted second upon additional column chromatography and isolated as a white solid. Mp = 129 °C (dec); $[\alpha]_D^{25} = -87.2$ (*c* 0.5, MeOH); IR absorption (nujol) 3298, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H), 0.94–1.98 (m, 17H), 2.24 (bd, *J* = 13.9 Hz, 1H), 2.56 (bd, *J* = 13.3 Hz, 1H), 3.23 (dd, *J* = 14.3, 8.4 Hz, 1H), 3.34 (dd, *J* = 14.3, 4.9 Hz, 1H), 3.77–3.85 (m, 1H), 4.89 (ddd, *J* = 8.7, 8.4, 4.9 Hz, 1H), 6.02 (d, *J* = 8.7 Hz, 1H), 7.11–7.37 (m, 7H), 7.31–7.42 (m, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.63–7.73 (m, 2H), 8.89 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 25.4, 25.7, 27.5, 27.7, 28.7, 29.6, 29.9, 32.4, 32.7, 32.8, 37.2, 47.8, 48.7, 54.5, 122.7, 127.1, 127.4, 128.2, 128.8, 129.2, 131.7, 132.1, 137.0, 138.5, 166.8, 167.7, 169.3. Elemental analysis calcd (%) for $C_{34}H_{45}N_3O_3$: C, 75.10; H, 8.34; N, 7.73; found: C, 74.98; H, 8.28; N, 7.79].

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References and notes

1. (a) Balaram, P. *Curr. Opin. Struct. Biol.* **1992**, *2*, 845–851. (b) Rizo, J.; Gierasch, L. M. *Annu. Rev. Biochem.* **1992**, *61*, 387–418. (c) Liskamp, R. M. J. *Recl. Trav. Pays-Bas* **1994**, *113*, 1–19. (d) McDowell, R. S.; Artis, R. D. *Annu. Rep. Med. Chem.* **1995**, *30*, 265–274. (e) Hanessian, S.; McNaughton Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854. (f) Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. *Biopolymers* **1997**, *43*, 219–266.
2. (a) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159–172. (b) Smith, M. J.; Kim, D.; Horenstein, B.; Nakanishi, K.; Kustin, K. *Acc. Chem. Res.* **1991**, *24*, 117–124.
3. (a) Gross, L. M.; Morell, P. M.; Craig, G. T. *Proc. Natl. Acad.*

Sci. U.S.A. **1969**, *62*, 953–961. (b) Stammer, C. H. In Weinstein, B., Ed.; Chemistry and Biochemistry of Amino Acids, Peptides and Proteins; Marcel Dekker: New York, 1982; Vol. 6, pp 33–74. (c) Aydin, M.; Lucht, N.; Koenig, W. A.; Lupp, R.; Jung, G.; Winkelmann, G. *Liebigs Ann. Chem.* **1985**, 2285–2300. (d) Fate, G. D.; Benner, C. P.; Grode, S. H.; Gilbertson, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 11363–11368.

4. (a) Chan, W. C.; Bycroft, B. W.; Lian, L.-Y.; Roberts, G. C. K. *FEBS Lett.* **1989**, *252*, 29–36. (b) Jung, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1051–1068.
5. Mihara, H.; Aoyagi, H.; Veno, T.; Kato, T.; Izumiya, N. *Bull. Chem. Soc. Jpn* **1986**, *59*, 2041–2043.
6. Noda, K.; Shimohigashi, Y.; Izumiya, N. In Gross, E., Meienhofer, J., Eds.; Peptides: Analysis, Synthesis, Biology; Academic: New York, 1983; Vol. 5, pp 285–339.
7. (a) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131–3152. (b) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers* **2001**, *60*, 396–419. (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011.
8. Hruby, V. J. *Acc. Chem. Res.* **2001**, *34*, 389–397.
9. (a) Shimohigashi, Y.; Stammer, C. H.; Costa, T.; von Voigtlander, P. F. *Int. J. Pept. Protein Res.* **1983**, *22*, 489–494. (b) Brady, S. F.; Cochran, D. W.; Nutt, R. F.; Holly, F. W.; Bennett, C. D.; Paleveda, W. J.; Curley, P. E.; Arison, B. H.; Saperstein, R.; Weber, D. *Int. J. Pept. Protein Res.* **1984**, *23*, 212–222. (c) Salvadori, S.; Marastoni, M.; Balboni, G.; Marzola, G.; Tomatis, R. *Int. J. Pept. Protein Res.* **1986**, *28*, 254–261. (d) Salvadori, S.; Marastoni, M.; Balboni, G.; Marzola, G.; Tomatis, R. *Int. J. Pept. Protein Res.* **1986**, *28*, 262–273. (e) Imazu, S.; Shimohigashi, Y.; Kodama, H.; Sakaguchi, K.; Waki, M.; Kato, T.; Izumiya, N. *Int. J. Pept. Protein Res.* **1988**, *32*, 298–306.
10. Shimohigashi, Y.; English, M. L.; Stammer, C. H.; Costa, T. *Biochem. Biophys. Res. Commun.* **1982**, *104*, 583–590.
11. (a) Jain, R. M.; Chauhan, V. S. *Biopolymers* **1996**, *40*, 105–119. (b) Broda, M. A.; Rzeszotarska, B.; Smelka, L.; Rospenk, M. *J. Pept. Res.* **1997**, *50*, 342–351. (c) Singh, T. P.; Kaur, P. *Prog. Biophys. Mol. Biol.* **1996**, *66*, 141–165. (d) Mathur, P.; Ramakumar, S.; Chauhan, V. S. *Biopolymers (Pept. Sci.)* **2004**, *76*, 150–161.
12. (a) Pieroni, O.; Montagnoli, G.; Fissi, A.; Merlino, S.; Ciardelli, F. *J. Am. Chem. Soc.* **1975**, *97*, 6820–6826. (b) Singh, T. P.; Narula, P.; Patel, H. C. *Acta Crystallogr.* **1990**, *B46*, 539–545. (c) Ciszak, E.; Pietrzynski, G.; Rzeszotarska, B. *Int. J. Pept. Protein Res.* **1992**, *39*, 218–222. (d) Pietrzynski, G.; Rzeszotarska, B.; Kubica, Z. *Int. J. Pept. Protein Res.* **1992**, *40*, 524–531. (e) Gupta, A.; Chauhan, V. S. *Int. J. Pept. Protein Res.* **1993**, *41*, 421–426. (f) Tuzi, A.; Ciajolo, M. R.; Guarino, G.; Temussi, P. A.; Fissi, A.; Pieroni, O. *Biopolymers* **1993**, *33*, 1111–1121. (g) Sharma, P.; Narula, P.; Singh, T. P. *Biopolymers* **1994**, *34*, 1243–1249. (h) Dey, S.; Mitra, S. N.; Singh, T. P. *Biopolymers* **1996**, *39*, 849–857. (i) Dey, S.; Mitra, S. N.; Singh, T. P. *Int. J. Pept. Protein Res.* **1996**, *48*, 123–128. (j) Pietrzynski, G.; Rzeszotarska, B.; Ciszak, E.; Lisowski, M.; Kubica, Z.; Boussard, G. *Int. J. Pept. Protein Res.* **1996**, *48*, 347–356. (k) Rajashankar, K. R.; Ramakumar, S.; Jain, R. M.; Chauhan, V. S. *Biopolymers* **1997**, *42*, 373–382. (l) Gupta, A.; Mehrotra, R.; Tewari, J.; Jain, R. M.; Chauhan, V. S. *Biopolymers* **1999**, *50*, 595–601. (m) Crisma, M.; Formaggio, F.; Toniolo, C.; Yoshikawa, T.; Wakamiya, T. *J. Am. Chem. Soc.* **1999**, *121*, 3272–3278. (n) Ramagopal, U. A.; Ramakumar, S.; Sahal, D.; Chauhan, V. S. *Proc. Natl. Acad. Sci.* **2001**, *98*, 870–874. (o) Inai, Y.; Ishida, Y.; Tagawa, K.; Takasu, A.; Hirabayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 2466–2473. (p) Inai, Y.; Oshikawa, T.; Yamashita, M.; Tagawa, K.; Hirabayashi, T. *Biopolymers* **2003**, *70*, 310–322. (q) Padyana, A. K.; Ramakumar, S.; Mathur, P.; Jagannathan, N. R.; Chauhan, V. S. *J. Pept. Sci.* **2003**, *9*, 54–63.
13. β-Turn conformers have been classified according to the rotational angles ϕ and ψ associated with the $i+1$ and $i+2$ residues, with βI, βII and βIII type turns being the most common. Less common are βI′ and βII′ type turns in which ϕ and ψ torsion angles of the central residues are opposite to those in the corresponding common turns, Venkatachalam, C. M. *Biopolymers* **1968**, *6*, 1425–1436.
14. Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron Lett.* **1999**, *40*, 1027–1030.
15. Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieux, R.; Schönholzer, P.; Spiègler, C.; Müller, K. *Helv. Chim. Acta* **1995**, *78*, 563–580.
16. IUPAC-IUB Commission on Biochemical Nomenclature. *J. Mol. Biol.* **1970**, *52*, 1–17.
17. Benedetti, E. In Weinstein, B., Ed.; Chemistry and Biochemistry of Amino Acids, Peptides and Proteins; Marcel Dekker: New York, 1982; Vol. 6, pp 105–184.
18. Evans, J. N. S. *Biomolecular NMR Spectroscopy*; Oxford University Press: New York, 1996.
19. Cung, M. T.; Marraud, M.; Neél, J. *Macromolecules* **1974**, *7*, 606–613.
20. Wüthrich, K. *NMR of Proteins and Nucleic Acids*; Wiley: New York, 1986.
21. Molecular mechanics calculations were performed using the MM2 Chem3D program force field. In starting conformations N- and C-terminal residues and amino acid side chains were situated based on crystallographic data. In these structures the α,β-didehydroamino acid side chain adopts a chair-like conformation with the C4 substituent in an equatorial position and the benzyl group of the phenylalanine residue in a (−) *gauche* conformation ($\chi_2^1 = -60°$. Moreover, each amide group was fixed to the more stable *trans* conformation ($\omega = 180°$ and ψ ϕ, torsion angles for the main chain that defined the β-turn conformation type (I, I′, II, II′) were fixed at their ideal values.
22. Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Su, G. *Arkivoc* **2004**, *iv*, 59–66.
23. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1993**, *26*, 343–350.
24. Sheldrick, G. M., (1997) *SHELXL97, Program for the Refinement of Crystal Structures*; University of Göttingen: Germany.

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Imide–amide rearrangement of oxazaphosphorimidates: studies towards the application to the synthesis of chiral Lewis bases

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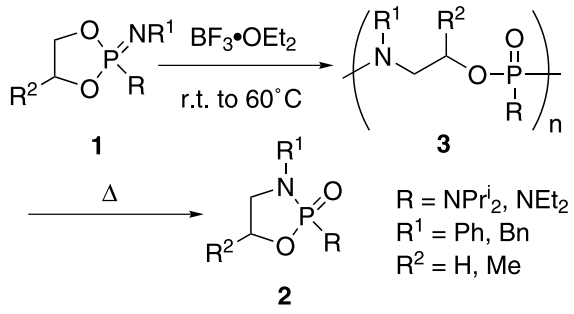
Abstract—The Lewis acid catalysed imide–amide rearrangement of oxazaphosphorimides to diazaphoshoramides is reported for the first time. In spite of the similarity to the previously reported Lewis acid catalysed imide–amide rearrangement of dioxaphosphorimides to oxazaphosphoramides we show that this rearrangement proceeds by a different mechanism, not involving the formation of an oligomeric intermediate. The oxazaphosphorimides are prepared in situ by the Staudinger reaction of the appropriate trivalent phosphorus compound with an azide and after the addition of $BF_3 \cdot OEt_2$, undergo rearrangement to the corresponding diazaphosphoramides. We have found that the rearrangement occurs with retention of configuration at the phosphorus atom and inversion of configuration at the rearranged carbon atom. When starting from chiral 1,2-aminoalcohol, substituted at the carbon atom that undergoes rearrangement, a mixture of diastereomers is obtained, but the diastereomeric ratio, initially obtained in the formation of the trivalent phosphorus compounds is maintained during the whole transformation. This implies that if the rearrangement is to be used for the preparation of chiral phosphoramides with defined stereochemistry at the phosphorus atom, a high diastereoselectivity during the preparation of the trivalent phosphorus precursors should be obtained.

1. Introduction

Catalytic processes involving Lewis base activation have been a topic of increasing interest.[1] Among the Lewis bases reported, phosphoramides have assumed a leading position. Chiral phosphoric triamides have been successfully employed as catalysts in a variety of transformations leading from moderately to good enantioselectivities.[1–7] In spite of the interest that these compounds have attracted, little or no effort has been devoted to the development of new synthetic methodologies for their preparation. The traditional coupling procedure between a reactive phosphorus reagent and a diamine ligand is still the best known synthetic choice when it comes to the preparation of the chiral catalysts employed in the majority of the transformations reported.[3] However, most of these are prepared from chiral C_2-symmetric diamines and therefore the phosphorus atom is not chiral. Due to our interest in the development of alternative synthetic pathways for the preparation of interesting chiral phosphoramides, we initiated a detailed study on the Lewis acid catalysed imide–amide rearrangement of cyclic phosphorimidates. As a result, we have reported a detailed mechanistic study of this reaction when applied to the rearrangement of dioxa **1** to oxaza **2** cyclic compounds. An intermolecular mechanism was found for this system and an oligomeric material **3**, resulting from a 1,4-addition-type ring-opening polymerisation (ROP) of the cyclic phosphorimidate **1**, was identified as being a stable intermediate of the rearrangement reaction, which occurs with retention of configuration at the carbon atom (Scheme 1).[8,9]

We have also established that the most probable mechanism for the 'oligomer–monomer' conversion involves an



Scheme 1.

Keywords: Imide–amide rearrangement; Phosphoramides; Lewis bases; Diazaphosphoramides.
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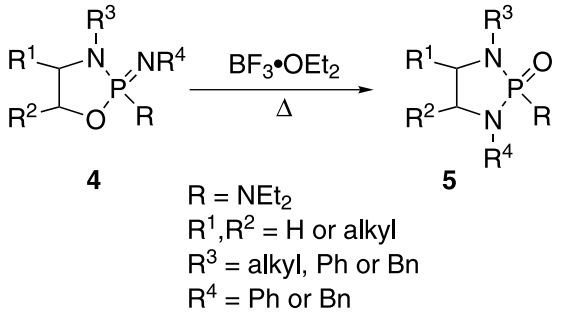


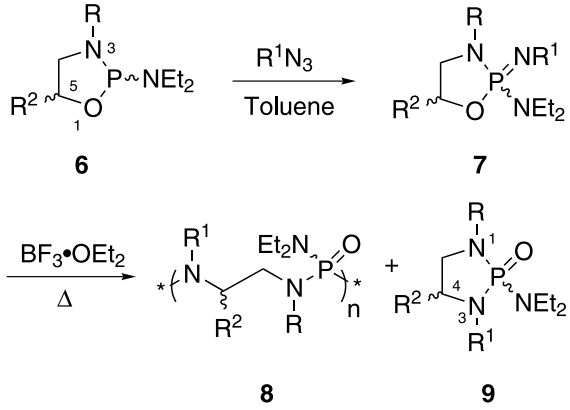
Scheme 2.

intramolecular nucleophilic attack of the chain oxygen to the phosphorus atom in a SNi chain reaction with P–O bond cleavage and formation of the cyclic product **2**.[9] The aim of the work now reported was to further explore the synthetic possibilities of the imide–amide rearrangement as a key step to the preparation of interesting cyclic chiral diazaphosphoramides.

We have found that chiral diazaphosphoramides **5** can be obtained from the imide–amide rearrangement of the corresponding oxazaphosphorimidate precursors **4** (Scheme 2), but also that the rearrangement reaction of this class of phosphorimides presents significant mechanistic differences from the parent dioxaphosphorimidates **1**, reported previously. The scope and limitations of the application of the imide–amide rearrangement reaction to the preparation of chiral phosphoramides are discussed in detail.

2. Results and discussion

As we have mentioned before, the Lewis acid catalysed imide–amide rearrangement of cyclic dioxaphosphorimidates **1** proceeds via a two step process, involving an oligomeric intermediate **3**, with the reaction being initiated by a ring opening polymerization (ROP) followed by the formation of a oxazaphospholidinone in a cyclisation step (Scheme 1). The formation of the stable phosphoryl bond plays an important role as a driving force for this ROP and we have shown that the presence or absence of substituents at the carbon atoms of the dioxaphospholane ring has a profound effect on the polymerisation. In the case of monosubstituted compounds, the polymerisation proceeds through the non-substituted carbon atom and, when a di-substituted compound is used, there is no reaction even under prolonged heating.[9] To probe the behaviour of structurally related oxazaphosphorimidates towards the imide–amide rearrangement, compounds **7a** and **7b** were prepared and subjected to Lewis acid catalysis (Scheme 3, Table 1). The formation of oligomer **8** was only detected for oxazaphosphorimidate **7a**, while for compound **7b** the cyclic rearranged product **9b** was directly obtained. This unexpected direct conversion of the more sterically hindered compound **7b**, to the rearranged cyclic phosphoramide **9b** with a good yield (approx. 60%), points to a different mechanism for the rearrangement of this class of compounds, when compared to the parent dioxaphosphorimidates **1**. In fact, this observation was confirmed in an



Scheme 3.

independent experiment where the thermal stability of compound **8a** was tested. Even after prolonged heating no rearranged product could be detected by ^{31}P NMR. This result is in accordance with the mechanism proposed for the oligomer–monomer conversion of the parent oligomer **3** and evidences that a phosphorous bonded oxygen is needed in the oligomeric chain for the reaction to occur.[9] As we have shown before for dioxaphosphorimidate substracts, the steric hindrance introduced by a methyl substituent at the carbon atom in the ring is sufficient to prevent the ROP to occur; the same seems to be valid for oxazaphosphorimidates. However, the most striking difference in the behaviour of these two classes of compounds is that for the oxazaphosphorimidates the conversion to a diazaphosphoramide can only be achieved by blocking the polymerization mechanism. This confirms the existence of an alternate mechanism for the imide–amide rearrangement of these compounds.

The introduction of a substituent (R^2) in the ring position 5 of compound **6** (Scheme 3) generates an extra asymmetric center, therefore a mixture of diastereoisomers is obtained (also called *cis*/*trans* when considering the relative position of the ring substituent R^2 to the phosphorous exocyclic substituent $-NEt_2$). In addition, the observation of the rearrangement of compound **7b** raises questions about the enantioselectivity of the rearrangement at the substituted carbon atom. With the aim of developing a synthetic route to enantiopure phosphoramides, a detailed study of this transformation was performed.

2.1. Study of the enantioselectivity of the imide–amide rearrangement of oxazaphosphorimidates

As a first approach, the reaction of racemic **6b** with benzylazide (formation of **7b**) and the subsequent evolution

Table 1. Outcome of the imide–amide rearrangement of compounds **7a**,**b** via Scheme 3

R	R^1	R^2	Imide **7**	Oligomer **8**	Diazaphosphoramide **9**
Bn	Bn	H	**a**	>90%[a]	Not detected
Bn	Bn	Me	**b**	Not detected	59%[b]

[a] Determined from the integration of the ^{31}P NMR signal in the reaction mixture.
[b] Global yield of isolated compounds after column chromatography (40% *cis*, 19% *trans*).

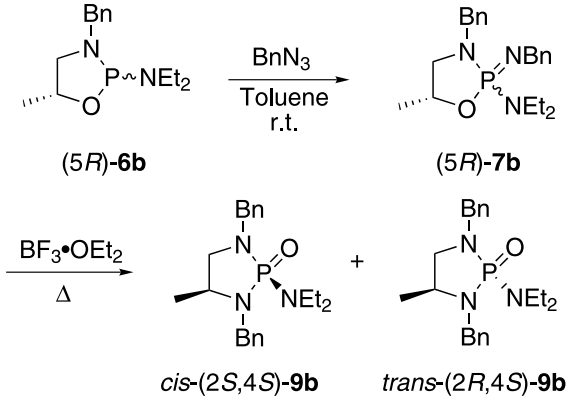
Table 2. ^{31}P NMR chemical shifts of the species involved in the imide–amide rearrangement and diastereomeric ratios as determined from the integration of the ^{31}P NMR signals

Compound	δ ^{31}P (ppm)	Diastereomers (%)
cis-**6b**	140.2	26
trans-**6b**	137.1	74
cis-**7b**	26.4	27
trans-**7b**	26.8	73
cis-**9b**	27.7	68
trans-**9b**	28.3	32

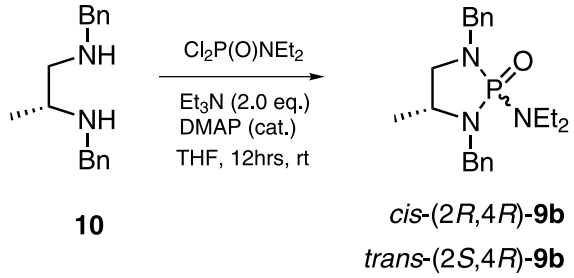
of the rearrangement reaction after the addition of $BF_3 \cdot OEt_2$, was followed by NMR; ^{31}P NMR was used to determine the diastereomeric ratio (dr) at every step of the reaction. The dr initially observed for the mixture of the trivalent phosphorus diastereomers **6b** (74:26) is not altered by the addition of the benzylazide and the formation of the imides **7b** (73:27). This result is in agreement with the fact that the Staudinger reaction proceeds with retention of configuration at the phosphorus centre and is also an indication of the configurational stability towards inversion, of the initial trivalent phosphorus compounds in the reaction conditions. The determined dr (Table 2) after the rearrangement reaction is complete (68:32, after 8 h under heating at 100 °C) is almost identical to the one from the initial trivalent phosphorus compounds.

Since there is no appreciable erosion of the dr, these results are a strong indication of a highly enantioselective transformation, occurring with retention or inversion of configuration at the rearranged centres (carbon and phosphorus). The determination of the relative configuration of the final products *cis*-**9b** and *trans*-**9b** was done based on the comparison of the ^1H NMR spectra of the isolated compounds after column chromatography. Due to the influence of the phosphoryl bond, the proton in position 4 in the *cis* configuration is more deshielded than the one in the *trans* configuration and its chemical shift can be used for the assignment of the relative configuration.[10–13]

In order to determine the enantioselectivity of the rearrangement, the reaction was repeated starting with the chiral phosphorimidates *cis*- and *trans*-(5*R*)-**7b**, derived from the chiral (*R*)-aminoalcohol ((*R*)-*N*-1-benzylaminopropan-2-ol) (Scheme 4). After rearrangement, the diastereomers were isolated and separated, and their relative



Scheme 4.



Scheme 5.

configuration (*cis*/*trans*) was determined by ^1H NMR as described before for the racemic compounds. The absolute configuration was determined by chiral HPLC, comparing the retention times of the rearrangement products **9**, starting from racemic **6b** and chiral 5*R*-**6b**, with the ones from reference chiral compounds *cis*-(2*R*,4*R*)-**9b** and *trans*-(2*S*,4*R*)-**9b**, prepared from a chiral diamine by an independent reaction (Scheme 5) (Table 3).

These results are a clear indication that the rearrangement proceeds with inversion of configuration at the rearranged carbon atom and, when analysed together with the values of the dr's shown before (Table 2), indicate that the reaction occurs with retention of configuration at the phosphorous atom. Due to the fact that the dr is maintained through all the reaction steps, starting from the trivalent phosphorus compounds until after the imide–amide rearrangement, the control of the stereochemistry at the phosphorous centre can be achieved by controlling the diastereomeric ratio during the synthesis of the trivalent phosphorus compounds.

As we have shown, the use of oxazaphosphorimidates **6a** derived from simple 1,2-aminoalcohols as substracts for the preparation of diazaphosphoramides, is limited by the fact that in these cases the favoured pathway for the reaction is the formation of oligomers. Therefore, the use of chiral 1-substituted-1,2-aminoalcohols (easily available from the reduction of natural aminoacids) as precursors should also be limited, since the favoured reaction pathway for the oxazaphosphorimidates derived from these compounds should be the oligomerization. However, in our previous studies about the imide–amide rearrangement of dioxaphosphorimidates we have determined that the polymerization reaction is very sensible to structural variations that influence the electronic nature of the phosphorus atom or the imidic nitrogen atom. Since the necessary condition to obtain diazaphosphoramides via the imide–amide rearrangement of ozaxaphosphorimidates seems to be the blocking of the polymerization mechanism, we decided to study the influence of the substituent nature at the

Table 3. Determination of the absolute configuration of the rearrangement product *cis*-**9b** by comparison of retention times as determined by HPLC using a chiral column for the separation of the enantiomers

Substract	t_R	ee (%)	Absolute configuration
Racemic **9b** (Scheme 3)	28.54	0	(2*R*,4*R*)
	30.53		(2*S*,4*S*)
Authenthic chiral *cis*-(2*R*,4*R*)-**9b**	28.80	>99	(2*R*,4*R*)
Chiral **9b** (Scheme 4)	30.87	>99	(2*S*,4*S*)

endocyclic and imidic nitrogen atoms in the polymerization of some selected oxazaphosphorimidates.

2.2. Imide–amide rearrangement of selected oxazaphosphorimidates

For this study the reaction of compounds **6a**,**c**–**g** with benzylazide and phenylazide, for the formation of the corresponding imides **7**, and their subsequent rearrangement under Lewis acid catalysis, were followed by NMR at 100 °C in toluene during 8 h. Table 4 summarizes the results obtained.

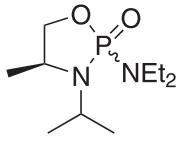
In all cases a complete conversion of the initial oxazaphospholidine **6** in the corresponding oxazaphosphorimidate **7** was observed. Independently of the formation of oligomer or diazaphosphoramide, in all cases the occurrence of rearrangement was confirmed by the inspection of the ^{13}C NMR spectra of the reaction mixtures. All the ^{13}C NMR spectra of the oxazaphosphorimidates **7a**,**c**–**g** showed a resonance around 60–63 ppm characteristic of oxygen bonded carbon. This resonance was absent in the ^{13}C NMR spectra obtained 8 h after the addition of $BF_3 \cdot OEt_2$ and was replaced by a new resonance in the region of 40–50 ppm, characteristic of a nitrogen bonded carbon.

The observation of the ^{1}H, ^{13}C and ^{31}P NMR spectra of the final reaction mixtures allowed a first identification of the products of the reactions either as diazaphosphoramides **9** or olygomers **8**, since these last show very characteristic and broad NMR spectra. The isolation and characterization of diazaphosphoramides **9c**–**e** by column chromatography and the characterization of oligomers **9a** and **9e** by MALDI, confirmed the assignments made in the reaction mixtures.

The results obtained with this study indicate that an alkyl substituent at the endocyclic nitrogen atom favours the formation of the diazaphosphoramide over the polymerization and, as was also observed for the dioxaphosphorimidates, a benzyl group at the imidic nitrogen accelerates the reaction but seems to favour the formation of olygomers.

Based on these results, and in order to test the possibility of employing ozaxaphospholidines derived from chiral 1-substituted-1,2-aminoalcohols as precursors for the preparation of chiral diazaphosphoramides, compounds **11a**–**b** were prepared. The *N*-monoalkylated-1,2-aminoalcohols, were obtained via the reductive monoalkylation of L-valine and L-alanine with acetone.[14] Compounds **11a** and **11b** were obtained as a mixture of diastereomers and were employed as such for the rearrangement (Table 5). The formation of the imides **12a** and **12b** was achieved, as before, via the Staudinger reaction, in this case with phenylazide. As was observed previously, the conversion of **11a**–**b** to **12a**–**b** was complete and without appreciable erosion of the dr (at the working temperature the oxazaphospholidines inversion rate must be very slow when compared to the rate of the Staudinger reaction for both isomers). After the addition of $BF_3 \cdot OEt_2$ the mixtures were heated to 100 °C, to promote the imide–amide rearrangement and the reactions were followed by ^{31}P NMR in order to monitor their progress. In both cases, as can be seen in Table 5, products **13** could be identified and isolated, with dr's very similar to the ones of the initial trivalent phosphorus compounds **11**. The relative configuration of the products was done as before for the diastereomeric pair **9b**.

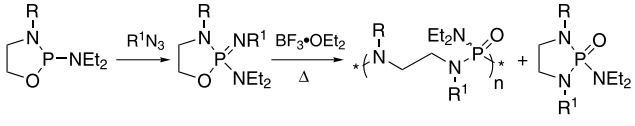
The reaction of **11a** gave a much lower yield of rearrangement but, in this case, compound **14a** was also isolated and as the major product of the reaction (64% total yield as a mixture of diastereomers 58:42). Its formation was detected by ^{31}P NMR in the reaction mixture before work-up. These results indicate that the imides **12a** are less prone to undergo rearrangement than **12b**.



14a

The importance of the substituent R at the ring, for the outcome of the reaction is also clear from the results

Table 4. Influence of the substituents at the endocyclic and imidic nitrogen atoms in the polymerization of some selected oxazaphosphorimides

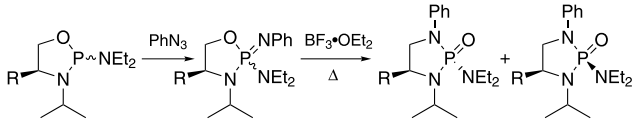


6 **7** **8** **9**

Entry	R	R^1	**7**	**8**	**9**		Conv. time
			δ ^{31}P	δ ^{31}P (%)[a]	δ ^{31}P (%)[a]	δ ^{31}P (%)[b]	
c	Me	Ph	18.4	[c]	20.4 (>80)	21.5 (36)	4 h[d]
d	Me	Bn	17.7	[c]	25.7 (>40)	27.3 (19)	40 min[d]
e	Ph	Ph	8.8	16.1 (>90)	12.6 (<5)	14.4 (3)	8 h
f	Ph	Bn	18.0	20.7 (>90)	—	—	4 h[d]
g	Bn	Ph	19.6	20.5 (>70)	—	—	7 h[d]
a	Bn	Bn	28.2	25.4 (>90)	—	—	40 min[d]

[a] ^{31}P NMR chemical shift (ppm) and conversion percentage (in brackets) determined by integration of the signals in the reaction mixture.
[b] ^{31}P NMR chemical shift (in ppm in $CDCl_3$) and yield (in brackets) after separation by column chromatography.
[c] The formation of oligomer was not detected.
[d] After 8 h at 100 °C no significant variation was detected by NMR.

Table 5. Imide-amide rearrangement of selected 4-substituted oxazaphosphorimidates derived from chiral 1,2-aminoalcohols



Entry	R	11	12	13			Time (h)
		δ ^{31}P (%)[a]	δ ^{31}P (%)[a]	Reaction[a], %, δ ^{31}P		Isolated[b], %, δ ^{31}P	
a	Me	139.0 (65) 127.9 (35)	19.9 (65) 16.1 (35)	35[c]	20.7 (40) 16.6 (60)	12 *cis* 18 *trans*	22.1 (40) 17.9 (60)	72
b	Pr^{i}	142.7 (37) 126.4 (63)	19.9 (39) 16.0 (61)	81[c]	21.5 (62) 17.6 (38)	32 *cis* 18 *trans*	22.9 (64) 18.6 (36)	48

[a] ^{31}P NMR chemical shift (ppm) and, in brackets, relative percentage of diastereomers as determined by integration of the ^{31}P NMR signals in the reaction mixture.
[b] Yield and relative stereochemistry of isolated products after column chromatography and ^{31}P NMR chemical shift (ppm, in $CDCl_3$), in brackets, calculated relative percentage of the isolated diastereomers.
[c] Percentage of **13** determined by ^{31}P NMR integration in the reaction mixture.

presented. In spite of the fact that the best results are achieved with the more bulky isopropyl group, it would be premature to withdraw more conclusions about the structural factors that influence the rearrangement without a more systematic study. However, the good conversion obtained for compound **11b** together with the fact that, as was already mentioned, the dr's of the final products are similar to the ones from the initial trivalent phosphorus, indicate that this reaction may constitute an alternative way to the preparation of chiral diazaphosphoramides with defined stereochemistry at the phosphorus atom. The factors that control the diastereoselectivity during the formation of these compounds are being studied.

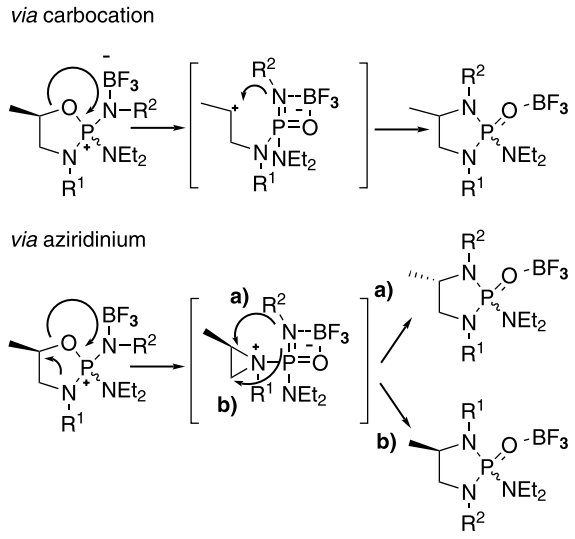
2.3. Mechanistic considerations

As was already mentioned, the most striking difference in the behaviour of the oxazaphosphorimidates **7** when compared to the parent dioxaphosphorimidates **1** is that, in contrary to these last, the imide–amide rearrangement of the oxazaphosphorimidates **7** does not involve a ROP and an oligomeric intermediate. For compounds of type **7** the conversion to a diazaphosphoramide can only be achieved by blocking the polymerization mechanism, either by increasing the steric hindrance at the electrophilic carbon atom, as in **7b**, or by introducing suitable substituents at the endocyclic and imidic nitrogen atoms, as in **7c**,**d** and **12**.

2.3.1. Polymerization versus diazaphosphoramide formation. The formation of oligomers **8** suggests that the reactivity of oxazaphosphorimidates **7** depends, at least to a certain extent, on the same activation requisites as those found for dioxophosphorimidates **1**, namely a fine balance between the nucleophilicity of the imidic nitrogen atom and the electrophilicity of the ring carbon atom, for the free and Lewis acid complexed imides, respectively. We have shown before that, for dioxophosphorimidates **1**, the BF_3 mediated electrophilic activation of the ring carbon atom is almost independent on the imidic nitrogen substituent. For these compounds the reactivity towards polymerization could be explained in terms of differences in the nucleophilic character of the imidic nitrogen atom and by the steric hindrance of the ring alkoxide carbon atom.[9] The same should be true for the oxazaphosphorimidates when concerning the polymerization reaction only. Nevertheless these effects do not explain the observed direct conversion to diazaphosphoramide and suggest that a different type of reaction might be involved. When a nitrogen atom substitutes an oxygen atom on the dioxophosphorimidate ring, to obtain an oxazaphosphorimidate, there are serious repercussions in the observed reactivity (Tables 4 and 5). The introduction of the nitrogen atom in the cycle has a direct influence over the electronic density at the phosphorus atom. This will indirectly affect both the nucleophilicity of the uncomplexed oxazaphosphorimidate imidic nitrogen atom and the electrophilicity of the ring carbon atom on the BF_3 adduct. For the oxazaphosphorimides the electrophilicity of the carbon atom might be an important factor to consider since it will be more directly affected by different substituents in the ring nitrogen atom. However, it seems clear that for compound **7b** the direct conversion to **9b** is depending on the blocking of the polymerization mechanism due to the steric hindrance of the ring methyl substituent. According to this the equivalent non-substituted compound **7a** is converted almost quantitatively to oligomer **8a** (Table 4, entry a).

In order to get some indication of the reaction pathway for the formation of the diazaphosphoramides we started by carefully studying the conversion of the methyl substituted compound **7b**.

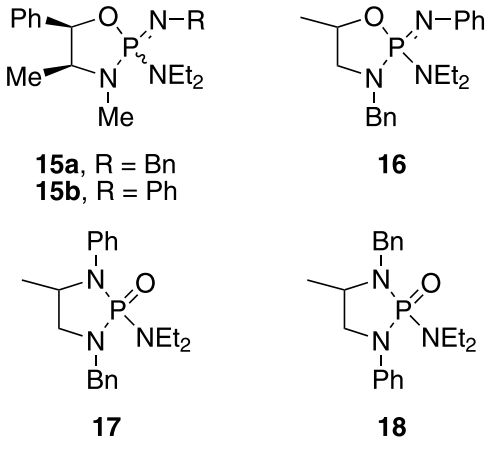
2.3.2. Direct conversion. The SNi mechanism hypothesis. The hypothesis of an intramolecular substitution was examined and two possibilities for the intramolecular reaction mechanism were considered (via carbocation or via aziridinium) (Scheme 6). Nevertheless, both had to be



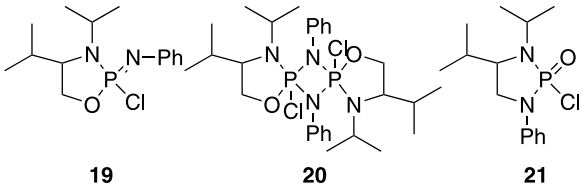
Scheme 6.

disregarded because, as we will show, neither of them could explain all the experimental data.

Both mechanisms have as driving force the formation of the stable phosphoryl bond and are analogous to the well known dealkylation reaction of phosphate esters that proceeds usually by a nucleophilic attack to the alkoxide carbon atom.[15] Also, the intramolecular dealkylation of phosphate esters, driven by nitrogen, sulfur or oxygen nucleophiles, is a very well known process that may lead to the degradation of the initial phosphate ester or to its rearrangement product.[15] After a close examination of the stereochemical outcome of the reaction for each one of the considered mechanisms a few directed experiments allowed us to test their validity. The mechanism involving a carbocation intermediate was the first to be disregarded based on two experimental observations: (1) the high enantioselective reaction of (5*R*)-**7b** proceeds with inversion of configuration at the carbon atom. If a carbocation was involved we would expect to observe at least some racemization; (2) we tried to perform the reaction with the ephedrine derived compounds **15a** and **15b**, that would stabilize the formation of a benzylic carbocation intermediate. No product was detected in these cases.[16] The mechanism involving an aziridinium intermediate was also disregarded based on the stereochemical analysis of the products and on some more additional experimental results. In fact the preferential attack for the aziridinium ring opening (attack to the less hindered carbon atom path (b) in Scheme 6) leads to retention of configuration at the carbon atom. This is the opposite to the experimentally observed result. However, and since the attack to the more hindered carbon atom (path (a) in Scheme 6) could explain the observed stereochemistry, we performed an additional experiment to test this hypothesis. As can be seen in Scheme 6, if the reaction is performed with an azide with a group R^2 different from the group R^1 at the ring nitrogen, then the products from the two ring opening possibilities differ not only in the stereochemistry at the carbon atom but also in the final localization of R^1 and R^2. When the reaction was performed with compound **16**, product **17** was obtained as a mixture of diastereoisomers and no traces of **18** could be detected,[17] thus excluding this path.

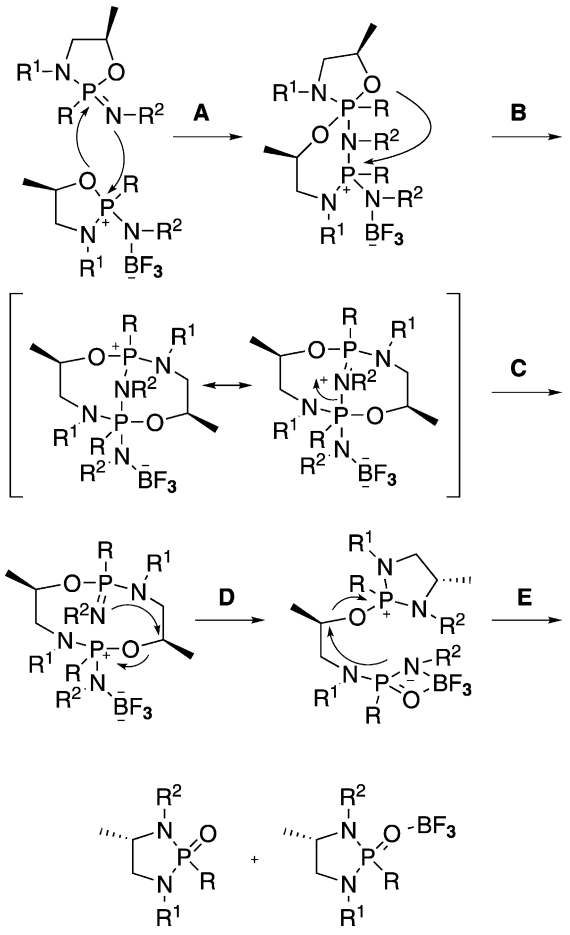


2.3.3. Mechanism proposal for the imide–amide rearrangement of oxazaphosphorimidates. Once excluded the intramolecular pathway, we turned our attention to a bimolecular mechanism. For the construction of a plausible proposal for a bimolecular mechanism, a crucial experimental observation drew our attention to a very important aspect of oxazaphosphorimides reactivity. When attempting to perform the imide–amide rearrangement of **19** we obtained, in addition to the corresponding rearranged product **21**, the dimeric diazadiphosphitidine **20**.[18]



The dimerization of imino derivatives of five-member ring phosphorous heterocycles has been reported previously.[19–21] According to the literature, the dimerization is highly dependent on the phosphorus substituents nature, being favoured by electronegative substituents such as fluorine or chlorine, that lead to a higher contribution of the betain (P^+–N^-) structure, thus activating the molecule for the dimerization. The reduction of the ring strain when going from **19** to **20**, due to the different geometry of the phosphorus atom in the dimeric form, was also pointed out as a factor contributing to this process. The dependency of the dimeric form stabilization on the substituents in the phosphorus atom, can originate equilibrium mixtures of the two forms, as was also described. However, it has also been reported that for compounds **7c** and **7e** the formation of dimers was not detected.[20] This information together with all the observed experimental facts lead us to propose a bimolecular mechanism, based on an initial nucleophilic attack of the imidic nitrogen atom of a free oxazaphosphorimidate to the phosphorus atom of a BF_3–oxazaphosphorimidate adduct (Scheme 7).

The formation of the BF_3–oxazaphosphorimidate adduct should increase the electrophilicity both of the phosphorus atom as well as the ring alkoxide carbon atom. According to the results in Table 4, there is a strong change in the reactivity



Scheme 7.

when the benzyl or the phenyl substituent at the ring nitrogen (R^1 in Scheme 7) is replaced with an alkyl group. The difference in reactivity can be explained if we consider that it depends on the relative activation of the phosphorus and the carbon atoms for a nucleophilic attack. The presence of a benzyl or a phenyl substituent at the ring nitrogen results in a stronger activation of the ring carbon atom, thus favoring the polymerization mechanism, while the presence of an alkyl group results in a greater electrophilic activation of the phosphorus atom. The first nucleophilic attack of the imidic nitrogen atom of a free oxazaphosphorimidate molecule to the phosphorus atom of a BF_3–oxazaphosphorimidate adduct (A, Scheme 7) is a process analogous to the dimerization referred previously.[19–21] In this case, and in contrast to the dimerization of **19**, we predict the migration of the oxygen atom of the attacked molecule instead of the imidic nitrogen, since this last is blocked by the BF_3. This can explain why the addition of BF_3 to a partially dimerized mixture of **19** and **20** leads to the formation of **21** stopping the formation of more **20**. The following two steps (B, C) can be considered as a substitution at the phosphorus atom, in which a bridged intermediate may be involved. The last two steps (D, E) lead to the final products, being the driving force the formation of the phosphoryl bond. Our proposal explains the observed inversion at the rearranged carbon center and is also consistent with other experimental observations, as is the partial formation of compound **14a** in the reaction mixture, by an alternative mechanism to the hydrolysis of the initial phosphorimide **12** during work-up. This compound can be obtained by decomposition of the initial dimer in an alternative path to B in Scheme 7. If the oxygen atom is not in a suitable position for the nucleophilic attack to the phosphorus atom, an attack from the bridged nitrogen atom to the alkoxide carbon may occur, leading to the decomposition of the dimer and the formation of **14a**.

3. Conclusions

We have shown that the Lewis acid catalysed imide–amide rearrangement of oxazaphosphorimidates to diazaphosphoramides is possible but, also, that the rearrangement reaction of this class of phosphorimidates presents significant mechanistic differences from the parent dioxaphosphorimidates, previously reported. In contrast to the mechanism proposed for these last compounds, the imide–amide rearrangement of oxazaphosphorimidates to diazaphosphoramides proceeds without the involvement of an oligomeric intermediate. We have also determined that the reaction occurs with retention of configuration at the phosphorus atom and inversion of configuration at the rearranged carbon atom, therefore, when applied to 4 or 5-substituted oxazaphosphorimidates, for the formation of 4 or 5-substituted diazaphosphoramides can constitute a possible route to the preparation of chiral diazaphosphoramides with defined stereochemistry at the phosphorus atom. Based in a number of experimental observations, we have proposed a mechanism for the imide–amide rearrangement of oxazaphosphorimidates that involves the formation of a dimer, through the nucleophilic attack of the imidic nitrogen of a free phosphorimidate to the phosphorus atom of a Lewis acid activated molecule. This dimer, upon internal rearrangement followed by two SNi reactions at the carbon atoms bearing oxygen, leads to the formation of the phosphoryl rearranged cyclic products with the correct stereochemistry. Overall, the possibility of an effective stereocontrol at the phosphorus atom is depending on the degree of stereocontrol during the preparation of the trivalent phosphorus precursors.

4. Experimental

4.1. General

All dried solvents were purified/dried before use, according to literature procedures.[22] Thin layer chromatography (TLC) was performed on aluminium sheets coated with silica gel 60 F_{254} (Merck 5554). Column chromatography was carried out on silica gel 60 (MN 815381, 230–400 Mesh). Melting points were determined on an Eletrothermal Mod. IA 6304 capillary melting point apparatus and are uncorrected. Observed rotations at the Na-D line were measured at 25 °C using an Optical Activity polarimeter Mod. AA-1000. Low- and high-resolution mass spectra (MS, HRMS) were obtained on a Fisons Autospec or Kratos apparatus. ^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker ARX400 spectrometer. HPLC analyses were performed using Merck and Hitachi components L-600A, L-4250, T-6300, D-6000 using Chiralcel OD column (0.46 cm, 25 cm) at 25 °C. The IR spectra were recorded

on a Unicam ATI Mattson Genesis Series FTIR as a film, obtained by evaporation of dichloromethane solutions on NaCl plates.

The following compounds were prepared, according to general reported procedures: dichloro diethylphosphoramidite,[23] diethylphosphoroamidous dichloride,[24] benzylazide,[25] phenylazide.[26,27]

4.2. Preparation of aminoalcohols

4.2.1. 1-*N*-Benzylamino-2-propanol and (*R*)-1-*N*-benzylamino-2-propanol. The title compounds were prepared from the corresponding aminoalcohol according to the general procedure for the monobenzylation of primary amines.[28]

4.2.2. (1*R*)-1-*N*,-2-*N*′-Dibenzylpropanodiamine 10. The title compound was prepared from the corresponding aminoalcohol according to the general procedure for the monobenzylation of primary amines.[28]

4.2.3. (*S*)-*N*-Isopropylalaninol. The title compound was prepared from (*S*)-alanine following general reported procedure.[14] Mp 28–29 °C (Et_2O), lit.[14] viscous oil; $[\alpha]_D^{25} = +31.3$ (*c* 1.04, MeOH), lit.[14] +34.6 (*c* 1, MeOH).

4.2.4. (*S*)-*N*-Isopropylvalinol. (*S*)-*N*-isopropylvalinol was prepared from (*S*)-valine following general reported procedure.[14] $[\alpha]_D^{25} = -3.5$ (*c* 1.04, EtOH), lit.[14] −3.3 (*c* 1, EtOH).

4.3. Preparation of 1,3,2-oxazaphospholidines

General procedure for the coupling of dichloro diethylphosphoramidite with aminoalcohols. To a stirred, ice-cold solution of dichloro diethylphosphoramidite in dry diethyl ether, under argon atmosphere, a solution of the appropriate dry aminoalcohol (1.0 equiv) and dry triethylamine (2.0 equiv) in dry diethyl ether was added dropwise. The addition was controlled in order to avoid that the temperature of the reaction would raise beyond 10 °C. After the addition was complete, the mixture was allowed to stir during 4 h at room temperature. The amine salts were then separated by filtration under argon atmosphere and washed repeatedly with dry ethylic ether. The liquid fractions were combined and the solvent removed by distillation under argon atmosphere. The residue obtained was purified by low pressure distillation.

4.3.1. 3-*N*-Benzyl-2-diethylamino-1,3,2-oxazaphospholidine 6a. The general procedure was followed using dichlorodiethylphosphoramidite (1.04 ml, 6.9 mmol), 2-*N*-benzylaminoethanol (1.03 g, 6.9 mmol) and dry triethylamine (1.92 ml, 13.8 mmol). Compound **6a** was obtained as slightly yellow viscous liquid (893 mg, 54%). Bp 150 °C (0.1 mmHg, KughelRohr); ^{1}H NMR (400 MHz, tol-d_8, 25 °C, tol): $\delta = 7.19$ (t, J(H,H) = 7.2 Hz, 2H, –CH–, *m*-Ar), 7.15 (d, J(H,H) = 7.7 Hz, 2H, –CH–, *o*-Ar), 7.07 (t, J(H,H) = 7.1 Hz, 1H, –CH–, *p*-Ar), 3.94 (q, J = 8.0 Hz, 1H, –OCH_2CH$_2$N–), 3.91 (d, J(H,H) = 7.3 Hz, 2H, –NCH_2Ph), 3.74 (qd, J = 8.7, 4.0 Hz, 1H, –OCH_2CH$_2$N–), 3.09–2.98 (m, 2H, –N(CH_2CH$_3$)$_2$), 2.93 (sxt, J = 7.1 Hz, 2H, –N(CH_2CH$_3$)$_2$), 2.76–2.70 (m, 1H, –OCH$_2$CH_2N–), 2.54–2.46 (m, 1H, –OCH$_2$CH_2N), 0.95 (t, J(H,H) = 7.0 Hz, 6H, –N(CH$_2$CH_3)$_2$); ^{13}C NMR (100 MHz, tol-d_8, 25 °C, tol-d_8): $\delta = 140.6$ (d, ^3J(P,C) = 6.9 Hz, –C–, Ar), 128.5 (–CH–, Ar), 128.3 (d, ^4J(P,C) = 1.6 Hz, –CH–, *o*-Ar,), 127.1 (–CH–, Ar), 67.0 (d, ^2J(P,C) = 12.2 Hz, –O*C*H$_2$CH$_2$N–), 50.7 (d, ^2J(P,C) = 26.5 Hz, –N*C*H$_2$Ph), 47.9 (–OCH$_2$*C*H$_2$N–), 38.7 (d, ^2J(P,C) = 19.7 Hz, –N(*C*H$_2$CH$_3$)$_2$), 15.4 (d, ^3J(P,C) = 3.5 Hz, –N(CH$_2$*C*H$_3$)$_2$); ^{31}P NMR (160 MHz, tol-d_8, 25 °C, H_3PO_4 external): $\delta = 135.4$.

4.3.2. 3-*N*-Benzyl-2-diethylamino-5-methyl-1,3,2-oxazaphospholidine 6b. The general procedure was followed using dichlorodiethylphosphoramidite (10.0 ml, 68.7 mmol), 1-*N*-benzylamino-2-propanol (11.36 g, 68.7 mmol) and dry triethylamine (19.2 ml, 137.4 mmol). Compound **6b** was obtained as a slightly viscous colourless liquid (13.34 g, 73%) as a mixture of *cis* and *trans* diastereomers (*cis*/*trans*, 26:74, as determined by ^{1}H and ^{31}P NMR). Bp 110 °C (0.1 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.27$–7.24 (m, 3H, –CH–, Ar, *cis* and *trans*), 7.19–7.18 (m, 2H, –CH–, Ar, *cis* and *trans*), 4.45 (m, J(H,H) = 8.5, 6.0, 5.4 Hz, J(P,H) = 1.1 Hz, 1H, –NCH$_2$-C*H*(CH$_3$)O–, *trans*), 4.23 (m, J(H,H) = 8.7, 6.7, 6.0 Hz, J(P,H) = 2.7 Hz, 1H –NCH$_2$C*H*(CH$_3$)O–, *cis*), 4.125 (dd, J(H,H) = 14.8 Hz, J(P,H) = 8.3 Hz, 1H, –CH_2Ph, *cis*), 4.02 (dd, J(H,H) = 14.6 Hz, J(P,H) = 8.5 Hz, 1H, –CH_2Ph, *trans*), 3.92 (dd, J(H,H) = 14.6 Hz, J(P,H) = 8.5 Hz, 1H, –CH_2Ph, *trans*), 3.687 (dd, J(H,H) = 14.8 Hz, J(P,H) = 3.8 Hz, 1H, –CH_2Ph, *cis*), 3.17–3.06 (m, 1H, –NCH_2 CH(CH$_3$)O *trans* and 2H, –NCH_2CH$_3$, *trans* and *cis*), 3.04–2.91 (m, 2H, –NCH_2CH$_3$, *trans* e *cis*), 2.82 (m, J(H,H) = 6.7, 8.7 Hz, J(P,H) = 15.1 Hz, 1H, –NCH_2 CH(CH$_3$)O–, *cis*), 2.67 (td, J(H,H) = 8.7, 8.7 Hz, J(P,H) = 1.0 Hz, 1H, –NCH_2CH(CH$_3$)O–, *cis*), 2.36 (td, J(H,H) = 8.5, 8.5 Hz, J(P,H) = 3.1 Hz, 1H, –NCH_2CH(CH$_3$)O–, *trans*), 1.17 (d, J(H,H) = 6.0 Hz, 3H, –NCH$_2$CH(CH_3)O–, *trans*), 1.00 (t, J(H,H) = 6.7 Hz, 6H, 2×–NCH$_2$CH_3, *cis* and *trans*); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): $\delta =$ 140.0 (d, ^2J(P,C) = 5.0 Hz, –C–, Ar), 128.19 (–CH–, Ar), 127.96 (–CH–, Ar), 127.7 (–CH–, Ar), 126.7 (–CH–, Ar), 74.9 (d, ^2J(P,C) = 11.4 Hz, –NCH$_2$*C*H(CH$_3$)O–, *cis*), 74.1 (d, ^2J(P,C) = 11.2 Hz, –NCH$_2$*C*H(CH$_3$)O–, *trans*), 54.8 (–N*C*H$_2$CH(CH$_3$)O–, *trans*), 53.25 (d, ^2J(P,C) = 2.6 Hz, –N*C*H$_2$CH(CH$_3$)O–, *cis*), 50.5 (d, ^2J(P,C) = 26.6 Hz, –*C*H$_2$Ph, *trans*), 49.2 (d, ^2J(P,C) = 19.5 Hz, –*C*H$_2$Ph, *cis*), 38.7 (d, ^2J(P,C) = 19.8 Hz, –N*C*H$_2$CH$_3$, *cis*), 38.3 (d, ^2J(P,C) = 19.4 Hz, –N*C*H$_2$CH$_3$, *trans*), 21.0 (d, ^3J(P,C) = 4.0 Hz, –NCH$_2$CH(*C*H$_3$)O–, *trans*), 20.0 (–NCH$_2$CH(*C*H$_3$) O–, *cis*), 15.3 (d, ^3J(P,C) = 2.6 Hz, –NCH$_2$*C*H$_3$, *cis*), 15.2 (d, ^3J(P,C) = 2.6 Hz, –NCH$_2$*C*H$_3$, *trans*); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): $\delta = 141.6$ (*cis*), 136.2 (*trans*).

4.3.3. (2*RS*,5*R*)-3-*N*-Benzyl-2-diethylamino-5-methyl-1,3,2-oxazaphospholidine (5*R*)-6b. The general procedure was followed using dichlorodiethylphosphoramidite (903.0 µl, 6.21 mmol), (*R*)-1-*N*-benzylamino-2-propanol (1.026 g, 6.21 mmol) and dry triethylamine (1.73 ml, 12.42 mmol). Compound (5*R*)-**6b** was obtained as a slightly viscous colourless liquid (900 mg, 55%) as a mixture of *cis* and *trans* diastereomers (*cis*/*trans*, 26:74, as determined by

^{1}H and ^{31}P NMR). Spectroscopic data identical to compound **6b**.

4.3.4. 2-Diethylamino-3-*N*-methyl-1,3,2-oxazaphospholidine 6c. The general procedure was followed using dichlorodiethylphosphoramidite (3.87 ml, 26.6 mmol), 2-*N*-methylaminoethanol (2.00 g, 26.6 mmol) and dry triethylamine (7.42 ml, 53.2 mmol). Compound **6c** was obtained as a slightly viscous colourless liquid (2.35 g, 50%). Bp 150 °C (5 mmHg, KughelRohr); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=4.20–4.13 (m, 1H, one of –OCH_2CH$_2$N–), 4.00–3.94 (m, 1H, one of –OCH_2CH$_2$N–), 3.15–3.11 (m, 1H, one of –OCH$_2$CH_2N–), 3.02–2.90 (m, 4H, –N(CH_2CH$_3$)$_2$), 2.88–2.83 (m, 1H, one of –OCH$_2$CH_2N–), 2.56 (d, J(P,H)=11.2 Hz, 1.5H, –NCH_3), 2.54 (d, J(P,H)=11.2 Hz, 1.5H, –NCH_3), 0.97 (t, J(H,H)=6.9 Hz, 3H, –N(CH$_2$CH_3)$_2$), 0.96 ((t, J(H,H)=6.9 Hz, 3H, –N(CH$_2$CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=66.8 (d, ^{2}J(P,C)=11.1 Hz, –OCH$_2$CH$_2$N–), 50.4 (–OCH$_2$$CH_2$N–), 38.3 (d, ^{2}J(P,C)=19.4 Hz, –N(CH$_2$CH$_3$)$_2$), 32.1 (d, ^{2}J(P,C)=25.0 Hz, –NCH$_3$), 15.2 (–N(CH$_2$$CH_3$)$_2$); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ=133.6.

4.3.5. 2-Diethylamino-3-*N*-phenyl-1,3,2-oxazaphospholidine 6e. The general procedure was followed using dichlorodiethylphosphoramidite (1.1 ml, 7.3 mmol), 2-phenylaminoethanol (1.03 g, 7.3 mmol) and dry triethylamine (2.9 ml, 14.6 mmol). Compound **6e** was obtained as a slightly yellow viscous liquid (971 mg, 56%). Bp 150 °C (0.1 mmHg, KughelRohr); ^{1}H NMR (400 MHz, tol-d$_8$, 25 °C, tol): δ=7.14 (t, J(H,H)=7.7 Hz, 2H, –CH–, Ar, *meta*), 6.86 (d, J(H,H)=8.1 Hz, 2H, –C-H–, *o*-Ar), 6.76 (t, J(H,H)=7.3 Hz, 1H, –CH–, *p*-Ar,), 3.99 (q, J(H,H)=9.2, 9.2, 6.8 Hz, ^{3}J(P,H)=1.5 Hz, 1H, –OCH_2CH$_2$N–), 3.82 (qd, J(H,H)=9.2, 7.8, 3.3 Hz, ^{3}J(P,H)=9.1 Hz, 1H, –OCH_2CH$_2$N–), 3.05–2.99 (m, J(H,H)=9.0, 6.8, 3.3 Hz, ^{3}J(P,H)=3.2 Hz, 1H, –OCH$_2$CH_2N–), 2.95–2.84 (m, 4H, –N(CH_2CH$_3$)$_2$), 2.82 (qd, J(H,H)=9.2, 9.0, 7.8 Hz, ^{3}J(P,H)=3.4 Hz, 1H, –OCH$_2$CH_2N–), 0.85 (t, J(H,H)=7.1 Hz, 6H, –N(CH$_2$CH_3)$_2$); ^{13}C NMR (100 MHz, tol-d$_8$, 25 °C, tol-d$_8$): δ=145.8 (d, ^{2}J(P,C)=13.8 Hz, –C–, Ar), 129.2 (–CH–, *m*-Ar,), 118.8 (–CH–, *p*-Ar,), 115.2 (d, ^{3}J(P,C)=11.0 Hz, –CH–, *o*-Ar,), 66.6 (d, ^{2}J(P,C)=11.3 Hz, –OCH$_2$CH$_2$N–), 45.3 (d, ^{2}J(P,C)=2.7 Hz, –OCH$_2$$CH_2$N–), 39.1 (d, ^{2}J(P,C)=19.5 Hz, –N(CH$_2$CH$_3$)$_2$), 18.9 (d, ^{3}J(P,C)=3.4 Hz, –N(CH$_2$$CH_3$)$_2$); ^{31}P NMR (160 MHz, tol-d$_8$, 25 °C, H_3PO_4 external): δ=121.3.

4.3.6. (2*RS*,4*S*)-2-Diethylamino-3-*N*-isopropyl-4-methyl-1,3,2-oxazaphospholidine 11a. The general procedure was followed using dichloro diethylphosphoramidite (534.0 µl, 3.67 mmol), (*S*)-*N*-isopropylalaninol (430.0 mg, 3.67 mmol) and dry triethylamine (1.02 ml, 7.34 mmol). Compound **11a** was obtained as a slightly viscous colourless liquid (346 mg, 43%) as a mixture of *cis* and *trans* diastereomers (*cis*/*trans*, 65:35, as determined by ^{1}H and ^{31}P NMR). Bp 120 °C (0.05 mmHg, KughelRohr); ^{1}H NMR (400 MHz, tol-d$_8$, 25 °C, tol): δ=4.02 (dd, J=6.4, 7.8 Hz, 1H, –OCH_2CH(R)N–, *trans*), 3.89–3.83 (m, 1H, –OCH_2CH(R)N–, *cis*), 3.54 (dd, J=9.0, 9.8 Hz, 1H, –OCH_2CH(R)N–, *cis*), 3.78–3.38 (m, 1H, –OCH_2CH(R)N–, *trans*), 3.33–3.24 (m, 2H, –OCH$_2$CH(R)NCH(CH$_3$)$_2$, *trans*), 3.21–3.10 (m, 1H, –OCH$_2$CH(R)NCH(CH$_3$)$_2$, *cis* and 2H, –N(CH_2CH$_3$)$_2$, *cis*), 3.08–2.95 (m, 2H, –N(CH_2CH$_3$)$_2$, *cis* and 1H, –OCH$_2$CH(R)NCH(CH$_3$)$_2$, *cis*), 2.91–2.76 (m, 4H, –N(CH_2CH$_3$)$_2$, *trans*), 1.26 (d, J(H,H)=6.7 Hz, 3H, –NCH(CH_3)$_2$, *trans*), 1.15 (d, J(H,H)=7.0 Hz, 3H, –NCH(CH_3)$_2$, *cis*), 1.12 (d, J(H,H)=6.4 Hz, 3H, –NCH(CH_3)$_2$, *cis*), 1.04 (d, J(H,H)=6.5 Hz, 3H, –NCH(CH_3)$_2$, *trans*), 0.97 (t, J(H,H)=6.4 Hz, 6H, –N(CH$_2$CH_3)$_2$, *cis*), 0.90 (t, J(H,H)=7.2 Hz, 6H, –N(CH$_2$CH_3)$_2$, *trans*), 0.88 (t, J(H,H)=5.8 Hz, 3H, –CH_3, *cis*), 0.83 (d, J(H,H)=6.1 Hz, 3H, –CH_3, *trans*); ^{13}C NMR (100 MHz, tol-d$_8$, 25 °C, tol-d$_8$): δ =74.0 (d, ^{2}J(P,C)=9.8 Hz, –OCH$_2$CH(R)N–, *cis*), 72.8 (d, ^{2}J(P,C)=10.0 Hz, –OCH$_2$CH(R)N–, *trans*), 52.3 (–OCH$_2$$C$H(R)N–, *cis*), 51.7 (d, ^{2}J(P,C)=3.6 Hz, –OCH$_2$$C$H(R)N–, *trans*), 45.8 (d, ^{2}J(P,C)=25.0 Hz, –OCH$_2$CH(R)NCH(CH$_3$)$_2$, *cis*), 44.7 (d, J(P,C)=15.5 Hz, –OCH$_2$CH(R)NCH(CH$_3$)$_2$, *trans*), 38.5 (d, ^{2}J(P,C)=20.5 Hz, –N(CH$_2$CH$_3$)$_2$, *cis*), 38.0 (d, ^{2}J(P,C)=6.5 Hz, –N(CH$_2$CH$_3$)$_2$, *trans*), 23.6 (d, ^{3}J(P,C)=11.0 Hz, –NCH(CH_3)$_2$, *cis*), 23.5 (d, ^{3}J(P,C)=2.7 Hz, –NCH(CH_3)$_2$, *trans*), 23.2 (d, ^{3}J(P,C)=13.9 Hz, –NCH(CH_3)$_2$, *trans*), 20.8 (d, ^{3}J(P,C)=6.9 Hz, –NCH(CH_3)$_2$, *cis*) 19.5 (d, ^{3}J(P,C)=2.6 Hz, –OCH$_2$CH(CH_3)N–, *trans*), 16.6 (d, ^{3}J(P,C)=3.0 Hz, –OCH$_2$CH(CH_3)N–, *cis*) 15.2 (d, ^{3}J(P,C)=3.7 Hz, –N(CH$_2$CH_3)$_2$, *cis*), 15.0 (d, ^{3}J(P,C)=2.8 Hz, –N(CH$_2$CH_3)$_2$, *cis*), 14.6 (–NCH$_2$CH_3, *trans*), 14.4 (d, ^{3}J(P,C)=2.0 Hz, –NCH$_2$CH_3, *trans*); ^{31}P NMR (160 MHz, tol-d$_8$, 25 °C, H_3PO_4 external): δ=139.0 (*cis*), 127.9 (*trans*).

4.3.7. (2*RS*,4*S*)-2-Diethylamino-3-*N*-, 4-di-isopropyl-1,3,2-oxazaphospholidine 11b. The general procedure was followed using dichlorodiethylphosphoramidite (2.0 ml, 13.8 mmol), (*S*)-*N*-isopropylvalinol (2.0 g, 13.8 mmol) and dry triethylamine (3.84 ml, 27.6 mmol). Compound **11b** was obtained as a slightly viscous colourless liquid (1.91 mg, 56%) as a mixture of *cis* and *trans* diastereomers (*cis*/*trans*, 37:63, as determined by ^{1}H and ^{31}P NMR). Bp 140 °C (0.1 mmHg, KughelRohr); ^{1}H NMR (400 MHz, tol-d$_8$, 25 °C, tol): δ=3.86 (dd, J(H,H)=8.8, 6.9 Hz, 1H, –OCH_2CH(R)N–, *trans*), 3.83–3.77 (m, 2H, –OCH_2CH(R)N–, *cis*), 3.76–3.70 (m, 1H, –OCH_2CH(R)N–, *trans*), 3.29–3.15 (m, 1H, –OCH$_2$CH(R)N–, *trans* and 1H, –NCH(CH$_3$)$_2$, *trans* and 2H, –N(CH_2CH$_3$)$_2$, *cis*), 3.08–2.96 (m, 1H, –OCH$_2$CH(R)N–, *cis* and 1H, –NCH(CH$_3$)$_2$, *cis*+2H, –N(CH_2CH$_3$)$_2$, *trans*), 2.88–2.80 (m, J(H,H)=7.0 Hz, 2H, –N(CH_2CH$_3$)$_2$, *trans*), 1.82–1.71 (m, 1H, –CH(CH$_3$)$_2$, *cis* and 1H, –CH(CH$_3$)$_2$, *trans*), 1.30 (d, J(H,H)=6.7 Hz, 3H, –NCH(CH_3)$_2$, *trans*), 1.21 (d, J(H,H)=7.0 Hz, 3H, –NCH(CH_3)$_2$, *cis*), 1.13 (d, J(H,H)=6.3 Hz, 3H, –NCH(CH_3)$_2$, *cis*), 1.05 (d, J(H,H)=6.4 Hz, 3H, –NCH(CH_3)$_2$, *trans*), 0.98 (t, J(H,H)=7.2 Hz, 6H, –N(CH$_2$CH_3)$_2$, *cis*), 0.96 (t, J(H,H)=7.1 Hz, 6H, –N(CH$_2$CH_3)$_2$, *trans*), 0.82 (d, J(H,H)=7.0 Hz, 3H, –CH(CH_3)$_2$, *cis*), 0.85 (d, J(H,H)=7.0 Hz, 3H, –CH(CH_3)$_2$, *trans*), 0. 72 (d, J(H,H)=7.0 Hz, 3H, –CH(CH_3)$_2$, *cis*), 0.64 (d, J(H,H)=7.0 Hz, 3H, –CH(CH_3)$_2$, *trans*); ^{13}C NMR (100 MHz, tol-d$_8$, 25 °C, tol-d$_8$): δ=67.5 (d, ^{2}J(P,C)=9.7 Hz, –OCH$_2$CH(R)N–, *cis*), 65.7 (d, ^{2}J(P,C)=11.1 Hz, –OCH$_2$CH(R)N–, *trans*), 61.6 (d, ^{2}J(P,C)=4.8 Hz, –OCH$_2$$C$H(R)N–, *trans*), 61.3 (–OCH2 CH(R)N–, *cis*), 46.1 (d, ^{2}J(P,C)=24.2 Hz, –NCH(CH$_3$)$_2$, *cis*), 44.5 (d, ^{2}J(P,C)=13.7 Hz, –NCH(CH$_3$)$_2$, *trans*), 38.6 (–N(CH$_2$CH$_3$)$_2$, *cis*), 38.3 (d, ^{2}J(P,C)=20.5 Hz,

–N(CH_2CH_3)$_2$, *trans*), 28.7 (d, ^3J(P,C)=2.6 Hz, –$CH(CH_3)_2$, *trans*), 27.9 (d, ^3J(P,C)=1.5 Hz, –$CH(CH_3)_2$, *cis*), 24.0 (d, ^3J(P,C)=13.2 Hz, –NCH(CH_3)$_2$, *cis*), 23.1 (d, ^3J(P,C)=2.0 Hz, –NCH(CH_3)$_2$, *trans*), 23.0 (d, ^3J(P,C)=14.0 Hz, –NCH(CH_3)$_2$, *trans*), 19.7 (–CH(CH_3)$_2$, *cis*), 19.3 (d, ^3J(P,C)=8.3 Hz, –NCH(CH_3)$_2$, *cis*), 18.7 (–CH(CH_3)$_2$, *trans*), 15.55 (–CH(CH_3)$_2$, *cis*), 15.2 (d, ^3J(P,C)=3.6 Hz, –N(CH_2CH_3)$_2$, *trans*), 15.1 (d, ^3J(P,C)=2.7 Hz, –NCH(CH_3)$_2$, *trans*), 15.00 (d, ^3J(P,C)=2.8 Hz, –N(CH_2CH_3)$_2$, *cis*); ^{31}P NMR (160 MHz, tol-d_8, 25 °C, H_3PO_4 external): δ=142.7 (*cis*), 126.4 (*trans*).

4.4. Preparation of diazaphosphoramides used as chiral standards *cis*-(2*R*,4*R*)-9b and *trans*-(2*S*,4*R*)-9b

4.4.1. *cis*-(2*R*,4*R*)- and *trans*-(2*S*,4*R*)-1-*N*-,3-*N′*-Dibenzyl-2-diethylamino-4-methyl-1,3,2-λ^5-diazaphospholidin-2-one 9b. The general method for the coupling of aminoalcohols with diethylphosphoramidous dichloride described previously was followed,[9] using (1*R*)-1-*N*-,2-*N′*-dibenzylpropanodiamine (103.0 mg, 0.405 mmol), diethylphosphoramidous dichloride (77.0 mg, 0.405 mmol) and dry triethylamine (113.0 μl, 0.810 mmol). The residue obtained was purified by column chromatography (*n*-Hex/AcOEt, 4:6), and two fractions corresponding to the two diastereomers *cis*-(2*R*,4*R*)-**9b** and *trans*-(2*S*,4*R*)-**9b** were obtained.

trans-(2*S*,4*R*)-**9b**. Colourless viscous oil (28.0 mg, 19%); R_f=0.45 (*n*-Hex/AcOEt, 1:1); $[\alpha]_D^{20}$=+1.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.41 (d, *J*(H,H)=7.3 Hz, 2H, –CH–, Ar), 7.30–7.25 (m, 8H, –CH–, Ar), 4.13–4.00 (m, 2H, one of –N(1)CH_2Ph and one of –N(3)CH_2Ph), 3.94–3.79 (m, 2H, one of –N(1)CH_2Ph and one of –N(3)CH_2Ph), 3.27–3.18 (m, *J*=7.3, 3.1 Hz, *J*(H,H)=6.2, 5.8, 1H, –NC*H*(CH_3)CH_2N–), 3.11–2.93 (m, 5H, one of –NCH(CH_3)CH_2N– and –N(CH_2C H$_3$)$_2$), 2.53 (ddd, 1H, *J*(P,H)=8.3 Hz, *J*(H,H)=10.9, 5.8 Hz, one of –NCH(CH_3)CH_2N), 1.02 (t, *J*(H,H)=7.1 Hz, 6H, –N(CH_2CH_3)$_2$), 0.96 (d, *J*(H,H)=6.1 Hz, 3H, –NCH(CH_3)CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ = 132.7 (d, *J*(P,C)=18.0 Hz, –C–, Ar), 128.1 (d, *J*(P,C)=3.6 Hz, –C–, Ar), 128.5 (–CH–, Ar), 128.4 (–CH–, Ar), 128.3 (–CH–, Ar), 128.1 (–CH–, Ar), 127.1 (–CH–, Ar), 127.0 (–CH–,Ar), 51.9 (d, *J*(P,C)=12.1 Hz, –NCH(CH_3)*C*H_2N–), 48.6 (d, *J*(P,C)=11.5 Hz, –N*C*H(CH_3)CH_2N–), 48.6 (d, *J*(P,C)=5.5 Hz, –N*C*H_2Ph), 46.2 (d, *J*(P,C)=5.5 Hz, –N*C*H_2Ph), 39.4 (d, *J*(P,C)=5.1 Hz, –N(*C*H_2CH_3)$_2$), 18.9. (d, *J*(P,C)=4.5 Hz, –NCH(*C*H_3)CH_2N–), 14.8 (–N(CH_2*C*H_3)$_2$); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ =28.3; IR (film): ν_{max} (cm^{-1})=2975.1 (CH), 1265.4 (P=O), 739.8 MS (70 eV, EI): *m*/*z* (%): 371 (25) [M^+], 356 (10) [M^+-CH_3], 299 (23) [M^+-NEt_2], 91 (100) [$^+CH_2Ph$], 72 (27), 57 (21), 41 (25), 28 (50); HRMS (EI): obtained 371.21270; M^+ $C_{21}H_{30}N_3OP$ requires 371.21265.

cis-(2*S*,4*R*)-**9b**. Colourless viscous oil (35.0 mg, 23%); R_f= 0.35 (*n*-Hex/AcOEt,1:1); $[\alpha]_D^{20}$=+11.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.34–7.15 (m, 10H, –CH–, Ar), 4.127 (dd, ^3J(P,H)=8.5 Hz, *J*(H,H)= 15.8 Hz, 1H, one of –N(1)CH_2Ph), 3.99 (dd, ^3J(P,H)= 6.9 Hz, *J*(H,H)=15.1 Hz, 1H, one of –N(3)CH_2Ph), 3.95 (dd, ^3J(P,H)=7.3 Hz, *J*(H,H)=15.1 Hz, 1H, one of –N(1)CH_2Ph), 3.85 (dd, ^3J(P,H)=8.5 Hz, *J*(H,H)= 15.8 Hz, 1H, one of –N(1)CH_2Ph), 3.35–3.26 (m, *J*=8.4, 5.1 Hz, *J*(H,H)=6.2, 5.9, 1H, –NC*H*(CH_3)CH_2N–), 3.14–2.98 (m, 5H, one of –NCH(CH_3)CH_2N– and –N(CH_2CH_3)$_2$), 2.55 (ddd, 1H, *J*(P,H)=5.9 Hz, *J*(H,H)= 8.6, 5.9 Hz, one of –NCH(CH_3)CH_2N), 1.04 (t, *J*(H,H)= 7.0 Hz, 6H, –N(CH_2CH_3)$_2$), 0.93 (d, *J*(H,H)=6.2 Hz, 3H, –NCH(CH_3)CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=128.6 (–CH–, Ar), 128.4 (–CH–, Ar), 128.3 (–CH, Ar), 127.8 (–CH–, Ar), 127.1 (–CH–, Ar), 126.9 (–CH–, Ar), 51.9 (d, ^2J(P,C)=11.7 Hz, –NCH(CH_3) *C*H_2N–), 51.6 (d, ^2J(P,C)=12.1 Hz, –N*C*H(CH_3)CH_2N–), 48.8 (d, ^2J(P,C)=5.2 Hz, –N*C*H_2Ph), 46.3 (d, ^2J(P,C)= 5.7 Hz, –N*C*H_2Ph), 39.1 (d, ^2J(P,C)=4.3 Hz, –N(*C*H_2 CH_3)$_2$), 19.3. (d, ^3J(P,C)=2.4 Hz, –NCH(*C*H_3)CH_2N–), 14.8 (–N(CH_2*C*H_3)$_2$); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ=27.7; IR (film): ν_{max} (cm^{-1})=2969.5 (CH), 1207.0 (P=O), 1153.1 (P–N–C), 1032.9, 732.2, 699.1; MS (70 eV, EI): *m*/*z* (%): 371 (39) [M^+], 356 (30) [M^+-CH3], 299 (34) [M^+-NEt_2], 224 (27), 91 (100)[$^+CH_2Ph$], 72 (27), 57 (47), 41 (27); HRMS (EI): obtained 371.21270; M^+ $C_{21}H_{30}N_3OP$ requires 371.21265.

4.5. Imide–amide rearrangement of oxazaphosphorimides of type 7 and 12 obtained in situ from the oxazaphospholanes of type 6 and 11

General method. Benzylazide or phenylazide was added dropwise to a toluene solution of oxazaphospholidine (approx. 1.0 M) in a dry, argon pre-filled, flask or NMR tube, stopped with a rubber septum (when using phenylazide the reaction was cooled in an ice-bath during the addition). Once the addition was completed, the mixture was heated to 40–60 °C until no more evolution of N_2 could be observed or until the total conversion of the oxazaphospholidine **6** or **11** in oxazaphosphorimide **7** or **12** was confirmed by ^{31}P NMR. $BF_3\cdot OEt_2$ (10 mol %) was then added and the reaction was heated to 100 °C and followed by NMR until the complete disappearance of the ^{31}P NMR signal of the oxazaphosphorimide **7** or **12**. At this point and after cooling down to room temperature dichloromethane was added, the resulting solution was washed with satd aq solution of $NaHCO_3$ and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried with anhyd $MgSO_4$ and the solvent removed under vacuum.

4.5.1. Reactions using 6a. *With benzylazide*. The general procedure was followed in a NMR tube using the oxazaphospholane **6a** (110 mg, 0.44 mmol) and benzylazide (54.5 μl, 0.44 mmol) in dry deuterated toluene (0.4 ml). The total conversion of **6a** (^{31}P NMR signal at 135.4 ppm) to the imide **7a** (^{31}P NMR signals at 28.2 ppm, ^{13}C NMR –O*C*H_2– at 62.7 ppm) was confirmed by NMR after 30 min at 40 °C. After the addition of $BF_3\cdot OEt_2$ (5.6 μl, 10 mol%) the total conversion of **7b** was observed by ^{31}P NMR after 40 min at 100 °C (^{31}P NMR signals at 25.9–25.4 and 21.4 and broad ^{1}H NMR and ^{13}C NMR signals, total disappearance of signal –O*C*H_2– at 62.7 ppm). After 8 h at 100 °C no variation was detected by NMR. The residue obtained after work-up was characterized without further purification and identified as poly-*N*-benzylamino-*N′*,*N′*-benzylethylamino-*N″*,*N″*-diethylaminophosphorotriamide **8a**; ^{1}H NMR (400 MHz, tol-d_8, 25 °C, tol): δ=7.42–7.22 (br, 4H, –CH–,

Ar), 7.15–7.06 (br, 6H, –CH–, Ar), 4.24–3.60 (br, 3H), 3.14–2.90 (br, 5H), 1.07–0.93 (m, 6H, $N(CH_2CH_3)_2$); ^{13}C NMR (100 MHz, tol-d_8, 25 °C, tol-d_8): $\delta=139.4$ (br), 128.6–126.3 (br), 52.2 (br), 50.9 (br), 46.1 (br), 45.1 (br), 39.8 (br), 14.3 (br), 14.1 (br); ^{31}P NMR (160 MHz, tol-d_8, 25 °C, H_3PO_4 external): $\delta=25.9$–25.4 (80%), 21.4 (20%); IR (film): ν_{max} (cm^{-1})=3379.1 (br, NH), 3228.8 (br), 2972.4 (C–H), 2931.6, 2871.1, 1454.2, 1214.6 (P=O), 1059.3, 1028.4 (P–N–C), 943.8, 732.8, 700.2; MS (MALDI): repeating unit: 357±1 Da; $M_n=3080$, $M_w=3480$, polydispersion index=1.028.

With phenylazide. The general procedure was followed in a NMR tube using the oxazaphospholane **6a** (110 mg, 0.44 mmol) and phenylazide (52 mg, 0.44 mmol) in dry deuterated toluene (0.4 ml). The total conversion of **6a** (^{31}P NMR signal at 135.4 ppm) to the imide **7g** (^{31}P NMR signals at 19.6 ppm, ^{13}C NMR –O*C*H_2– at 63.1 ppm) was confirmed by NMR after 30 min at 40 °C. After the addition of $BF_3\cdot OEt_2$ (5.6 μl, 10 mol%) the total conversion of **7g** was observed by ^{31}P NMR after 7 h at 100 °C (^{31}P NMR signals at 21.6, 20.5 (70%) and 15.3 and broad ^1H NMR and ^{13}C NMR signals, total disappearance of signal –O*C*H_2– at 62.7 ppm). The residue partly decomposed during work-up but, due to its spectral characteristics in the reaction mixture, was identified as poly-*N*-benzylethylamino-*N′*,*N′*-diethylamino-*N″*,*N″*-phenylaminophosphorotriamide **8g**.

4.5.2. Reaction using 6b. The general procedure was followed using the racemic oxazaphospholane **6b** (260 mg, 0.976 mmol) and benzylazide (122 μl, 0.976 mmol) in dry toluene (1.0 ml). The total conversion of **6b** (^{31}P NMR signals at 140.2 and 137.1 ppm, in a 26:74 ratio) to the imide **7b** (^{31}P NMR signals at 26.8 and 26.4 ppm, in a 73:27 ratio) was confirmed by NMR after 12 h at room temperature. After the addition of $BF_3\cdot OEt_2$ (12 μl, 10 mol%), the total conversion of **7b** was observed by ^{31}P NMR after 8 h at 100 °C. The residue obtained after work-up was purified by column chromatography (Et_2O) and two fractions corresponding to the two diastereomers *cis*-**9b** and *trans*-**9b** were obtained.

trans-**9b**. Colourless viscous oil (70.1 mg, 19%); $R_f=0.13$ (Et_2O); other spectroscopic data identical to the already described *trans*-(2*S*,4*R*)-**9b**.

cis-**9b**. Colourless viscous oil (144.0 mg, 40%); $R_f=0.10$ (Et_2O); other spectroscopic data identical to the already described *cis*-(2*S*,4*R*)-**9b**.

4.5.3. Reaction using (5*R*)-6b. The general procedure was followed using the chiral oxazaphospholane (5*R*)-**6b** (81.5 mg, 0.306 mmol) and benzylazide (38.2 μl, 0.306 mmol) in dry toluene (0.4 ml). The total conversion of **6b** (^{31}P NMR signals at 140.2 and 137.1 ppm, in a 26:74 ratio) to the imide **7b** (^{31}P NMR signals at 26.8 and 26.4 ppm, in a 73:27 ratio) was confirmed by NMR after 12 h at room temperature. The total conversion of **7b** was observed by ^{31}P NMR after 8 h at 100 °C. The residue obtained after work-up was purified by column chromatography (Et_2O) and two fractions corresponding to the two diastereomers *cis*-**9b** and *trans*-**9b** were obtained.

trans-(2*R*,4*S*)-**9b**. Colourless viscous oil (10.2 mg, 9%); $R_f=0.13$ (Et_2O); $[\alpha]_D^{20}=-0.9$ (*c* 0.2, $CHCl_3$); other data identical to the already described *trans*-(2*S*,4*R*)-**9b**.

cis-(2*S*,4*S*)-**9b**. Colourless viscous oil (26.4 mg, 23%); $R_f=0.10$ (Et_2O); $[\alpha]_D^{20}=-10.4$ (*c* 1.1, $CHCl_3$); ee >99% determined by HPLC (*n*-Hex/*i*-PrOH; 98:2, 1 ml/min, λ_{max} 254 nm). The determination of the absolute configuration of *cis*-(2*S*,4*S*)-**9b** was performed by comparison of its retention time (30.87 min) with the ones from the chiral authentic *cis*-(2*S*,4*R*)-**9b** (28.80 min) and the racemic *cis*-**9b** (28.54 and 30.53 min). The retention times are the average values obtained in three HPLC runs; other data identical to the already described *cis*-(2*S*,4*R*)-**9b**.

4.5.4. Reactions using 6c. *With phenzylazide*. The general procedure was followed in a NMR tube using the oxazaphospholane **6c** (77.5 mg, 0.45 mmol) and phenzylazide (53 mg, 0.44 mmol) in dry deuterated toluene (0.4 ml). The total conversion of **6c** (^{31}P NMR signal at 135.0 ppm) to the imide **7c** (^{31}P NMR signals at 28.2 ppm, ^{13}C NMR –O*C*H_2– at 62.7 ppm) was confirmed by NMR after 30 min at 40 °C. After the addition of $BF_3\cdot OEt_2$ (5.6 μl, 10 mol%) the total conversion of **7c** was observed by ^{31}P NMR after 4 h at 100 °C (conversion to ^{31}P NMR signal at 20.4 (approx. 85%), 18.0, 15.0 and 14.0 ppm). After 8 h at 100 °C no variation was detected by NMR. The residue obtained after work-up was purified by column chromatography (*n*-Hex/AcOEt, 1:9) and 2-diethylamino-3-*N′*-methyl-1-*N*-phenyl-1,3,2-λ^5-diazaphospholidin-2-one **8c** was obtained as a yellow solid (42.9 mg, 36%). Mp 35–37 °C; ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=7.18$ (t, J(H,H)=7.4 Hz, 2H, –CH–, Ar), 6.96 (d, J(H,H)=7.4 Hz, 2H, –CH–, Ar), 6.83 (t, J(H,H)=7.4 Hz, 1H, –CH–, Ar), 3.87–3.52 (m, 1H, one of NCH_2–), 3.43 (q, $J=8.4$ Hz, 1H, one of –NCH_2–), 3.37–3.27 (m, 1H, one of –NCH_2–), 3.19–3.08 (m, 1H, one of –NCH_2–), 3.08–2.98 (m, 2H, two of –N(C$H_2$$CH_3$)$_2$), 2.92–2.82 (m, 2H, two of –N(C$H_2$$CH_3$)$_2$), 2.54 (d, J(H,H)=10.5 Hz, 3H, –NCH_3), 0.87 (t, J(H,H)=7.0 Hz, 6H; –N(CH_2CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): $\delta=142.2$ (d, ^2J(P,C)=6.7 Hz, –C–), 128.8 (CH–, Ar), 120.4 (–CH–, Ar), 115.4 (d, ^2J(P,C)=5.4 Hz, –CH–, Ar), 45.7 (d, ^2J(P,C)=10.9 Hz, one of –N*C*H_2–), 43.7 (d, ^2J(P,C)=12.3 Hz, one of –NCH_2–), 39.3 (d, ^2J(P,C)=5.4 Hz, one of –N(*C*$H_2$$CH_3$)$_2$), 30.9 (d, ^2J(P,C)=5.4 Hz, –N*C*H_3), 14.0 (–N(CH_2*C*H_3)$_2$); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): $\delta=21.54$; IR (KBr): ν_{max} (cm^{-1})=2978.2 (C–H, Ar), 1603.9, 1499.3, 1312.4, 1216.6 (P=O), 1183.3, 1033.3 (P–N–C), 761.7; MS (FAB): *m*/*z* (%): 268 (100) [MH^+], 195 (54) [M^+-HNEt_2], 106 (10) [CH_2=$NHPh^+$], 72 (12) [NEt_2^+]; HMRS (EI): obtained 267.150765; M^+ $C_{13}H_{22}N_3OP$ requires 267.150051.

With benzylazide. The general procedure was followed in a NMR tube using the oxazaphospholane **6c** (84.2 mg, 0.48 mmol) and benzylazide (60.0 μl, 0.48 mmol) in dry deuterated toluene (0.4 ml). The total conversion of **6c** (^{31}P NMR signal at 135.0 ppm) to the imide **7d** (^{31}P NMR signal at 17.7 ppm, ^{13}C NMR –O*C*H_2– at 62.6 ppm) was confirmed by NMR after 30 min at 40 °C. After the addition of $BF_3\cdot OEt_2$ (5.6 μl, 10 mol%) the total conversion of **7c** was observed by ^{31}P NMR after 40 min at 100 °C (conversion to ^{31}P NMR signals at 25.7 (approx. 40%),

23.1 and 18 ppm, ^{13}C NMR –N*C*H$_2$– duplet at 43.9 ppm). After 8 h at 100 °C no variation was detected by NMR. The residue obtained after work-up was purified by column chromatography (*n*-Hex/AcOEt, 1:9) and 2-diethylamino-1-*N*-benzyl-3-*N*′-methyl-1,3,2-λ^5-diazaphospholidin-2-one **8d** was obtained as a slightly yellow viscous oil (24.9 mg, 19%); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.31–7.26 (m, 4H, –CH–, Ar), 7.195 (t, *J*(H,H)=7.0 Hz,. –CH–, Ar), 3.98 (dd, *J*(H,H)=14.9 Hz, *J*(P,H)=6.1 Hz, 1H, one of –NC*H*$_2$Ph), 3.89 (dd, *J*(H,H)=14.9 Hz, *J*(P,H)=7.6 Hz, 1H, one of –NC*H*$_2$Ph), 3.11–2.91 (m, 8H, NC*H*$_2$C*H*$_2$N– and –N(C*H*$_2$CH$_3$)$_2$), 2.52 (d, *J*(H,H)=9.7 Hz, 3H, –NC*H*$_3$), 1.06 (t, *J*(H,H)=7.1 Hz, 6H, –N(CH$_2$C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=138.1 (d, ^{2}*J*(P,C)=5.9 Hz, –C–), 128.3 (–CH–, Ar), 128.0, (–CH–, Ar) 127.0 (–CH–, Ar), 48.8 (d, ^{2}*J*(P,C)=5.3 Hz, –N*C*H$_2$Ph), 47.0 (d, ^{2}*J*(P,C)=12.5 Hz, one of –N*C*H$_2$–), 44.1 (d, ^{2}*J*(P,C)=12.4, one of –N*C*H$_2$–), 39.0 (d, ^{2}*J*(P,C)=4.6 Hz, –N(*C*H$_2$CH3)$_2$), 31.0 (d, ^{2}*J*(P,C)=5.6 Hz, –N*C*H$_3$), 14.6 (–N(CH$_2$*C*H$_3$)$_2$); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): d=27.3; IR (KBr): ν_{max} (cm^{-1})=2934.0 (C–H), 1229.8 (P=O), 1209.4, 1188.4, 1019.72 (P–N–C), 998.5, 701.0.

4.5.5. Reactions using 6e. *With phenylazide*. The general procedure was followed in a NMR tube using the oxazaphospholane **6e** (110.0 mg, 0.46 mmol) and phenylazide (55 mg, 0.46 mmol) in dry deuterated toluene (0.4 ml). The total conversion of **6e** (^{31}P NMR signal at 121.3 ppm) to the imide **7e** (^{31}P NMR signals at 8.8 ppm, ^{13}C NMR –O*C*H$_2$– at 62.2 ppm) was confirmed by NMR after 30 min at 40 °C. After the addition of $BF_3\cdot OEt_2$ (5.6 μl, 10 mol%) the total conversion of **7e** was observed by ^{31}P NMR after 8 h at 100 °C (conversion to ^{31}P NMR signal at 16.1 (approx. 90%), 18.0, 15.0 and 14.0 ppm). The residue obtained after work-up was purified by thin layer chromatography (*n*-Hex/AcOEt, 1:1) and two fractions were isolated.

2-Diethylamino-1-*N*-,-3-*N*′-diphenyl-1,3,2-λ^5-diazaphospholidin-2-one **8e**. White needles (4.0 mg, 3%); R_f=0.5 (*n*-Hex/AcOEt, 1:1). Mp 190–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.16 (t, *J*(H,H)=7.2 Hz, 2H, –CH–, *m*-Ar), 7.01 (d, *J*(H,H)=7.2 Hz, 2H, –CH–, *o*-Ar), 6.84 (t, *J*(H,H)=7.2 Hz, 1H, –CH–, *p*-Ar), 3.74–3.65 (m, 4H, –NC*H*$_2$C*H*$_2$N–), 3.01–2.96 (m, *J*(H,H)=7.0 Hz, *J*(P,H)=11.6 Hz, 4H, –N(C*H*$_2$CH$_3$)$_2$), 0.83 (t, *J*(H,H)=7.0 Hz, 6H, –N(CH$_2$C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=141.8 (d, *J*(P,C)=7.1 Hz, –C–, Ar), 129.1 (–CH–, Ar), 121.5 (–CH–, Ar), 116.5 (d, *J*(P,C)=5.5 Hz, –CH–, *o*-Ar), 42.7 (d, *J*(P,C)=11.4 Hz, –N*C*H$_2$–), 39.3 (d, *J*(P,C)=4.8 Hz, –N(*C*H$_2$CH$_3$)$_2$), 13.3 (–N(CH$_2$ *C*H$_3$)$_2$); IR (KBr): ν_{max} (cm^{-1})=2964.0 (C–H), 1599.9, 1499.8, 1279.9, 1262.2, 1227.3 (P=O), 1103.8, 1028.7 (P–N–C), 749.4 ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ=14.43; MS (EI): *m*/*z* (%): 329 (83) [M$^+$], 314 (52) [M$^+$ CH$_3$], 257 (100) [M$^+$ −NEt$_2$], 152 (38), 119 (23) [C$_2$H$_4$NPh$^+$], 106 (50), 72 (25) [NEt$_2^+$]; HMRS (EI): obtained 329.165660; M$^+$ C$_{18}$H$_{24}$N$_3$OP requires 329.165701.

Poly-diethylamino-*N*′,*N*′-ethylphenylamino-*N*″,*N*″-phenylaminophosphorotriamide **9e**. White solid (109.0 mg, 72%); recovered from the application point; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.18–6.91 (br, approx. 7H, –CH–, Ar), 6.78 (br, approx. 3H, –CH–, Ar), 3.01–2.37 (br, approx. 8H, –NCH$_2$CH$_2$N– and –N(CH$_2$C H$_3$)$_2$), 0.53–0.44 (br, approx. 6H, –N(CH$_2$CH$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=142.7 (br), 128.8 (br), 125.3 (br), 48.5 (br), 40.4 (br), 13.3 (br); IR (KBr): ν_{max} (cm$_{-1}$)=3400.2 (br, NH), 2972.3, (C–H), 1595.9, 1492.5, 1216.8 (P=O), 1097.2, 1028.1 (P–N–C), 950.1, 698.3; ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ=15.79 (broad, 87%), 11.17 (broad, 7%), 10.80 (broad, 3%); MS (MALDI): repeating unit: 329±1 Da; M_n=5990, M_w=6156, polydispersion index=1.028.

With benzylazide. The general procedure was followed in a NMR tube using the oxazaphospholane **6e** (104.0 mg, 0.44 mmol) and benzylazide (54.0 μl, 0.44 mmol) in dry deuterated toluene (0.4 ml). The total conversion of **6e** (^{31}P NMR signal at 121.3 ppm) to the imide **7f** (^{31}P NMR signal at 18.0 ppm, ^{13}C NMR –O*C*H$_2$– at 61.6 ppm) was confirmed by NMR after 30 min at 40 °C. After the addition of $BF_3\cdot OEt_2$ (5.6 μl, 10 mol%) the total conversion of **7** was observed by ^{31}P NMR after 40 min at 100 °C (conversion to ^{31}P NMR signals at 20.7 (approx. 90%) broad ^{1}H NMR and ^{13}C NMR signals, total disappearance of signal –O*C*H$_2$– at 61.6 ppm). After 8 h at 100 °C no variation was detected by NMR. The residue obtained after work-up was characterized without further purification and identified as poly-*N*-benzylamino-*N*′,*N*′-diethylamino-*N*″,*N*″-benzylphenylaminophosphorotriamide **8f**; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.36–7.07 (br, 9H, –CH–, Ar), 6.76 (br, 1H, –CH–, Ar), 3.95 (br, 2H), 3.76–3.40 (br, 2H), 2.98–2.66 (6H, br, –N(CH$_2$CH$_3$)$_2$), 0.68 (br, 6H, –N(CH$_2$CH$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=143.0 (–C–, Ar), 139.6 (–C–, Ar), 128.8 (–CH–, Ar), 128.5–127.9 (br, –CH–, Ar), 127.0 (br, –CH–, Ar), 51.8, 48.5 e 46.1 (very broad signals), 40.0 (br, –N(CH$_2$CH$_3$)$_2$), 14.7 (br, –N(CH$_2$CH$_3$)$_2$); ^{31}P NMR (160 MHz, $CD_3C_6D_5$, 25 °C, H_3PO_4 external): δ=20.5 (br, 90%), 17.3 (br, 10%); IR (film): ν_{max} (cm^{-1})=3393.8 (br, NH), 2974.2 (C–H), 1598.6, 1493.6, 1217.3 (P=O), 1193.9, 1068.9, 1029.3 (P–N–C), 949.9, 736.4, 700.4.

4.5.6. Reaction using 11a. The general procedure was followed in a NMR tube using the oxazaphospholane **11a** (38.0 mg, 0.174 mmol) and phenylazide (20.7 mg, 0.174 mmol) in dry deuterated toluene (0.4 ml). The total conversion of **11a** to the imide **12a** (^{31}P NMR signals at 19.86 and 16.09 ppm, in a 65:35 ratio) was confirmed by NMR after 30 min at 40 °C. After the addition of $BF_3\cdot OEt_2$ (3.6 μl, 10 mol %), the total conversion of **11b** was observed by ^{31}P NMR after 72 h at 100 °C. The residue obtained after work-up was purified by column chromatography (*n*-Hex/AcOEt, 6:4). Three fractions were obtained, the first two corresponding to the two diastereomers *cis*-**13a** and *trans*-**13a** and the third fraction corresponding to a mixture of *cis* and *trans*-**14a**.

cis-**13a**. Colourless viscous oil (6.3 mg, 12%); R_f=0.21 (*n*-Hex:AcOEt, 6:4); $[\alpha]_D^{20}$=+43.8 (*c* 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.17 (t, *J*(H,H)=7.5 Hz, 1H, –CH–, *m*-Ar), 6.99 (d, *J*(H,H)=7.5 Hz, 1H, –CH–, *o*-Ar), 6.83 (t, *J*(H,H)=7.5 Hz, 1H, –CH–, *p*-Ar), 3.79–3.71 (m, *J*(H,H)=9.2, 6.0 Hz, 1H, –NC*H*(CH$_3$)CH$_2$N–), 3.52–3.37 (m, 2H, one of –NCH

(CH_3)CH_2N– and –NCH(CH_3)$_2$), 3.09–2.96 (m, 3H, one of –NCH(CH_3)CH_2N– and two of –N(C$H_2$$CH_3$)$_2$), 2.94–2.84 (m, 2H, two of –N(C$H_2$$CH_3$)$_2$), 1.31 (d, J(H,H)=6.9 Hz, 3H, –NCH(CH_3)CH_2N–), 1.22 (d, J(H,H)=6.0 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$), 1.20 (d, J(H,H)=6.0 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$), 0.82 (t, J(H,H)=7.0 Hz, 6H, –N(CH_2CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=128.8 (–CH–, *m*-Ar), 120.5 (–CH–, *p*-Ar), 115.8 (d, ^3J(P,C)=4.7 Hz, –CH–, *o*-Ar), 51.6 (d, $_2J$(P,C)=12.3 Hz, –NCH(CH_3)CH_2N–),45.5 (d, ^2J(P,C)=11.1 Hz, (d, ^2J(P,C)=4.3 Hz, –NCH(CH_3)CH_2N–), 44.7 (–NCH(CH_3)$_2$), 39.3 (d, ^2J(P,C)=5.3 Hz, –N(C$H_2$$CH_3$)$_2$), 21.9 (d ^3J(P,C)=3.5 Hz, one CH_3 of NCH(CH_3)$_2$), 20.6 (d, ^3J(P,C)=8.8 Hz, one CH_3 of –NCH(CH_3)$_2$), 20.1 (–NCH(CH_3)CH_2N–), 13.6 (N(CH_2CH_3)$_2$); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 externo): δ=22.13; IR (film): ν_{max} (cm^{-1})=2974.0 (C–H), 1600.8, 1499.7, 1304.8, 1218.1 (P=O), 1193.5, 1031.6 (P–N–C); MS (70 eV, EI): *m*/*z* (%): 309 (92) [M^+], 294 (100) [M^+-CH_3], 237 (84) [M^+-NEt_2], 223 (66) [HCNPhP(O)NEt_2^+], 195 (34), 133 (40) [$C_3H_6NPh^+$], 72 (56) [NEt_2^+].

trans-**13a**. Colourless viscous oil (9.3 mg, 18%); R_f=0.17 (*n*-Hex/AcOEt, 6:4); $[\alpha]_D^{20}=-18.5$ (*c* 0.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.17 (t, J(H,H)=7.8 Hz, 1H, –CH–, *m*-Ar), 6.99 (d, J(H,H)=7.8 Hz, 1H, –CH–, *o*-Ar), 6.82 (t, J(H,H)=7.8 Hz, 1H, –CH–, *p*-Ar), 3.69–3.60 (m, 2H, one of –NCH(CH_3)CH_2N– and –NCH(CH_3)CH_2N–), 3.50–3.40 (m, J(H,H)=6.6 Hz, 1H, –NCH(CH_3)$_2$), 3.14–2.97 (m, 3H, one of –NCH(CH_3)CH_2N– and two of –N(C$H_2$$CH_3$)$_2$), 2.94–2.92 (m, 2H, two of –N(C$H_2$$CH_3$)$_2$), 1.33 (d, J(H,H)=6.1 Hz, 3H, –NCH(CH_3)CH_2N–), 1.25 (d, J(H,H)=6.6 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$), 1.21 (d, J(H,H)=6.6 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$), 0.82 (t, J(H,H)=7.1 Hz, 6H, –N(CH_2CH_3)$_2$); δH4=3.63 ppm (from HMQC); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=142.8 (d, J(P,C)=7.0 Hz, –C–, Ar), 128.9 (–CH–, *m*-Ar), 120.2 (–CH–, *p*-Ar), 115.6 (d, ^3J(P,C)=4.7 Hz, –CH–, *o*-Ar), 51.8 (d, ^2J(P,C)=12.4 Hz, –NCH(CH_3)CH_2N–), 47.0 (d, ^2J(P,C)=6.3 Hz, –NCH(CH_3)CH_2N–), 44.3 (d, ^2J(P,C)=12.0 Hz, –NCH(CH_3)$_2$), 39.3 (d, ^2J(P,C)=5.1 Hz, –N(C$H_2$$CH_3$)$_2$), 23.8 (d ^3J(P,C)=2.4 Hz, one CH_3 of –NCH(CH_3)$_2$), 21.7 (–NCH(CH_3)CH_2N–), 21.1 (d, ^3J(P,C)=4.5 Hz, one CH_3 of –NCH(CH_3)$_2$), 13.6 (–N(CH_2CH_3)$_2$); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ=17.95; IR (film): ν_{max} (cm^{-1})=2968.6 (C–H), 1602.5, 1500.9, 1304.9, 1203.7 (P=O), 1029.7 (P–N–C); MS (70 eV, EI): *m*/*z* (%): 309 (89) [M^+], 294 (100) [M^+-CH_3], 237 (55) [M^+-NEt_2], 223 (71) [HCNPhP(O)NEt_2^+], 195 (35), 133 (39) [$C_3H_6NPh^+$], 72 (44) [NEt_2^+]. HMRS (EI): obtained 309.196851; M^+ $C_{16}H_{28}N_3OP$ requires 309.197001.

cis-**14a** and *trans*-**14a** (mixture of diastereoisomers 58:42, respectively, as determined by ^{31}P and ^{1}H NMR). Colourless viscous oil (26 mg, 64%); R_f=0.1 (*n*-Hex/AcOEt, 6:4); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=4.21 (q, J=8.8 Hz, 1H, one of –NCH(CH_3)CH_2O–, *cis*), 4.08 (q, J=8.8 Hz, 1H, one of –NCH(CH_3)CH_2O–, *trans*), 3.78–3.59 (m, 1H, one of –NCH(CH_3)CH_2O–, *trans*, 1H, –NCH(CH_3)$_2$, *trans* and 1H, –NCH(CH_3)$_2$, *cis*), 3.50 (q, J=8.8 Hz, 1H, one of –NCH(CH_3)CH_2O–, *cis*), 3.42–3.27 (m, 1H, one of –NCH(CH_3)CH_2O–, *cis* and 1H, one of –NCH(CH_3)CH_2O–, *trans*), 3.12–2.30 (m, 4H, –N(C$H_2$$CH_3$)$_2$, *trans* and 4H, –N(C$H_2$$CH_3$)$_2$, *cis*), 1.26–1.25 (m, 3H, –NCH(CH_3)CH_2N–, *cis* and 3H, one –CH_3 of –NCH(CH_3)$_2$, *trans*), 1.22 (d, J(H,H)=5.5 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$, *trans*), 1.17 (d, J(H,H)=6.4 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$, *cis*), 1.14 (d, J(H,H)=7.2 Hz, 3H, –NCH(CH_3)CH_2N–, *trans*), 1.11 (d, J(H,H)=6.4 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$, *cis*), 1.04 (t, J(H,H)=7.0 Hz, 6H, N(CH_2CH_3)$_2$, *trans* and 6H, –N($CH_2$$CH_3$)$_2$, *cis*); δ H4 (from HMQC) δ H4=3.68 ppm (major diastereoisomer—*cis*) δ H4=3.62 ppm (minor diastereoisomer—*trans*); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=70.2 (–NCH(CH_3)CH_2O–, *trans*), 69.9 (NCH(CH_3)CH_2O–, *cis*), 51.2 (d, ^2J(P,C)=16.3 Hz, –NCH(CH_3)$_2$, *trans*), 49.5 (d, ^2J(P,C)=15.2 Hz, –NCH(CH_3)$_2$, *cis*), 45.0 (d, ^2J(P,C)=4.4 Hz, –NCH(CH_3)CH_2N–, *cis*), 44.1 (d, ^2J(P,C)=5.7, –NCH(CH_3)CH_2N–, *trans*), 39.6 (d, ^2J(P,C)=5.4 Hz, –N(C$H_2$$CH_3$)$_2$, *cis*), 39.4 (d, ^2J(P,C)=4.6 Hz, –N(C$H_2$$CH_3$)$_2$, *trans*), 22.8 (–NCH(C$H_3$)$CH_2$N–, *trans*), 21.9 (d, ^3J(P,C)=3.0 Hz, one CH_3 of –NCH(CH_3)$_2$, *cis*), 20.8 (d, ^3J(P,C)=4.0 Hz, one CH_3 of –NCH(CH_3)$_2$, *trans*), 20.6 (–NCH(CH_3)CH_2N–, *cis*), 19.8 (d, ^3J(P,C)=7.0 Hz, one CH_3 of NCH(CH_3)$_2$, *cis*), 19.7 (d, ^3J(P,C)=2.2 Hz, one CH_3 of –NCH(CH_3)$_2$, *trans*), 14.2 (d, ^3J(P,C)=2.0 Hz, –N(CH_2CH_3)$_2$, *cis*), 14.1 (–N(CH_2CH_3)$_2$, *trans*); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ=28.54 (*cis*), 25.12 (*trans*);IR (film): ν_{max} (cm_{-1})=2972.9 (C–H), 1381.0, 1245.1 (P=O), 1210.3, 1024.3 (P–N–C), 808.9, 720.8.

4.5.7. Reaction using 11b. The general procedure was followed in a NMR tube using the oxazaphospholane **11b** (72.0 mg, 0.292 mmol) and phenylazide (35.0 mg, 0.292 mmol) in dry deuterated toluene (0.4 ml). After the addition of $BF_3\cdot OEt_2$ (3.6 μl, 10 mol%), the total conversion of **11b** to the imide **12b** (^{31}P NMR signals at 19.92 and 15.99 ppm, in a 39:61 ratio) was confirmed by NMR after 40 min at 40 °C. The total conversion of **11b** was observed by ^{31}P NMR after 48 h at 100 °C. The residue obtained after work-up was purified by column chromatography (*n*-Hex/AcOEt, 7:3 until 1:1) and two fractions corresponding to the two diastereomers *cis*-**13b** and *trans*-**13b** were obtained.

trans-**13b**. White crystals (18.0 mg, 18%); higher R_f diastereomer; mp 115–117 °C; $[\alpha]_D^{20}=+7.2$ (*c* 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.18 (t, J(H,H)=7.6 Hz, 1H, –CH–, *m*-Ar), 7.03 (d, J(H,H)=7.6 Hz, 1H, –CH–, *o*-Ar), 6.81 (t, J(H,H)=7.6 Hz, 1H, –CH–, *p*-Ar), 3.50–3.40 (m, 3H, –NCH(R)CH_2N–, –NCH(CH_3)$_2$ and one of –NCH(R)CH_2N–), 3.23 (t, J=9.5 Hz, 1H, one of –NCH(R)CH_2N–), 3.09–2.97 (m, 2H, two of –N(C$H_2$$CH_3$)$_2$), 2.94–2.83 (m, 2H, two of –N(C$H_2$$CH_3$)$_2$), 2.08–2.00 (m, J(H,H)=6.9, 6.8, 3.2 Hz, 1H, –CHCH(CH_3)$_2$), 1.28 (d, J(H,H)=6.9 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$), 1.22 (d, J(H,H)=6.7 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$), 0.96 (d, J(H,H)=6.8 Hz, 3H, one –CH_3 of –CHCH(CH_3)$_2$), 0.86 (d, J(H,H)=6.9 Hz, 3H, one –CH_3 of –CHCH(CH_3)$_2$), 0.82 (t, J(H,H)=7.2 Hz, 6H, –N(CH_2CH_3)$_2$); δH_4=3.48 ppm (from HMQC); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=128.9 (–CH–, *m*-Ar), 120.0 (–CH–, *p*-Ar), 115.4 (d, ^3J(P,C)=4.1 Hz, –CH–, *o*-Ar), 56.1 (d, ^2J(P,C)=11.1 Hz, –NCH(R)CH_2N–), 44.3

(d, ^2J(P,C)=7.9 Hz, –NCH$(CH_3)_2$), 43.7 (d, ^2J(P,C)=13.4 Hz, –NCH(R)CH_2N–), 39.4 (d, ^2J(P,C)=5.2 Hz, –N($CH_2CH_3)_2$), 30.5 (–CH$CH(CH_3)_2$), 23.7 (one –CH_3 of –NCH($CH_3)_2$), 20.7 (d, ^3J(P,C)=5.5 one –CH_3 of –NCH($CH_3)_2$), 19.05 (one –CH_3 of –CHCH($CH_3)_2$), 14.5 (one –CH_3 of –CHCH($CH_3)_2$), 13.7 (–N($CH_2CH_3)_2$); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ=18.62; IR (KBr): ν_{max} (cm^{-1})=2970.2 (C–H), 1603.4, 1502.2, 1312.9, 1220.3 (P=O), 1187.8, 1033.7 (P–N–C),755.4; MS (70 eV, EI): *m*/*z* (%): 337 (16) [M^+], 308 (10) [$M^+-C_2H_5$], 294 (100) [M^+-*i*-Pr], 265 (10) [M^+-NEt_2],252 (31) [M^+-*i*-Pr–CH_2=$CHCH_3$], 223 (45) [HCNPhP(O)NEt_2^+].

cis-**13b**. Colourless viscous oil (31.0 mg, 32%); $[\alpha]_D^{20}=+19.8$ (*c* 0.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.17 (t, *J*(H,H)=7.6 Hz, 1H, –CH–, *m*-Ar), 7.02 (d, *J*(H,H)=7.6 Hz, 1H, –CH–, *o*-Ar), 6.84 (t, *J*(H,H)=7.6 Hz, 1H, –CH–, *p*-Ar), 3.67–3.61 (m, 1H, –NC*H*(R)CH_2N–), 3.35–3.14 (m, 3H, –NC*H*($CH_3)_2$ and –NCH(R)CH_2N), 3.03–2.86 (m, 4H, –N($CH_2CH_3)_2$), 2.17–2.03 (m, *J*(H,H)=6.9, 6.8, 2.0 Hz, 1H, –CHC*H*($CH_3)_2$), 1.35 (d, *J*(H,H)=6.9 Hz, 3H, one –CH_3 of –NCH($CH_3)_2$), 1.23 (d, *J*(H,H)=6.6 Hz, 3H, one –CH_3 of –NCH($CH_3)_2$), 0.91 (d, *J*(H,H)=6.9 Hz, 3H, one –CH_3 of –CHCH($CH_3)_2$), 0.87 (d, *J*(H,H)=6.8 Hz, 3H, one –CH_3 of –CHCH($CH_3)_2$), 0.89 (t, *J*(H,H)=7.0 Hz, 6H, N($CH_2CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=142.27 (d, ^2J(P,C)=7.2 Hz, –C–, Ar), 128.7 (–CH–, *m*-Ar), 120.5 (–CH–, *p*-Ar), 116.0 (d, ^3J(P,C)=4.1 Hz, –CH–, *o*-Ar), 56.8 (d, ^2J(P,C)=8.6 Hz, –N*C*H(R)CH_2N–), 45.1 (d, ^2J(P,C)=2.2 Hz, –N*C*H($CH_3)_2$), 43.5 (d, ^2J(P,C)=11.1 Hz, –NCH(R)*C*H_2N–), 39.1 (d, ^2J(P,C)=4.6 Hz, –N(*C*H_2 $CH_3)_2$), 27.1 (d, ^2J(P,C)=8.1 Hz, CH*C*H($CH_3)_2$), 20.4 (one –CH_3 of –NCH(*C*$H_3)_2$), 20.0 (one –CH_3 of –NCH (*C*$H_3)_2$), 18.2 (one *C*H_3 of –CHCH(*C*$H_3)_2$), 14.04 (one –CH_3 of –CHCH(*C*$H_3)_2$), 13.35 (–N($CH_2CH_3)_2$); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ=22.91; IR (film): ν_{max} (cm^{-1})=2968.9 (C–H), 1603.6, 1502.8, 1223.3 (P=O), 1203.8, 1184.3, 1033.5 (P–N–C); MS (70 eV, EI): *m*/*z* (%): 337 (31) [M^+], 294 (100) [M^+-*i*-Pr], 265 (8) [M^+-NEt_2], 252 (30) [M^+-*i*-Pr–CH_2=$CHCH_3$], 223 (39) [HCNPhP(O)NEt_2^+]; HMRS (EI): obtained 337.227622; M^+ $C_{18}H_{32}N_3OP$ requires 337.228301.

4.6. Reactions towards the elucidation of the mechanism of the imide–amide rearrangement of oxazaphosphorimidates

4.6.1. Imide–amide rearrangement of 16. The general procedure (Section 4.5) was followed using the racemic oxazaphospholane **6b** (226 mg, 0.85 mmol) and phenylazide (101 mg, 0.85 mmol) in dry toluene (1.0 ml). After 12 h at room temperature $BF_3\cdot OEt_2$ (10.4 μl, 10 mol%) was added and the mixture heated to 100 °C. The total conversion of **16** was observed by ^{31}P NMR after 12 h at 100 °C. The residue obtained after work-up was purified by column chromatography ($CHCl_3$/Et_2O, 5:95 until 1:1) affording an inseparable mixture of the two diastereomers (minor/major, 37:63) *cis*- and *trans*-1-*N*-benzyl-2-diethylamino-3-*N*′-phenyl-4-methyl-1,3,2-λ^5-diazaphospholidine-2-one **17**.

cis and *trans*-**17**. Colourless viscous oil (168.8 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.31–7.25 (m, 4H minor and 4H major, –CH–, Ar), 7.22–7.16 (m, 4H minor and 4H major, –CH–, Ar), 7.08 (d, *J*(H,H)=8.0 Hz, 2H minor, –CH–, Ar), 6.92 (d, *J*(H,H)=8.0 Hz, 2H major, –CH–, Ar), 6.89 (t, *J*(H,H)=8.0 Hz, 1H minor, –CH–, Ar), 6.824 (t, *J*(H,H)=8.0 Hz, 1H minor, –CH–, Ar), 4.10–3.97 (m, 2H major, one of –N(CH_3)CHC*H*$_2$N– and –N(CH_3) C*H*CH_2N– and 2H minor, one of –N(CH_3)CHC*H*$_2$N– and –N(CH_3)C*H*CH_2N–), 3.97–3.87 (m, 1H major, one of –N(CH_3)CHC*H*$_2$N– and 1H minor, one of –N(CH_3)CHC*H*$_2$-N–), 3.15–3.32 (m, 2H major, two of –N(C$H_2CH_3)_2$), 3.29–3.24 (m, 1H major, one of –NCH_2Ph and 1H minor, one of –NCH_2Ph), 3.09–2.97 (m, 2H major, two of –N(C$H_2CH_3)_2$), 2.97–2.83 (m, 4H minor, –N(C$H_2CH_3)_2$), 2.72 (t, *J*(H,H)=8.4 Hz, *J*(P,H)=8.4 Hz, 1H minor, one of –NCH_2Ph), 2.61 (dd, *J*=21.8, 8.7 Hz, 1H major, one of –NCH_2Ph), 1.25 (d, *J*(H,H)=6.1 Hz, 3H major, –N(CH_3) HCH_2N–), 1.15 (d, *J*(H,H)=6.0 Hz, 3H minor, –N(CH_3) HCH_2N–), 1.01 (t, *J*(H,H)=7.0 Hz, 6H major, –N(CH_2 C$H_3)_2$), 0.74 (t, *J*(H,H)=7.1 Hz, 6H minor, –N(CH_2C$H_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=140.9 (d, *J*(P,H)=7.2 Hz, –C–, Ar, major), 140.7 (d, *J*(P,H)=5.7 Hz, –C–, Ar, minor), 137.6 (d, *J*(P,H)=7.0 Hz, –C–, Ar, minor.), 137.4 (d, *J*(P,H)=8.3 Hz, –C–, Ar, major), 129.0 (–CH–, Ar), 128.7 (–CH–, Ar), 128.5 (–CH–, Ar), 128.4 (–CH–, Ar), 128.2 (–CH–, Ar), 127.3 (–CH–, Ar), 127.2 (–CH–, *p*-Ar), 121.7 (–CH–, Ar), 120.4 (–CH–, *p*-Ar, minor), 119.2 (–CH–, Ar, major), (d, *J*(P,C)=4.2 Hz, –CH–, *o*-Ar, minor), 116.8 (d, *J*(P,C)=5.1 Hz, –CH–, *o*-Ar, major), 50.6 (d, *J*(P,C)=11.1 Hz, –N*C*H_2Ph, minor), 49.9 (d, *J*(P,C)=11.4 Hz, –N*C*H_2Ph, major), 49.6 (d, *J*(P,C)=11.4 Hz, –N(CH_3)*C*HCH_2N–, minor), 49.1 (d, *J*(P,C)=11.6 Hz, –N(CH_3)*C*HCH_2N–, major), 48.5 (d, *J*(P,C)=5.0 Hz, –N(CH_3)CH*C*H_2N–, minor), 48.1 (d, *J*(P,C)=5.3 Hz, –N(CH_3)CH*C*H_2N–, major), 39.2 (d, *J*(P,C)=5.4 Hz, –N(*C*$H_2CH_3)_2$, major), 39.8 (d, *J*(P,C)=5.1 Hz, –N(*C*H_2 $CH_3)_2$, minor), 18.9 (–N(*C*H_3)CHCH_2N–, major), 18.8 (–N(*C*H_3)CHCH_2N–, minor), 14.1 (–N(CH_2*C*$H_3)_2$, major), 13.8 (–N(CH_2*C*$H_3)_2$, minor); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ=24.08 (minor, 37%), 22.33 (major, 63%); IR (KBr): ν_{max} (cm^{-1})=2965.0 (C–H), 1602.3, 1497, 1305.8, 1299.6 (Ph–N–R), 1225.0 (P=O), 1203.5, 1034.7 (P–O–C), 753.9, 756.5.

4.6.2. Preparation of *cis*- and *trans*-3-*N*′-benzyl-2-diethylamine-1-*N*-phenyl-4-methyl-1,3,2-λ^5-diazaphospholidin-2-one 18. The general method for the coupling of aminoalcohols with diethylphosphoramidous dichloride described previously was followed,[9] using 2-*N*-benzyl-1-*N*′-phenylpropanodiamine (202.0 mg, 0.84 mmol), diethylphosphoramidous dichloride (160.0 mg, 0.84 mmol) and dry trietilamine (235.0 μl, 1.68 mmol). The residue obtained was purified by column chromathography (*n*-Hex/AcOEt, 8:2), and two fractions corresponding to the two diastereomers *cis*-**18** and *trans*-**18** were obtained.

cis-**18**. Colourless crystals (60.6 mg, 20%); R_f=0.32 (*n*-Hex/AcOEt, 1:1). Mp 123–125 °C (isolated from chromatography); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.47 (d, *J*(H,H)=7.4 Hz, 2H, –CH–, *o*-Ar), 7.25 (t, *J*(H,H)=7.4 Hz, 2H, –CH–, *m*-Ar), 7.18 (t, *J*(H,H)=7.4 Hz, 3H, two –CH–, *m*-Ar and one –CH–, *p*-Ar), 7.01

(d, J(H,H)=7.4 Hz, 2H, –CH–, *o*-Ar), 6.83 (t, J(H,H)=7.4 Hz, 1H, –CH–, *p*-Ar), 4.15 (dd, ^3J(P,H)=10.2 Hz, J(H,H)=15.3 Hz, 1H, one of –NCH_2Ph), 4.00 (t, ^3J(P,H)=15.3 Hz, J(H,H)=15.3 Hz, 1H, one of –NCH_2Ph), 3.55–3.43 (m, 2H, –NCH(CH$_3$)CH_2N– and one of –NCH(CH$_3$)CH_2N–), 3.11–3.00 (m, 3H, one of –NCH(CH$_3$)CH_2N– and one –CH_2– of –N(CH_2CH$_3$)$_2$), 2.92–2.80 (m, 2H, one –CH_2– of –N(CH_2CH$_3$)$_2$), 1.08 (d, J(H,H)=5.6 Hz, 3H, –NCH(CH_3)CH$_2$N–), 0.80 (t, J(H,H)=7.1 Hz, 6H, –N(CH$_2$CH_3)$_2$); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C, CDCl$_3$): δ=142.0 (d, ^2J(P,C)=6.8 Hz, –C–, Ar), 137.4 (–C–, Ar), 128.8 (–CH–, *m*-Ar), 128.7 (–CH–, *o*-Ar), 128.3 (–CH–, *m*-Ar), 127.1 (–CH–, *p*-Ar), 120.5 (–CH–, *p*-Ar), 115.6 (d, ^3J(P,C)=5.1 Hz, –CH–, *o*-Ar), 51.6 (d, ^2J(P,C)=11.3 Hz, –NCH(CH$_3$)CH_2N–), 47.7 (d, J(P,C)=11.9 Hz, –NCH(CH$_3$)CH$_2$N–), 45.8 (d, ^2J(P,C)=5.5 Hz, –NCH_2Ph), 39.5 (d, ^2J(P,C)=4.8 Hz, –N(CH_2CH$_3$)$_2$), 18.8 (d, ^3J(P,C)=7.5 Hz, –NCH(CH_3)CH$_2$N–), 14.0 (–N(CH$_2$CH_3)$_2$); ^{31}P NMR (160 MHz, CDCl$_3$, 25 °C, H$_3$PO$_4$ external): δ=22.7; IR (KBr): ν_{max} (cm^{-1})=2967.0 (C–H, Ar), 1602.9, 1496.9, 1330.1 (Ph–N–R), 1305.8, 1225.1 (P=O), 1203.1, 1030.3 (P–O–C), 756.5; MS (70 eV, EI): *m*/*z* (%): 357 (46) [M$^+$], 342 (56) [M$^+$−CH$_3$], 285 (76) [M$^+$−NEt$_2$], 181 (36), 134 (55) [CH$_3$CH$_2$CH$_2$NHPh$^+$], 106 (34), 91 (100) [PhCH$_2^+$], 72 (49); HMRS (EI): obtained 357.197240; M$^+$ $C_{20}H_{28}N_3OP$ requires 357.1970011.

trans-**18**. Colourless crystals (30.9 mg, 10%); R_f=0.21 (*n*-Hex/AcOEt, 1:1). Mp 64–66 °C (isolated from chromatography); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ=7.31–7.18 (m, 7H, –CH–, Ar), 7.00 (d, J(H,H)=8.0 Hz, 2H, –CH–, *o*-Ar), 6.85 (t, J(H,H)=7.3 Hz, 1H, –CH–, *p*-Ar), 4.09 (dd, ^3J(P,H)=7.7 Hz, J(H,H)=15.2 Hz, 1H, one of –NCH_2Ph), 4.03 (t, ^3J(P,H)=4.8 Hz, J(H,H)=15.2 Hz, 1H, one of –NCH_2Ph), 3.66 (td, J(P,H)=8.5 Hz, J(H,H)=6.8, 2.3 Hz, 1H, one of –NCH(CH$_3$)CH_2N–), 3.46–3.36 (m, 1H, J(P,H)=18.0 Hz, J(H,H)=7.4, 6.8, 6.0 Hz, –NCH(CH$_3$)CH$_2$N–), 3.20–3.09 (m, 3H, one of –NCH(CH$_3$)CH_2N– and one –CH_2– of –N(CH_2CH$_3$)$_2$), 2.97–2.85 (m, 2H, one –CH_2– of –N(CH_2CH$_3$)$_2$), 1.21 (d, J(H,H)=6.3 Hz, 3H, –NCH(CH_3)CH$_2$N–), 0.84 (t, J(H,H)=7.1 Hz, 6H, –N(CH$_2$CH_3)$_2$); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C, CDCl$_3$): δ=142.5 (d, ^2J(P,C)=6.7 Hz, –C–, Ar), 138.0 (d, ^2J(P,C)=7.9 Hz, –C–, Ar), 128.9 (–CH–, *m*-Ar), 128.5 (–CH–, *o*-Ar), 128.2 (–CH–, *m*-Ar), 127.3 (–CH–, *p*-Ar), 120.4 (–CH–, *p*-Ar), 115.5 (d, ^3J(P,C)=4.0 Hz, –CH–, *o*-Ar), 51.2 (d, ^2J(P,C)=12.2 Hz, –NCH(CH$_3$)CH_2N–), 48.3 (d, ^2J(P,C)=10.5 Hz, –NCH(CH$_3$)CH$_2$N–), 45.2 (d, ^2J(P,C)=5.6 Hz, –NCH_2Ph), 39.2 (d, J(P,C)=3.5 Hz, –N(CH_2CH$_3$)$_2$), 18.55 (–NCH(CH_3)CH$_2$N–), 14.0 (–N(CH$_2$CH_3)$_2$); ^{31}P NMR (160 MHz, CDCl$_3$, 25 °C, H$_3$PO$_4$ external): δ=20.09; IR (KBr): ν_{max} (cm^{-1})=2970.0 (C–H, Ar), 1602.3, 1497.1, 1299.6 (Ph–N–R), 1224.2 (P=O), 1203.7, 1034.7 (P–O–C), 753.9, 726.9; MS (70 eV, EI): *m*/*z* (%): 357 (76) [M$^+$], 342 (57) [M$^+$−CH$_3$], 285 (66) [M$^+$−NEt$_2$], 271 (23), 171 (28), 134 (33) [CH$_3$CH$_2$CH$_2$NHPh$^+$], 91 (100) [PhCH$_2^+$].

4.7. Imide–amide rearrangement of 19

4.7.1. Preparation of (4*S*)-2-chloro-3-*N*-,4-di-isopropil-1,3,2-oxazaphospholidine—precursor of 19. To a stirred, ice-cold solution of phosphorus trichloride (1.20 ml, 13.8 mmol) and dry triethylamine (3.84 ml, 24.6 mmol) in dry diethyl ether (30 ml), under argon atmosphere, (*S*)-*N*-isopropylvalinol (2.0 g, 13.8 mmol) was added dropwise. The addition was controlled in order to avoid that the temperature of the reaction would rise beyond 10 °C. After the addition was complete, the mixture was allowed to stir during 3 h at room temperature. The amine salts were then separated by filtration under argon atmosphere and wash repeatedly with dry ethylic ether. The liquid fractions were combined and the solvent removed by distillation under argon atmosphere. The residue obtained was purified by low pressure distillation affording a colourless slightly viscous liquid, corresponding to the 2-chloro-oxazaphospholidine (1.23 g, 43%) as a mixture of *cis* and *trans* diastereomers (*cis*/*trans*; 10:90, as determined by ^{31}P NMR). Bp 140 °C (0.05 mmHg, KughelRohr); ^{1}H NMR (400 MHz, tol-d$_8$, 25 °C, tol): δ=4.25 (br, ^{1}H, –OCH_2CH(R)N–), 3.92 (br, ^{1}H, –OCH_2CH(R)N–), 3.10 (bl, 1H, –OCH$_2$CH(R)N–), 3.03 (bl, –NCH(CH$_3$)$_2$), 1.53 (br, 1H, –CH(CH$_3$)$_2$), 1.26 (dd, J(H,H)=6.7 Hz, J(P,H)=2.0 Hz, 3H, –NCH(CH_3)$_2$), 1.06 (br, 3H, NCH(CH_3)$_2$), 0.52 (br, 6H, –CH(CH_3)$_2$); ^{13}C NMR (100 MHz, tol-d$_8$, 25 °C, tol-d$_8$): δ=70.6 (br, –OCH_2CH(R)N–), 59.9 (br, –OCH$_2$CH(R)N–), 45.71 (d, ^2J(P,C)=9.0 Hz, –NCH(CH$_3$)$_2$), 27.0 (br, –CH(CH$_3$)$_2$), 23.3 (d, ^3J(P,C)=19.7 Hz, –NCH(CH_3)$_2$), 20.6 (br, –CH(CH_3)$_2$), 19.2 (–NCH(CH_3)$_2$), 14.4 (bl, –CH(CH_3)$_2$); ^{31}P NMR (160 MHz, tol-d$_8$, 25 °C, H$_3$PO$_4$ external): δ=180.7 (*cis*), 171.2 (*trans*).

4.7.2. Imide–amide rearrangement of 19. The general procedure (Section 4.5) was followed in a NMR tube using the previous described (4*S*)-2-chloro-3-*N*-,4-di-isopropil-1,3,2-oxazaphospholidine (89.0 mg, 0.424 mmol) and phenylazide (50.5 mg, 0.424 mmmol) in dry toluene-d$_8$ (0.5 ml). After heating the NMR tube for 30 min at 40 °C, no N_2 evolution could be seen (indicating that the Staudinger product **19** was not being formed) and therefore the temperature was slowly raised until N_2 evolution started (80 °C). After 40 min N_2 evolution ceased and ^{31}P NMR spectrum was acquired (^{31}P NMR: δ=−2.31 and −3.23 ppm, in 86:14 ratio) confirming the formation of **19**. BF$_3$·OEt$_2$ was then added (5.2 µl, 10 mol%) and the mixture was allowed to react for 18 h. The ^{31}P NMR spectrum acquired at this point revealed that all **19** had been consumed and three new signals could be seen, two signals corresponding to *cis*- and *trans*-**21** the products of the rearrangement (^{31}P NMR: δ=21.38 and 17.63 ppm, in 72:28 ratio) and one broad signal at −0.7 ppm, that was afterwards identified as the dimeric compound **20**. The residue obtained after work-up was purified by column chromatography (*n*-Hex/AcOEt, 8:2) and three fractions corresponding to the two diastereomers *cis*-(2*S*,4*S*)- and *trans*-(2*R*,4*S*)-2-chloro-1-*N*-phenyl-3-*N*′-4,4-diisopropyl-1,3,2-λ^5-diazaphospholidine-2-one **21** and the dispiro[(3-*N*-,4-diisopropyl-1,3,2-λ^5-oxazaphospholidine)-2,2′-(2′,4′-dichloro-1′,3′-diphenyl-1′,3′,2′-λ^5-diazadiphosphitidine)-4′,2″-(3″-*N*-,4″-diisopropyl-1″,3″,2″-λ^5-oxazaphospholidine)] **20** were obtained.

Compound **20**. Colourless crystals (19.4 mg, 15%); R_f=0.63 (*n*-Hex/AcOEt, 8:2). Mp 164–166 °C (AcOEt/*n*-Hex); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ=7.36–7.23 (br, 7H, –CH–, Ar), 713–7.06 (br, 3H, –CH–, Ar), 4.14

(br, 1H, one of –OCH_2–), 4.38 (br, 1H, one of –OCH_2–), 3.60–3.50 (br, 4H, –OCH_2– and 2×–N(R)CH), 2.99 (br, 1H, –N(R)CH–), 266–2.59 (br, 1H, –N(R)CH–), 2.33–2.26 (br, 1H, –CH(CH_3)$_2$), 1.91 (br, 1H, –CH(CH_3)$_2$), 1.40 (br, 6H, 2×–CH_3), 1.04–0.99 (br, 3H, 1×–CH_3), 0.80–0.68 (m, 9H, 3×–CH_3), 0.53 (br, 3H, 1×CH_3), 0.40 (br, 3H, 1×–CH_3); ^{13}C –NMR (100 MHz, $CDCl_3$, −40 °C, $CDCl_3$): δ=136.9, 135.9, 135.6, 130.2, 129.7, 125.3, 125.1, 124.8, 124.1, 122.6, 120.8, 120.3, 118.9, 62.3 (–N(R)CH–), 61.8 (–N(R)CH–), 49.0 (–OCH$_2$–), 48.5 (–OCH$_2$–), 47.3 (–CH(CH_3)$_2$), 33.3 (–CH(CH_3)$_2$), 23.3, 25.1, 24.2, 22.7, 22.2, 21.6, 21.3, 20.8, 20.1, 19.8; ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ=−0.72 (bl), −1.72 (bl); IR (KBr): ν_{max} (cm^{-1})=2976.9 (C–H), 1596.2, 1490.3, 1270.8, 1244.7, 1159.1, 1042.5 (P–N–C), 971.1, 948.4, 757.5, 698.1; MS (70 eV, EI): *m/z* (%): 604 (5), [M^++4], 602 (25) [M^++2], 600 (30) [M^+], 557 (100) [M^+−*i*-Pr], 515 (25) [M^+−*i*-Pr–CH=CH_2CH_3], 473 (15) [M^+−CH_2 CH(*i*-Pr)N-*i*-Pr], 122 (30).

cis-(2*S*,4*S*)-**21**. 73.2 mg, 57%, R_f=0.37 (*n*-Hex/AcOEt, 8:2); white crystals; Mp 128–130 °C (from chromatography; $[\alpha]_D^{20}$=−28.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.29–7.22 (m, 4H, –CH–, *o*-Ar and *m*-Ar), 7.01 (t, *J*(H,H)=7.0 Hz, 1H, –CH–, *p*-Ar), 3.69.3.63 (m, ^{3}*J*(P,H)=9.6 Hz, *J*(H,H)=7.0, 6.5, 4.4 Hz, 1H, –NCH(R)CH_2N–), 3.56–3.42 (m, 2H, –NCH(CH_3)$_2$ and one of –NCH(R)CH_2N–), 3.23 (td, *J*(P,H)=8.9 Hz, *J*(H,H)=8.9, 1.9 Hz, 1H, one of –NCH(R)CH_2N–), 2.19–2.08 (m, *J*(H,H)=7.7, 6.9, 4.4 Hz, 1H, –CHCH(CH_3)$_2$), 1.52 (d, *J*(H,H)=7.0 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$), 1.29 (d, *J*(H,H)=6.5 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$), 0.91 (d, *J*(H,H)=7.7 Hz, 3H, one –CH_3 of –CHCH(CH_3)$_2$), 0.891 (d, *J*(H,H)=6.9 Hz, 3H, one –CH_3 of –CHCH (CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ= 139.9 (d, ^{2}*J*(P,C)=4.7 Hz, –C–, Ar), 129.3 (–CH–, *m*-Ar), 123.1 (–CH–, *p*-Ar), 117.5 (d, ^{3}*J*(P,C)=5.4 Hz, –CH–, *o*-Ar), 56.9 (d, ^{2}*J*(P,C)=10.9 Hz, –NCH(R)CH_2N–), 48.8 (d, ^{2}*J*(P,C)=5.1 Hz, –NCH(CH_3)$_2$), 42.5 (d, ^{2}*J*(P,C)= 14.5 Hz, –NCH(R)CH$_2$N–), 28.1 (d, ^{3}*J*(P,C)=3.6 Hz, –CHCH(CH_3)$_2$–), 21.2 (–NCH(CH_3)$_2$), 20.6 (d, ^{3}*J*(P,C)= 2.3 Hz, –NCH(CH$_3$)$_2$), 17.7 (–CHCH(CH$_3$)$_2$), 14.8 (–CHCH(CH$_3$)$_2$); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 externo): δ=22.25; IR (KBr): ν_{max} (cm^{-1})= 2967.6 8 (C–H), 1602.8, 1502.5, 1267.1 (P=O), 1184.2, 754.6; MS (70 eV, EI): *m/z* (%): 302 (13) [M^++2], 300 (27) [M^+], 257 (58) [M^+−*i*-Pr], 215 (97) [M^+−*i*-Pr–CH=CH_2CH_3], 179 (15) [M^+−2×*i*-Pr–Cl], 104 (31), 83 (100) [HPClNPh$^+$].

trans-(2*R*,4*S*)-**21**. 16.2 mg, 13%, R_f=0.29 (*n*-Hex/AcOEt, 8:2); colourless viscous oil; $[\alpha]_D^{20}$=+68.4 (*c* 1.41, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.29–7.22 (m, 4H, –CH–, *o*-Ar and *m*-Ar), 7.01 (t, *J*(H,H)=7.0 Hz, 1H, –CH–, *p*-Ar), 3.67–3.55 (m, ^{3}*J*(P,H)=19.5 Hz, *J*(H,H)=6.8, 6.7 Hz, 1H, –NCH(CH_3)$_2$), 3.51–3.32 (m, 3H, –NCH(R)CH_2N– and –NCH(R)CH_2N–), 2.10–2.02 (m, *J*(H,H)=7.9, 7.7, 4.0 Hz, 1H, –CHCH(CH_3)$_2$), 1.43 (d, *J*(H,H)=6.8 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$), 1.32 (d, *J*(H,H)=6.7 Hz, 3H, one –CH_3 of –NCH(CH_3)$_2$), 0.93 (d, *J*(H,H)=7.7 Hz, 3H, one –CH_3 of –CHCH(CH_3)$_2$), 0.91 (d, *J*(H,H)=7.9 Hz, 3H, one –CH_3 of –CHCH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ=129.32 (–CH–, *m*-Ar), 123.0 (–CH–, *p*-Ar), 117.5 (d, ^{3}*J*(P,C)= 4.8 Hz, –CH–, *o*-Ar), 55.7 (d, ^{2}*J*(P,C)=10.5 Hz, –NCH(R)CH_2N–), 46.4 (d, ^{2}*J*(P,C)=5.5 Hz, –NCH (CH_3)$_2$), 42.8 (d, ^{2}*J*(P,C)=15.8 Hz, –NCH(R)CH$_2$N–), 29.9 (d, ^{3}*J*(P,C)=3.2 Hz, –CHCH(CH_3)$_2$), 21.7 (–NCH (CH$_3$)$_2$), 20.6 (–NCH(CH$_3$)$_2$), 18.7 (–CHCH(CH$_3$)$_2$), 14.4 (–CHCH(CH$_3$)$_2$); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C, H_3PO_4 external): δ=18.81; IR (KBr): ν_{max} (cm^{-1})= 2974.2 (C–H), 1598.6, 1501.5, 1269.0 (P=O), 1197.9, 1043.1 (P–N–C), 759.6; MS (70 eV, EI): *m/z* (%): 302 (9) [M^++2], 300 (22) [M+], 257 (68) [M^+−*i*-Pr], 215 (100) [M^+−*i*-Pr–CH=CH_2CH_3], 179 (15) [M^+−2×*i*-Pr–Cl], 104 (16), 77 (27) [$C_6H_5^+$]; HRMS (EI): obtained 300.115979; M^+ $C_{14}H_{22}N_2OPCl$ requires 300.115830.

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References and notes

1. Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2003**, *125*, 2208–2216.
2. Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, 432–440.
3. Denmark, S. E.; Su, X.; Nishigaichi, Y.; Coe, D. M.; Wong, K.-T.; Winter, S. B. D.; Choi, J. Y. *J. Org. Chem.* **1999**, 1958–1967 and references therein.
4. Legrand, O.; Brunel, J. M.; Buono, G. *Tetrahedron Lett.* **1998**, *39*, 9419–9422.
5. Brunel, J. M.; Constantieux, T.; Legrand, O.; Buono, A. *Tetrahedron Lett.* **1998**, *39*, 2961–2964.
6. Hulst, R.; Heres, H.; Fitzpatrick, K.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2755–2760.
7. Iseki, T.; Kuroki, Y.; Takahashi, M.; Kobayashi, Y. *Tetrahedron Lett.* **1996**, *29*, 5149–5150.
8. Cabrita, E. J.; Candeias, S. X.; Ramos, A. M.; Afonso, C. A. M.; Santos, A. G. S. *Tetrahedron Lett.* **1999**, *40*, 137–140.
9. Cabrita, E. J.; Afonso, C. A. M.; Santos, A. G. S. *Chem. Eur. J.* **2001**, *7*, 1455–1467.
10. Setzer, W.; Black, B. G.; Hovanes, B. A. *J. Org. Chem.* **1989**, *54*, 1709–1713.
11. Boulet, C. A.; Tregear, S. J.; Hansen, A. S. *Heterocycles* **1991**, *32*, 2105–2110.
12. Cooper, D. B.; Hall, C. R.; Harrison, J. M.; Inch, T. D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1969–1980.
13. Verkade, J. G.; Quin, L. D. Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis. In *Methods in Stereochemical Analysis*; VCH: Deerfield Beach, FL, 1987; Vol. 8, pp 297–330.
14. Ando, A.; Shiori, T. *Tetrahedron* **1989**, *45*, 4969–4988.
15. *Nitrogen Compounds, Carboxylic acids, Phosphorus Compounds*; Sutherland, I. O., Ed.; Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds; Pergamon: Oxford, 1979; Vol. 2, pp 1121–1300; University of Liverpool.

16. The imide–amide rearrangement was performed starting from the corresponding ephedrine derived oxazaphospholidine and generating in situ the phosphorimide with benzylazide or phenylazide, following the general procedure described in Section 4.5 of Section 4. Compounds **15a** and **15b** were allowed to react for 12 h. The ^{31}P NMR of the crude showed a complex mixture with multiple signals. After work-up and column chromatography the only products isolated were the phosphorus oxides (30–70% yield) corresponding to the several possibilities of hydrolysis of **15a** and **15b**, namely hydrolysis by loss of NPh or NBn, by loss of NEt_2, and even loss of the ephedrine moiety.
17. Since compounds **17** and **18** are very similar, compound **18** was also prepared by an independent way, by the coupling of diethylphosphoramidous dichloride with 2-*N*′-benzyl-1-*N*-phenylpropanodiamine. The comparison of the spectral data confirmed structure **17** as the product of the rearrangement.
18. By warming-up **19** in the absence of $BF_3 \cdot OEt_2$ the conversion to **20** is almost quantitative. An experiment was also made in order to determine if **20** could be involved in the mechanism of the rearrangement; **19** was allowed to react until approximately 50% conversion to **20** was observed, at this point $BF_3 \cdot OEt_2$ was added and the reaction followed by ^{31}P NMR. After the addition of the Lewis acid, the concentration of **20** remain practically unaltered and the remaining **19** was converted to product **21**.
19. Kukhar, V. P.; Kasheva, T. N.; Kasukhin, L. F.; Ponomarchuk, M. P. *J. Gen. Chem. USSR (Engl. Transl.)* **1984**, *54*, 1360–1364.
20. Kukhar, V. P.; Gilyarov, V. A. *Pure Appl. Chem.* **1980**, *52*, 891–904.
21. Gilyarov, V. A.; Tikhonina, N. A.; Andrianov, V. G.; Struchkov, Yu. T.; Kabachnik, M. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1978**, *48*, 671–677.
22. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: London, 1980.
23. Perich, J. W.; Johns, R. B. *Synthesis* **1988**, 142.
24. Katriztky, A. R.; Meth-Cohn, O. Synthesis: Carbon with One Heteroatom Attached by a Single Bond. In Ley, S. V., Ed.; Comprehensive Organic Functional Group Transformations; Elsevier: Oxford, 1995; Vol. 2.
25. Koziara, A.; Osowaka-Pacewicka, K.; Zawadzki, S.; Zwierzac, A. *Synthesis* **1985**, 202.
26. Alajarin, M.; Molina, P.; Sánchez-Andrada, P. *J. Org. Chem.* **1999**, *64*, 1121–1130.
27. Smith, P. A. S.; Brown, B. B. *J. Am. Chem. Soc.* **1951**, *73*, 2438–2441.
28. White, E. H.; Field, K. W.; Hendrickson, W. H.; Dzadzic, P.; Roswell, D. F.; Paik, S.; Mullen, P. W. *J. Am. Chem. Soc.* **1992**, *114*, 8008.

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Synthesis of highly substituted *meso*-tetraarylporphyrins

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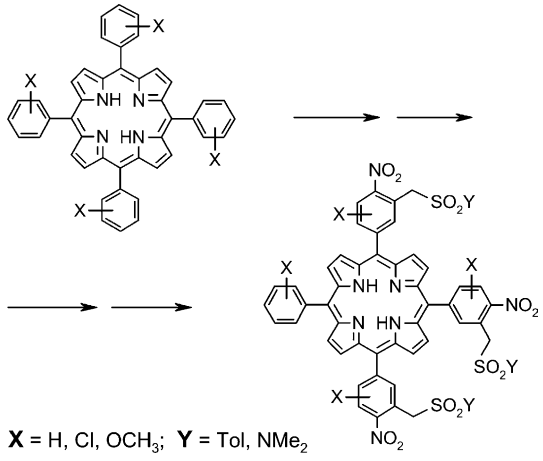
Abstract—*meso*-Tetraphenylporphyrin (and its derivatives), in the reaction with fuming yellow nitric acid ($d=1.53$), form either 5-(4-nitroaryl)-10,15,20-triarylporphyrin, 5,10-bis(4-nitroaryl)-15,20-diarylporphyrin, or 5,10,15-tris(4-nitroaryl)-20-arylporphyrin, depending on the reaction temperature (0–20 °C), amounts of the acid used, and reaction time. The above nitroporphyrins react, in the presence of a base (*t*-BuOK) at 0 °C, with carbanions (which bear nucleophugal groups at the carbanionic center: $^{-}CH(Cl)SO_2Tol$, $^{-}CH(Br)SO_2Tol$, and $^{-}CH(Cl)SO_2NMe_2$), leading to the nucleophilic substitution of hydrogen in one or more of the *meso*-nitroaryl rings. By this route, the preparation of the highly substituted 'synthetic' porphyrins (bearing up to ten *O*-, *N*-, *Cl*-, or *C*-substituents) was demonstrated.

1. Introduction

The porphyrin system is present in well-known biological materials (e.g., chlorophyll, heme, vitamin B_{12}).[1] Many porphyrin derivatives are of significant importance due to their potential use as photosensitizers in photodynamic therapy (PDT),[2] molecular-based multi-bit memory storage,[3] electron-donor parts in artificial photosynthetic models,[4] etc. Their precursors are usually isolated from naturally occurring substances and transformed into compounds possessing a high degree of complexity. On the other hand, a similar effect can be achieved by the selective functionalization of the easily available (in one-step cyclocondensation) 'synthetic' *meso*-tetraphenylporphyrin,[5] or its derivatives. From this process, the hydrophobic moieties can be transformed into hydrophilic compounds. The latter, being soluble in physiological milieu, may be considered, for example, as potential PDT agents.

We present herein a method for the selective derivatization of *meso*-tetraarylporphyrins, leading to highly substituted derivatives (mono-, di-, and tri-) on one or more of the *meso*-aryl rings. By this method, the synthesis of the *meso*-tetraarylporphyrins bearing *O*-, *N*-, *Cl*-, or *C*-substituents was demonstrated (Scheme 1). Usually, the first substituent (Cl, OCH_3, and CH_3) was introduced to the system due to cyclocondensation of pyrrole with the respective substituted aromatic aldehydes. Introduction of the next substituent (NO_2 in this case, with the possibility for the subsequent transformation to other nitrogen functionality) was achieved by the direct electrophilic nitration of the system. The nitro group, which lends the possibility for further transformations (reduction to NO and NH_2, further functionalization via diazotization, substitution of hydrogen in position *ortho*-,[6] many types of cyclizations,[7] etc.), is one of the most versatile substituents for this purpose.



Scheme 1.

Keywords: *meso*-Tetraarylporphyrins; Nitration; Carbanions; Nucleophilic substitution of hydrogen.
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2. Results and discussion

2.1. Selective transformation of *meso*-tetraarylporphyrins into polynitrated derivatives

The electrophilic nitration of *meso*-tetraarylporphyrins may lead to mono-substitution in the *para*-position of one of the *meso*-aryl rings (e.g., compounds **2a–c**). This was observed for the first time by Kruper et al.,[8] and similar results were obtained by other groups[9] (also in our laboratory[10]). In the case of 5-(3-methoxy-4-nitrophenyl)-10,15,20-tris(3-methoxyphenyl)porphyrin (**2a**), which was used for further functionalization in this work, some aspects need to be clarified. The mentioned product was identified and characterized earlier[8] in a mixture of two compounds [5-(3-methoxy-4-nitrophenyl)- and 5-(3-methoxy-6-nitrophenyl)-substituted porphyrin derivatives). Our investigations are contradictory to those results. We obtained as a major product the desired compound **2a** (34%), accompanied by the dinitrated moiety—5,10-bis(3-methoxy-4-nitrophenyl)-15,20-bis(3-methoxyphenyl)porphyrin (**3a**; 11%). We easily separated both products chromatographically and the structure determination was rather a trivial problem. We note that in the cited paper[8] some mistakes were made, for example, it is rather difficult to explain the occurrence of extremely large coupling constants (above 14 Hz) in the 3-methoxy-4-nitrophenyl moiety.

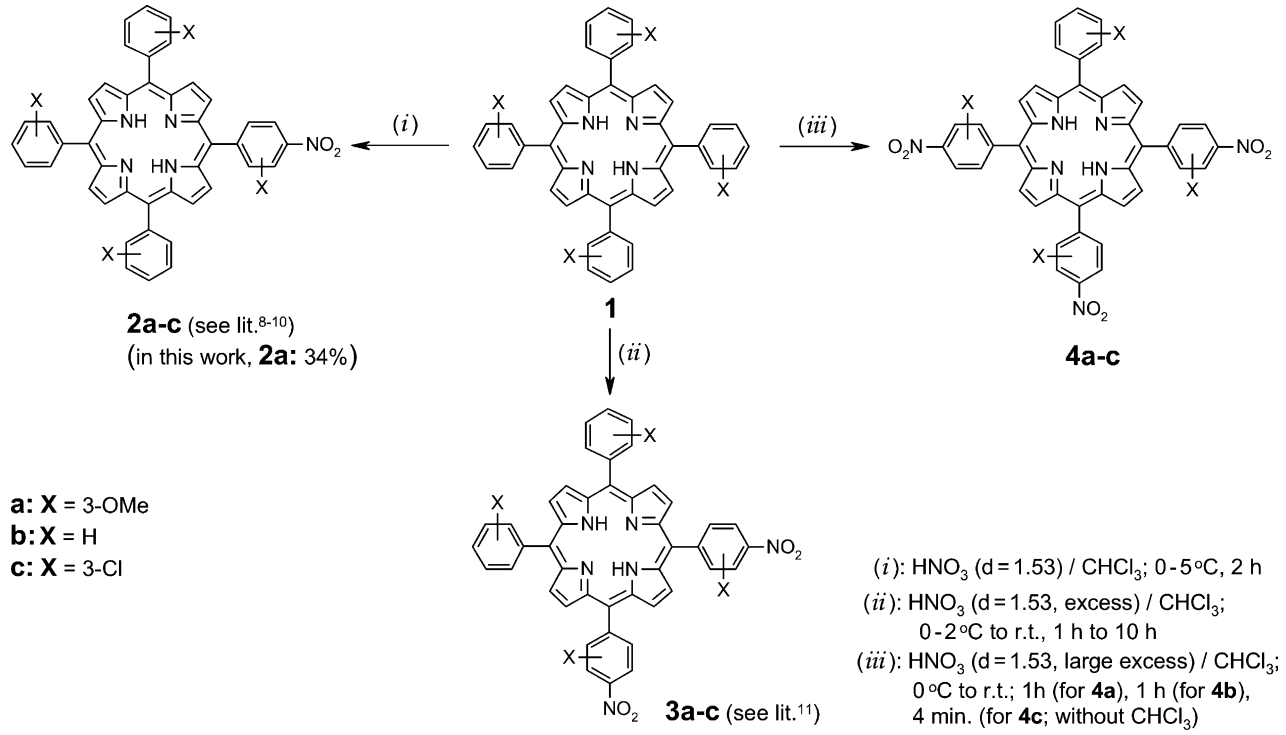
Recently, we also published a paper concerning the selective nitration of *meso*-tetraarylporphyrins in two neighbouring aromatic rings[11] (e.g., compounds **3a–c**). Now, we found that the exhaustive nitration of these systems allows, in some cases, the preparation of higher nitro-substituted products (tri- or even tetranitro-derivatives) with moderate yields. The above polynitration could be realized with the use of fuming yellow nitric acid ($d=1.53$, Fluka), when the temperature, amount of the acid, and reaction time were manipulated. In the nitration of TPP, the desired trisubstituted product **4b** was obtained in a reasonable yield (35%) and with better selectivity as compared to the previous investigations.[8] Additionally, this compound was, for the first time, isolated in a pure form and fully characterized (Scheme 2).

Conversely, nitration of *meso*-tetrakis(3-methoxyphenyl)-porphyrin (**1a**), effectively activated for electrophilic substitution by the OCH_3 group, leads to a mixture of polynitrated products, from which the fraction containing mainly the trinitro-product **4a** was isolated (ca. 30% yield). Similar results were obtained for 5,10,15,20-tetrakis(3-chlorophenyl)porphyrin (**1c**); however, all the possible products were isolated and identified in this case (**2c**: 22%; **3c**: 26%; **4c**: 15%; and also 5,10,15,20-tetrakis(3-chloro-4-nitrophenyl)porphyrin, **5**, in a yield of 2%).

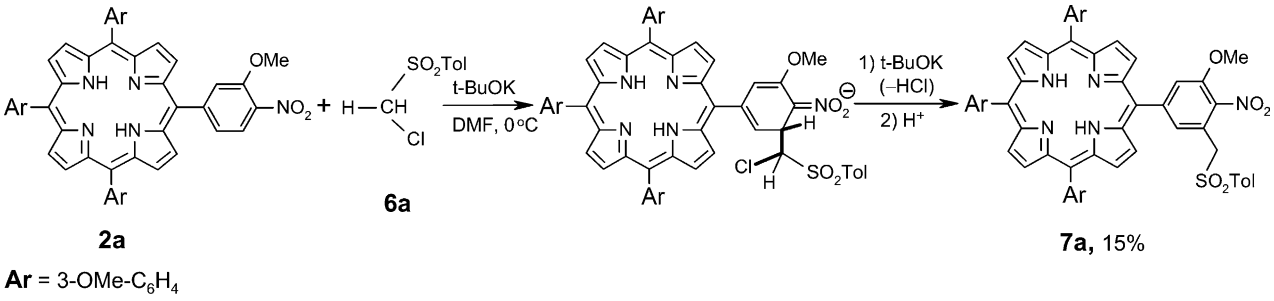
The nitroporphyrins synthesized were used for further functionalization. Their preparation from the corresponding aldehyde(s) and pyrrole is an extremely difficult (or impossible) task (yields $<3\%$).[12]

2.2. Introduction of carbon substituents into nitro- and dinitro- *meso*-tetraaryl-porphyrins

We published some papers in the recent past concerning the nucleophilic functionalization of mono-nitroaryl-substituted porphyrin zinc and copper complexes.[10,13] Subsequently we proved that this nucleophilic reaction [the so-called vicarious nucleophilic substitution (VNS)[6b]] can be also realized for unprotected porphyrins.[14] We have



Scheme 2.



Scheme 3.

now combined our observations concerning nitration (dinitration, polynitration) and nucleophilic substitution with the possibility of preparing the corresponding highly substituted porphyrins. Carbanions generated from chloromethyl *para*-tolyl sulphone (**6a**), from *N*,*N*-dimethyl-(chloromethane)sulphonamide (**6b**), and from bromomethyl *para*-tolyl sulphone (**6c**) (standard nucleophiles for the VNS process) were selected for these reactions. Compounds **6a**–**6c** were the carbanion precursors of choice, because they allow the synthesis of porphyrin derivatives containing sulphur(VI) substituents. These types of compounds may lead to moieties which could have potential bioactive properties (prior research has revealed several sulphonyl TPP derivatives to have anti-cancer activity[15]). On the other hand, as electrophilic partners, mono- and dinitrated *meso*-tetraarylporphyrins (**2a** and **3a**,**b**) were used.

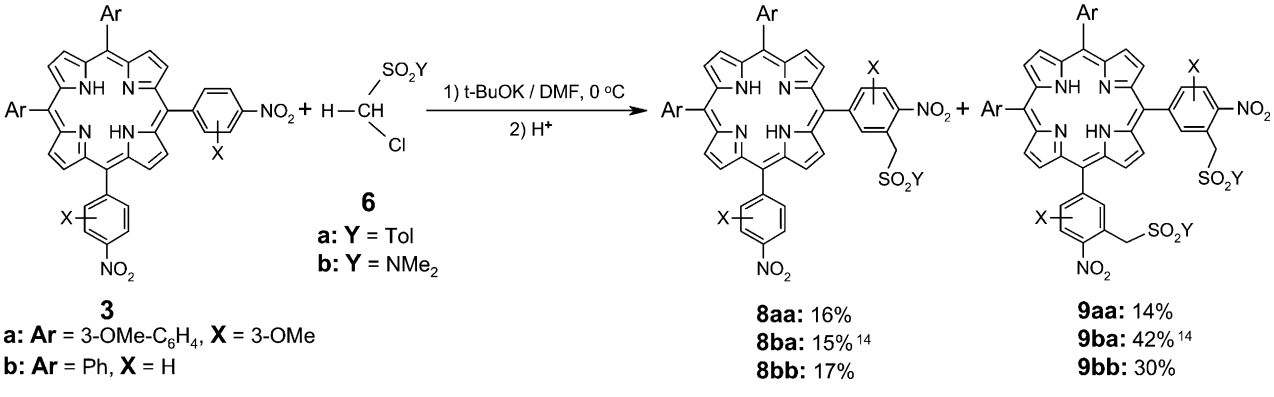
The nucleophilic substitution of hydrogen in unprotected mono-nitrated porphyrin, demonstrated herein for a more complicated model—5-(3-methoxy-4-nitrophenyl)-10,15,20-tris(3-methoxyphenyl)porphyrin (**2a**) (in the reaction with **6a**), leads to the desired product **7a** (containing three different substituents in one aryl ring), however with moderate yield (15%, Scheme 3).

The same reaction in porphyrins dinitrated on two neighbouring *meso*-aryl rings [5,10-bis(3-methoxy-4-nitrophenyl)- and 5,10-bis(4-nitrophenyl)-porphyrins, **3a** and **3b**] (Scheme 4) allows the possibility for synthesis of tetrasubstituted or even octasubstituted systems in fully-controlled transformations. Previously, we demonstrated this for the reaction of **3b** with chloromethyl *para*-tolyl sulphone (**6a**), leading to a mixture of products substituted in one or two of the *meso*-nitrophenyl rings, **8ba** and **9ba**.[14]

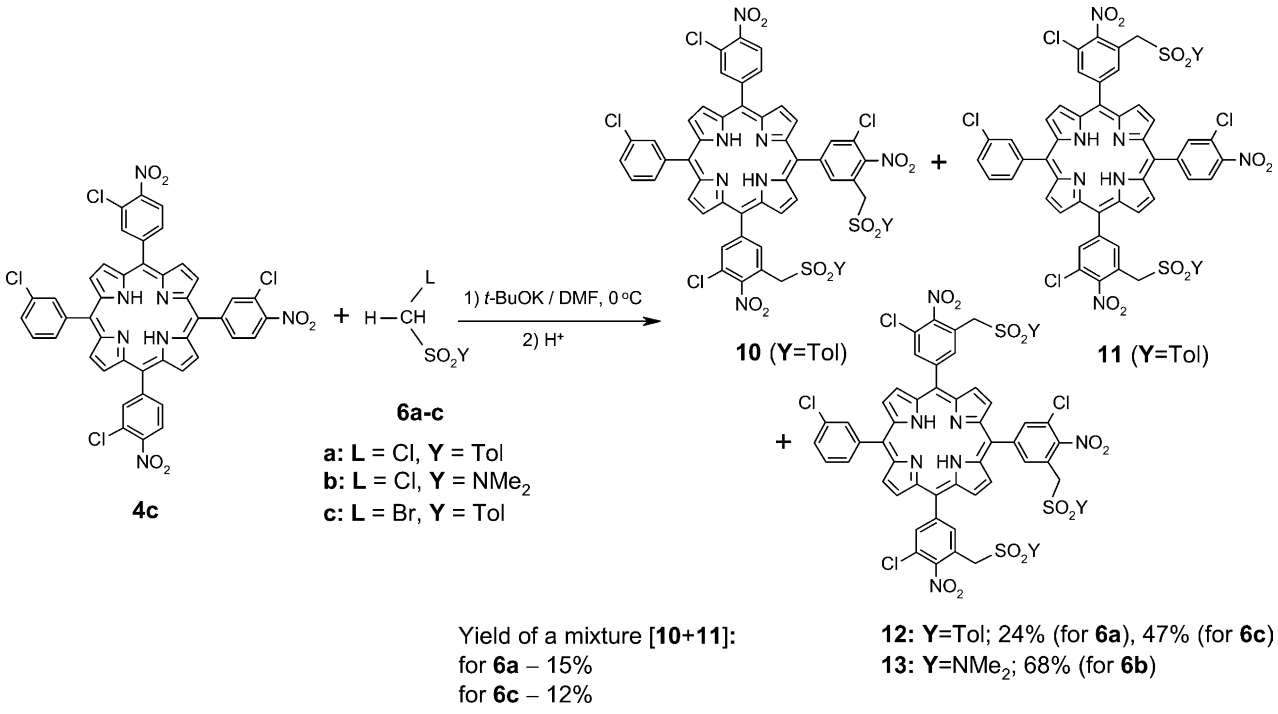
A more recent example of this reaction is that of **3b** with *N*,*N*-dimethyl-(chloromethane)sulphonamide **6b**. Thus, in the reaction with the above substrates, if performed in the presence of *t*-BuOK in DMF at 0 °C, the substitution takes place mainly on the two nitrophenyl rings to give compound **9bb** as a major product in moderate yield (30%); accompanied by the monosubstituted derivative **8bb** (yield 17%). Analogously, in the reaction of dinitroporphyrin **3a** with chloromethyl *para*-tolyl sulphone (**6a**), under the same reaction conditions, a mixture of compounds **8aa** (16%) and **9aa** (14%) was obtained. The preparation of the above compounds is impossible to realize effectively by the alternative Rothemund and Adler–Longo method[16] (and its cross-condensation modifications[17]) or by the synthesis via dipyrromethane methodology.[18]

2.3. Substitution of hydrogen in trinitro- *meso*-tetraarylporphyrins

We present the nucleophilic substitution of hydrogen reaction in this class of compounds for unprotected 5,10,15-tris(3-chloro-4-nitrophenyl)-20-(3-chlorophenyl)-porphyrin (**4c**). Attempts to prepare porphyrins possessing high degree of complexity were undertaken herein. We found that porphyrin **4c**, in the reaction with carbanion of $ClCH_2SO_2Tol$ (**6a**), in *t*-BuOK/DMF system at 0 °C, leads to a complicated mixture of three products: two inseparable disubstituted compounds (**10** and **11**; $R_f=0.38$, in $CHCl_3$; total yield 15%), and **12** ($R_f=0.21$; yield 24%). The disubstituted products **10/11** were identified by MS [the only molecular ion $m/z=1222$ (M+H) by the ESI method was detected] and confirmed by ^1H NMR investigations (a broad signal originating from several diverse CH_3-Tol groups was observed at ca. 2.40 ppm). However, in this



Scheme 4.



Scheme 5.

case, the formation of considerable amounts of the product substituted on all of the *meso*-nitroaryl rings (**12**; 24%) was observed. In the similar process of **4c** with sulphonamide **6b** (with a prolonged reaction time) only one product was formed in high yield (**13**; 68%)—an unexpected outcome (Scheme 5).

The differentiation of the above reaction courses is not clear—possibly the bulkiness of the carbanion generated from $ClCH_2SO_2Tol$ is crucial for this process, thus causing considerable steric hindrances when the carbanion approaches the porphyrin. One can suppose, that a leaving group can also play important role herein. Indeed, in the reaction of **4c** with bromomethyl *para*-tolyl sulphone (**6c**), bearing an excellent leaving group (–Br), the yield was relatively higher (as compared to the case of very similar carbanion precursor **6a**) to give mainly the trisubstituted product **12** (47%), accompanied with only a small amount of the mixture of **10** and **11** (Y=Tol; 12%).

Probably, both the above factors operate herein; however, in the latter case an every attack of carbanion moiety could be the effective one—because the next step of the VNS reaction (elimination of HBr) is an easier process as compared to elimination of HCl, thus allowing the exhaustive substitution on all of the nitroaryl rings.

3. Conclusions

The ability to access new types of porphyrin derivatives is of great importance due to the biological activity of these systems. In this paper, we presented the methodology for the functionalization of *meso*-tetraaryl porphyrins by tandem electrophilic/nucleophilic reactions in these systems. The introduction, in a controlled process, of many *Cl*-, *N*-, *O*-, and *C*-substituents into the *meso*-aryl moieties, was demonstrated to give compounds bearing up to 10 functional groups. These compounds could be of higher hydrophilicity (or could be a precursors for such derivatives); hence may be of potential use as the photosensitizers in photodynamic therapy.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded with a Varian GEMINI-200 spectrometer operating at 200 MHz. Coupling constants *J* are expressed in hertz (Hz). Mass spectra were measured with an AMD 604 (AMD Intectra GmbH, Germany) spectrometer (electron impact and LSIMS methods) and MARINER (ESI-TOF) PerSeptive Biosystems spectrometer (ESI method); *m/z* intensity values for peaks are given as a % of relative intensity. UV/Vis spectra were measured with a Beckman DU-68 spectrometer. TLC analysis was performed on aluminium foil plates pre-coated with silica gel (60F 254, Merck). Silica gel, 200–300 mesh and 230–400 mesh (Merck AG), was used for column chromatography.

Some nitroporphyrins used and the starting carbanion precursors, were obtained according to methods described in the earlier literature: 5,10-bis(3-methoxy-4-nitrophenyl)-15,20-bis(3-methoxyphenyl)porphyrin (**3a**),[11] 5,10-bis(4-nitrophenyl)-10,15-diphenylporphyrin (**3b**),[11] chloromethyl *para*-tolyl sulphone (**6a**),[19] *N*,*N*-dimethyl-(chloromethane)-sulphonamide (**6b**),[20] bromomethyl *para*-tolyl sulphone (**6c**).[21]

All the porphyrin derivatives described herein were deep purple solids.

4.2. 5-(3-Methoxy-4-nitrophenyl)-10,15,20-tris(3-methoxyphenyl)porphyrin (2a)

meso-Tetrakis(3-methoxyphenyl)porphyrin (**1a**; 50 mg, 0.068 mmol) was dissolved in dry $CHCl_3$ (10 mL), and the solution was stirred under argon and cooled to ca. 0–2 °C. To this mixture nitric acid (310 mg, 0.2 mL, $d=1.53$) was added via syringe. After 15 min, the next portion of HNO_3 (0.2 mL) was added and the reaction was continued for 0.5 h (TLC monitoring). The reaction mixture was washed with water (2×50 mL) and dried with $MgSO_4/Na_2CO_3$. After evaporating the solvent, the crude residue was chromatographed using a mixture of *n*-hexane/$CHCl_3$ as eluent (1:5) to give: 5-(3-methoxy-4-nitrophenyl)-10,15,20-tris(3-methoxyphenyl)porphyrin (**2a**)—18 mg (34%) and 5,10-bis(3-methoxy-4-nitrophenyl)-15,20-bis(3-methoxyphenyl)porphyrin (**3a**)—6 mg (11%; for data see lit.[11]).

Compound 2a. Mp >300 °C. ^{1}H NMR ($CDCl_3$): $\delta=8.94$ (d, $J=4.9$ Hz, 2H, H^β-pyrrole), 8.91 (s, 4H, H^β-pyrrole), 8.82 (d, $J=4.9$ Hz, 2H, H^β-pyrrole), 8.29 (d, $J=8.2$ Hz, 1H, H-5 of Ar(OCH_3)(NO_2)), 7.98 (d, $J=1.5$ Hz, 1H, H-2 of Ar(OCH_3)(NO_2)), 7.94 (dd, $J=8.2$, 1.5 Hz, 1H, H-6 of Ar(OCH_3)(NO_2)), 7.84–7.14 (m, 12H, H-Ar), 3.99 (s, 9H, $3\times OCH_3$), 3.98 (s, 3H, OCH_3), −2.81 (broad s, 2H, $2\times$NH). UV/Vis ($CHCl_3$): $\lambda_{max}=645$, 589.5, 551, 516, 420 nm (Soret). MS (ESI): *m/z* (% rel. int.)=783 (2), 782 (8), 781 (53), 780 (100) [isotopic M+H]. HR-MS (ESI) calcd for $C_{48}H_{38}N_5O_6$ (M+H)—780.2822, found—780.2829.

4.3. 5,10,15-Tris(3-methoxy-4-nitrophenyl)-20-(3-methoxyphenyl)porphyrin (4a)

meso-Tetrakis(3-methoxyphenyl)porphyrin (**1a**; 12 mg, 0.016 mmol) was dissolved in dry $CHCl_3$ (5 mL), and the solution was stirred under argon and cooled to ca. 0–2 °C. To this mixture nitric acid (153 mg, 0.1 mL, $d=1.53$) was added via syringe. After 0.5 h to 1 h (TLC monitoring), the reaction mixture was washed with water (4×5 mL) and dried with $MgSO_4/Na_2CO_3$. After evaporating the solvent, the crude residue was chromatographed on preparative TLC (eluent: $CHCl_3$) to give the fraction containing mainly 5,10,15-tris(3-methoxy-4-nitrophenyl)-20-(3-methoxyphenyl)porphyrin (**4a**)—4.5 mg (ca. 30%). An analytical sample was purified by several rechromatographies.

Mp >300 °C. ^{1}H NMR ($CDCl_3$): $\delta=9.05$ (d, $J=4.8$ Hz, 2H, H^β-pyrrole), 9.03–8.84 (m, 6H, H^β-pyrrole), 8.30–8.20 (m, 3H, H-5 of Ar(OCH_3)(NO_2)), 7.98–7.31 (m, 10H, H-Ar), 4.10–3.95 (m, 12H, $4\times OCH_3$), −2.78 (broad s, 2H, $2\times$NH). UV/Vis ($CHCl_3$): λ_{max} (log ε)=646 (3.58), 590 (3.91), 550 (4.12), 515 (4.33), 421.5 nm (5.66, Soret). MS (EI): *m/z* (% rel. int.)=872 (0.2), 871 (0.5), 870 (1.4), 869 (2.6) [isotopic $M^{+\cdot}$], 44 (100, CO_2^+). MS (ESI): *m/z* (% rel. int.)=873 (1), 872 (10), 871 (48), 870 (100) [isotopic M+H]. HR-MS (ESI) calcd for $C_{48}H_{36}N_7O_{10}$ (M+H)—870.2524, found—870.2444.

4.4. 5,10,15-Tris(4-nitrophenyl)-20-phenylporphyrin (4b)

meso-Tetraphenylporphyrin (**1b**; 20 mg, 0.033 mmol) was dissolved in dry $CHCl_3$ (5 mL), and the solution was stirred under argon at room temperature (ca. 5 min). To this mixture nitric acid (2.3 g, 1.5 mL, $d=1.53$) was added via syringe. After 0.5 h the next portion of HNO_3 (0.77 g, 1.5 mL) was added, and the reaction was continued for 0.5 h (TLC monitoring). The reaction mixture was washed with water (3×50 mL) and dried with $MgSO_4/Na_2CO_3$. After evaporating the solvent, the crude residue was chromatographed using a mixture of $CHCl_3$/*n*-hexane as eluent (3:1) to give 5,10,15-tris(4-nitrophenyl)-20-phenylporphyrin (**4b**) as a main product, 6 mg (25%).

Mp >300 °C. ^{1}H NMR ($CDCl_3$): $\delta=8.94$–8.73 (m, 8H, H^β-pyrrole), 8.71–8.53 and 8.45–8.36 ($2\times$m, 12H, H-Ar(NO_2)), 8.24–7.74 (m, 5H, H-Ph), −2.80 (broad s, 2H, $2\times$NH). UV/Vis ($CHCl_3$): λ_{max} (log ε)=647 (2.95), 591.5 (3.18), 553 (3.35), 517.5 (3.65), 422.5 nm (4.80, Soret). MS (EI): *m/z* (% rel. int.)=750 (0.5, M+H), 749 (0.5, $M^{+\cdot}$), 535 (1), 207 (6), 107 (22), 77 (40), 44 (100, CO_2^+). LSIMS (+): *m/z* (% rel. int.)=754 (0.2), 753 (0.3), 752 (0.6), 751 (1.2), 750 (2.8), 749 (1.9) [isotopic M^+ and M+H]. HR-MS (ESI) calcd for $C_{44}H_{28}N_7O_6$ (M+H)—750.2101, found—750.2098 (100%).

4.5. 5,10,15-Tris(3-chloro-4-nitrophenyl)-20-(3-chlorophenyl)porphyrin (4c)

To 5,10,15,20-(3-chlorophenyl)porphyrin (**1c**; 51 mg, 0.068 mmol) 1.5 g of nitric acid (ca. 1.0 mL; $d=1.53$) was added at room temperature and stirred for 4 min. Then, $CHCl_3$ (10 mL) was added and it was poured onto ice water (30 mL). The organic layer was separated and washed with water (5×10 mL). After drying over $MgSO_4/Na_2CO_3$ and evaporation of the solvent the crude residue was chromatographed ($CHCl_3$/*n*-hexane; from 1:1 to 4:1, then with $CHCl_3$) to give the starting 5,10,15,20-(3-chlorophenyl)-porphyrin (**1c**)—6 mg (12%), 5-(3-chloro-4-nitrophenyl)-10,15,20-tris(3-chlorophenyl)porphyrin (**2c**)—12 mg (22%), 5,10-bis(3-chloro-4-nitrophenyl)-15,20-bis(3-chlorophenyl)-porphyrin (**3c**)—15 mg (26%), 5,10,15-tris(3-chloro-4-nitrophenyl)-20-(3-chlorophenyl)porphyrin (**4c**)—15 mg (25%), and 5,10,15,20-tetrakis(3-chloro-4-nitrophenyl)porphyrin (**5**)—1.5 mg (2%).

Data for porphyrins **2c** and **3c**—see lit.[11]

4.5.1. 5,10,15-Tris(3-chloro-4-nitrophenyl)-20-(3-chlorophenyl)porphyrin (4c). Mp >300 °C. ^{1}H NMR ($CDCl_3$): $\delta=8.94$ (d, $J=5.0$ Hz, 2H, H^β-pyrrole), 8.89–8.78 (m, 6H, H^β-pyrrole), 8.42 (s, 3H, H-2 of H-Ar(Cl)(NO_2)), 8.34 (part of AB, $J=8.2$ Hz, 3H, H-5 of H-Ar(Cl)(NO_2)), 8.30–8.18 (m, 4H, H-Ar), 8.10 (apparent d, $J=7.2$ Hz, 1H, H-4 of Ar-Cl), 7.84–7.68 (m, 2H, H-5 and H-6 of Ar-Cl), −2.90 (broad s, 2H, $2\times$NH). UV/Vis ($CHCl_3$): λ_{max} (log ε)=645 (3.26), 590 (3.70), 556.5 (3.75), 516 (4.15), 421.5 nm (5.36, Soret). LSIMS (+): *m/z* (% rel. int.)=893 (0.7), 892 (2), 891 (2), 890 (4), 889 (5), 888 (8), 887 (5), 886 (5), 885 (3) [isotopic M^+ and M+H]. HR-LSIMS (+) calcd for $C_{44}H_{23}N_7O_6^{35}Cl_3^{37}Cl$ (M^+)—887.0434, found—887.0358.

4.5.2. 5,10,15,20-Tetrakis(3-chloro-4-nitrophenyl)porphyrin (5). Mp >300 °C. ^{1}H NMR ($CDCl_3$): δ=8.89 (s, 8H, H$^\beta$-pyrrole), 8.42 (d, J=1.6 Hz, 4H, H-2 of H-Ar(Cl)(NO_2)), 8.33 (part of AB, J=8.2 Hz, 4H, H-5 of H-Ar(Cl)(NO_2)), 8.27 (part of AB coupled with another proton, J=8.2, 1.6 Hz, 4H, H-6 of Ar(Cl)(NO_2)), −2.93 (broad s, 2H, 2×NH). UV/Vis ($CHCl_3$): λ_{max} (log ε)= 646.5 (3.68), 591 (3.96), 549 (4.03), 515.5 (4.35), 422.5 nm (5.47, Soret). LSIMS (+): *m/z* (% rel. int.)=936 (0.4), 935 (0.5), 934 (0.5), 933 (1.4), 932 (1.2), 931 (0.2) [isotopic M+H]. MS (ESI): *m/z* (% rel. int.)=938 (8), 937 (15), 936 (27), 935 (54), 934 (55), 933 (100), 932 (41), 931 (56) [isotopic M+H]. The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M+H]^+$ ion ($C_{44}H_{23}N_8O_8Cl_4$)—found to be identical within the experimental error limits.

4.6. Reactions of porphyrins 2a and 3a with $ClCH_2SO_2Tol$

To a stirred solution of *t*-BuOK (30 mg, 0.27 mmol) in anhydrous DMF (6 mL, under argon), a solution of corresponding methoxyporphyrin (**2a**, **3a**; 0.042 mmol) and chloromethyl *para*-tolyl sulphone (**6a**; 18 mg, 0.088 mmol) in DMF (3 mL) was added dropwise via syringe at 0 °C during ca. 10 min. After an additional 5 h of stirring at this temperature the mixture was poured into 3% HCl containing ice (100 mL). The precipitate was filtered, washed with water, and then dissolved in $CHCl_3$ (50 mL). After drying with anhydrous $MgSO_4$ and evaporation of the solvent, the crude products were purified by column chromatography or by preparative TLC (eluent: $CHCl_3$/*n*-hexane, 1:1). The yields of the pure products: **7a**, 6 mg (15%)—from **2a**; **8aa**, 6.5 mg (16%), and **9aa**, 6.6 mg (14%)—from **3a**.

4.6.1. 5-[3-Methoxy-4-nitro-5-(toluene-4-sulphonylmethyl)phenyl]-10,15,20-tris(3-methoxyphenyl)porphyrin (7a). Mp >300 °C. ^{1}H NMR ($CDCl_3$): δ=9.06–8.88 (m, 8H, H$^\beta$-pyrrole), 8.00–7.32 (m, 18H, H-Ar), 4.72 (s, 2H, CH_2), 4.15–3.98 (four lines, 12H, 4×OCH_3), 2.36 (s, 3H, CH_3), −2.89 (s, 2H, 2×NH). UV/Vis ($CHCl_3$): λ_{max}=644.5, 592, 555, 516, 414 nm (Soret). MS (ESI): *m/z* (% rel. int.)=952 (3), 951 (6), 950 (21), 949 (67), and 948 (100) [isotopic M+H], 761 (5), 760 (14), 759 (29), 668 (1), 417 (11). HR-MS (ESI) calcd for $C_{56}H_{46}N_5O_8S$ (M+H)—948.3067, found—948.3129.

4.6.2. 5-(3-Methoxy-4-nitrophenyl)-10-[(3-methoxy-4-nitro-5-(toluene-4-sulphonylmethyl)-phenyl]-15,20-bis(3-methoxyphenyl)porphyrin (8aa). Mp >300 °C. ^{1}H NMR ($CDCl_3$): δ=9.10–8.72 (m, 8H, H$^\beta$-pyrrole), 8.27 (d, J=8.1 Hz, 1H, H-5 of H-Ar(NO_2)), 7.99–7.60 and 7.42–7.30 (2×m, 16H, H-Ar), 4.72 (s, 2H, CH_2), 4.08–3.99 (m, 12H, 4×OCH_3), 2.36 (s, 3H, CH_3), −2.85 (s, 2H, 2×NH). UV/Vis ($CHCl_3$): λ_{max}=644.5, 591, 552, 516, 421.5 nm (Soret). MS (ESI): *m/z* (% rel. int.)=996 (2), 995 (12), 994 (57), and 993 (100) [isotopic M+H]. HR-MS (ESI) calcd for $C_{56}H_{45}N_6O_{10}S$ (M+H)—993.2918, found—993.2929.

4.6.3. 5,10-Bis[3-methoxy-4-nitro-5-(toluene-4-sulphonylmethyl)phenyl]-15,20-bis(3-methoxyphenyl)porphyrin (9aa). Mp >300 °C. ^{1}H NMR ($CDCl_3$): δ=9.10–8.86 (m, 8H, H$^\beta$-pyrrole), 8.00–7.31 (m, 20H, H-Ar), 4.82 (s, 4H, 2×CH_2), 4.10–4.00 (m, 12H, 4×OCH_3), 2.33 (s, 6H, 2×CH_3), −2.85 (s, 2H, 2×NH). UV/Vis ($CHCl_3$): λ_{max}=644.5, 590.5, 553.5, 516, 413 nm (Soret). MS (ESI): *m/z* (% rel. int.)=1164 (4), 1163 (16), 1162 (47), and 1161 (45) [isotopic M+H], 761 (4), 760 (33), 759 (100). HR-MS (ESI) calcd for $C_{64}H_{53}N_6O_{12}S_2$ (M+H)—1161.3163, found—1161.3500.

4.7. Reaction of porphyrin 3b with $ClCH_2SO_2NMe_2$

t-BuOK (24 mg, 0.21 mmol) was dissolved in anhydrous DMF (2 mL). The solution was stirred under argon and cooled to 0 °C. To this mixture, a solution of 5,10-bis(4-nitrophenyl)-15,20-diphenylporphyrin (**3b**; 20 mg, 0.028 mmol) and *N*,*N*-dimethyl-(chloromethane)sulphonamide (**6b**; 17 mg, 0.11 mmol) in DMF (3 mL) was added via syringe (ca. 5 min). After an additional 2 h of stirring at this temperature (TLC monitoring), the mixture was poured into 3% HCl containing ice (50 mL). The precipitate was filtered, washed with water, and then dissolved in $CHCl_3$ (40 mL). After drying with anhydrous $MgSO_4$ and evaporation of the solvent, the residue was chromatographed (eluent: $CHCl_3$/*n*-hexane—2:1 to 3:1, then $CHCl_3$) to give: **8bb** (4 mg, 17%) and **9bb** (8 mg, 30%).

4.7.1. *N*,*N*-Dimethyl-*C*-{2-nitro-5-[10-(4-nitrophenyl)-15,20-diphenylporphyrin-5-yl]phenyl}-methanesulphonamide (8bb). Mp >300 °C. ^{1}H NMR ($CDCl_3$): δ=8.97–8.81 (m, 8H, H$^\beta$-pyrrole), 8.79–8.34 (m, 7H, H-Ar(NO_2)), 8.25–8.17 (m, 4H, H-Ph), 7.83–7.72 (m, 6H, H-Ph), 5.03 (s, 2H, CH_2), 2.96 (s, 6H, N(CH_3)$_2$), −2.81 (s, 2H, 2×NH). UV/Vis ($CHCl_3$): λ_{max}=660.5, 595.5, 553, 516.5, 420 (Soret), 358 nm. MS (EI): *m/z* (% rel. int.)=828 (1), 827 (1), 826 (3), 825 (5) [isotopic $M^{+\cdot}$], 412 (13), 209 (6), 207 (21), 81 (48), 64 (100), 44 (63), 43 (85). HR-MS (ESI) calcd for $C_{47}H_{36}N_7O_6S$ (M+H)—826.2448, found—826.2462.

4.7.2. Compound 9bb. Mp >300 °C. ^{1}H NMR ($CDCl_3$): δ=8.98–8.82 (m, 8H, H$^\beta$-pyrrole), 8.54–8.33 (m, 6H, H-Ar(NO_2)), 8.26–8.17 (m, 4H, H-Ph), 7.84–7.75 (m, 6H, H-Ph), 5.03 (s, 4H, 2×CH_2), 2.96 (s, 12H, 2×N(CH_3)$_2$), −2.83 (s, 2H, 2×NH). UV/Vis ($CHCl_3$): λ_{max}=660.5, 609, 560, 516.5, 425.5 (Soret), 365.5, 356 nm. MS (EI): *m/z* (% rel. int.)=947 (1, M+H), 946 (0.5, $M^{+\cdot}$).

4.8. Reactions of porphyrin 4c with $ClCH_2SO_2Y$ (Y=Tol, NMe_2)

To a stirred solution of *t*-BuOK (26 mg, 0.24 mmol) in anhydrous DMF (3 mL, under argon), a solution of 5,10,15-tris(3-chloro-4-nitrophenyl)-20-(3-chlorophenyl)porphyrin (**4c**; 30 mg, 0.034 mmol) and the proper carbanion precursor (**6a**, **6b**, or **6c**; 0.11 mmol) in DMF (1 mL) was added dropwise via syringe at 0 °C during ca. 10 min. After an additional 2.5 h of stirring at this temperature the mixture was poured into 3% HCl containing ice (40 mL). The precipitate was filtered, washed with water, and then dissolved in $CHCl_3$ (40 mL). After drying with anhydrous $MgSO_4$ and evaporation of the solvent, the residue was chromatographed (eluent: $CHCl_3$/*n*-hexane, 2:1), to give, respectively:

(1) a mixture of **10** and **11** (6.5 mg, 15%), and **12** (11 mg, 24%)—from **6a**

(2) a mixture of **10** and **11** (5 mg, 12%), and **12** (23 mg, 47%)—from **6c**
(3) **13** as the only product (29 mg, 68%)—from **6b**.

4.8.1. Mixture of 5,10-bis[3-chloro-4-nitro-5-(toluene-4-sulphonylmethyl)phenyl]-15-(3-chloro-4-nitrophenyl)-20-(3-chlorophenyl)porphyrin (10) and 5,15-bis[3-chloro-4-nitro-5-(toluene-4-sulphonylmethyl)phenyl]-10-(3-chloro-4-nitrophenyl)-20-(3-chlorophenyl)porphyrin (11). ^{1}H NMR ($CDCl_3$): δ=9.02–8.84 (m, 8H, H^{β}-pyrrole), 8.44–8.34, 8.25–8.08, 8.00–7.97, 7.89–7.66, and 7.46–7.33 (5×m, 19H, H-Ar), 4.71 (s, 4H, CH_2 groups), ca. 2.41 (broad s, 6H, CH_3 groups), −2.94 (broad s, 2H, NH groups). MS (ESI): *m/z* (% rel. int.)=1230 (7), 1229 (10), 1228 (20), 1227 (34), 1226 (65), 1225 (57), 1224 (100), 1223 (36), and 1222 (47) [isotopic M+H]. The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M+H]^+$ ion ($C_{60}H_{40}N_7O_{10}Cl_4S_2$)—found to be identical within the experimental error limits.

4.8.2. 5,10,15-Tris[3-chloro-4-nitro-5-(toluene-4-sulphonylmethyl)phenyl]-20-(3-chlorophenyl)porphyrin (12). Mp >300 °C. ^{1}H NMR ($CDCl_3$): δ=9.01–8.82 (m, 8H, H^{β}-pyrrole), 8.44–8.32 (broad s, 3H, H-2 of H-Ar(Cl)(NO_2)), 8.27–8.06, 7.89–7.67, and 7.46–7.31 (3×m, 19H, H-Ar), 4.71 (s, 6H, 3×CH_2), 2.41 (s, 6H, 2×CH_3), 2.39 (s, 3H, CH_3), −2.90 and −2.94 (2×s, 2H, 2×NH). UV/Vis ($CHCl_3$): λ_{max} (log ε)=646 (3.92), 589 (4.14), 550 (4.17), 516 (4.48), 422.5 nm (5.67, Soret). MS (ESI): *m/z* (% rel. int.)=1397 (2), 1396 (3), 1395 (4), 1394 (5.5), 1393 (6), 1392 (7), 1391 (4), and 1390 (3.5) [isotopic M+H]. The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M+H]^+$ ion ($C_{68}H_{48}N_7O_{12}Cl_4S_3$)—found to be identical within the experimental error limits.

4.8.3. Compound 13. Mp >300 °C. ^{1}H NMR ($CDCl_3$): δ=9.00–8.85 (m, 8H, H^{β}-pyrrole), 8.56–8.35, 8.29–7.98, and 7.90–7.64 (3×m, 10H, H-Ar), 4.55 (s, 6H, 3×CH_2), 3.04–2.93 (m, 18H, 3×$N(CH_3)_2$), −2.95 (broad s, 2H, 2×NH). UV/Vis ($CHCl_3$): λ_{max} (log ε)=643.5 (3.97), 590.5 (4.12), 555.5 (4.16), 515 (4.42), 422.5 nm (5.54, Soret). MS (ESI): *m/z* (% rel. int.)=1257 (3), 1256 (5), 1255 (14), 1254 (25), 1253 (59), 1252 (52), 1251 (100), 1250 (27), and 1249 (45) [isotopic M+H]. HR-MS (ESI) calcd for $C_{53}H_{45}N_{10}O_{12}Cl_4S_3$ (M+H)—1249.1135, found—1249.1152.

References and notes

1. *The Porphyrin Handbook*; Kadish, K. M.; Smith, K. M.; Guilard, R.; Eds.; Academic: San Diego, CA, 2000; Vols. 1 and 13.
2. (a) Hsi, R. A.; Rosenthal, D. I.; Glatstein, E. *Drugs* **1999**, *57*, 725–734. (b) Sternberg, E. D.; Dolphin, D.; Brückner, Ch. *Tetrahedron* **1998**, *54*, 4151–4202. (c) DeLaney, T. F.; Glatstein, E. *Compr. Ther.* **1988**, *14*, 43–55.
3. Clausen, Ch.; Gryko, D. T.; Dabke, R. B.; Dontha, N.; Bocian, D. F.; Kuhr, W. G.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7363–7370; and refs. cited therein.
4. (a) Imahori, H.; Hagiwara, K.; Aoki, M.; Akiyama, T.; Taniguchi, S.; Okada, T.; Shirakawa, M.; Sakata, Y. *J. Am. Chem. Soc.* **1996**, *118*, 11771–11782. (b) Cheng, P.; Wilson, S. R.; Schuster, D. I. *Chem. Commun.* **1999**, 89–90. (c) Zheng, G.; Dougherty, T. J.; Pandey, R. K. *Chem. Commun.* **1999**, 2469–2470. (d) Lee, J.-Ch.; Kim, T.-Y.; Kang, S. H.; Shim, Y. K. *Bull. Kor. Chem. Soc.* **2001**, *22*, 257–258. (e) Ostrowski, S.; Mikus, A. *Mol. Divers.* **2003**, *6*, 315–321.
5. (a) Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969–4970. (b) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827–836.
6. (a) Bartoli, G. *Acc. Chem. Res.* **1984**, *17*, 109–115. (b) Mąkosza, M.; Wojciechowski, K. *Liebigs Ann./Recueil* **1997**, 1805–1816. (c) Kienzle, F. *Helv. Chim. Acta* **1978**, *61*, 449–452. (d) Hamana, M.; Iwasaki, G.; Saeki, S. *Heterocycles* **1982**, *17*, 177–181.
7. (a) Davis, R. B.; Pizzini, L. C. *J. Org. Chem.* **1960**, *25*, 1884–1888. (b) Kimura, M.; Obi, N.; Kawazoi, M. *Chem. Pharm. Bull.* **1972**, *20*, 452–458. (c) Danikiewicz, W.; Mąkosza, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1792. (d) Wróbel, Z.; Mąkosza, M. *Tetrahedron* **1997**, *53*, 5501–5514. (e) Wróbel, Z.; Mąkosza, M. *Synlett* **1993**, 597–598.
8. Kruper, W. J., Jr.; Chamberlin, T. A.; Kochanny, M. *J. Org. Chem.* **1989**, *54*, 2753–2756.
9. (a) Meng, G. G.; James, B. R.; Skov, K. A.; Korbelik, M. *Can. J. Chem.* **1994**, *72*, 1894–1909. (b) Matthews, S. E.; Pouton, C. W.; Threadgill, M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 1809–1811. (c) Faustino, M. A. F.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S.; Neumann, M.; Brauer, H.-D.; Jori, G. *Photochem. Photobiol.* **2000**, *72*, 217–225.
10. (a) Ostrowski, S.; Shim, Y. K. *Bull. Kor. Chem. Soc.* **2001**, *22*, 9–10. (b) Ostrowski, S.; Mikus, A.; Shim, Y. K.; Lee, J.-Ch.; Seo, E.-Y.; Lee, K.-I.; Olejnik, M. *Heterocycles* **2002**, *57*, 1615–1626.
11. Ostrowski, S.; Łopuszyńska, B. *Synth. Commun.* **2003**, *33*, 4101–4110.
12. (a) Tsuchida, E.; Hasegava, E.; Kanayama, T. *Macromolecules* **1978**, *11*, 947–955. (b) Thomas, D. W.; Martell, A. E. *J. Am. Chem. Soc.* **1956**, *78*, 1335–1343.
13. (a) Ostrowski, S. *Abh. al-Yarmouk, Basic Sci. Eng.* **2003**, *12*, 523–539. (b) Ostrowski, S.; Mikus, A. *Molbank* **2003**, M329.
14. Ostrowski, S.; Urbańska, N.; Mikus, A. *Tetrahedron Lett.* **2003**, *44*, 4373–4377.
15. Dougherty, T. J. *Photochem. Photobiol.* **1993**, *58*, 895–900.
16. (a) Rothemund, P. *J. Am. Chem. Soc.* **1936**, *58*, 625–627; *J. Am. Chem. Soc.* **1939**, *61*, 2912–2915. (b) Kim, J. B.; Adler, A. D.; Longo, F. R. In *The Porphyrins*; Dolphin, D., Ed.; Academic: New York, 1978; Vol. 1, pp 85–100.
17. Lindsey, J. S. In *The Porphyrin Handbook*; Kadish, K. M.; Smith, K. M.; Guilard, R.; Eds.; Academic: San Diego, CA, 2000; Vol. 1, pp 45–118.
18. Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323–7344.
19. Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1987**, 711–715.
20. Jakobsen, H. J.; Senning, A.; Kaae, S. *Acta Chem. Scand.* **1971**, *25*, 3031–3036.
21. Mąkosza, M.; Goliński, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488–1494.

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9-Anthroylacetone and its photodimer

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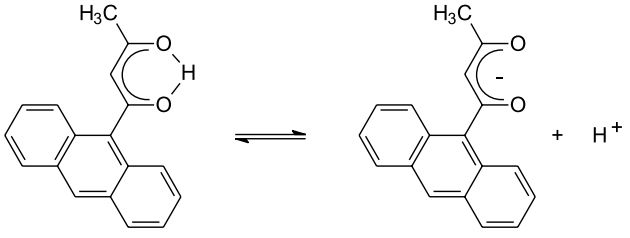
Abstract—9-Anthroylacetone undergoes a head-to-tail [4π+4π] photo-dimerisation reaction that leads to the formation of 5,11-bis(1,3-diketobutyl)-5,6,11,12-tetrahydro-5,12,6,11-di-*o*-benzeno-dibenzo[*a*,*e*]cyclooctene both in solution and in the solid state when irradiated with different sources (sunlight, tungsten lamp, xenon lamp, UV laser beam 351–364 nm), the reaction being accompanied by a colour variation from bright yellow to colourless. Quantum yields >0.023 mol/Einstein are evaluated for the solid state reaction. Interestingly, the dimer dissociates to give 9-anthroylacetone, both thermally (T>130 °C) and photochemically, by short UV wavelength irradiation. The single-crystal X-ray structure of 9-anthroylacetone and its dimer are reported.

1. Introduction

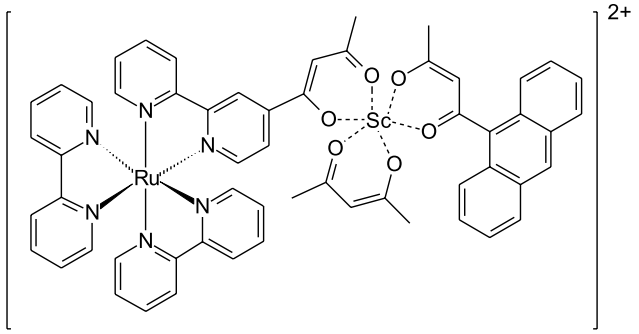
9-Anthroylacetone **1**, reported first by Evans in 1961,[1] has been the object of attention since its conjugate base, i.e. 9-anthroylacetonate **2**, gave rise to various boron[2] and rare earth derivatives[3] showing potentially interesting photophysical properties (Scheme 1).



1 2

Scheme 1.

More recently, the self assembled compound **3** has been described in which energy and electron transfer can take place between $Ru(bipy)_3^{2+}$, the donor sub-unit, and the ligand **2**, the acceptor component, under photo-activation conditions.[4]



3

During the last years, some of us have studied whether and how the anthrylic fluorophore communicates with different metal–ligand sub-units, like metal–β-ketoenolato or metal–cyclopentadienyl systems, under those conditions (chemical, photochemical, and electrochemical) that can induce the intramolecular transmission of electronic effects.[5] In this context, we prepared **1** as reported by Evans[1] with the aim to synthesise new rhodium(I) and iridium(I) derivatives of **2**.[6] We observed that freshly prepared bright yellow solid samples of 9-anthroylacetone gave rise to a new colourless compound, when they were exposed to laboratory light in the presence of air and this drew our attention towards the photochemistry of **1**. We succeeded in isolating the colourless compound and found that it has the structure **4** resulting from the [4π+4π] photo-dimerisation of **1**. To our knowledge, such a reaction of **1** has not yet reported in the literature. A similar behaviour has instead been documented for 9-benzoylanthracene.[7]

Keywords: Anthracene derivatives; Anthracene photo-dimerisation; Photochromism.
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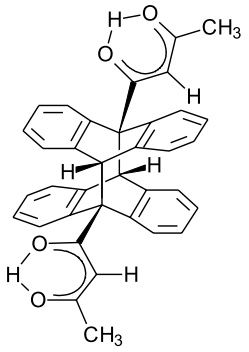
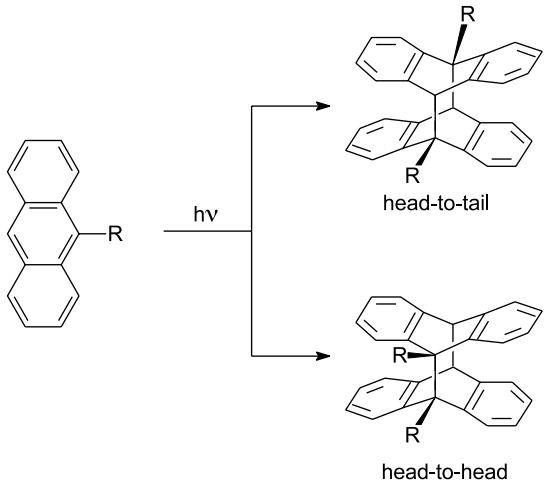


4

The [4π+4π] photo-dimerisation of anthracene as well as of several anthracene derivatives is a very well known reaction that has been studied extensively since 1950.[8] The reaction takes place both in solution,[8,9] in a variety of organic solvents and in the solid state,[7,9c,10] although the reaction in the solid state is less documented. Photo-excitation of *meso*-substituted anthracene derivatives in solution typically leads to the head-to-tail dimers, though evidence for the concomitant formation of the thermally more labile head-to-head dimers has been obtained in some cases (Scheme 2).[8b,9e,10b,11] Bimolecular reactions are expected to take place in the solid state only between nearest neighbours. Thus, the molecular structure of the dimer is expected to reflect the geometric relationship lying between the neighbours in the crystal lattice.[12] As a result of these restrictions, solid state reactions are generally more selective then those in solution.



Scheme 2.

One of the most interesting features of the photo-dimerisation of anthracene derivatives is the reversibility, this being the prerequisite for the development of new logic devices that operate at the molecular level.[9a,b,13] The photo-dimer can be reverted to the monomer by thermal and photochemical dissociation. While the first process is quantitative, a steady state mixture of monomer and dimer is obtained by photochemical dissociation, at least under the irradiation conditions used until now.[8a] Compounds that interconvert between one form and another upon irradiation with convenient light (photo-chromic molecules)[8b,9b,14] can be useful, at least in principle, to project various photonic devices, such as erasable optical memory media and photo-optical switch components. For this reason it is important that the direct and inverse photoreactions are not limited to the solution phase but also occur in the solid state.

All these facts prompted us to study in some detail the photochemical dimerisation of **1** to **4** and the thermal and photochemical dissociation of **4**, both in solution and in the solid state. The results of this study are presented herein.

2. Result and discussion

2.1. The photo-dimerisation of 9-anthroylacetone 1

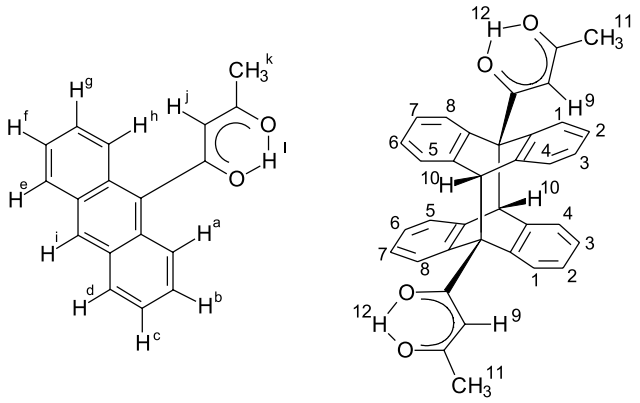
As described in the Section 4, when a d_2-dichloromethane solution of **1** (ca. 10^{-2} M) was irradiated for 3 h, under dinitrogen atmosphere, with a xenon lamp, about 50% of **1** was converted into **4**. Exposure of **1** to sunlight, at the same concentration, gave **4** in about 28% yield. The photo-dimerisation took place also when a d_2-dichloromethane solution of **1** was irradiated with a near-UV laser beam, although in this case the conversion of **1** into **4** was about 11%. Since each experiment was carried out under very different irradiation conditions (irradiation geometries, light source, energy), it is not possible to draw any conclusion regarding the relative efficiency of the different irradiation techniques. Nevertheless, the photo-conversion of **1** into **4** appears a relatively simple clean reaction. A new, unidentified, species were formed only when the irradiation is carried out on chloroform solutions.

Mixtures of **1** and **4** can be separated by taking advantage of their different solubility in diethyl ether.

The main pattern of the ^{1}H NMR spectrum of **4** (Table 1) looks like that reported in the literature for other anthracene photodimers,[7,15] but in this spectrum a peak at $\delta = 14.8$ ppm is present due to the enolic proton of **4**. In the ^{1}H NMR spectrum of **1** (Table 1), the enolic peak is observed at $\delta = 16.0$ ppm, thus showing that **1** is moderately more acid than **4**. Both compounds are in their enolic form and the keto-enol equilibrium cannot be shifted by changing the solvent polarity.

As anticipated in the introduction, solid samples of **1** show the presence of increasing amounts of **4** when they are exposed to laboratory light. With the aim to better define the photo-dimerisation of **1** in the solid state some experiments were carried out. Irradiation experiments of solids are less straightforward than experiments on solutions. In particular, the irradiation geometry (i.e. the relative position and orientation of the light source and of the sample), the emission characteristics of the source and the spatial extension of its light-generating volume, the dimension of the particles being irradiated and their reflective and scattering properties and the optics make a precise evaluation of photochemical quantities difficult. However, we attempted to estimate the limit values of quantum yields of the photochemical reactions.

Table 1. [1]H NMR spectroscopy data for compound **1** and **4**[a]



Compound	δ (ppm), J/Hz
1	16.10 (1H, s, H^l); 8.54 (1H, s, H^i); 8.20–8.12 (2H, m, H^a, H^h); 8.06–8.02 (2H, m, H^d, H^e); 7.60–7.50 (4H, m, H^b, H^c, H^f, H^g); 5.99 (1H, s, H^j); 2.27 (3H, s, H^k)
4	14.76 (2H, s, H^{12}); 6.98 (4H, d, J=4 Hz, H^1, H^8); 6.88–6.66 (12H, m, H^2, H^3, H^4,H^5, H^6, H^7); 5.92 (2H, s, H^9); 5.31 (2H, s, H^{10}); 1.94 (6H, s, H^{11})

[a] Spectra recorded in $CDCl_3$; s=singlet; m=multiplet; d=doublet.

A variety of irradiation experiments successfully transform **1** into **4** (see Section 4). Irradiation with a tungsten lamp (24 h), with a xenon arc lamp (4 h) or with a near-UV Argon-ion laser (2 h) produced the photo-transformation up to high conversion values: in our experiments, 70% yields were easily obtained without any detectable formation of other products. The irradiation of 50 mg of **1** with the 351–364 nm emission lines of an Argon-ion laser (**1**→**4** conversion, 31%) allowed us to estimate the minimum value ($\Phi_{\mathbf{1}\rightarrow\mathbf{4}}>0.023$ mol of **4**/Einstein) of the quantum yield of photo-production of **4**. This value was obtained on the hypothesis that all incident light was absorbed by the sample, thus ignoring scattering and reflection of light, which are more and more intense with the increasing amount of white microcrystals of **4** on the sample surface. Thus, the above calculated value is a lower limit of the true quantum yield.

The **1** to **4** transformation in the solid state (UV Argon-ion laser beam) (see Section 4.6, Experiment *D*) can be followed by direct analysis using front-surface absorption spectroscopy.[16] Figure 1(A), that shows the spectra of pure micro-crystalline **1**, registered before and after irradiation, as well as the spectrum of pure **4**, demonstrates clearly that **1** photo-dimerises, at least partially, giving rise to **4**. All the spectra show saturation effects[16] at absorbance >0.8 which are due to the strong absorbing features of pure **1** and **4**. To avoid the saturation effects it is necessary to dilute the sample with non-absorbing powder species to lower the concentration of absorbing centres. A comparison between the spectra reported in Figure 1(A) and those of Figure 1(B), which were recorded on diluted mixtures of **1** or **4** in $BaSO_4$, supports the above conclusion, the spectrum of pure **4** looking like that of diluted **4**, although, because of saturation at absorbance >0.8, the absorbance in the range 350–400 nm seems proportionally higher than that expected on the base of the absorbance of the band at ca. 300 nm shown by diluted **4**. On the other hand, the spectrum of diluted **1** (Fig. 1(B)) clearly shows the dramatic effect of dilution, and now it looks similar to that obtained in solution (see Section 2.2, Fig. 6).

In order to gain insight into the topochemical aspects of the photo-dimerisation reaction, single crystals of **1** and **4** were analysed by X-ray diffraction. The molecular structure of **1** is shown in Figure 2. Bond distances and angles are provided in Supporting Information. The molecule lies on two planes, one being defined by the 9-anthryl moiety (max deviating atom being C(8), 0.06 Å) and the other by the 1,3-diketobutyl moiety (max deviating atom being C(3), 0.002 Å). The two planes intersect each other along a line almost coincident with the C(4)–C(5) bond and make a dihedral angle of about 64.7°. The wideness of the C(2)–C(3)–C(4) angle (121.5°) and the presence of only one hydrogen maximum beside C(3) in the difference Fourier map both suggest the essential sp^2 nature of this carbon atom, which supports the enolic form for the 1,3-diketobutyl moiety. Anyway, the equal lengths within the C(2)–C(3)/C(3)–C(4) and C(2)–O(1)/C(4)–O(2) bonds do not establish reliably which oxygen atom carries the enolic hydrogen atom, which probably is statistically

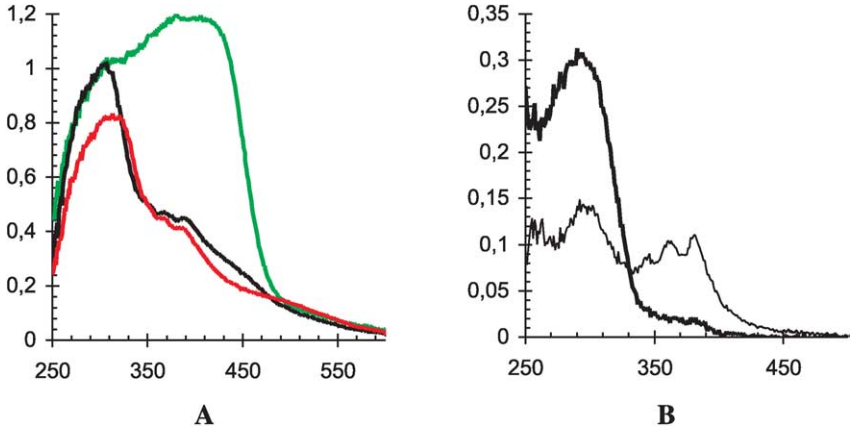


Figure 1. Front surface absorbance spectra (absorbance vs λ, nm); (A) spectrum of pure micro-crystalline 9-anthroylacetone **1** (—); spectrum of the same sample after 5 min of irradiation (—); spectrum of pure **4** (—); (B) spectrum of 9-anthroylacetone **1** in $BaSO_4$ (1 mg in 5 g of $BaSO_4$) (—); spectrum of pure **4** in $BaSO_4$ (1 mg in 0.5 g of $BaSO_4$) (—).

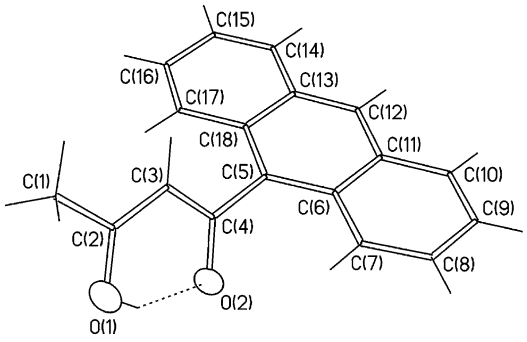


Figure 2. View of the molecular structure of **1**. Thermal ellipsoids of O atoms are at 30% probability, those of C atoms have been omitted for clarity.

bonded to either O(1) or O(2) atoms. However, according to the finding of a maximum in the difference Fourier map, we have introduced in our model the hydrogen atom bonded to O(1). The resulting OH group behaves as a donor in an intramolecular hydrogen bond (O(1)···O(2) distance 2.516 Å). Figure 3 suggests the crystal structure of **1** by showing the contents of the unit cell. The molecules are arranged in pairs, related by the inversion centre placed at ½, ½, ½. The 9-anthryl moieties of each pair overlap each other in such a way that C(5) faces C(12′) and, consequently, C(12) faces C(5′), at a distance of 3.794 Å, where the primed atoms belong to the second molecule of the pair.

The molecular structure of **4** is shown in Figure 4. Bond distances and angles are provided in Supporting Information. Compound **4** results from the cycloaddition of two molecules of **1** that are linked to each other by the new bonds C(5)–C(12′) and C(12)–C(5′). As a consequence, the central rings of the two original 9-anthryl moieties lose their aromaticity and bend along the axes C(5), C(12) and C(5′), C(12′), respectively, assuming the shape of flying wings. The molecule has an inversion centre, which allows us to confine our description to only one half of compound **4**. The

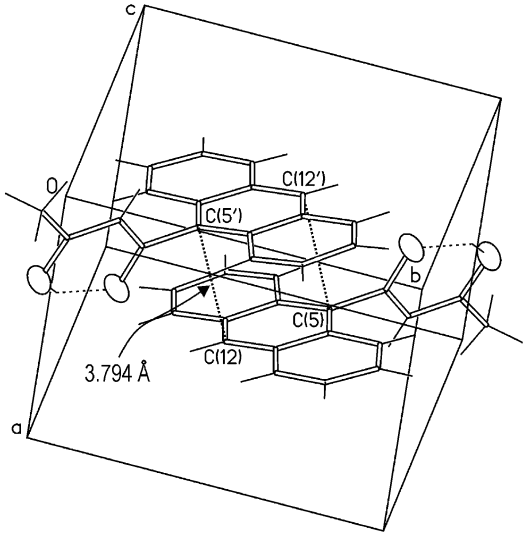


Figure 3. View of the crystal packing of **1**, projected approximately along the [101] direction. The molecules of the pair are related by the inversion center at ½, ½, ½. $' = 1-x, 1-y, 1-z$.

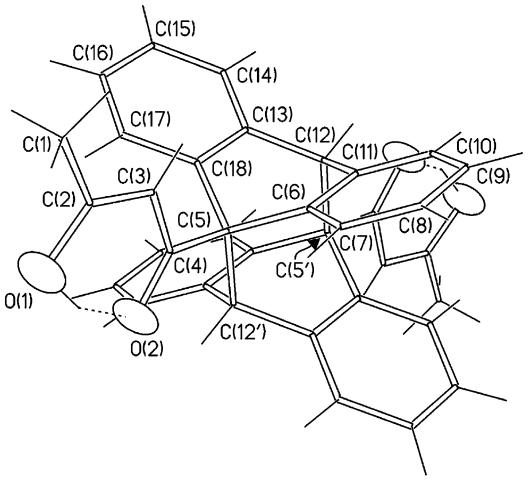


Figure 4. View of the molecular structure of **4**. Thermal ellipsoids of O atoms are at 30% probability, those of C atoms have been omitted for clarity. $' = -x+1/2, -y+1/2, -z+1$.

wings derived from the bending of the 9-anthryl group make in **4** a dihedral angle of 133.1°, while the 1,3-diketobutyl moiety maintains its approximately planar conformation, and, rotating around C(4)–C(5) bond, becomes coplanar with the C(5)–C(12′) bond.

Looking at Figures 3 and 4, the topological relationship between the pair of molecules in the crystal structure of **1** and the molecular structure of **4** appears evident. Moreover, it is important to underline that although the distance of 3.794 Å between C(5) and C(12′) and C(5′) and C(12) in the crystal structure of **1** should be thought to be too long for the cycloaddition to take place in the solid state,[7] nevertheless such a reaction indeed occurs in the case of **1**, as reported above. The cycloaddition of **1** to **4** does not follow a topotactic reaction pathway: in fact, when a single crystal of **1** was exposed to a near-UV laser the yellow colour disappeared and **4** was formed, but the crystal flaked off. This shows that the molecules of **4** cannot move in the crystal of **1** so to assemble in the packing required by the new single crystal. The occurrence of any thermal effect caused by the laser beam was discarded since the crystal was maintained at room temperature during the irradiation.

2.2. Thermal and photochemical dissociation of 4

When a solution of **4** in benzene was maintained at 80 °C for 4 h no appreciable decomposition of the sample was observed. This fact prompted us to heat solid-state samples. Thus, we observed that when a solid sample of **4** was heated at a temperature near the melting point of **1** (127–129 °C), it started to dissociate to give **1**, and, at 180 °C, it was converted almost quantitatively into **1** in about 25 min.

Since at 150 °C the reaction is slower, it can be easily followed by ^{1}H NMR spectroscopy. The profile of the thermal dissociation of **4** (containing a small amount of **1**, ca. 1%) as a function of time (Fig. 5) shows that, after an induction period, the reaction is fast. On the other hand, the thermal dissociation of a solid sample of **4** which did not contain any traces of **1** had a completely different course. In this case, after 200 min of heating at 150 °C, an amount of **1**

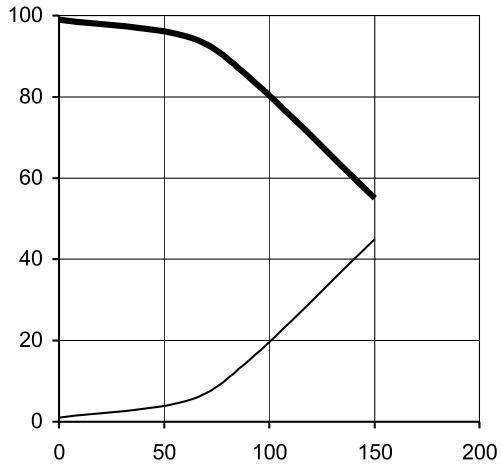


Figure 5. Thermal dissociation at 150 °C of **4** as a function of time (min): % of **1** (—),% of **4** (▬).

(only 35%), smaller than that predictable based on the data reported in Figure 5, was obtained. We are inclined to conclude that small amounts of **1** in solid samples of **4** play some catalytic role in the thermal dissociation of **4**. The fact that, at 150 °C, **1** is melted while **4** is still solid can favour the thermal decomposition of **4**. At this temperature the thermal dissociation of crystalline **4** can be kinetically impeded; while, the solubilisation of **4** into **1** can be favoured: as a result, a new reaction pathway can be available.

The photochemical dissociation of **4** to give **1** was followed by UV–vis absorption spectroscopy and was carried out on an ethanol solution of pure **4** (4.27×10^{-6} M) which was irradiated by a medium pressure mercury lamp adopting an unusual technique (see below). Before analysing the results of these experiments it is necessary to consider the UV–vis spectra of pure **1** and **4** (Fig. 6). The spectrum of **1** is characterised by an intense absorption band at 254 nm, a shoulder at ca. 280 nm and the typical anthracene vibrational structure in the range 330–390 nm.[4,8b] An evident feature of the UV–vis spectrum of **4** is the lack of any absorption in the spectral zone where the typical vibrational structure of anthracene is located. In involving the 9,10-positions, the photo-dimerisation interrupts the conjugation of anthracene, generating four *o*-xylene chromophores. This was observed first by Coulson who showed that the molar extinction coefficient at 270 and 280 nm are equal to four times that of *o*-xylene.[17]

One of the most intense emission bands of a medium pressure mercury lamp is centred at 254 nm.[18] Exactly at this wavelength 9-anthroylacetone **1** has an extinction maximum significantly higher than the extinction of **4** at the same wavelength. Compound **4** has the extinction maximum at 290 nm whose value is ca. double with respect to the extinction exhibited by **1** at the same wavelength. Finally, at $\lambda<240$ nm the extinction of **4** becomes much larger than that of **1**. Then, irradiation in the $\lambda<240$ nm zone is strongly recommended. Moreover, assuming that the quantum yield of the photodissociation of **4** is higher than the quantum yield of dimerisation of **1**, as reported for most anthracene derivatives in solution,[8a] we profited from both the quantum yield and the favourable absorption features to shift the photo-equilibrium towards **1**. In this connection, it is important to underline that it is known that several anthracene photodimers partially photodissociate into two anthracene nuclei when they are irradiated in the range 250–290 nm. However, at these wavelengths the monomer can re-dimerise and a steady state mixture is obtained by prolonged irradiation,[8a,9l] characterised by the presence of high amounts of photodimer (up to 94%, under 254 nm irradiation).[9l]

In our case, we succeeded in shifting the photo-equilibrium towards **1** taking advantage of the favourable absorption properties of **4** in the $\lambda<240$ nm region and by adopting an unconventional use of the mercury lamp, i.e. by switching the lamp on/off at regular intervals of time to avoid the strong increase of Hg vapour pressure which parallels the warming of the lamp. Indeed, when the cool lamp is just switched on, it strongly emits at wavelengths shorter than 254 nm because of the low density of Hg vapour. In addition, the temperature of the lamp was kept as low as possible by ventilation. Finally, operating on rigorously deareated ethanol solutions, the occurrence of the photochemical reaction of anthracene with dioxygen, that leads to anthraquinone and anthracene endoperoxide,[4,7,8b,9d,19] was avoided.

The UV–vis absorption spectra of ethanol solutions of **4**, registered after 2, 5, 7, 12 and 15 min of irradiation, are reported in Figure 7. These spectra clearly show the progressive growth of the absorption bands due to

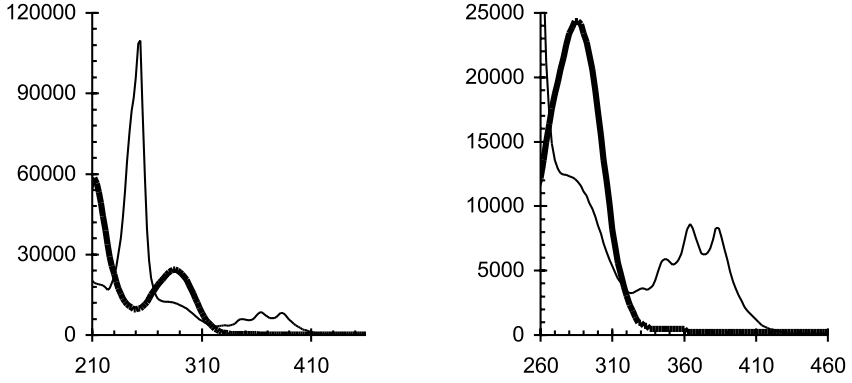


Figure 6. Absorption spectra (ε vs λ, nm) of: 9-anthroylacetone **1** (—) and **4** (▬); the spectra were recorded in 4×10^{-6} M ethanol solutions.

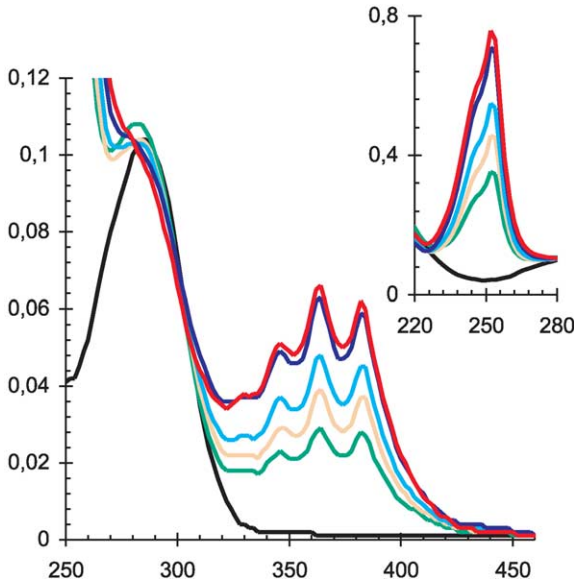


Figure 7. Absorption spectra (absorbance vs λ, nm) of **4** in ethanol; successive spectra taken after 0 (▬), 2 (▬), 5 (▬), 7 (▬), 12 (▬), and 15 min (▬) of irradiation with a medium pressure mercury lamp.

9-anthroylacetone **1**. Since at 384 nm the photodimer **4** does not absorb and **1** exhibits an absorption maximum ($\varepsilon=8300$), the concentration of **1** in each sample can be calculated from absorption at this wavelength (Table 2). Interestingly, the amount of **1** formed for short irradiation times is proportionally higher than that formed for long exposure times. Evidently, the photochemical dissociation of **4** tends to a steady state with excellent yields of **1** (>80%) that can be reached in 15 min of effective irradiation.

Further evidence of the photo-dissociation of **4** to give **1** was obtained by analysing the irradiated sample by Ion Spray Mass Spectroscopy (IS-MS). The IS-MS data for pure **1** and **4** are reported in Table 3.

Both the spectra show only the pseudo molecular peaks and noteworthy in the IS-MS spectrum of **4** no peaks are present in the range $m/z=263$–285, where the spectrum of **1** has its pseudo molecular peaks. It is interesting to underline that rarely are the molecular peaks of anthrachene photodimers detected,[8b] because generally the photodimer fragments to anthracene, under electron impact conditions. Only recently, by FAB(+) analysis[9e] and by GC-MS (EI mode),[9d] the molecular peak of a photodimer has been identified. The IS-MS spectrum of the ethanolic solution of **4**, irradiated for 15 min with the medium pressure mercury lamp, shows four pseudo molecular peaks at $m/z=263$ (14.3%), 301 (79%), 542 (3%) and 547 (3%). The peaks at

Table 2. Concentration of **1** formed by irradiation of an ethanol solution of **4** with a medium pressure mercury lamp

	2 min[a]	5 min[a]	7 min[a]	12 min[a]	15 min[a]
A_{384}[b]	0.027	0.037	0.047	0.058	0.060
C_1[c]	3.2×10^{-6}	4.5×10^{-6}	5.4×10^{-6}	7.0×10^{-6}	7.2×10^{-6}
1 (%)	37	53	63	82	84

[a] Total irradiation time.
[b] Absorbance at 384 nm.
[c] Molar concentration of **1** calculated by Lambert–Beer law ε_1 at 384 nm = 8300.

Table 3. IS-MS data of compounds **1** and **4**[a]

Compound	$[M+H]^+$	$[M+NH_4]^+$	$[M+Na]^+$
1	263 (100)	280 (7.5)	285 (20)
4	525 (12.5)	542 (70)	547 (100)

[a] m/z (% relative intensity of peak).

$m/z=263$ and 301 are attributable to the ions $[M(\mathbf{1})+H]^+$ and $[M(\mathbf{1})+K]^+$, respectively, M(**1**) being the molecular mass of 9-anthroylacetone **1** (262). The other two peaks at $m/z=542$ and 547 are associated with $[M(\mathbf{4})+NH_4]^+$ and $[M(\mathbf{4})+Na]^+$, respectively, M(**4**) being the molecular mass of **4** (524). These results clearly show that **4** photo-dissociates in solution, and **1** can be obtained in high yields in few minutes.

The photochemical dissociation in the solid state was carried out on a solid sample of pure **4** placed in a 1 mm optical path spectrophotometric quartz cell which was irradiated with a medium pressure mercury lamp for 30 min. During the first 15 min the lamp was switched on and off at regular intervals; whereas, during the last 15 min of irradiation the lamp was left on. The front surface absorption spectra registered after 5, 15 and 30 min of effective exposure to light are reported in Figure 8.

For the first 15 min of irradiation the amount of **1** increased whereas the spectrum registered after 30 min of irradiation was less intense than that registered after 15 min. This should be connected to the short-wavelengths emission-lines of the lamp during the cold period, i.e. the first 15 min of irradiation, with respect to the emission of the Hg stationary plasma during the last 15 min. As previously noted, at 254 and 366 nm the absorption of **1** is much higher than that of **4**. Evidently, for prolonged exposition of the sample to these wavelengths part of **1**, which is formed during the first 15 min of irradiation, reverts to **4**. The genesis of **1** was confirmed by UV–vis absorption spectroscopy of the irradiated solid sample upon dissolution in dichloromethane.

The definitive confirmation of the presence of **1** came once again from the IS-MS analysis of the reaction mixture that

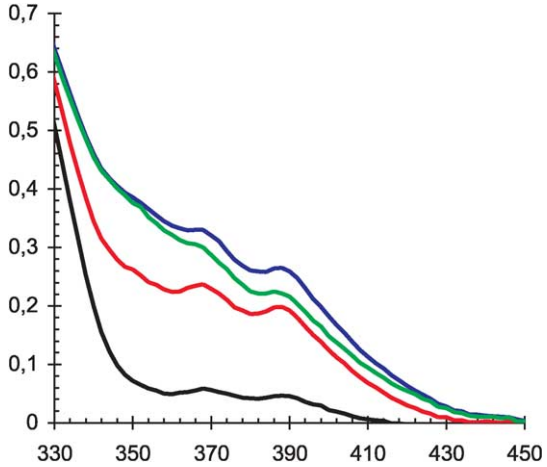


Figure 8. Front surface absorption spectra (absorbance vs λ, nm) of a solid sample of **4**; successive spectra taken after 0 (▬), 5 (▬), 15 (▬), and 30 min (▬) of irradiation by a medium pressure mercury lamp.

was dissolved in dichloromethane and diluted with methanol. The IS-MS spectrum shows one peak at $m/z=$ 263 (42.5%) attributable to $[M(\mathbf{1})+H]^+$ (M(**1**) is the molar mass of **1**) and two peaks, of the same intensity (47.5%), at $m/z=542$ and 547 attributable to $[M(\mathbf{4})+NH_4]^+$ and $[M(\mathbf{4})+Na]^+$ (M(**4**) is the molar mass of **4**), respectively. All these results clearly show that **4** photo-dissociates to give **1** even in the solid state; although, in this case, the process takes place only at the surface level and then the overall conversion is not high.

3. Conclusions

For the first time the photodimerisation of 9-anthroylacetone **1** to give the photodimer **4** has been observed and studied. The ^{1}H NMR spectra and the X-ray analysis reveal that both **1** and **4** are in their enolic form in solution as well as in the solid state.

1 photodimerises in solution as well as in the solid state by irradiation with different sources, the reaction being accompanied by a colour variation from bright yellow to colourless, a manifestation of the deep spectroscopic differences between **1** and **4**. No appreciable amounts of other products are detected although, in same cases, small quantities of anthraquinone are present, probably due to the presence of oxygen.[4,7,8a,9d,19]

The crystal structure of a 9-substituted anthracene derivative can be classified into three types according to the geometric relationship between neighbouring molecules (Fig. 9).[12] In the γ type structure the central ring of the two anthracene units are not superimposed and anthracene derivatives which crystallise with this structure hardly photodimerise in the solid state; on the other hand, when anthracene derivatives crystallise in the α or β type structure the photodimerisation can take place.[10c] The X-ray analysis of **1** reveals that it crystallises in the α-type structure, this allowing compound **1** to undergo the photodimerisation to **4** in the solid state.

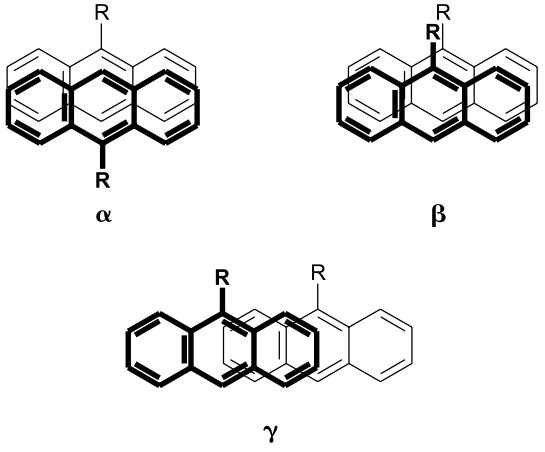
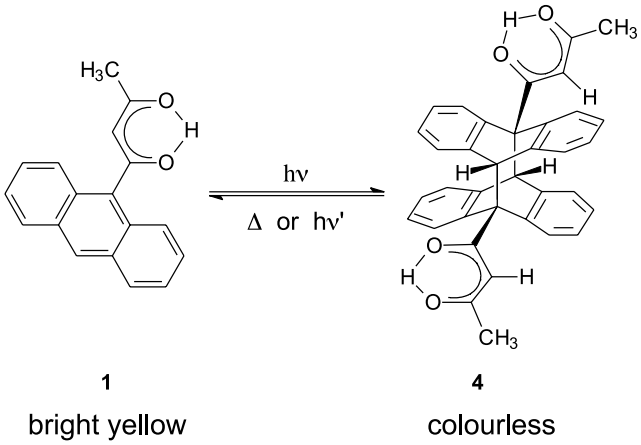


Figure 9. Main crystalline packing modes found in the case of 9-substituted anthracene derivatives.



Scheme 3.

Compound **4** dissociates to give **1**, both thermally and photochemically (Scheme 3).

The thermal dissociation is a well known phenomenon extensively documented in the literature,[7,9a,b,g,i] and **4** behaves like many other anthracene photodimers although the accelerating effect on thermal dissociation played by the presence of even small amounts of **1** had not been reported previously. The photochemical dissociation of **4** is particularly interesting because it can be carried out in solution as well as in the solid state by irradiation with a medium pressure mercury lamp. Some examples of this reaction carried out in solution are reported in the literature,[9a,c,d,l] but in all cases the samples were irradiated at wavelengths that seem to favour the photo-recombination of monomers since a steady state is reached characterised by the prevalent presence of the photodimer. Instead, under the irradiation conditions adopted here, >80% yield of **1** can be obtained. As said, **4** in the solid state can photo-dissociate. It is noticeable that only a very few examples of photochemical dissociation in this phase are reported in the literature.[9j,10d,20]

4. Experimental

4.1. General

All solvents were used as received. The HPLC grade or spectrophotometric grade solvents were used in the spectrophotometric measurements. Microanalyses were performed by the Laboratorio di Microanalisi, Facoltà di Farmacia, Università di Pisa, Italy. 9-Anthroylacetone was prepared as reported.[1]

^{1}H NMR spectra were run at 200 MHz on a Varian Gemini 200 instrument. Ion Spray Mass Spectra (IS-MS) were performed on a Perkin–Elmer Sciex API III plus triple quadrupole mass spectrometer (Sciex Co., Thornhill, ONT, Canada) equipped with an API ion source and an ionspray interface. The spectra were obtained under the following experimental conditions: ionspray voltage, 5.5 kV; orifice voltage, 35 or 60 V. The samples were dissolved in a very small amount of dichloromethane and diluted with methanol to obtain a concentration ca. 10 mM. The irradiation of solid

samples or solutions of **1** were carried out with a tungsten lamp (100 W), with a xenon lamp (150 W) which emits at $\lambda > 250$ nm and with a Argon-Ion laser Coherent Innova 600 ($\lambda_1 = 351$ nm; $\lambda_2 = 364$ nm, jointly). The irradiations of solid samples or solutions of **4** were carried out with a medium pressure mercury lamp (125 W).

4.2. Crystal structure determination of 1 and 4

The X-ray diffraction experiments were carried out at room temperature ($T = 293$ K) by means of a Bruker P4 diffractometer, operating with a graphite-monochromated Mo-K_α radiation. The intensity data collection was carried out with the $\omega/2\theta$ scan mode, collecting a redundant set of data. Three standard reflections were measured every 97 measurements to check sample decay. The intensities were corrected for Lorentz and polarisation effects and for absorption by means of a ψ-scan method.[21] The absorption correction was not applied due to the low absorption coefficient. The structure solutions were obtained by means of the automatic direct methods contained in SHELXS97[22] programme and the refinements, based on full-matrix least-squares on F^2, were done by means of the SHELXL97[22] programme. Some other utilities contained in the WINGX suite[23] were also used. The more relevant crystal parameters are listed in Table 4.

The crystals of compound **1** are yellow platelets flattened on (100). One of them, glued at the end of a glass fibre, was used for intensity data collection. Table 4 lists the essential collection statistics. The structure solution was obtained in the centrosymmetric $P\bar{1}$ space group. The hydrogen atoms were observed in the difference Fourier map, they was, however, introduced in idealised positions and refined letting them 'to ride' on the connected heavy atoms. The final refinement cycle gave the reliability factors listed in Table 4.

The crystals of compound **2** are colourless prisms. The intensity data collection was done on one of them, glued on the tip of a glass fibre, giving the results summarised in Table 4. The structure solution was found in the centrosymmetric $C2/c$ space group. The asymmetric unit resulted to be done by one half molecule placed beside an inversion centre. The hydrogen atoms were localised in the difference Fourier map and refined without constraints. The reliability factors resulting from the final refinement cycle are listed in Table 4.

Table 4. Crystal data and structure refinements

Compound	**1**	**4**
Empirical formula	$C_{18}H_{14}O_2$	$C_{36}H_{28}O_4$
Formula weight	262.29	524.58
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$ (no. 2)	$C2/c$ (no. 15)
a/Å	8.521(2)	23.784(3)
b/Å	8.980(2)	9.180(1)
c/Å	10.079(2)	16.553(2)
α/Å	71.34(1)	
β/Å	68.67(1)	132.13(1)
γ/Å	74.24(2)	
U/Å^3	670.0(2)	2680.3(6)
Z	2	4
D_{calcd}/Mg M^{-3}	1.300	1.300
μ/mm^{-1}	0.084	0.084
No. measured	2864	2186
No. unique [R_{int}]	2346 [0.0259]	1749 [0.0168]
No. parameters	183	237
R_1, wR_2 [$I > 2\sigma(I)$]	0.0550, 0.1254	0.0399, 0.1022
Goodness of fit on F^2	1.032	0.961

$R_1 = \sum ||F_o| - |F_c|| / \sum F_o$; $wR_2 = [\sum[w(F_o^2 - F_c^2)^2] / \sum[w(F_o^2)^2]]^{1/2}$; $w = 1/[\sigma^2(F_o^2) + BQ]$ where $Q = [\mathrm{MAX}(F_o^2, 0) + 2F_c^2]/3$; Goodness-of-fit $= [\sum[w(F_o^2 - F_c^2)^2]/(N-P)]^{1/2}$, where N, P are the numbers of observations and parameters, respectively.

Further details of crystal characterisations and structure refinements have been deposited in the form of CIF files with the Cambridge Crystallographic Data Centre. Deposition references: CCDC 237079 and CCDC 237080 for **1** and **4**, respectively. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Rd, Cambridge CB21EZ UK (fax: +44 1223 336 033); e-mail: deposit@ccdc.cam.ac.uk. Bond distances and angles for both **1** and **4** are provided in Supporting Information.

4.3. Spectrophotometric measurements

The UV–vis absorption spectra were measured at room temperature in ethanol or dichloromethane solutions using a Perkin–Elmer UV/VIS LAMDA EZ 201 spectrophotometer with a spectral bandwidth of 1 nm. Front-surface absorbance measurements in the UV–vis spectral region (250–500 nm) were performed on powder samples of **1** and **4** using the method reported by one of us.[16] Experiments were carried out on a conventional spectrofluorimeter (ISA Fluoromax II with photon counting detection) suitably set to detect light scattered from powder samples. The samples, ca. 1 mm thick, were enclosed in a cell-holder suitably designed to avoid specular reflections into the emission monochromator in measurements on powders.[24] Thus, the incident angle was 35°. Powdered $BaSO_4$ was used as reference light scatterer.[25] The front-surface absorbance measurements reported in Figure 1(A) were performed on powder samples of **1** and **4** obtained by mixing a dichloromethane solution of **1** or **4** with $BaSO_4$. The slurries so obtained were dried under vacuum, re-powdered by a mortar and examined. The relative ratios were of 1 mg **1**/5 g of $BaSO_4$ and 1 mg **4**/0.5 g of $BaSO_4$, respectively.

4.4. Purification of 4

To 200 mg of a mixture of **1** (about 60%) and **4** (about 40%) was added of diethyl ether (20 mL). The resulting suspension was stirred for 1 min and decanted. The residual solid was treated twice with diethyl ether (5 mL). The ethereal extracts contains **1** with minor amounts of **4** and the solid residue is constituted by almost pure **4**. A further amount of **4** was recovered by drying the ethereal extracts under reduced pressure and then suspending the resulting solid residue in 10 mL of diethyl ether. The ethereal solution was collected and dried under reduced pressure. The solid so obtained was further extracted with 5 mL of diethyl ether and, once again, the solution was separated from the solid and dried. The last sequence was repeated 2 times. All residual solid phases were dissolved in dichloromethane and dried under reduced pressure. About 100 mg almost pure **4** was so obtained which can be further purified by two methods. (A) 1 mL of a benzenic solution of impure **4** was purified by column (internal diameter, 15 mm; length,

150 mm) chromatography on silica gel 60 (230–400 mesh, Merck) using benzene as eluant, the first band eluted was collected and dried. The obtained solid is colourless and very pure. By this method a small amount of **4** can be obtained because **4** is slightly soluble in benzene. (B) About 100 mg of impure **4** was dissolved in about 25 mL of dichloromethane. The solution was extracted with portions of aqueous NaOH 2% (3×25 mL). The organic phase was discarded. Each aqueous phase was acidified with a few drops of HCl 35%, which caused the precipitation of a white solid. The resulting suspensions were extracted (2×20 mL) with dichloromethane. The organic extracts were then dried over anhydrous Na_2SO_4, then concentrated to 2 mL under reduced pressure (17 mmHg), and finally, chromatographated over a column (internal diameter, 5 mm; length, 30 mm) of silica gel 60 (230–400 mesh, Merck), using dichloromethane as eluant. A colourless solution was collected and dried under reduced pressure (17 mmHg) to give pure **4**. Anal. Calcd for $C_{36}H_{28}O_4$ (524) C, 82.4; H, 5.3%. Found: C, 82.4; H, 5.2%.

4.5. Photo-dimerisation of 1 in solution

Three ^{1}H NMR tubes, each containing 3 mg of **1** in 0.5 mL of d_2-dichloromethane, were irradiated with three different sources and analysed by ^{1}H NMR. Sample A was irradiated with a xenon lamp for 3 h: the analysis of the sample indicated the conversion of 50% of **1** to **4**. Sample B was exposed to sun light for 3 h: the conversion of **1** to **4** was about 28%. Sample C was exposed to the near-UV Argon-ion laser beam (0.010 W) for 4 h: the conversion of **1** to **4** was about 11%.

4.6. Photo-dimerisation of 1 in the solid state

Experiment A. 2 mg of **1** was placed in a ^{1}H NMR tube under dinitrogen atmosphere and was irradiated for 24 h by a 100 W tungsten lamp, at 15 °C, the distance between the sample and the lamp being about 10 cm. At the end of irradiation, the solid sample was dissolved in d_1-chloroform and the ^{1}H NMR spectrum was registered. **4** was formed in a 35% yield.

Experiment B. **1** (ca. 5 mg) was placed between two thin glass slides and irradiated by a 150 W xenon lamp (collocated at about 15 cm from the sample) for 4 h. The ^{1}H NMR analysis of the irradiated sample, dissolved in d_1-chloroform, revealed the presence of 70% of **4**.

Experiment C. 50 mg of **1**, containing ca. 7% of **4**, was placed in a watch glass horizontally disposed and irradiated with a vertical UV laser beam (0.088 W) that was enlarged by means of a quartz lens up to 2 cm diameter. The sample was periodically stirred in order to expose to radiation fresh portions of solid. During irradiation the well shaped yellow crystals of **1** turned opaque white and flaked off. After 2 h of irradiation, ^{1}H NMR analysis of the sample in d_1-chloroform showed the presence of 38% of **4**. The temperature of the sample remained practically unchanged by irradiation.

Experiment D. About 100 mg of **1**, placed in a quartz spectrophotometric cuvette (1 mm optical path), was exposed perpendicular to the UV laser beam (0.005 W) whose spot was about 2 mm^2, at the centre of the cell window. During the irradiation the cell was vertically moved. After 5 min, the portion exposed to laser beam showed a well defined white strip. The reaction was monitored by front surface absorption spectroscopy with illumination of the above strip.

4.7. Thermal dissociation of 4

All tests were run on 2 mg of **4** placed in a ^{1}H NMR tube which was heated at various temperatures as shown in the Section 2. Analysis of the samples, dissolved in d_1-chloroform, were performed by ^{1}H NMR.

4.8. Photochemical dissociation of 4 in solution

Three millilitres of an ethanol solution (4.27×10^{-6} M) of **4** was placed, under dinitrogen atmosphere, in a quartz 10×10 mm spectrophotometric cuvette and irradiated by a medium pressure mercury lamp. The sample was placed about 3 cm far from the lamp in an equatorial position and oriented so to optimise the interception of the light rays. Both sample and lamp were cooled by a ventilator. The lamp was switched on for 30 s, then switched off for at least 1 min. After 2, 5, 7, 12 and 15 min of effective irradiation, the sample was analysed by UV–vis absorption spectra. At the end of the experiment the sample was analysed by IS MS.

4.9. Photochemical dissociation of 4 in the solid state

About 130 mg of pure **4** were placed in a 1 mm thick spectrophotometric cell and irradiated in the same geometric arrangement as above, with the only difference that the distance from the plasma source was larger (ca. 6 cm). The sample was irradiated as before, the lamp being switched on and off at regular intervals during the first 15 min of irradiation; finally, during the last 15 min, the lamp was left on. After 5, 15 and 30 min of irradiation the sample was analysed by front surface absorption spectroscopy. Spectral bandwidths of 0.25 and 4 mm were employed for the excitation and emission slits, respectively. The integration time was 0.5 s. 10 mg of the irradiated sample was used to prepare a 3.85×10^{-3} M dichloromethane solution which was analysed by UV–vis spectroscopy. The irradiated sample was also analysed by IS MS.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at 10.1016/j.tet.2004.09.070

References and notes

1. Evans, D. F. *J. Chem. Soc.* **1961**, 1987–1993.
2. Hartmann, H. *J. Prakt. Chem.* **1986**, *328*, 755–762. (b) Ilge, H.-D.; Birckner, E.; Fassler, D.; Kozmenko, M. V.; Kuz'min, M. G.; Hartmann, H. *J. Photochem.* **1986**, *32*, 177–189. (c) Ilge, H.-D.; Fassler, D.; Hartmann, H. *Z. Chem.* **1984**, *24*, 218–219.
3. Akutsu, B.; Nakano, Y.; Usui, Y. *Anal. Sci.* **1990**, *6*, 827–831. (b) Sato, S.; Wada, M. *Bull. Chem. Soc. Jpn* **1970**, *43*, 1955–1962. (c) Sato, S.; Wada, M.; Seki, T. *Jpn. J. Appl. Phys.* **1968**, *7*, 7–13.
4. Kercher, M.; König, B.; Zieg, H.; De Cola, L. *J. Am. Chem. Soc.* **2002**, *124*, 11541–11551.
5. Carano, M.; Cicogna, F.; D'Ambra, I.; Gaddi, B.; Ingrosso, G.; Marcaccio, M.; Paolucci, D.; Paolucci, F.; Pinzino, C.; Roffia, S. *Organometallics* **2002**, *21*, 5583–5593. (b) Carano, M.; Cicogna, F.; Houben, J. L.; Ingrosso, G.; Marchetti, F.; Mottier, L.; Paolucci, F.; Pinzino, C.; Roffia, S. *Inorg. Chem.* **2002**, *41*, 3396–3409. (c) Carano, M.; Careri, M.; Cicogna, F.; D'Ambra, I.; Houben, J. L.; Ingrosso, G.; Marcaccio, M.; Paolucci, F.; Pinzino, C.; Roffia, S. *Organometallics* **2001**, *20*, 3478–3490. (d) Cicogna, F.; Colonna, M.; Houben, J. L.; Ingrosso, G.; Marchetti, F. *J. Organomet. Chem.* **2000**, *593–594*, 251–266.
6. Cicogna, F.; Ingrosso, G. Unpublished results.
7. Becker, H.-D.; Langer, V.; Becker, H.-C. *J. Org. Chem.* **1993**, *58*, 6394–6396.
8. Bouas-Laurent, H.; Castellan, A.; Desvergne, J.-P.; Lapouyade, R. *Chem. Soc. Rev.* **2001**, *30*, 248–263. (b) Bouas-Laurent, H.; Castellan, A.; Desvergne, J.-P.; Lapouyade, R. *Chem. Soc. Rev.* **2000**, *29*, 43–55. (c) Becker, H.-D. *Chem. Rev.* **1993**, *93*, 145–172.
9. Nakatsuji, S.; Ojima, T.; Akutsu, H.; Yamada, J. *J. Org. Chem.* **2002**, *67*, 916–921. (b) McSkimming, G.; Tucker, J. H. R.; Bouas-Laurent, H.; Desvergne, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2167–2169. (c) Mori, Y.; Maeda, K. *J. Chem. Soc., Perkin Trans. 2* **1996**, 113–119. (d) Schottelius, M. J.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 4896–4903. (e) Becker, H.-D.; Langer, V. *J. Org. Chem.* **1993**, *58*, 4703–4708. (f) Becker, H.-D.; Amin, K. A. *J. Org. Chem.* **1989**, *54*, 3182–3188. (g) Becker, H.-D.; Elebring, T.; Sandros, K. *J. Org. Chem.* **1982**, *47*, 1064–1068. (h) Castellan, A.; Desvergne, J.-P.; Bouas-Laurent, H. *Chem. Phys. Lett.* **1980**, *76*, 390–397. (i) Bergmark, W. R.; Jones, G. II; Reinhardt, T. E.; Halpern, A. M. *J. Am. Chem. Soc.* **1978**, *100*, 6665–6673. (j) Ferguson, J.; Morita, M.; Puza, M. *Chem. Phys. Lett.* **1976**, *42*, 288–292. (k) Bradshaw, A. W.; Chapman, O. L. *J. Am. Chem. Soc.* **1967**, *89*, 2372–2375. (l) Livingston, R.; Wei, K. S. *J. Am. Chem. Soc.* **1967**, *89*, 3098–3100.
10. Ihmels, H.; Leusser, D.; Pfeiffer, M.; Stalke, D. *Tetrahedron* **2000**, *56*, 6867–6875. (b) Ito, Y.; Olovsson, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 127–133. (c) Kaupp, G. *Angew. Chem. Int. Ed.* **1992**, *31*, 595–598. (d) Chandross, E. A.; Ferguson, J. *J. Chem. Phys.* **1966**, *45*, 3564–3567. (e) Ito, Y.; Craig, D. P.; Sarti-Fantoni, P. *Chem. Commun.* **1966**, *20*, 742–743.
11. Wu, D.-Y.; Zhang, L.-P.; Wu, L.-Z.; Wang, B.-J.; Tung, C.-H. *Tetrahedron Lett.* **2002**, *43*, 1281–1283. (b) Grimme, S.; Peyerimhoff, S. D.; Bouas-Laurent, H.; Desvergne, J.-P.; Becker, H.-D.; Sarge, S. M.; Dreeskamp, H. *Phys. Chem. Chem. Phys.* **1999**, *1*, 2457–2462. (c) Tung, C.-H.; Guan, J.-Q. *J. Org. Chem.* **1998**, *63*, 5857–5862.
12. Cohen, M. D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 386–393.
13. Trouts, T. D.; Tyson, D. S.; Pohl, R.; Kozlov, D. V.; Waldron, A. G.; Castellano, F. N. *Adv. Funct. Mater.* **2003**, *13*, 398–402. (b) Hiraga, H.; Morozumi, T.; Nakamura, H. *Tetrahedron Lett.* **2002**, *43*, 9093–9095. (c) Ojima, T.; Akutsu, H.; Yamada, J.; Nakatsuji, S. *Polyhedron* **2001**, *20*, 1335–1338.
14. Irie, M. *Chem. Rev.* **2000**, *100*, 1683–1684. (b) Irie, M. *Chem. Rev.* **2000**, *100*, 1685–1716.
15. Becker, H.-D.; Andersson, K. *J. Org. Chem.* **1983**, *48*, 4542–4549.
16. Zandomeneghi, M.; Festa, C.; Carbonaro, L.; Galleschi, L.; Lenzi, A.; Calucci, L. *J. Agric. Food Chem.* **2000**, *48*, 2216–2221.
17. Coulson, C. A.; Orgel, L. E.; Taylor, W.; Weiss, J. *J. Chem. Soc.* **1955**, 2961–2962.
18. Calvert, J. G.; Pitts, J. N., Jr. *Photochemistry*; Wiley: New York, 1966; p. 297.
19. Toshima, N.; Sugano, T.; Hirai, H. *Can. J. Chem.* **1984**, *62*, 2047–2053.
20. Anderson, B. F.; Ferguson, J.; Morita, M.; Robertson, G. B. *J. Am. Chem. Soc.* **1979**, *101*, 1832–1840.
21. North, C. T.; Phillips, C.; Mathews, F. S. *Acta Crystallogr. A* **1968**, *24*, 351–359.
22. Sheldrick, G. M. *SHELXTL-Plus*, Rel. 5.1; Brucker A.X.S. Instruments Inc.: Madison, Wisconsin, USA, 1997.
23. Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837–838.
24. Zandomeneghi, M. *J. Agric. Food Chem.* **1999**, *47*, 878–882.
25. Hapke, B. In *Theory of Reflectance and Emittance Spectroscopy*; Arvidson, R. E., Rycroft, M. J., Eds.; Cambridge University Press: Cambridge, UK, 1993; Chapters 10 and 11.

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Reactivity of TEMPO anion as a nucleophile and its applications for selective transformations of haloalkanes or acyl halides to aldehydes

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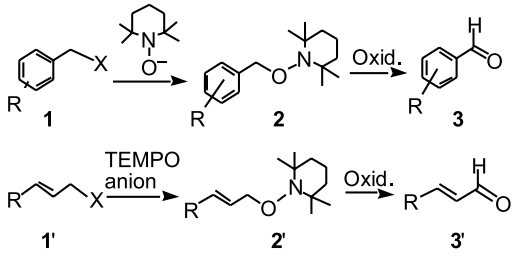
Abstract—Sodium 2,2,6,6-tetramethylpiperidine-*N*-oxide ($TEMPO^-Na^+$), generated by reduction of TEMPO· with sodium naphthalenide in THF, reacted with alkyl halides or acyl halides to produce *O*-alkylated or acylated TEMPOs, which were in turn oxidized with *m*CPBA or reduced with DIBAL-H to afford the corresponding aldehydes, thus accomplishing a new protocol for the halides-carbonyls conversion.

1. Introduction

Selective oxidation of the benzylic and allylic positions of arenes and alkenes to the corresponding carbonyl compounds is an important task especially in the synthesis of bioactive and medicinally significant compounds.[1] Radical halogenation at the benzylic and allylic positions, followed by the oxidation of the resulting halides **1** is one of the most practical methods leading to the desired carbonyl compounds **3**. However, the most conventional method of this conversion,[2] relied on acyloxylation followed by successive hydrolysis and oxidation of the hydroxy group, is a time-consuming procedure.[3] We, therefore, developed an efficient method for the conversion of **1** to **3** by way of the intermediate **2**, by utilizing the 2,2,6,6-tetramethylpiperidine-*N*-oxy (TEMPO)-substituted carbon of **2** as a latent carbonyl function (Scheme 1).[4,5] Furthermore, we found that the reduction of *O*-acylated TEMPOs with DIBAL-H produced primarily the corresponding aldehydes **3**.

A variety of methods for the preparation of TEMPO-based molecules have thus far been investigated by trapping the carbon centered radical with 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical[6–11] (abbreviated as TEMPO·) and by the reaction of its *N*-oxoammonium salts with ketones and aldehydes.[5a,12,13] On the other hand, 2,2,6,6-tetramethylpiperidine-*N*-oxide (the TEMPO anion), a reduced form of TEMPO·, is also useful species to produce *O*-alkyl TEMPOs. However, the TEMPO anion was usually generated in aqueous media by treatment with sodium or calcium ascrobates followed by deprotonation of the resulting 1-hydroxyTEMP (TEMPOH) with NaH in THF[14,6b] and the reactivity of the TEMPO anion as a nucleophile has not been well explored.[6c] We, therefore, utilized a direct method to generate this anionic species by reduction of TEMPO· with sodium naphthalenide in THF, which is featured by the repeated use of naphthalene, and applied it to the nucleophilic substitution of a variety of alkyl halides **1** including benzylic and allylic halides. Subsequently, oxidation of the resulting *O*-alkylated TEMPOs **2** and **2′** to the corresponding carbonyl compounds **3** and **3′** was examined.



Scheme 1. Benzylic and allylic C–X bond oxidation via substitution with the TEMPO anion.

Keywords: TEMPO and compounds; Oxidation; Reduction; *m*CPBA; DIBAL-H; Aldehyde.
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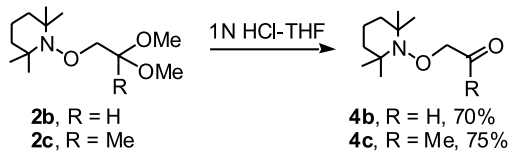
2. Result and discussion

Although reduction of TEMPO· to the TEMPO anion with sodium metal or lithium naphthalenide in DME was reported by Whitesides et al.,[6c] we devised a catalytic procedure with respect to naphthalene (2–10 mol%) by stirring with a stoichiometric amount of sodium as a real reducing reagent in THF, during which the red brown color of TEMPO· faded as it was converted to the TEMPO anion. The resulting TEMPO anion-containing solution was used for the S_N2 reactions of a variety of primary and secondary halides **1**, giving the corresponding *O*-alkyl TEMPOs **2**.

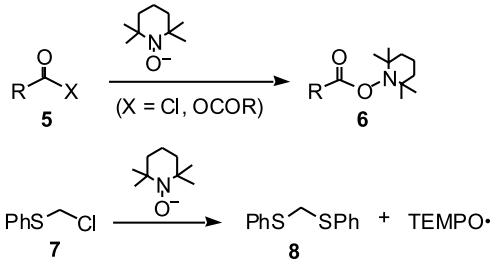
As shown in Table 1, primary alkyl halides **1** reacted with the TEMPO anion to give the corresponding alkoxyamines **2** in good to excellent yields (runs 1–7). The lower reactivity of 2-halo acetals **1b**,**c**, presumably due to some steric hindrance, was improved by adding dimethylpropyleneurea (DMPU) or 1,3-dimethyl-2-imidazolidinone (DMI) as a co-solvent (runs 2 and 3). Similar additive effect was also attained with HMPA. *O*-Alkylation with primary benzylic (runs 4 and 5) and allylic halide (runs 6 and 7) proceeded smoothly. On the other hand, secondary halides were less reactive and moderate yield was obtained with benzylic halide (run 8).

Our attempts at the substitution reaction of 2-halo ketones and esters such as bromoacetophenone and bromoacetate with the TEMPO anion were unsuccessful. However, a synthetically equivalent and/or useful class of aldehyde **4b** and ketone **4c** was obtained in 70–75% yields by hydrolysis of the acetals **2b** and **2c**, prepared by the present method (Scheme 2).



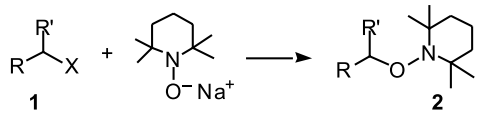
Scheme 2. Hydrolysis of α-TEMPO substituted acetals **2**.

The reactivity of the TEMPO anion toward different electrophiles such as acyl halides or acid anhydrides **5** and others was also examined. The *O*-acyl TEMPOs **6** were easily produced (75–88%) by nucleophilic acyl substitution of **5**.[15] The reaction of the TEMPO anion with phenylthiomethyl chloride **7** led quantitatively to bis(phenylthio)methane **8** instead of the expected *O*-phenylthiomethylTEMPO, which is in sharp contrast to substitution of **7** with sodium alkoxide (Scheme 3).[16]



Scheme 3. Reactions of the TEMPO anion with acyl halides or acid anhydrides **5** and $PhSCH_2Cl$ (**7**).

Table 1. *O*-Alkylations of 2,2,6,6-tetramethylpiperidine-*N*-oxide anion



Entry	**1**	Temp/time[a]	Product, **2**	Yield/% (method)[b]
1	**a**, X=Br	Reflux/18 h	$C_{10}H_{21}$–OTEMP	92 (A)
2	**b**, X=Br	rt/17 h, 70 °C/65 h[c]	CH_3O, CH_3O, OTEMP	43 (B)
3	**c**, X=Br	Reflux/110 h[d]	CH_3O, OCH_3, OTEMP	67 (B)
4	**d**, X=Br	rt/0.5 h[d]	C_6H_5–OTEMP	99 (A)
5	**e**, X=Br	rt/10 h[d]	C_6H_5–OTEMP	99 (A)
6	**f**, X=Cl	Reflux/20 h	C_6H_5–OTEMP	89 (A)
7	**g**, X=Cl	Reflux/24 h	OTEMP	76 (B)
8	**h**, X=Br	Reflux/89 h	C_6H_5–OTEMP	45 (A)

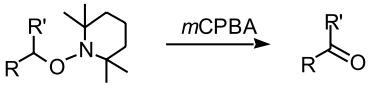
[a] The reactions were carried out in THF under Ar.
[b] Yields are based on isolated products and calculated based on (A) the halides or (B) TEMPO·.
[c] Carried out in the presence of DMPU.
[d] Carried out in the presence of 1,3-dimethyl-2-imidazolidinone (DMI).

As shown in Table 2, selected *O*-benzyl- and *O*-allyl-TEMPOs **2** were transformed to carbonyl compounds **3**. We examined a variety of oxidizing reagents such as $Mn(OAc)_3$, $Cu(OAc)_2$, *tert*-BuOOH[4b] for this purpose, but it turned out that *m*-chloroperbenzoic acid (*m*CPBA) was highly efficient to complete quickly the reaction at 0–5 °C and the corresponding **3**, conjugated with arenes and C=C double bond, were obtained in excellent yields (runs 1–3).[5a] In the *m*CPBA oxidation, 1-hydroxyTEMP (TEMPOH) along with a small amount of TEMPO· was produced as the one of fragments from **2**.[17]

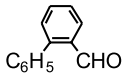
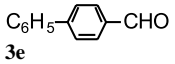
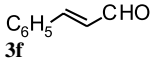
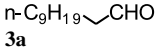
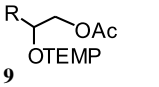
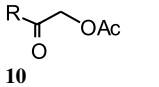
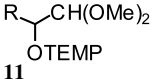
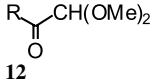
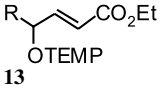
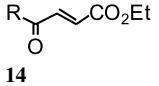
Furthermore, in addition to the case of a simple alkanal **3a** from **2a** (run 4), this reaction was successfully applied to the synthesis of diverse carbonyl compounds[18] including 2-acetoxyketone **10** (run 5), acetal of 1,2-dione **12** (run 6), and 4-oxo-2-enoate **14**[19] (run 7) from the corresponding precursors **9**, **11**, and **13**, derived from 2-TEMPO-substituted undecanal as a common starting material.[12]

The allylic oxidation of the prenyl derivative **15** was examined by employing the present protocol (Scheme 4). Thus, the electrochemical ene-type chlorination[20] of **15** and the subsequent protection of the hydroxy group as a THP ether, giving **16**, was followed by the Cl/I exchange reaction with NaI to afford the allylic iodide **17** (*E*:*Z*=ca. 2:1). The S_N2 reaction of **17** with the TEMPO anion afforded **18** in 45% yield. The enal **19** was obtained by oxidation with *m*CPBA as a ca. 2:1 *E*/*Z* mixture in 78% yield, which, on standing in $CDCl_3$, converged to *E*-isomer.

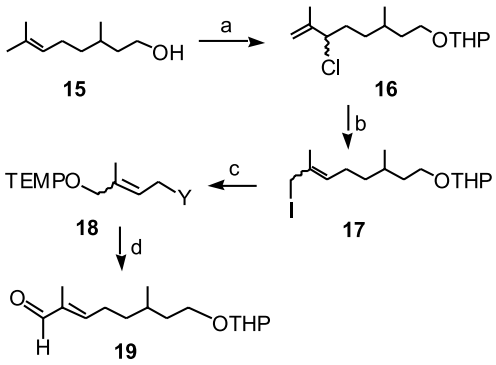
Table 2. Oxidations of (2,2,6,6-tetramethylpiperidinyl-1-oxy)alkanes to aldehydes and ketones[a]



2 **3**

Entry	Substrates	Products	Yield/%[b]
1	**2d**	 **3d**	99
2	**2e**	 **3e**	86
3	**2f**	 **3f**	86
4	**2a**	 **3a**	88
5[c]	 **9**	 **10**	90
6[c]	 **11**	 **12**	96
7[c]	 **13**	 **14**	89

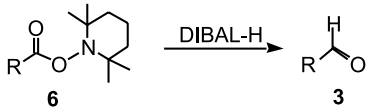
[a] Carried out by using slightly excess *m*CPBA in CH_2Cl_2 with cooling at 0–5 °C for 30 min.
[b] Yields are based on isolated products.
[c] R=*n*-C_9H_{19}.



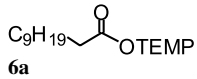
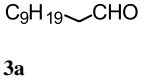
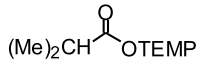
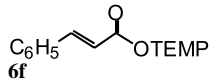
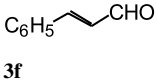
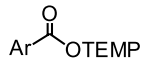
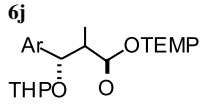
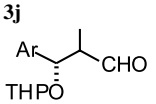
Scheme 4. Allylic oxidation via halogenation and substitution with the TEMPO anion followed by *m*CPBA oxidation. a: (1) Electrolysis, −2e, CH_2Cl_2—aq. NaCl/1 N HCl (81%), (2) DHP, *p*TsOH, CH_2Cl_2 (81%), b: NaI, acetone, heated (74%), c: $TEMPO^-Na^+$, THF, reflux, 20 h (45%) (Y=$CH_2CH(Me)CH_2CH_2OTHP$), *E*:*Z*=ca. 2:1, d: *m*CPBA, CH_2Cl_2 (78%).

Alternatively, the conversion of *O*-acylated TEMPOs **6** to the corresponding aldehydes **3** was examined by a hydride reduction.[21] Thus, the treatment of **6f** (R=PhCH=CH) with DIBAL-H (3 equiv) at −78 to −50 °C for 75 min afforded cleanly the corresponding aldehyde **3f** (91% yield) (run 3), the overreduction to carbinol was negligibly small, while ethyl *trans*-cinnamate, an analogue of **6f**, produced the corresponding primary alcohol under the same conditions.[22] Examples of the selective reduction of **6** to aldehydes, including aldol derivative (run 5), are shown in Table 3.

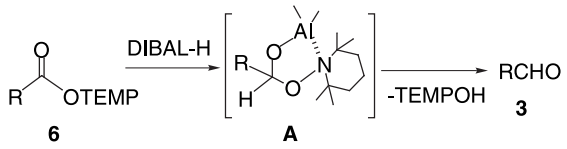
Table 3. Reduction of *O*-acylated 2,2,6,6-tetramethylpiperidinyl-1-oxyls with DIBAL-H to aldehydes[a]



6 **3**

Entry	Substrates	Products	Yield/%[b]
1	 **6a**	 **3a**	95
2	 **6i**	$(Me)_2CH–CHO$ **3i**	72[c]
3	 **6f**	 **3f**	91
4[d]	 **6j**	Ar–CHO **3j**	92
5[d,e]	 **20**	 **21**	94[f]

[a] Carried out by using excess DIBAL-H (2–3 equv.) in toluene at −78 ~ −50 °C for 30 min to 1 h.
[b] Yields are based on isolated products.
[c] Yield calculated by comparing with an internal standard (PhCH=CHCHO, added after the reaction) due to volatility of the product.
[d] Ar=4-$MeOC_6H_4$.
[e] The substrate *anti*-**20** was prepared by the aldol reaction of **6** (R=Et) and 4-$MeOC_6H_4CHO$ with LDA (ca. 7:1 ds. mixture) followed by protection of the *anti*-adduct, purified by recrystallization, as a THP either.
[f] Overreduction to the carbinol (4%) was found.



Scheme 5. A proposed mechanism for reduction of *O*-acyl TEMPOs **6** with DIBAL-H.

Accordingly, it is conceived that the DIBAL-H reduction of **6** proceeds through the chelated intermediate **A** with close resemblance with the case of *N*-methoxy-*N*-methylamdies developed by Weinreb et al.,[23] which explain the lack of over-reduction (Scheme 5).

3. Conclusion

The TEMPO-attached carbon was shown to be a synthon of carbonyl group. Haloalkanes were efficiently converted to aldehyde via *O*-alkylated TEMPOs by oxidation with *m*CPBA (up to 98% yields for two steps). The *O*-acyl TEMPOs were selectively reduced to the aldehydes even with excess DIBAL-H owing to chelating ability of tetramethylpiperidine group for stabilization of the hydride-adduct intermediate.

4. Experimental

4.1. General

IR spectra were obtained with a Horiba, Model FT-210, or a JASCO, Model FT/IR-230, fourier transform infrared spectrometer instrument, and only major absorptions are cited. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-AL400 and Varian Mercury-300 instruments with $CDCl_3$ as a solvent unless otherwise indicated.

4.2. General procedure for preparation of *O*-alkyl TEMPOs 2

In a 50 mL one-necked flask were placed $C_{10}H_8$ (221 mg, 1.72 mmol), TEMPO· (2.7 g, 17.3 mmol), and THF (15 mL). To this solution was added Na metal (477 mg, 20.7 mmol) and the mixture was stirred at room temperature until Na dissolved and blue-black color of $Na^+[C_{10}H_8]^{-\cdot}$ persisted. To a solution of n-$C_{11}H_{23}Br$ (**1a**, 3.66 g, 15.5 mmol) in THF (5 mL), placed in a 100 mL one-necked flask, was transferred by double-ended needle the above TEMPO anion with cooling at 0–4 °C. The mixture was allowed to warm gradually to room temperature and to 50 °C, stirred for 2 h, and then heated at reflux for 18 h. The reaction was quenched with cold aqueous $NaHCO_3$ and products were extracted with AcOEt. Extracts were washed with brine, dried ($MgSO_4$), and concentrated. The products were purified by distillation and the fraction of boiling range 137–138 °C (0.15 Torr, bath temperature 150–155 °C) was collected; 4.47 g (92% yield).

4.2.1. Compound 2a. IR (neat) 1467, 1373, 1263, 1133, 1047, 759, 711 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.88 (complex t, J=6.9 Hz, 3H), 1.09, 1.14 (s, 12H), 1.23–1.56 (m, 24H, brs at 1.26), 3.71 (t, J=6.6 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 14.1, 17.2, 20.1 (2C), 22.7, 26.5, 28.7, 29.4, 29.6, 29.7 (2C), 29.8, 31.9, 33.0 (2C), 39.6 (2C), 59.5 (2C), 76.8. HRMS (EI) calcd for $C_{20}H_{41}NO$ 311.3188, found 311.3205.

Similarly, the compound **2c** was prepared as follows. A solution of the TEMPO anion, prepared from TEMPO· (2.59 g, 16.6 mmol), $C_{10}H_8$ (240 mg, 1.87 mmol), and Na (420 mg, 18.3 mmol) in THF (20 mL), was added to a solution of $BrCH_2C(OMe)_2CH_3$ (**1c**, 3.5 g, 19.2 mmol) in THF (10 mL) and DMI (3.6 mL) at 0 °C. The mixture was gradually raised to room temperature and then heated at reflux for 110 h, during which solids precipitated. Usual workup and the removal of volatile materials including the unreacted TEMPO· (1.65 g) by distillation of the crude product at 62 °C (1.5 Torr, bath temperature 90 °C), which was followed by column chromatography (SiO_2, hexane and hexane-AcOEt 10:1) of the residual oil to give the TEMPO substituted acetal **2c** (2.9 g, 67% yield based on the starting TEMPO·): IR (neat) 2933, 2829, 1469, 1454, 1375, 1360, 1261, 1242, 1178, 1132, 1090, 958, 849, 800, 702 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.13, 1.19 (s, 12H), 1.41(s, 3H), 1.42–1.59 (m, 6H), 3.23 (s, 6H), 3.77 (s, 2H); ^{13}C NMR (75.5 MHz) δ 16.9, 20.0, 20.3, 32.9 (2C), 39.7 (2C), 48.1 (2C), 59.8 (2C), 77.4, 100.0. HRMS (EI) calcd for $C_{14}H_{29}NO_3$ 259.2147, found 259.2169.

4.2.2. Compound 2b. Bp 78–82 °C (0.1 Torr); IR (neat) 2831, 1469, 1359, 1245, 1135, 1081, 970, 923, 856, 786, 713 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.10, 1.17 (s, 12H), 1.25–1.55 (m, 6H), 3.39 (s, 6H), 3.84 (d, J=5.2 Hz, 2H), 4.49 (t, J=5.2 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 16.6, 19.5 (2C), 32.4 (2C), 39.1 (2C), 53.3 (2C), 59.3 (2C), 76.7, 101.9. HRMS (EI) calcd for $C_{13}H_{27}NO_3$ 245.1991, found 245.1959.

4.2.3. Compound 2d. Mp 82.5–83.5 °C; IR (KBr) 3003, 2976, 2927, 2868, 1477, 1360, 1263, 1186, 1132, 1039, 933, 829, 775, 750, 706 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.04, 1.08 (s, 12H), 1.20–1.59 (m, 6H), 4.72 (s, 2H), 7.19–7.65 (m, 9H); ^{13}C NMR (100 MHz) δ 17.5, 20.7 (2C), 33.2 (2C), 40.1 (2C), 60.2 (2C), 77.5, 127.1, 127.3, 127.4, 128.1 (2C), 129.1, 129.4 (2C), 129.9, 135.8, 141.2, 141.8. HRMS (EI) calcd for $C_{22}H_{29}NO$ 323.2249, found 323.2277.

4.2.4. Compound 2e. Mp 88–89 °C; IR (KBr) 3003, 2974, 2931, 2889, 1485, 1469, 1448, 1373, 1360, 1261, 1182, 1132, 1030, 991, 862, 823, 764, 702 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.25, 1.37 (s, 12H), 1.20–1.70 (m, 6H), 4.95 (s, 2H), 7.37–7.47 (m, 9H); ^{13}C NMR (100 MHz) δ 17.2, 20.4 (2C), 33.2 (2C), 39.8 (2C), 60.0 (2C), 78.4, 126.8 (2C), 126.9 (2C), 127.0, 127.7 (2C), 128.5 (2C), 137.1, 140.1, 140.8. HRMS (EI) calcd for $C_{22}H_{29}NO$ 323.2249, found 323.2216.

4.2.5. Compound 18 (*E*/*Z* mixture). IR (Neat) 2929, 1454, 1373, 1358, 1261, 1201, 1184, 1134, 1078, 1030, 991, 908, 870, 814, 735 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.87, 0.90 (d, J=6.8 Hz, 3H), 1.09, 1.15, 1.19 (s, 12H), 1.65, 1.79 (s, 3H), 1.25–2.12 (m, 19H), 3.33–3.52 (m, 2H), 3.70–3.90 (m, 2H), 4.11, 4.25 (s, 2H), 4.56, 4.81 (s, 1H, OCH), 5.25, 5.37 (t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz) δ 14.3, 17.0, 19.5, 20.0 and 20.1 (2C), 24.8, 25.3, 29.5, 30.6 (2C), 32.8 and 32.9,

36.4 and 36.5, 37.2 and 37.3, 39.5 (2C), 59.5 (2C), 62.0, 65.6 and 65.7, 75.1, 82.3, 98.4 and 98.6, 128.3, 131.4 and 131.5. HRMS (EI) calcd for $C_{24}H_{45}NO_4$ 395.3399, found 395.3310.

4.3. General procedure for oxidation of *O*-alkyl TEMPOs 2 to aldehydes and ketones 3

To a solution of the *O*-alkyl TEMPO **2a** (R=$C_{10}H_{21}$, 311 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added portionwise *m*CPBA (70–75% assay, 296 mg, 1.2 equivalent) over 10 min at 0–4 °C. The reaction was exothermic and the temperature was kept under 8 °C. The mixture was stirred at the same temperature for 30 min, and the reaction was quenched with cold aqueous $Na_2S_2O_3$, and the products were extracted with CH_2Cl_2 (first) and AcOEt (second). Extracts were washed with aqueous $NaHCO_3$ and with brine, dried ($MgSO_4$), and concentrated. The crude products were purified by column chromatography (SiO_2, hexane-AcOEt, 7:1, 5:1, 3:1, 2:1, then 1:1) to give 150 mg (88%) of the aldehyde **3a** (R=$C_{10}H_{21}$, R_f=0.52, hexane-AcOEt 7:1), 10 mg of TEMPO·, and 101 mg (64%) of a mixture of TEMPO· and the *N*-hydroxypiperidine (R_f=0.12, hexane-AcOEt 7:1).

4.3.1. 2-Phenylbenzaldehyde 3d. IR (neat) 3062, 2848, 2754, 2252, 1655, 1597, 1473, 1394, 1254, 1196, 1009, 910, 827, 733, 704, 646 cm^{-1}; ^1H NMR (400 MHz) δ 7.35–8.04 (m, 9H, Ph), 9.97 (s, 1H, CHO); ^{13}C NMR (100 MHz) δ 127.4, 127.6, 128.0, 128.3 (2C), 129.9 (2C), 130.6, 133.4, 133.5, 137.5, 145.8, 192.2.

4.3.2. 4-Phenylbenzaldehyde 3e. IR (neat) 3059, 3032, 2827, 2735, 2252, 1699, 1604, 1566, 1487, 1450, 1412, 1385, 1308, 1215, 1171, 1007, 910, 839, 762, 731, 696 cm^{-1}; ^1H NMR (400 MHz) δ 7.35–7.96 (m, 9H, Ph), 10.04 (s, 1H, CHO); ^{13}C NMR (100 MHz) δ 127.1 (2C), 127.4 (2C), 128.2, 128.5 (2C), 130.0 (2C), 134.9, 139.4, 146.9, 191.5.

4.3.3. 1-Acetoxy-2-undecanone 10. Mp 51.5–52.5 °C; IR (KBr) 1862, 1724, 1467, 1409, 1378, 1232, 1130, 1079, 1037, 985, 873, 838, 717 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (complex t, J=6.2 Hz, 3H), 1.26 (brs, 12H), 1.60 (m, 2H), 2.17 (s, 3H), 2.40 (t, J=7.4 Hz, 2H), 4.65 (s, 2H); ^{13}C NMR (75.5 MHz) δ 14.1, 20.5, 22.6, 23.3, 29.1, 29.2, 29.28, 29.33, 31.8, 38.8, 67.9, 170.2, 204.0 HRMS (EI) calcd for $C_{13}H_{24}O_3$ 228.1725, found 228.1772.

4.3.4. Ethyl 4-oxotridec-2-enoate 14. IR (neat) 1727, 1689, 1635, 1465, 1367, 1301, 1182, 1095, 1031, 981, 867, 723 cm^{-1}; ^1H NMR (300 MHz) δ 0.88 (complex t, J=6.9 Hz, 3H), 1.27 (brs, 12H), 1.32 (t, J=7.1 Hz, 3H), 1.64 (m, 2H), 2.63 (t, J=7.4 Hz, 2H), 4.27 (q, J=7.1 Hz, 2H), 6.67 (d, J=15.9 Hz, 1H), 7.07 (d, J=15.9 Hz, 1H); ^{13}C NMR (300 MHz) δ 12.1, 12.2, 20.6, 21.7, 27.1, 27.2, 27.3, 27.4, 29.8, 39.5, 59.4, 128.6, 137.3, 163.5, 197.8.

4.3.5. Enal 19 (*E*-isomer). IR (neat) 2943, 2871, 1685, 1645, 1454, 1381, 1354, 1265, 1201, 1184, 1136, 1120, 1076, 1034, 910, 868, 812, 733 cm^{-1}; ^1H NMR (400 MHz) δ 0.92 (d, J=6.4 Hz, 3H), 1.73 (s, 3H), 1.25–1.82(m, 11H), 2.25–2.40 (m, 2H), 3.33–3.50 (m, 2H), 3.70–3.85 (m, 2H), 4.50–4.55 (m, 1H), 6.45 (t, J=7.2 Hz, 1H), 9.35 (s, 1H); ^{13}C NMR (100 MHz) δ 9.3, 19.4 and 19.5, 19.6 and 19.8, 25.6, 26.6, 29.8, 30.8, 35.5 and 35.7, 36.5, 62.4, 65.5 and 65.6, 98.7 and 99.0, 139.0, 154.7, 194.9

4.4. Hydrolysis of 2c to 4c

To a solution of **2c** (3.96 g, 15.3 mmol) in THF (80 mL) was added at 0–4 °C cold 1N HCl (15 mL). The mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched with aqueous $NaHCO_3$ and products were extracted with AcOEt. Usual workup followed by purification on column chromatography (SiO_2, hexane-AcOEt 10:1 and 7:1) gave 2.44 g (75%) of the TEMPO-substituted acetone **4c**: IR (neat) 1720, 1359, 1234, 1133, 1081, 995, 923, 702 cm^{-1}; ^1H NMR (300 MHz) δ 1.13, 1.15 (s, 12H), 1.30–1.60 (m, 6H), 2.21 (s, 3H), 4.38 (s, 2H); ^{13}C NMR (75.5 MHz) δ 16.8, 19.9 (2C), 27.0, 32.7 (2C), 39.4 (2C), 59.8 (2C), 83.1, 206.6.

4.4.1. Compound 4b. Yield 70%; IR (neat) 2976, 2933, 1736, 1469, 1375, 1362, 1263, 1246, 1134, 1080, 912, 735 cm^{-1}; ^1H NMR (400 MHz) δ 1.12 (s, 12H), 1.20–1.67 (m, 6H), 4.41 (s, 2H), 9.73 (s, 1H); ^{13}C NMR (100 MHz) δ 17.1, 20.2 (2C), 32.9 (2C), 39.7 (2C), 60.2 (2C), 83.6, 200.6.

4.5. Preparation of *O*-acyl TEMPOs 6

To a cooled (0–4 °C) solution of *p*-anisoyl chloride **5j** (R=4-$MeOC_6H_4$, 3.5 g, 20.5 mmol) in THF (10 mL) was added dropwise a chilled solution of the TEMPO anion, prepared from TEMPO· (3.12 g, 20 mmol), $C_{10}H_8$ (150 mg, 1.17 mmol), and Na metal (506 mg, 22 mmol). The mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched with cold aqueous $NaHCO_3$ and products were extracted with AcOEt, worked up in a usual manner, and purified by distillation; fraction of 147–152 °C (0.03 Torr) was collected: 5.12 g (88% based on TEMPO·).

4.5.1. Compound 6j. Mp 89–91 °C (from hexane-AcOEt); IR (KBr) 1747, 1604, 1510, 1459, 1442, 1317, 1249, 1160, 1130, 1072, 1024, 912, 846, 765, 692, 607 cm^{-1}; ^1H NMR (300 MHz) δ 1.10, 1.26 (s, 12H), 1.42–1.48 (m, 1H), 1.54–1.84 (m, 5H), 3.87 (s, 3H), 6.94 (d, J=9.1 Hz, 2H), 8.03 (d, J=9.1 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 16.9, 20.7 (2C), 31.8 (2C), 38.9 (2C), 55.3, 60.2 (2C), 113.6 (2C), 121.8, 131.3 (2C), 163.2, 166.0. HRMS (EI) calcd for $C_{17}H_{25}NO_3$ 291.1834, found 291.1849.

4.5.2. Compound 6a. Yield 85%; IR (neat) 2927, 2854, 1770, 1466, 1377, 1363, 1265, 1246, 1209, 1182, 1134, 1101, 1045, 935, 721 cm^{-1}; ^1H NMR (400 MHz) δ 0.85 (complex t, J=6.8 Hz, 3H), 1.02, 1.12 (s, 12H), 1.20–1.73 (m, 22H), 2.31 (t, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz) δ 14.2, 17.1, 20.6 (2C), 22.8, 25.4, 29.3, 29.4, 29.5 (2C), 29.6, 32.0 (2C), 33.1 (2C), 39.0 (2C), 59.9 (2C), 173.0. HRMS (EI) calcd for $C_{20}H_{39}NO_2$ 325.2981, found 325.2986.

4.5.3. Compound 6f. Yield 75%; mp 104–105 °C; IR (KBr) 3066, 1739, 1575, 1450, 1307, 1203, 1124, 1042, 1012, 973, 923, 864, 804, 767, 715, 675 cm^{-1}; ^1H NMR (300 MHz) δ 1.10, 1.22 (s, 12H), 1.40–1.48 (m, 1H), 1.53–1.80 (m, 5H), 6.49 (d, J=16.0 Hz, 1H), 7.37–7.42 (m, 3H), 7.55–7.59 (m,

2H), 7.76 (d, $J=16.0$ Hz, 1H); ^{13}C NMR (75.5 MHz) δ 16.8, 20.4 (2C), 31.8 (2C), 38.8 (2C), 60.0 (2C), 116.5, 127.9 (2C), 128.7 (2C), 130.1, 134.3, 144.9, 167.0. HRMS (EI) calcd for $C_{18}H_{25}NO_2$ 287.1885, found 287.1924.

4.6. General procedure for reduction of *O*-acyl TEMPOs 6 to aldehydes 3

To a cooled (−78 °C) solution of **6f** (R=PhCH=CH, 723 mg, 2.5 mmol) in toluene (10 mL) was added dropwise DIBAL-H (1.0 N in toluene, 7.9 mL, 3.1 equivalents) over 5 min. The mixture was stirred at −78 to −50 °C for 75 min and excess DIBAL-H was decomposed with AcOEt and the reaction was quenched with aqueous $NaHCO_3$ (1.0 mL). The mixture was diluted with AcOEt, treated with a Celite, and filtered from a short Celite pad. The filtrate was washed with cold 2N HCl, brine, dried ($MgSO_4$), and concentrated. The crude products were analyzed by ^{1}H NMR (300 MHz) to ensure the amount of aldehyde over carbinol and purified by column chromatography (SiO_2, hexane-AcOEt, 10:1, 7:1, 5:1, 3:1, 2:1, then 1:1) to give 308 mg (91%) of **3f** ($R_f=0.36$, hexane-AcOEt 5:1), identical in all respects with that obtained above. The structures of the aldehydes **3a**, **3i**, **3f**, and **3j** in Table 3 were confirmed by comparison of their spectral data with those of authentic samples.

4.6.1. Aldol 21. IR (neat) 2715, 1727, 1612, 1586, 1513, 1303, 1251, 1116, 1035, 1022, 968, 906, 869, 817 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.85 (d, $J=6.9$ Hz, 3H), 1.35–1.85 (m, 6H), 2.70–2.85 (m, 1H), 3.15–3.80 (m, 2H), 3.809 and 3.813 (s, 3H), 4.40 and 4.80 (m, 1H), 4.64 (d, $J=8.5$ Hz) and 4.78 (d, $J=9.6$ Hz, 1H), 6.85–6.90 (m, 2H), 7.21–7.28 (m, 2H), 9.82 (d, $J=2.5$ Hz) and 9.90 (d, $J=3.3$ Hz, 1H). HRMS (EI) calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1484.

Acknowledgements

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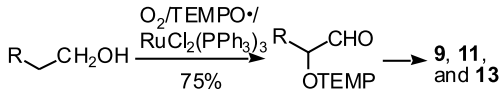
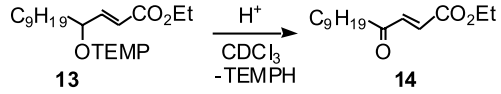
References and notes

1. Page, P. C. B.; McCarthy, T. J. In *Comprehensive Organic Synthesis*, Vol. 7; Pergamon: New York, 1991; pp 83–117.
2. (a) Hudlicky, M. Oxidation in Organic Chemistry In *ACS Monograph 186*; American Chemical Society: Washington, DC, 1990; pp 109–114. (b) Kilenyi, S. N. In *Comprehensive Organic Synthesis*, Vol. 7; Pergamon: New York, 1991; pp 653–670. Recent examples on C—halogen oxidation: (c) Paquette, W. D.; Taylor, R. E. *Org. Lett.* **2004**, *6*, 103–106 and references cited therein.
3. Saunders, J. *Top Drugs: Top Synthetic Routes*; Oxford University Press: Oxford, 2000; Chapter 2.
4. (a) Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A. *Tetrahedron Lett.* **1986**, *27*, 1119–1122. (b) Rossi, I.; Venturini, A.; Zedda, A. *J. Am. Chem. Soc.* **1999**, *121*, 7914–7917.
5. (a) Hunter, D. H.; Barton, D. H. R.; Motherwell, W. J. *Tetrahedron Lett.* **1984**, *25*, 603–606. (b) Skene, W. G.; Connolly, T. J.; Scaiano, J. C. *Tetrahedron Lett.* **1999**, *40*, 7297–7302.
6. Use of Grignard reagents or organolithium reagents: (a) Sholle, V. D.; Golubev, V. A.; Rozantsev, E. G. *Dokl. Akad. Nauk SSSR* **1971**, *200*, 137. *Chem. Abstr.* **1972**, *76*, 25049e. (b) Hawker, C. J.; Barclay, G. G.; Orellana, A.; Dao, J.; Devonport, W. *Macromolecules* **1996**, *29*, 5245–5254. (c) Whitesides, G. M.; Newirth, T. L. *J. Org. Chem.* **1975**, *40*, 3448–3450.
7. Oxidation of enolates; use of Cu(II): (a) Braslau, R.; Burrill, L. C. II; Siano, M.; Naik, N.; Howden, R. K.; Mahal *Macromolecules* **1997**, *30*, 6445–6450. (b) Wetter, C.; Jantos, C.; Woithe, K.; Studer, A. *Org. Lett.* **2003**, *5*, 2899–2902. Use of ferroceniu salt: (c) Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2001**, 3333–3335.
8. Use of radical initiators; Bu_3SnH: (a) Boger, D. L.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 1271–1275. Cu(II)(cat.)/Cu(0): (b) Matyjaszewski, K.; Woodworth, B. E.; Zhang, X.; Gaynor, S. G.; Metzner, Z. *Macromolecules* **1998**, *31*, 5955–5957. *B*-Alkylcatecholborane: (c) Ollivier, C.; Chuard, R.; Renaud, P. *Synlett* **1999**, 807–809.
9. Irradiation with radical initiators; use of $Mn_2(CO)_{10}$: Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E. *Tetrahedron Lett.* **1999**, *40*, 6095–6098. Use of $[Cp(CO)_2Fe]_2$, $(PhS)_2$, (*tert*-$BuO)_2$ and others, see Refs. 6b,7a.
10. Irradiation of [(alkylcarbonyloxy)iodo]benzene: Togo, H.; Aoki, M.; Kuramochi, T.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2417–2427.
11. Addition to ketene: Allen, A. D.; Cheng, B.; Fenwick, M. H.; Huang, W.-w.; Missiha, S.; Tahmassebi, D.; Tidwell, T. *Org. Lett.* **1999**, *1*, 693–696.
12. Inokuchi, T.; Nakagawa, K.; Torii, S. *Tetrahedron Lett.* **1995**, *36*, 3223–3226.
13. (a) Ren, T.; Liu, Y.-C.; Guo, Q.-X. *Bull. Chem. Soc. Jpn* **1996**, *69*, 603–606.(b) Church, K. M.; Holloway, L.; Matley, R.; Brower, R. J. *Abstracts of Papers*, 224th ACS National Meeting, Boston, MA, August 18–22, 2002; MEDI-378. AN 2002; 618229. (c) Schämann, M.; Schäfer, H. J. *Synlett* **2004**, 1601–1603.
14. (a) Anderson, J. E.; Casarini, D.; Corrie, J. E. T.; Lunazzi, L. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1299–1304. (b) Studer, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1108–1111. (c) Henry-Riyad, H.; Tidwell, T. T. *J. Phys. Org. Chem.* **2003**, *16*, 559–563.
15. Braslau, R.; Anderson, M. O.; Rivera, F.; Jimenez, A.; Haddad, T.; Axon, J. *Tetrahedron* **2002**, *58*, 5513–5523.
16. (a) Kruse, B.; Brückner, R. *Chem. Ber.* **1989**, *122*, 2023–2025. (b) Kersey, I. D.; Fishwick, C. W. G.; Findlay, J. B. C.; Ward, P. *Tetrahedron* **1995**, *51*, 6819–6834.
17. The liberated TEMPOH can be recovered and reused.
18. The 2-TEMPO-substituted undecanal was prepared by the reaction of undecanol with the TEMPO·/$RuCl_2(PPh_3)_3/O_2$ system in toluene.[12] This compound was converted to **9** by treatment with $NaBH_4$ (94% yield) followed with Ac_2O (95%

yield), to **11** with $CH(OMe)_3$/*p*TsOH in MeOH (82% yield), and to **13** with $(i\text{-PrO})_2P(O)CH_2CO_2Et$/NaH (97% yield).



19. The same compound **14** was produced on standing **13** under very weak acidic conditions (in $CDCl_3$) at room temperature for a long period.[5]



20. Uneyama, K.; Hasegawa, N.; Kawafuchi, H.; Torii, S. *Bull. Chem. Soc. Jpn* **1983**, *56*, 1214–1218.
21. Johnstone, R. A. W. In *Comprehensive Organic Synthesis*, Vol. 8; Pergamon: New York, 1991; pp 259–81.
22. Winterfeldt, E. *Synthesis* **1975**, 617–630.
23. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

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Assignment of the relative and absolute configurations of acyclic secondary 1,2-diols

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Abstract—The NMR profiles (^{13}C-δ, ^{1}H-δ, ^{1}H(OH)-δ, and $^{3}J_{H,H}$) of *syn*- and *anti*-diols—**3a**,**b** in achiral solvents were found to be very similar to each other. Contrarily, their $\Delta\delta$ ($\Delta\delta = \delta_{(R,R)\text{-}\mathbf{2}} - \delta_{(S,S)\text{-}\mathbf{2}}$) behaviors in chiral bidentate NMR solvent (*R*,*R*)- and (*S*,*S*)-BMBA-*p*-Me (**2**) were found to be significantly different. On the basis of this NMR characteristic, a method has been developed to predict both the relative and absolute configurations of acyclic secondary 1,2-diols.

1. Introduction

We have advanced the concept and logic of a universal NMR database approach for assignment of the relative and absolute configuration of unknown compounds without degradation and/or derivatization work. The feasibility, reliability, and applicability of this approach was demonstrated through the stereochemical assignment of several classes of natural products.[2] Using a generalized molecule, we first outline the concept and logic used in the universal NMR database approach. Given an unmanageably complex structure such as the one in Figure 1, one would seek a way of breaking it into a collection of smaller molecules, solving their structures and assembling them to solve the structure of the original molecule.[3] However, as evident from the palytoxin case,[4] this approach would require extensive synthetic and degradation work, and our primary research goal has been to advance and develop the concept and logic for establishing the relative and absolute configuration of unknown compounds without degradation and/or derivatization work. The generalized molecule is composed of stereoclusters **A**–**E**, which are connected by a varying number of methylene bridges. We hypothesized, and experimentally demonstrated, that: (1) the structural properties of these stereoclusters are inherent to the specific stereochemical arrangement of the (small) substituents on the carbon backbone and (2) the structural properties of these stereoclusters are independent from the rest of molecule, when they are sufficiently separated from each other. Through the work on AAL toxins and maitotoxin,[5,6] we then put forward the guidelines for selecting imaginary sites to dissect a given large molecule to a collection of smaller stereoclusters. For the case of $n \geq 2$, primary steric and/or stereoelectronic interactions between functional groups X and Y can, at least at the first approximation,[1c,h] be ignored and therefore the structural moieties containing X and Y can be treated as independent stereoclusters. On the other hand, as primary steric and/or stereoelectronic

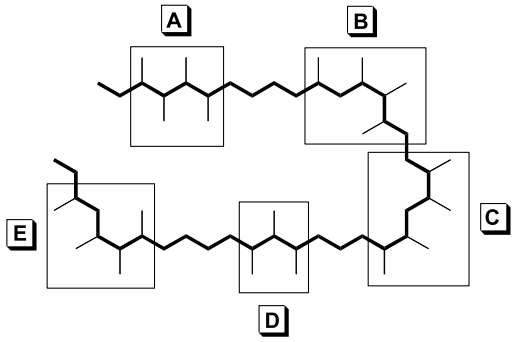
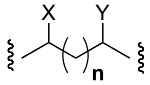


Figure 1. A generalized structure.



n = 0 or 1:
Primary steric and/or stereoelectronic interactions.
n = 2:
No primary steric and/or stereoelectronic interactions.

Figure 2. The guidelines for selecting an imaginary dissecting site.

Keywords: Relative configuration; Absolute configuration; Chiral NMR solvent; Diols.
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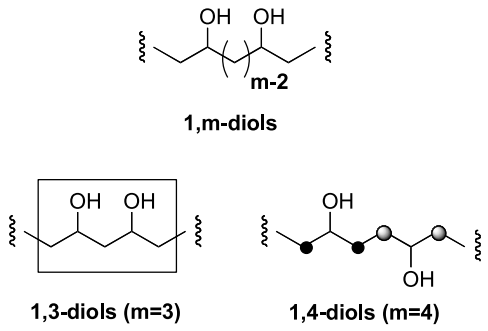

Figure 3. 1,*m*-Diols.

interactions between X and Y are significant for a case of $n=0$ or 1, the structural moiety containing X and Y needs to be treated as one stereocluster (Fig. 2).[1c,3]

Specifically related to the subject reported in this paper, we consider a generalized structure of 1,*m*-diols (Fig. 3). The guidelines suggest that the two alcoholic groups present in 1,3-diols ($m=3$) should be treated as one stereocluster, cf., the boxed structural moiety of 1,3-diols in Figure 3. We anticipated, and experimentally demonstrated, that the 1,3-diol stereocluster exhibits a unique NMR profile dependent on relative configuration in achiral solvents (DMSO-d_6 or CD_3OD). Importantly, the NMR profile of 1,3-*syn*-diols are significantly different from the NMR profile of 1,3-*anti*-diols, thereby allowing us to deduce the relative configuration of a given 1,3-diol.[1c] In principle, the NMR profiles in chiral NMR solvents contain not only the relative, but also absolute, stereochemical information. In practice, it was required to find a chiral NMR solvent(s) suitable for our purposes and, through an extensive search, we found that (*R*)- and (*S*)-DMBA (**1**, Fig. 4) meets our needs well.[1d–f] The NMR profiles of 1,3-*syn*- and 1,3-*anti*-diols in **1** are very similar to their corresponding NMR profiles in DMSO-d_6 or CD_3OD. Thus, these profiles can be used to predict the relative stereochemistry of 1,3-diols. As anticipated, the NMR profile observed for 1,3-*syn*-diols in (*R*)-DMBA is the mirror image of the NMR profile observed in (*S*)-DMBA and, importantly, the difference in the two profiles well exceeds the limit of measurement. Thus, these profiles can be used to predict the absolute configuration of 1,3-*syn*-diols.[1e,f] The NMR behaviors of 1,3-*anti*-diols in (*R*)- and (*S*)-DMBA are parallel to those described for 1,3-*syn*-diols.

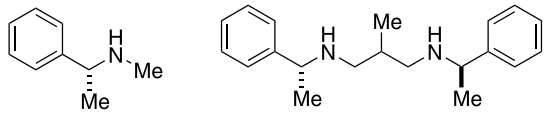

Figure 4. Chiral monodentate NMR solvent DMBA (**1**) and chiral bidentate NMR solvent BMBA-*p*-Me (**2**).

The guidelines summarized in Figure 1 suggest that the two alcoholic groups present in 1,4-diols (Fig. 3) can, at least at first approximation,[1c,h] be treated as two isolated mono-ols. Therefore, the stereochemistry of 1,4-diols can be established through deducing the absolute configuration of two isolated alcohols independently. We demonstrated that the absolute configuration of isolated secondary and tertiary

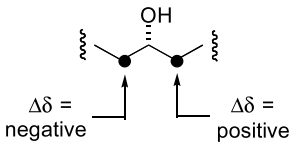

Figure 5. The ^{13}C chemical shift behaviors of saturated secondary alcohols in **2**.

alcohols can be established from analysis of the chemical shift behaviors of the adjacent carbons in bidentate chiral solvent (*R*,*R*)- and (*S*,*S*)-BMBA-*p*-Me (**2**) (Figs. 4 and 5).[1g,i] With this method, the absolute configuration of the left-side and right-side alcohols present in 1,4-diols can be deduced from analysis of the $\Delta\delta$ ($\Delta\delta=\delta_{(R,R)\text{-}\mathbf{2}}-\delta_{(S,S)\text{-}\mathbf{2}}$) behaviors of: (1) the adjacent two carbons marked by solid dots and (2) the adjacent two carbons marked by shadowed dots, respectively, in the chiral bidentate solvent **2**, thereby allowing us to establish the relative and absolute stereochemistries of 1,4-diols.[1g] In summary, the relative and absolute configurations of 1,*m*-diols, where $m\geq 4$, can also be established through the procedure given for 1,4-diols.

2. Results and discussion

With this background, we studied the NMR behaviors of 1,2-diols. The guidelines summarized in Figure 1 suggest that the 1,2-diol structural moiety should be treated as one stereocluster. We anticipated that, like 1,3-diols, 1,2-diols would exhibit unique NMR profiles dependent on their relative configuration. With this anticipation, we chose (4*R*,5*R*)-4,5-*syn*-diol **3a** and (4*R*,5*S*)-4,5-*anti*-diol **3b** (Fig. 6) and examined their ^{13}C, ^{1}H, and $^{1}H(OH)$ chemical shift profiles in DMSO-d_6.[1h] Table 1 summarizes the ^{13}C, ^{1}H, and $^{1}H(OH)$ chemical shifts observed for *syn*-**3a** and *anti*-**3b**. Based on these experimental data, the ^{13}C, ^{1}H, and $^{1}H(OH)$ chemical shift profiles were created by using a deviation in chemical shift for each nucleus of *syn*-**3a** or *anti*-**3b** from the average chemical shift of the nucleus in question. As seen from the graphs shown in Figure 7, *syn*-diol **3a** and *anti*-diol **3b** exhibited different profiles but the differences in the profiles are disappointingly small, thereby casting a doubt on their usefulness/dependability to predict the relative stereochemistry of 1,2-diols. We also paid attention to the

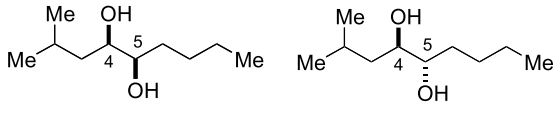

Figure 6. (4*R*,5*R*)-4,5-*syn*-diol **3a** and (4*R*,5*S*)-4,5-*anti*-diol **3b**.

Table 1. ^{13}C and ^{1}H chemical shifts of *syn*-**3a** and *anti*-**3b** in ppm in DMSO-d_6

		syn-**3a**	*anti*-**3b**
^{13}C-δ	C3	41.37	41.78
	C4	71.06	71.78
	C5	73.49	74.25
	C6	31.88	32.19
^{1}H-δ	H4	3.30	3.22
	H5	3.16	3.11
$^{1}H(OH)$-δ	OH4	4.10	4.16
	OH5	4.15	4.20

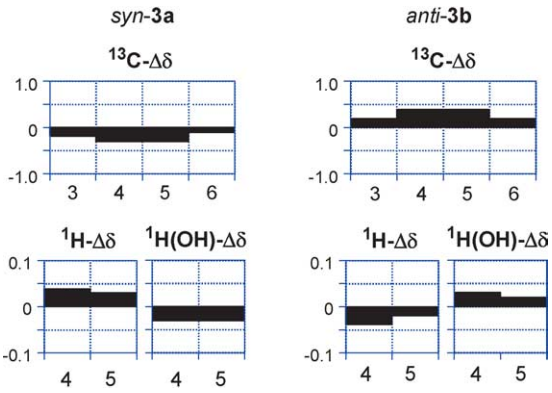

Figure 7. Difference in ^{13}C-δ, ^{1}H-δ, and ^{1}(OH)-δ between the average and the values for *syn*-**3a** and *anti*-**3b** in DMSO-d_6. The *x* and *y* axes represent carbon or proton number and $\Delta\delta=\delta_{each}-\delta_{ave}$ in ppm, respectively.

vicinal ^{1}H/^{1}H spin-coupling constants[1h] but found that both *syn*- and *anti*-diols **3a**,**b** exhibit the identical $^{3}J_{H4,H5}$ (4.9 Hz) in pyridine-d_5. Literature examples also reveal that the differences in the relevant $^{3}J_{H,H}$ of 1,2-*syn*- and 1,2-*anti*-diols are very small (typically less than 1.0 Hz) in polar solvents.[7] In summary, any one of the NMR profiles (^{13}C-δ, ^{1}H-δ, ^{1}H(OH)-δ, and $^{3}J_{H,H}$) in achiral solvents does not appear to provide a useful and dependable tool to predict the relative configuration of 1,2-diols.

Under this circumstance, we shifted our attention to the NMR database of 1,2-diols in chiral NMR solvents. As reported previously, an analysis of the ^{13}C chemical shift profiles observed in chiral monodentate NMR solvent **1** (Fig. 4) allows us to deduce the absolute, as well as relative, configuration of various structural motifs.[1d,e] Recognizing that 1,2-*syn*- and 1,2-*anti*-diols have an opposite combination of the absolute configuration at the two alcoholic centers, cf., **3a** and **3b**, we were interested in examining the usefulness of the NMR profiles in a chiral NMR solvent to predict the relative stereochemistry of 1,2-diols. Thus, we studied the ^{13}C chemical shift (^{13}C-δ) profiles of (4*R*,5*R*)-4,5-*syn*-diol **3a** and (4*R*,5*S*)-4,5-*anti*-diol **3b** in chiral monodentate NMR solvent (*R*)- and (*S*)-**1** but found that the differences in the ^{13}C-δ profiles were still small (Fig. 8).[8] We then turned our attention to their $\Delta\delta$ ($\delta_{(R)\text{-}\mathbf{1}}-\delta_{(S)\text{-}\mathbf{1}}$) behaviors and made interesting observations; (4*R*,5*R*)-*syn*-diol **3a** gave positive $\Delta\delta$ both at C4 ($\Delta\delta=+0.008$) and C5 ($\Delta\delta=+0.016$), whereas (4*R*,5*S*)-*anti*-diol **3b** gave positive and negative $\Delta\delta$ both at C4 ($\Delta\delta=+0.015$) and C5 ($\Delta\delta=-0.015$).[9] These observations were intriguing and encouraging but, in our view, the magnitudes of observed $\Delta\delta$ were still too small for our purposes. In order to boost the

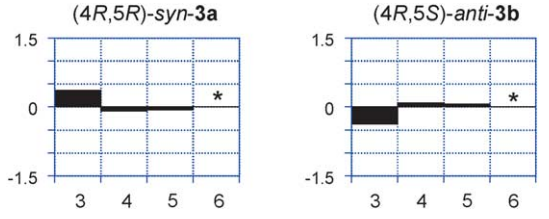

Figure 8. Difference in ^{13}C-δ between the average and the values for (4*R*,5*R*)-*syn*-**3a** and (4*R*,5*S*)-*anti*-**3b** in (*R*)-DMBA (**1**). The *x* and *y* axes represent carbon number and $\Delta\delta=\delta_{each}-\delta_{ave}$ in ppm, respectively. The ^{13}C-δ at C6 of **3a**,**b** indicated by an asterisk is hidden under the solvent signal.

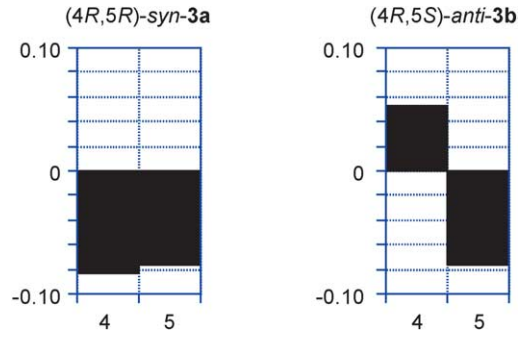

Figure 9. Difference in ^{13}C-δ of (4*R*,5*R*)-*syn*-**3a** and (4*R*,5*S*)-*anti*-**3b** between in (*R*,*R*)- and (*S*,*S*)-**2**/$CDCl_3$ (5/2 w/w). The *x* and *y* axes represent carbon number and $\Delta\delta=\delta_{(R,R)\text{-}\mathbf{2}}-\delta_{(S,S)\text{-}\mathbf{2}}$ in ppm, respectively.

magnitudes of $\Delta\delta$, we then tested chiral bidentate NMR solvent (*R*,*R*)- and (*S*,*S*)-**2**. Figure 9 presents the $\Delta\delta$ ($\delta_{(R,R)\text{-}\mathbf{2}}-\delta_{(S,S)\text{-}\mathbf{2}}$) behaviors of the two alcoholic carbons observed for 1,2-*syn*-diol **3a** and 1,2-*anti*-diol **3b** in bar graphs. These results deserve several comments. First, the observed magnitudes of $\Delta\delta$ are significantly boosted and are certainly large enough to use these profiles for establishing the relative stereochemistry of 1,2-diol stereoclusters. Second, as (4*S*,5*S*)-4,5-*syn*-diol (the antipode of **3a**) and (4*S*,5*R*)-4,5-*anti*-diol (the antipode of **3b**) should give a mirror image of the graphs shown in Figure 9, respectively, these $\Delta\delta$ profiles can be used for establishing the absolute configuration of 1,2-*syn*-diols and 1,2-*anti*-diols. Third, the $\Delta\delta$ behavior of **3a** in a 5:2 mixture of **2** and pyridine-d_5 was found to be almost identical with the $\Delta\delta$ behaviors in a 5:2 mixture of **2** and $CDCl_3$, except that the magnitudes of $\Delta\delta$ in the former solvent system are smaller than those in the latter solvent system. However, they are still large enough for our purposes. Forth, to test the trend in the $\Delta\delta$ behaviors observed on **3a** and **3b**, (3*R*,4*R*)-3,4-*syn*-**4a** and (3*R*,4*S*)-3,4-*anti*-**4b** were synthesized and subjected to NMR studies, thereby demonstrating their $\Delta\delta$ profiles shown in Figure 10 to be very similar to those in Figure 9. Lastly, we have used ^{13}C-δ profiles in both achiral and chiral solvents to predict the relative configuration of unknown compounds. However, this is the first example in which the $\Delta\delta$ behaviors in

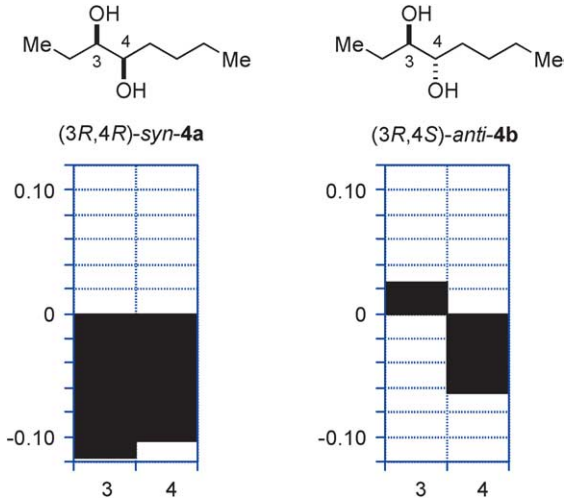

Figure 10. Difference in ^{13}C-δ of (3*R*,4*R*)-*syn*-**4a** and (3*R*,4*S*)-*anti*-**4b** between in (*R*,*R*)- and (*S*,*S*)-**2**/$CDCl_3$ (5/2 w/w). The *x* and *y* axes represent carbon number and $\Delta\delta=\delta_{(R,R)\text{-}\mathbf{2}}-\delta_{(S,S)\text{-}\mathbf{2}}$ in ppm, respectively.

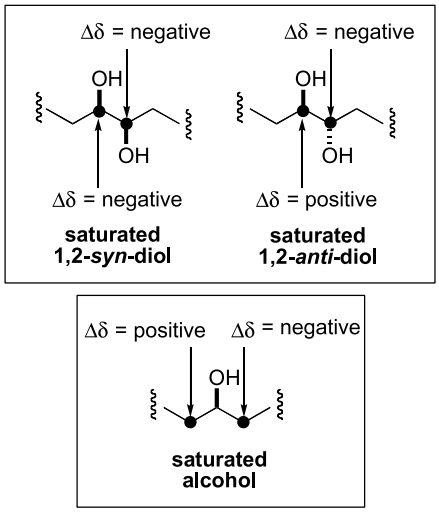

Figure 11. Empirical behavior of the signs of ^{13}C-$\Delta\delta$ for saturated 1,2-*syn*-diol and 1,2-*anti*-diol and that for saturated alcohol in (*R*,*R*)- and (*S*,*S*)-**2**. $\Delta\delta = \delta_{(R,R)\text{-}\mathbf{2}} - \delta_{(S,S)\text{-}\mathbf{2}}$.

chiral solvents are useful for predicting the relative configuration.

The $\Delta\delta$ behaviors observed for saturated 1,2-*syn*-diol and 1,2-*anti*-diol in chiral bidentate NMR solvent (*R*,*R*)- and (*S*,*S*)-**2** are summarized in Figure 11. 1,2-*syn*-Diols exhibit a $\Delta\delta$ profile with both alcoholic carbons having the same sign, whereas 1,2-*anti*-diols exhibit a $\Delta\delta$ profile with both alcoholic carbons having opposite signs. The signs of $\Delta\delta$ profiles are correlated with their absolute configuration. Intriguingly, we recognized a possible correlation between the $\Delta\delta$ behaviors of 1,2-diols with the $\Delta\delta$ behaviors of isolated secondary alcohols (Fig. 11).[1g] With two assumptions: (1) the two alcohols of 1,2-diols are independently recognized by bidentate chiral solvents (*R*,*R*)- and (*S*,*S*)-**2** and (2) the empirical rule developed for isolated mono-ols is applicable for analysis of 1,2-diols, we would predict the $\Delta\delta$ for the left- and right-side alcoholic carbons to be (predominantly) affected by the right- and left-side alcohols, respectively. Interestingly, the trend in the $\Delta\delta$ behaviors observed for 1,2-diols is consistent with this prediction. This picture is very speculative, and we need further experimental work to entertain such a proposal. Nonetheless, we make three additional comments. First, we have previously proposed a cyclic hydrogen-bonded network for recognition of an isolated alcohol by the chiral bidentate NMR solvent **2**, and it may not be totally unreasonable to suggest such a recognition mode for the two alcohols independently. Second, with these assumptions, we would expect that the $\Delta\delta$ behaviors of the C3 and C6 carbons of **3a** and **3b** are correlated to the absolute configuration of C4 and C5 alcohols, respectively, and the observed results are consistent with this prediction.[10] Third, the $\Delta\delta$ behaviors found for 1,3-diols in the chiral bidentate NMR solvent **2** are not inconsistent with this analysis.[1g]

3. Conclusion

In summary, we have, for the first time, demonstrated that the relative and absolute configurations of saturated secondary 1,2-diol stereocluster can be deduced by use of the ^{13}C-$\Delta\delta$ behaviors in chiral bidentate NMR solvent (*R*,*R*)- and (*S*,*S*)-BMBA-*p*-Me (**2**). We are currently extending the reported method to saturated and unsaturated secondary 1,2-diol stereoclusters as well as saturated tertiary 1,2-diol stereoclusters.

4. Experimental

4.1. General procedures and methods

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 spectrometer and a Mercury 400 spectrometer, respectively. The residual solvent-signal [^{1}H NMR spectrum: 2.49 ppm (DMSO-d_6), 7.19 ppm (pyridine-d_5); ^{13}C NMR spectrum: 39.5 ppm (DMSO-d_6), 123.5 ppm (pyridine-d_5)] was used as the internal reference for the measurement in achiral solvents. The residual solvent-signal of co-solvents ($CDCl_3$: 77.0 ppm; pyridine-d_5: 123.5 ppm) was used as the internal reference and a lock-signal for the measurement in BMBA-*p*-Me/$CDCl_3$ (350 mg/140 mg) or BMBA-*p*-Me/pyridine-d_5 (350 mg/140 mg) with readout of NMR spectral being adjusted to 0.001 ppm/point (sw=23,980.8, fn=524,288). Analytical thin chromatography (TLC) was performed with E. Merk pre-coated TLC plates, silica gel, 60F-254, layer thickness 0.25 mm. Flash chromatography separations were performed on E. Merk kieselgel 60 (230–400) mesh silica gel, or on Silica (KP-Sil) by Biotage, Inc. Horizon™ HPFC System. Reagents and solvents were commercial grade and were used as supplied. All reactions were conducted under an argon or nitrogen atmosphere. Reaction vessels were oven-dried and cooled under an inert atmosphere. [2*R*,2(1*R*)]- and [2*R*,2(1*S*)]-2-(1-benzyloxy-pentyl)-oxiranes **5a**, **b** were prepared by the procedure reported in Ref. 11 and silica-gel chromatographic separation of the intermediate [4*R*,4(1*RS*)]-4-(1-benzyloxy-pentyl)-2,2-dimethyl-[l,3]dioxolane.

4.1.1. (4*R*,5*R*)-2-Methyl-nonane-4,5-diol 3a. 2-Propenyl magnesium bromide was prepared from 2-bromo-propen (242 μl, 2.72 mmol) and magnesium turnings (66.2 mg, 2.72 mmol) in THF (3.5 ml) at 0 °C–rt. CuI (259 mg, 1.36 mmol) was added to the suspension of 2-propenyl magnesium bromide at 0 °C and the reaction mixture was stirred at 0 °C for 15 min. [2*R*,2(1*R*)]-**5a** (100 mg, 0.454 mmol) in THF (1 ml) was added to the mixture and the reaction was stirred at 0 °C for 30 min. The reaction mixture was quenched by aqueous ammonium chloride. The mixture was extracted by ether (3 ml×3) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered through Celite, and evaporated in vacuo. The crude product was purified by silica-gel chromatography (0–8% Et_2O/hexane) to give pure (4*R*,5*R*)-4,5-dibenzyloxy-2-methyl-non-1-ene **6a** (105 mg, 66%). To a suspension of 20% Pd$(OH)_2$ on charcoal (10 mg) in ethanol (1 ml), **6a** (105 mg, 0.298 mmol) in ethanol (1 ml) was added under Ar atmosphere. The atmosphere was replaced by hydrogen and the reaction mixture was stirred vigorously for 5 h. The mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by silica-gel chromatography (30% AcOEt/hexane) to give pure (4*R*,5*R*)-**3a**

(52 mg, quant.). ^{1}H NMR (DMSO-d_6) δ 4.15 (5-OH), 4.10 (4-OH), 3.30 (H.4), 3.16 (H.5); (pyridine-d_5) δ 3.88 (H.4, $^3J_{H.4,H.5}$=4.9 Hz), 3.74 (H.5, $^3J_{H.4,H.5}$=4.9 Hz). ^{13}C NMR (DMSO-d_6) δ 73.487 (C.5), 71.060 (C.4), 41.366 (C.3), 31.877 (C.6); (pyridine-d_5) δ 75.094 (C.5), 72.599 (C.4), 43.154 (C.3), 33.757 (C.6); [(*R*,*R*)-BMBA-*p*-Me/$CDCl_3$] δ 73.230 (C.5), 70.826 (C.4), 42.148 (C.3); [(*S*,*S*)-BMBA-*p*-Me/$CDCl_3$] δ 73.306 (C.5), 70.909 (C.4), 42.087 (C.3); [(*R*,*R*)-BMBA-*p*-Me/pyridine-d_5] δ 74.973 (C.5), 72.523 (C.4), 43.542 (C.3); [(*S*,*S*)-BMBA-*p*-Me/pyridine-d_5] δ 75.003 (C.5), 72.561 (C.4), 43.526 (C.3). LR-MS (EI) *m*/*z* 197.7 $(M+Na)^+$.

4.1.2. (4*R*,5*S*)-2-Methyl-nonane-4,5-diol 3b. (4*R*,5*S*)-4,5-Dibenzyloxy-2-methyl-non-1-ene **6b** (97 mg, 61%) was prepared from [2*R*,2(1*S*)]-**5b** (100 mg, 0.454 mmol) by following the same procedure for [2*R*,2(1*R*)]-**5a** with 2-propenyl magnesium bromide (2.72 mmol) in THF and CuI (259 mg, 1.36 mmol). (4*R*,5*S*)-**6b** (97 mg, 0.277 mmol) was hydrogenated by 20% $Pd(OH)_2$ on charcoal (10 mg) in ethanol (2 ml) in same procedure for (4*R*,5*R*)-**6a** and the crude product was purified by silica-gel chromatography (30% AcOEt/hexane) to give pure (4*R*,5*S*)-**3b** (48 mg, quant.). ^{1}H NMR (DMSO-d_6) δ 4.20 (5-OH), 4.16 (4-OH), 3.22 (H.4), 3.11 (H.5); (pyridine-d_5) δ 3.99 (H.4, $^3J_{H.4,H.5}$=4.9 Hz), 3.89 (H.5, $^3J_{H.4,H.5}$=4.9 Hz). ^{13}C NMR (DMSO-d_6) δ 74.246 (C.5), 71.781 (C.4), 41.775 (C.3), 32.188 (C.6); (pyridine-d_5) δ 75.655 (C.5), 73.137 (C.4), 42.388 (C.3), 33.051 (C.6); [(*R*,*R*)-BMBA-*p*-Me/$CDCl_3$] δ 73.526 (C.5), 71.205 (C.4), 39.857 (C.3), 30.672 (C.6); [(*S*,*S*)-BMBA-*p*-Me/$CDCl_3$] δ 73.602 (C.5), 71.152 (C.4), 39.842 (C.3), 30.695 (C.6). LR-MS (EI) *m*/*z* 197.5 $(M+Na)^+$.

4.1.3. (4*R*,5*R*)-Octane-3,4-diol 4a. To a suspension of CuI (259 mg, 1.36 mmol) in ether (2 ml), MeLi (1.6 M, 2.72 mmol) in ether was added at 0 °C. The mixture was stirred at 0 °C for 10 min. [2*R*,2(1*R*)]-**5a** (100 mg, 0.454 mmol) in ether (2 ml) was added to the mixture and the reaction was stirred at 0 °C for 30 min. The reaction mixture was quenched by aqueous ammonium chloride. The mixture was extracted by ether (3 ml×3) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered through Celite, and evaporated in vacuo. The crude product was purified by silica-gel chromatography (0–10% Et_2O/hexane) to give pure (3*R*,4*R*)-3,4-dibenzyloxyoctane **7a** (87 mg, 59%). To a suspension of 20% $Pd(OH)_2$ on charcoal (10 mg) in ethanol (1 ml), **7a** (87 mg, 0.266 mmol) in ethanol (1 ml) was added under Ar atmosphere. The atmosphere was replaced by hydrogen and the reaction mixture was stirred vigorously for 5 h. The mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by silica-gel chromatography (30% AcOEt/hexane) to give pure (4*R*,5*R*)-**4a** (39 mg, quant.). ^{1}H NMR [(*R*,*R*)-BMBA-*p*-Me/$CDCl_3$] δ 74.080 (C.3), 72.354 (C.4), 25.747 (C.2); [(*S*,*S*)-BMBA-*p*-Me/$CDCl_3$] δ 74.197 (C.3), 72.457 (C.4), 25.709 (C.2). LR-MS (EI) *m*/*z* 169.4 $(M+Na)^+$.

4.1.4. (4*R*,5*S*)-Octane-3,4-diol 4b. (3*R*,4*S*)-3,4-Dibenzyloxyoctane **7** (230 mg, 57%) was prepared from [2*R*,2(1*S*)]-**5b** (270 mg, 1.22 mmol) by following the same procedure for [2*R*,2(1*R*)]-**5a** with MeLi (4.6 ml, 7.36 mmol) in ether and CuI (700 mg, 3.68 mmol). (4*R*,5*S*)-**7b** (230 mg, 0.705 mmol) was hydrogenated by 20% $Pd(OH)_2$ on charcoal (20 mg) in ethanol (3 ml) in same procedure for (4*R*,5*R*)-**7b** and the crude product was purified by silica-gel chromatography (30% AcOEt/hexane) to give pure (4*R*,5*S*)-**4b** (103 mg, quant.). ^{1}H NMR [(*R*,*R*)-BMBA-*p*-Me/$CDCl_3$] δ 74.709 (C.3), 72.908 (C.4), 30.817 (C.6); [(*S*,*S*)-BMBA-*p*-Me/$CDCl_3$] δ 74.683 (C.3), 72.973 (C.4), 30.806 (C.2). LR-MS (EI) *m*/*z* 169.6 $(M+Na)^+$.

Acknowledgements

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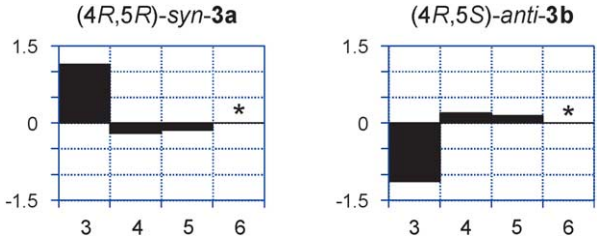
References and notes

1. (a) Lee, J.; Kobayashi, Y.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2177–2180. (b) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2181–2184. (c) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562–2571. (d) Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2245–2248. (e) Hayashi, N.; Kobayashi, Y.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2249–2252. (f) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2253–2255. (g) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* **2002**, *4*, 411–414. (h) Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379–14393. (i) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Tetrahedron Lett.* **2003**, *44*, 7489–7491.
2. For the desertomycin/oasomycin class of natural products, see: (a) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 4279–4281. (b) Tan, C.-H.; Kobayashi, Y.; Kishi, Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 4282–4284. (c) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, *123*, 2076–2078. For mycolactones A and B, see: (d) Benowitz, A. B.; Fidanze, S.; Small, P. L.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, *123*, 5128–5129. (e) Fidanze, S.; Song, F.; Szlosek-Pinaud, M.; Small, P. L.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10117–10118. For tetrafibricin, see: (f) Kobayashi, Y.; Czechtizky, W.; Kishi, Y. *Org. Lett.* **2003**, *5*, 93–96.
3. Kishi, Y. *Tetrahedron* **2002**, *58*, 6239–6258.
4. (a) Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W. Jr.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, 104, 7369–7371 and the preceding papers. (b) Kishi, Y. *Current Trends in Organic Synthesis (IUPAC)*; Pergamon: Oxford, 1983; pp 115–130.
5. (a) Boyle, C. D.; Harmange, J.-C.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4995–4996. (b) Boyle, C. D.; Kishi, Y. *Tetrahedron Lett.* **1995**, *36*, 5695–5698 and references cited therein.
6. (a) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946–7968. (b) Cook, L. R.; Oinuma, H.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 7928–7937.
7. For examples, see: (a) Oikawa, H.; Matsuda, I.; Ichihara, A.; Kohmoto, K. *Tetrahedron Lett.* **1997**, *35*, 1223–1226. (b) Kugel, C.; Lellouche, J.-P.; Beaucourt, J.-P.; Niel, G.; Girard, J.-P.; Rossi, J.-C. *Tetrahedron Lett.* **1989**, *30*, 4949–4950.

8. As seen from the graphs shown below, the ^{13}C-δ profile differences between **3a** and **3b** in **2** are more noticeable than those in **1**, thereby suggesting a possibility that these differences could be useful for our purposes. However, we have not yet explored this possibility.



Difference in ^{13}C-δ between the average and the values for *syn*-**3a** and *anti*-**3b** in (*R*,*R*)-BMBA-*p*-Me (**2**). The *x* and *y* axes represent carbon number and $\Delta\delta=\delta_{each}-\delta_{ave}$ in ppm, respectively. The ^{13}C-δ at C.6 of **3a**,**b** indicated by an asterisk is hidden under the solvent signal.

10. The ^{13}C-$\Delta\delta$ profile of a symmetric 1,2-*anti*-diol stereocluter in (*R*)- and (*S*)-DMBA (**1**) was reported in Ref. 1f.
11. The C3 carbon of **3a** and the C3 and C6 carbons of **3b** exhibited $\Delta\delta=+0.061$, $+0.015$ and -0.023, respectively. However, because of the overlapping with solvent signals, we were unable to establish the $\Delta\delta$ for the C6 carbon of **3a**.
12. Mori, K.; Otsuka, T.; Oda, M. *Tetrahedron* **1994**, *40*, 2929–2934.

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Corrigendum

Corrigendum to "Synthetic studies on bradykinin antagonist martinellines: construction of a pyrrolo[3,2-*c*]quinoline skeleton using silicon-tether RCM reaction and allylic amination" [Tetrahedron 60 (2004) 9381]

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Available online 19 October 2004

The formal synthesis of martinelline by a very different route to that we described has been previously published[2g] and should be cited in the References on page 9390.

References

2. (g) Takeda, Y.; Nakabayashi, T.; Shirai, A.; Fukumoto, D.; Kiguchi, T.; Naito, T. *Tetrahedron Lett.* **2004**, *45*, 3481–3484.

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