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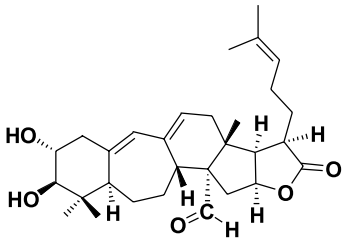
Contents

REPORT

ARTICLES



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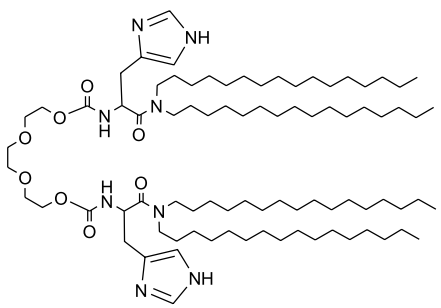
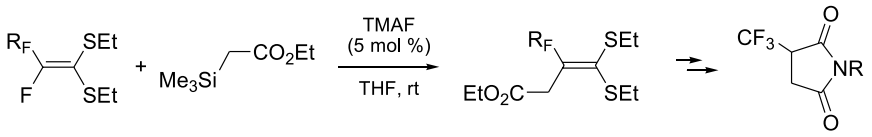
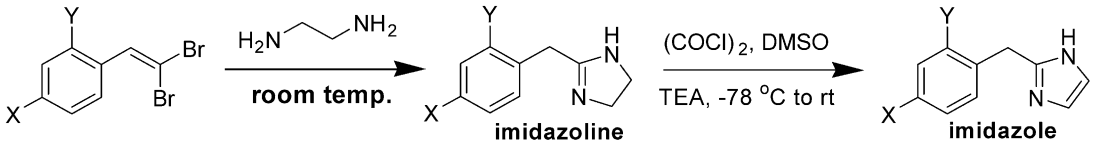
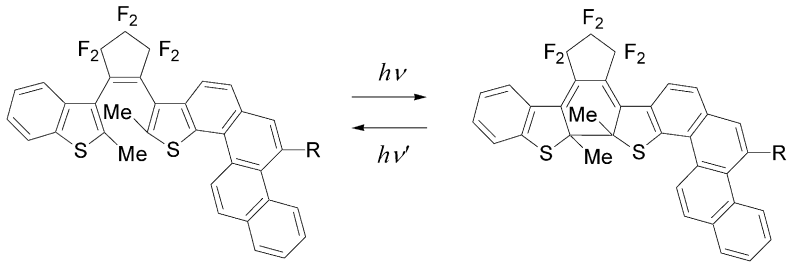
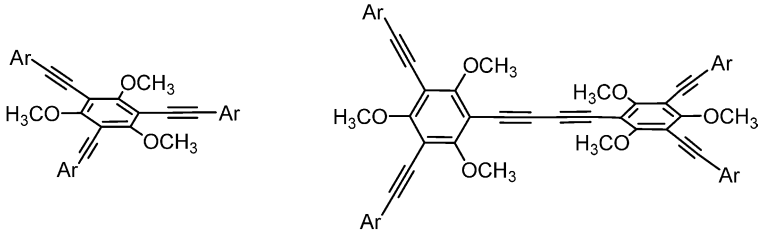
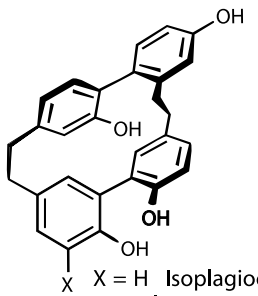


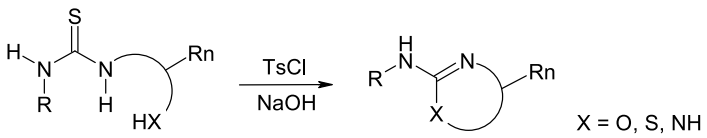


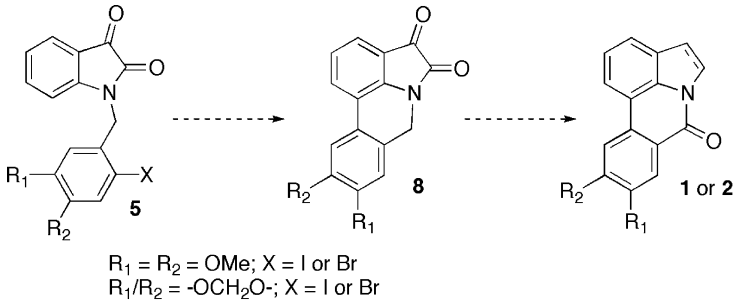


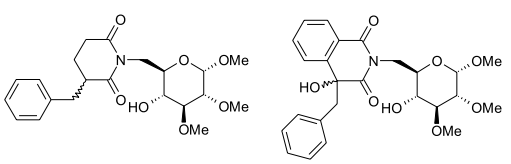


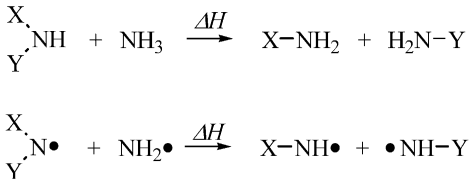


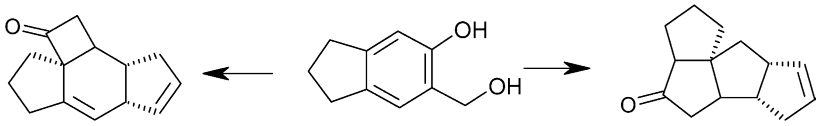


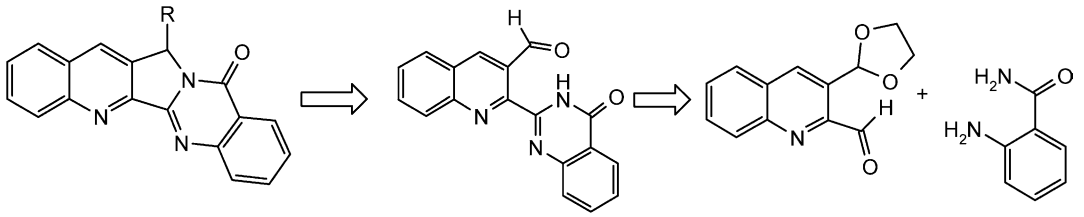


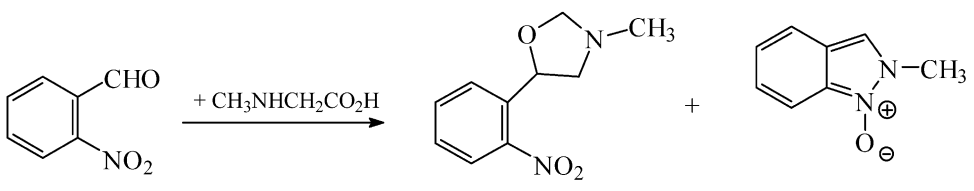




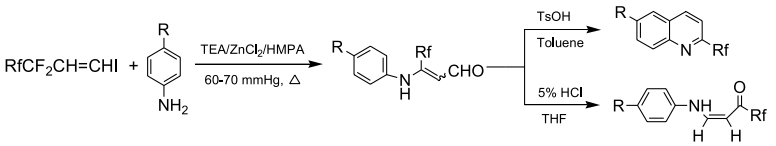


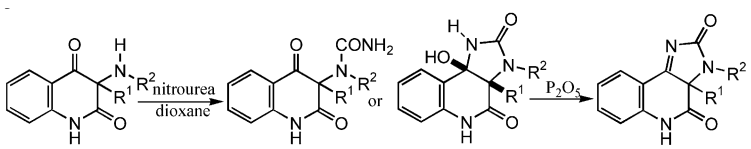


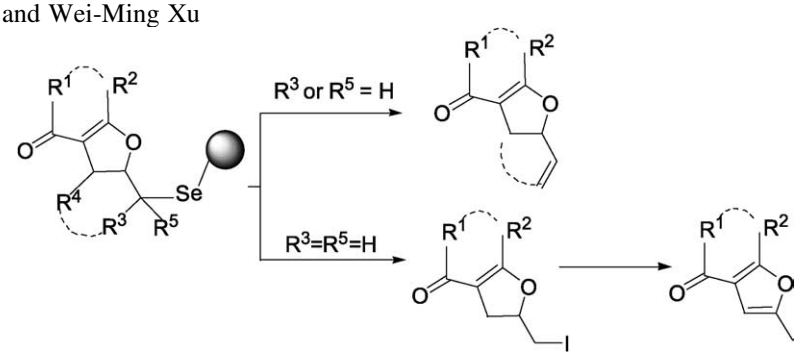


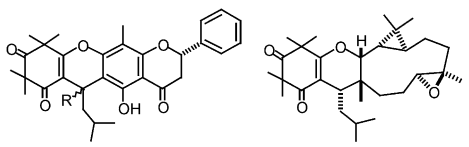


1a **5a** (43 %) **7a** (40 %)

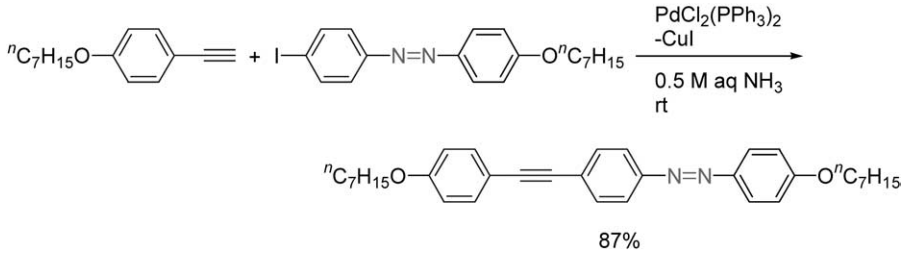


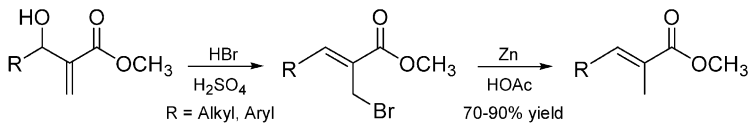






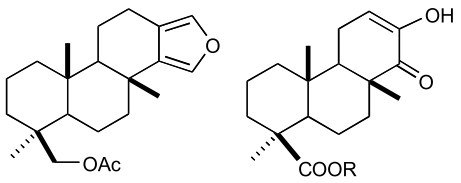
Three novel compounds, kunzeanones A–C (**1**–**3**) were isolated from the dried leaves of *Kunzea ambigua* (Myrtaceae), and their structures were characterized on the basis of spectroscopic analyses. The stereochemistries of kunzeanones A and B were established by X-ray chrystallographic analysis.



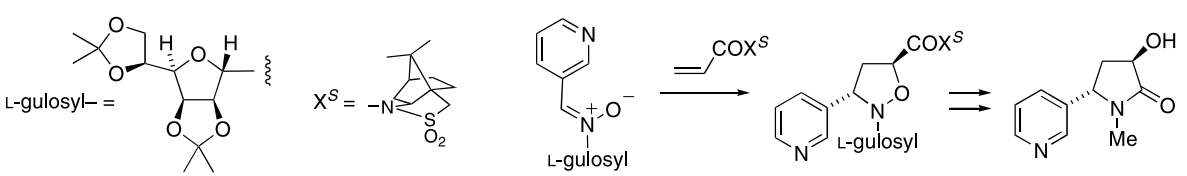


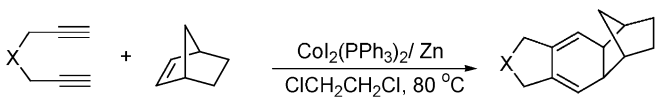
(*E*)-2-Methylacrylates are easily prepared by zinc-promoted reduction of 2-(bromomethyl)alkenoates derived from Baylis–Hillman adducts. Synthesis of the male ant pheromone (*E*)-2,4-dimethyl-2-hexenoic acid was performed using this simple methodology.

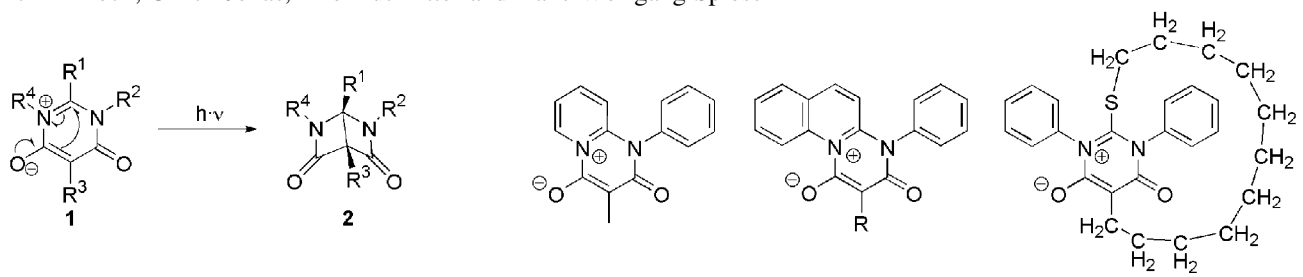
Bioassay-directed fractionation of a $CHCl_3$ extract of an unidentified sponge of the family Demospongiae resulted in the isolation of the new diterpenoid **1**, the new bis-norditerpenoids **2**–**3**, and two known compounds. All the isolated compounds were weak inhibitors of the lyase activity of DNA polymerase β.



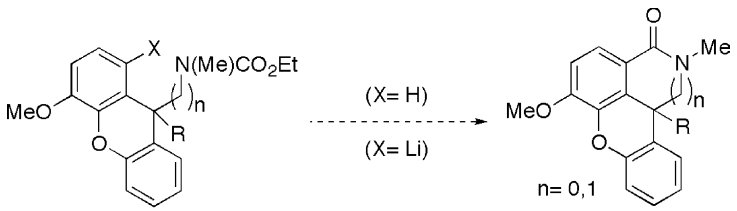
1 **2** R = CH_3 **3** R = H

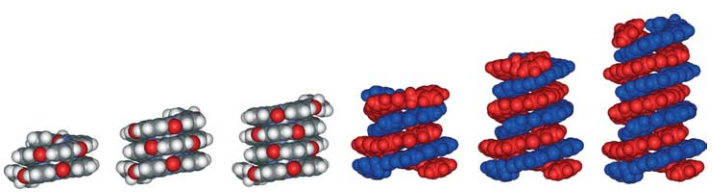


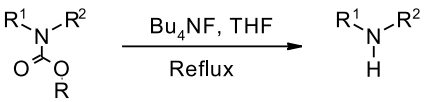




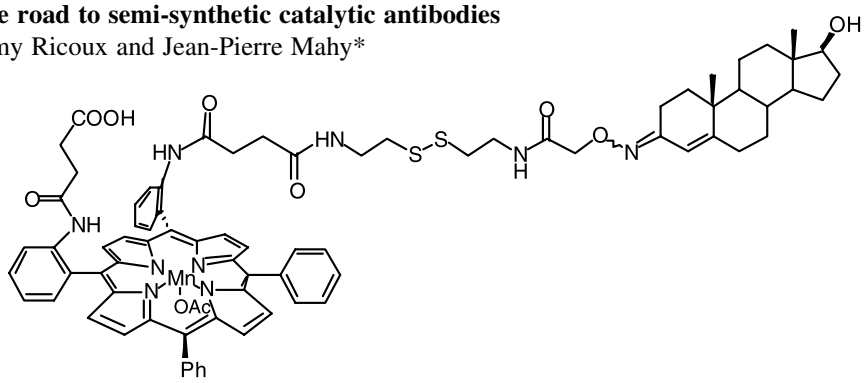
The synthesis and photochemical behavior of polycyclic and macrocyclic mesoions is investigated.

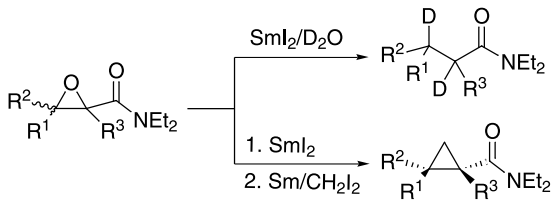


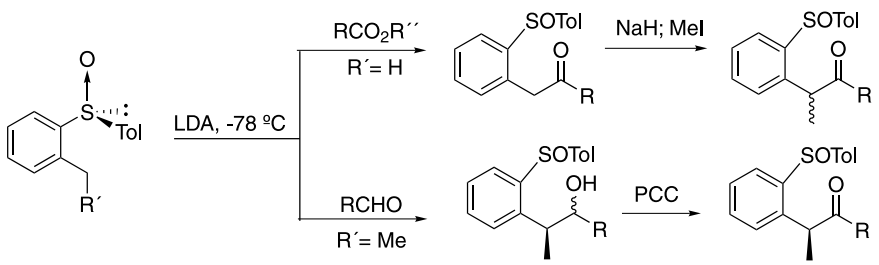


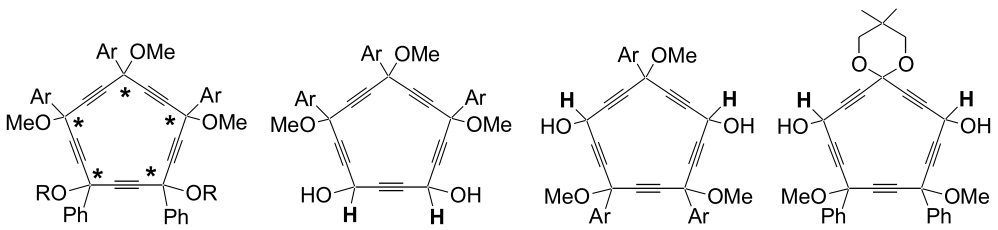


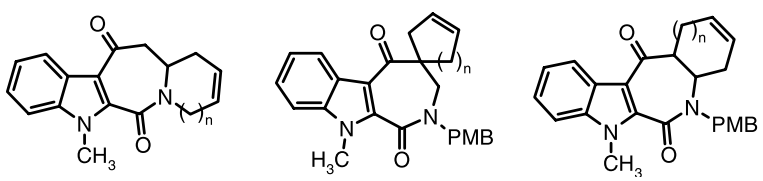
R = Me, Et, t-Bu, benzyl, allyl, phenyl
R^1 = Alkyl, aryl
R^2 = H, alkyl, aryl

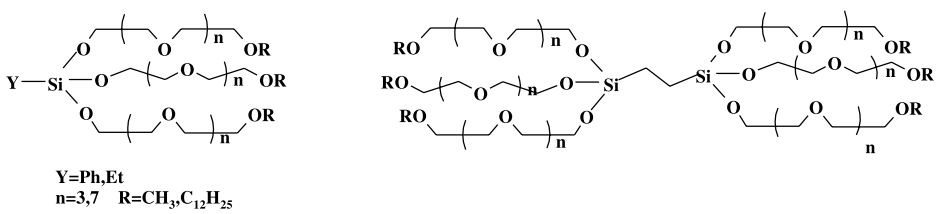












OTHER CONTENTS

*Corresponding author
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When the Pauson–Khand and Pauson–Khand type reactions go awry: a plethora of unexpected results

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Dedicated with appreciation and utmost respect to Professor Peter L. Pauson for his outstanding and pioneering contributions to the field of Organometallic Chemistry

Contents

1. Introduction

The synthesis of cyclopentenones is most frequently achieved via an organometallic approach. The widely studied route, the Pauson–Khand reaction (PKR), incorporates three components in a formal [2+2+1] cycloaddition process—an alkene, an alkyne and a carbon monoxide molecule—with the aid of cobalt carbonyl complexes.[1–15]

Keywords: Cyclopentenones; Pauson–Khand reaction; Alkyne; Cycloaddition.

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Discovered using $Co_2(CO)_8$, this transformation can now be promoted by complexes of titanium, zirconium, molybdenum, tungsten, iron, ruthenium, rhodium, nickel and iridium (Pauson–Khand-type reactions). These reactions continue to be investigated extensively, now reaching a level unimaginable when cyclopentenone formation was first reported by Pauson and co-workers in 1971.[14,16,17] The scope of the reaction has broadened, catalysis has been achieved, milder reactions have been developed and its application in organic synthesis has been realized. The impetus originates from its high value in transforming simple components into the synthetically useful cyclopentenone unit, in which a high degree of molecular complexity can be achieved in a single step, with impressive stereochemical and regiochemical control.

Interestingly, a multitude of compounds and unconventional results have also been observed, yet attracted less attention. For example, alternative pathways in the PKR mechanistic manifold, or reactions of starting unsaturated groups and PK cycloadducts have led to side products, such as dienes, monocyclic enones, saturated ketones, and cyclopropanes. Stereo- and regiochemical outcomes that are atypical in the PKR have also been reported. With this information in hand, we felt that a comprehensive review of these results is essential and timely. Similar unexpected observations noted under the PK-type cyclizations have also been included.

This work, covering the period from 1971 to mid-2004, is intended to complement recent reviews on the PKR, and to increase awareness of the potential for discovering more exciting and unexpected results under these conditions. Having been overlooked for a long time, and essentially left out of all previous reviews, an organized compilation of such accounts can serve as a primary guide on this subject. Some of these reactions have now been explored and developed into useful synthetic methods. Depending on the researcher's desired outcome, we believe that this review can serve as a useful reference to other possible reactions that can occur with the PKR. Finally, of equal importance are the solutions commonly used to minimize, if not eliminate the formation of these side products, and promote the formation of the PKR cycloadduct, that are found in this review.

2. Pauson–Khand reaction

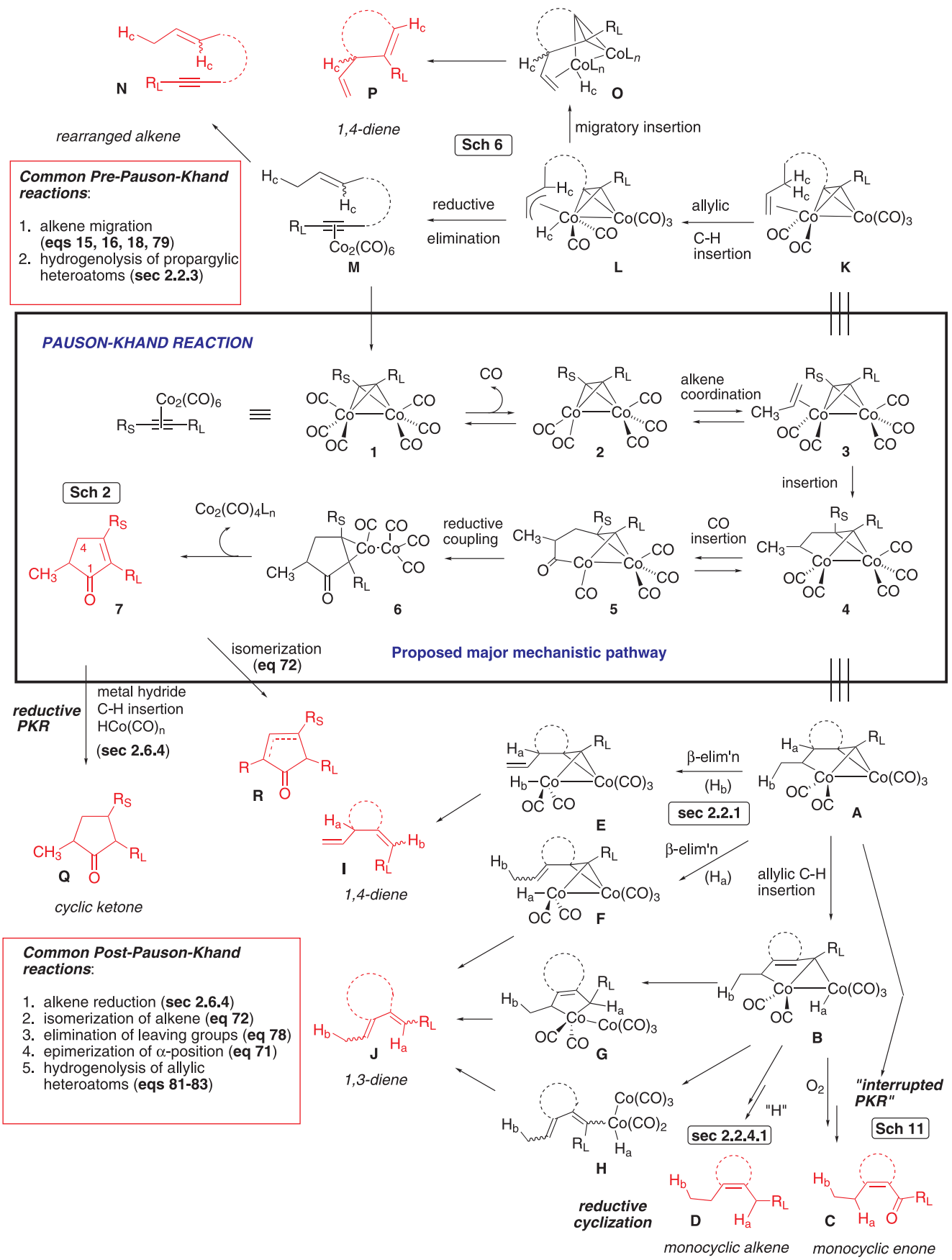
The Pauson–Khand cyclopentenone formation was itself an unexpected finding that was discovered while attempting to synthesize new organometallic complexes.[14,16,17] Following this initial finding, numerous unanticipated new organic and organometallic compounds have since been identified as products derived from Pauson–Khand reaction conditions, thus adding to the excitement of investigating this reaction. These unexpected results include: (a) formation of dienes and alkenes, (b) isomerization of the alkene moiety in the starting material and in the cyclopentenone adduct, (c) Diels–Alder reactions, (d) hydrogenolysis, (C–heteroatom bond reduction), (e) ionization of propargylic alcohols, (f) formation of other products, such as monocyclic enones, arenes, cyclopropyl ketones and other ketonic products, (g) cycloisomerization, (h) a metallo-ene reaction, (i) homocoupling of terminal alkynes, (j) reduction of alkynes to alkenes, (k) formation of other organometallic complexes, (l) dry state adsorption conditions inducing PKR, (m) formation of cyclopentanones, (n) tandem reactions, and (o) unusual stereo- and regiochemical outcomes in the PKR adduct.

2.1. Proposed mechanism

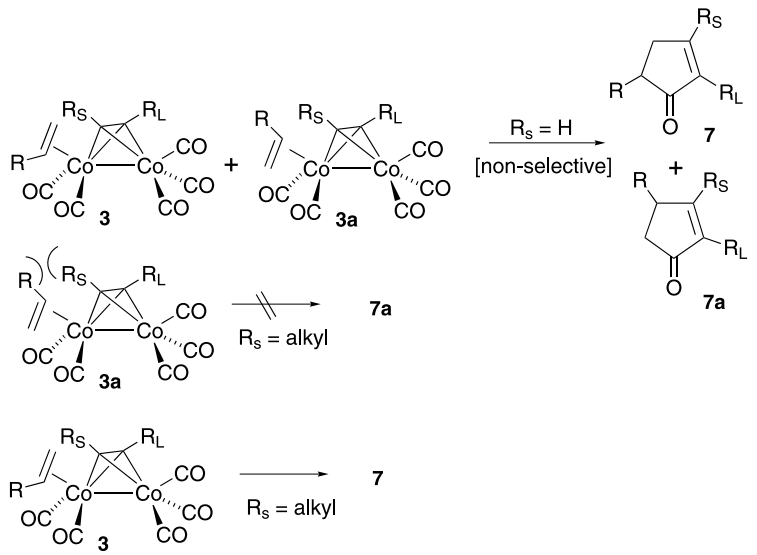
Depicted in Scheme 1 is the widely accepted mechanistic pathway proposed by Magnus[18–20] and Schore[21] for the stoichiometric Pauson–Khand reaction. Although no direct evidence has been provided for intermediates beyond **2**, the current level of mechanistic understanding accommodates only the main experimental observations, and is inferred from the regio- and stereochemistry observed in the products.[6] These observations include characterization of isolable alkyne–$Co_2(CO)_6$ complexes **1**, an isolable pentacarbonyl complex **2** stabilized by chelation of a bishomopropargylic-sulfide group,[22–25] and an intercepted intermediate **4**.[26] According to this proposal, the reaction involves five main steps from the initial complex **1**: (a) decarbonylation of **1**, (b) coordination of an olefin onto a coordinatively unsaturated cobalt center in **2**, (c) insertion of the π-complexed olefin into a Co–C bond, (d) insertion of CO into a Co–C sp^3 bond, and (e) reductive elimination and subsequent loss of a dicobaltcarbonyl fragment to give the final cyclopentenone **7**.

Loss of CO from **1** to form a coordinatively unsaturated complex **2** can be achieved thermally, photochemically, oxidatively, or by ultrasonication. Subsequent irreversible insertion of the complexed face of the alkene π bond into one of the formal Co–C bonds of complex **3** gives **4**. This step is believed to be both rate- and product-determining,[6] and can be used to explain the regiochemistry with respect to both the alkyne and alkene in the intermolecular version, where the incipient C–C bond is most susceptible to steric crowding. For unsymmetrical alkynes (both terminal and internal), insertion and C–C bond formation occur exclusively at the alkyne carbon bearing the smaller substituent, R_S (**3** to **4**). As a consequence, the larger substituent of the alkyne, R_L, always ends up at C2 of the cyclopentenone ring. In contrast, regiochemistry with respect to the alkene component is generally less predictable (Scheme 2). In reactions with terminal alkynes, monosubstituted alkenes generally lead to a 1:1 mixture of regioisomeric cyclopentenones. However, reactions of monosubstituted alkenes with internal alkynes lead to the 2,3,5-trisubstituted isomer as the major product. Recent reports have further suggested that Lewis bases as additives facilitate decarbonylation and stabilize putative intermediates along the reaction pathway.[27–30]

Further understanding of the mechanistic interpretation of the Pauson–Khand reaction have also incorporated theoretical studies, which have led to practical models for predicting the diastereoselectivity of the cycloaddition.[25,31–40] A composite of some of the major mechanistic pathways that have been proposed to account for the formation of unusual by-products is summarized in Scheme 1. These pathways include mechanistic diversions that occur prior to, during or after PK cycloaddition.



Scheme 1. Major mechanistic pathways and diversions observed under Pauson–Khand reaction conditions.



Scheme 2.

2.2. Alternative pathways

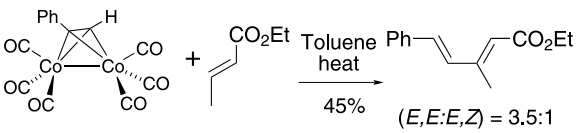
Accounts of other products derived from reactions occurring under the Pauson–Khand reaction conditions can generally be classified according to the following:

(a) Other modes of reactions of the presumed metallacycles in the PK mechanistic manifold, with the exclusion of CO insertion, for example, β-hydride elimination, reductive and oxidative cyclizations, cycloisomerization, carbene insertion, and cobalt-mediated ene and Diels–Alder reactions;
(b) Reduction of alkynes and heteroatom functionalities in the propargylic or resulting allylic position;
(c) Isomerization of the alkene moiety, either before or after cycloaddition;
(d) Tandem reactions, with and without the PKR; and
(e) Other reactions of alkynes, for example, diyne coupling reaction and aminocarbonylation.

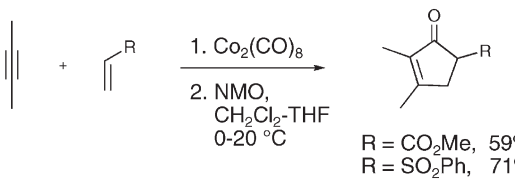
Secondary reactions, such as epimerization α to the carbonyl, cyclotrimerization, co-trimerization and formation of other heterocycles (spirofuran, cyclopentadienone, and bifurandiones) are also discussed. Some of these reactions have already been exploited to understand the mechanism of the transformation, and optimized to be synthetically useful.

2.2.1. Diene formation. Examination of the proposed mechanism shows that other pathways are readily available to cobaltacyclopentene intermediate **4**, besides insertion of carbon monoxide, which could potentially generate products other than the cyclopentenone (Scheme 1). When the structure or nature of the substrate and/or reaction conditions permit, the most common divergent pathway involves β-elimination to give 1,3- or 1,4-dienes from the metallacyclic intermediate.[41–44] Under thermal conditions, either the presence of polarizing groups on the alkene or alkyne, or a high degree of substitution in the enyne can destabilize the metallacycle and favor β-elimination to provide dienes (Scheme 1: **A→F→J**, 1,3-diene; **A→E→I**, 1,4-diene).

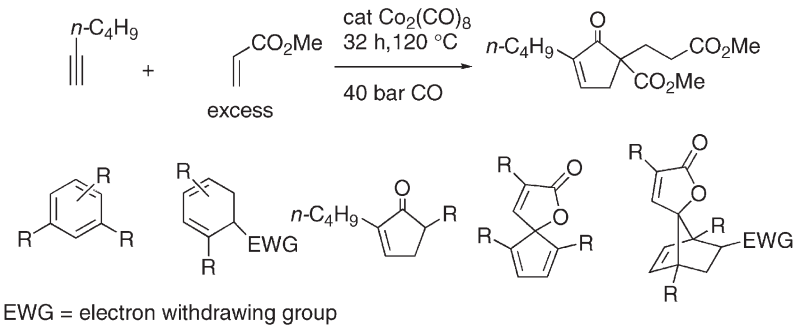
The first surprise was from the Pauson group, where conjugated 1,3-dienes were obtained from attempted thermal cycloadditions of activated alkenes with dicobalthexacarbonyl-complexed alkynes (Eq. 1).[45] The dienes were formed highly regioselectively, with the alkene activating group and the alkyne substituent oriented at the terminal positions of the resulting 1,3-diene. The putative metallacyclic intermediate **4** apparently underwent β-elimination instead of CO insertion under these conditions (Scheme 1). However, it was shown that promotion of the reaction under mild conditions using amine oxides, diene formation from some activated alkenes can be prevented in favor of an intermolecular PKR (40–70% yields, Eq. 2).[46] In other cases, even these mild conditions still led to the exclusive formation of a 1,3-diene,[47] for example, from an enyne bearing a modestly polarized alkyne group (Eq. 3).[48] Yet when the cyclization in Eq. 3 was conducted under mild conditions at 0 °C diene formation was minimized, yielding the PK cycloadduct and the diene in a 2:1 ratio in 84% yield.[49]



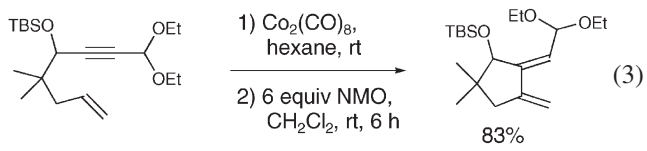
(1)



(2)

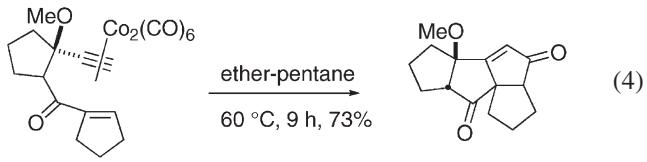


Scheme 3.



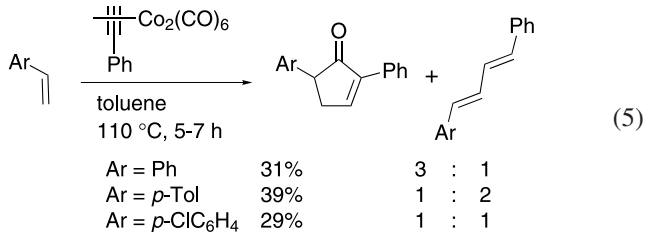
(3)

However, when the alkene substitution pattern prevents β-elimination, an activated alkene can undergo an intramolecular PKR (Eq. 4).[50] Under 40 bar of CO pressure, cyclopentenones were isolated in moderate yields when using an excess of the activated alkene (Scheme 3). The enone also underwent a subsequent Michael addition due to the presence of excess alkene. Numerous interesting by-products, the nature of which depended on the substituent on the alkyne, were also isolated in 3–35% yields. It was speculated that the Michael addition occurred at the stage of the metallacyclic intermediate after carbonyl insertion.[51]



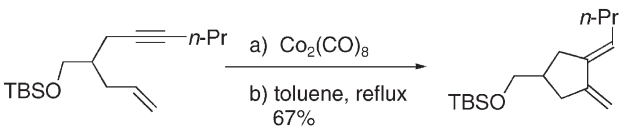
(4)

In addition to PK cycloadducts, 1,3-dienes were generated from the PKR of substituted styrenes (Eq. 5).[1–3,52–57] The cycloaddition is highly regioselective, with the 2,5-disubstituted regioisomer being formed as the exclusive cyclopentenone product. The relationship between chemoselectivity and electronic nature of the arene is not supported by the experimental evidence, and there is also no consistent pattern of reactivity.



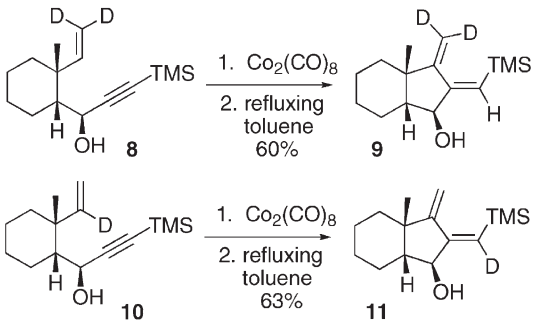
(5)

In the heteroatom-directed thermal intermolecular Pauson–Khand reactions dienes were isolated at elevated temperatures (e.g., 110 °C).[58] Consequently, the thermolysis of hexacarbonyldicobalt complexes of unactivated 1,6- and 1,7-enynes in refluxing toluene was developed into a general synthetic route, yielding monocyclic 1,3-dienes with a number of different substrates in 50–70% yields (Eq. 6).[59]



(6)

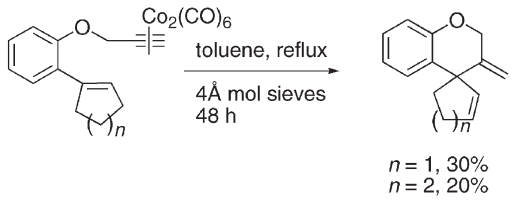
The origin of 1,3-diene formation was studied in an attempt to elucidate its mechanism. It is generally accepted that the PK cycloadduct and the corresponding diene arise from the same metallacyclic intermediate **A** (Scheme 1: **A→F→J**; **A→B→H** or **G→J**). In addition, the β-elimination route was speculated to occur via direct removal of the hydrogen adjacent to the M–C bond (**A→F**) or via an allylic C–H insertion (**A→B**) followed by rearrangement.[59,60] The latter pathway is preferred due to the conformational restraint associated with a β-elimination in the five-membered metallacycle **A**. Deuterium labeling studies suggested a β-elimination rather than an α-elimination mechanistic manifold (Scheme 4).[59] Lack of deuterium scrambling in the cyclization of enyne **8**, and the exclusive migration of deuterium in the cyclization of **10** indicated a β-elimination mechanistic manifold.



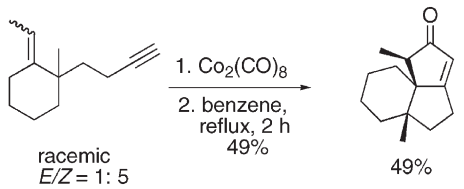
Scheme 4.

Steric requirements of substituents on or adjacent to the alkene or alkyne also presented reactivity problems preventing the formation of the PK cycloadduct. While some sterically congested enynes managed to give PK cycloadducts, in spite of the presence of steric bulk, a number of them have reacted via alternative reaction pathways under the forcing conditions generally required for metallacycle formation.[61] In one case, a 1,4-diene was formed rather than the 1,3-diene due to the quaternary center in the incipient diene (Eq. 7). It was speculated that the steric demand imposed by the quaternary center in this

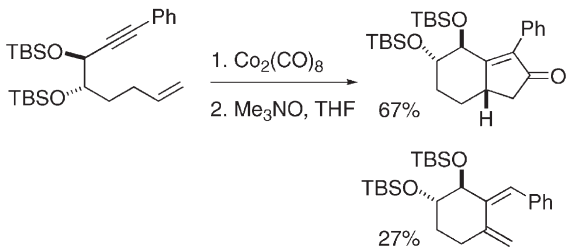
substrate favored an elimination process. On the other hand, quaternary centers in cyclopentenones were successfully formed in a number of cases using the PK reaction (Eq. 8).[62,63] In the cyclization of 1,7-enynes bearing bulky groups on the tether, 1,3-dienes were generated along with bicyclo[4.3.0]nonanones, when using amine-oxides as promoters of the reaction (Eq. 9).[64]



(7)

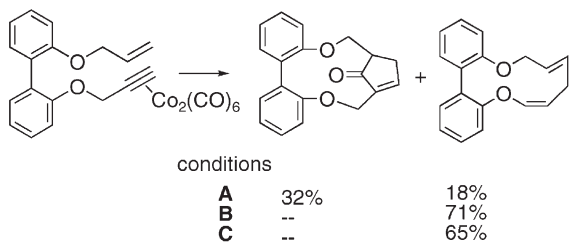


(8)



(9)

1,4-Dienes were also obtained in the NMO-promoted cyclizations of 1,11-enynes templated on a 2,2′-biphenol scaffold. A 1.6:1 ratio of the 11-membered bridged enone and 12-membered diene macrocycle was obtained from these reactions (Eq. 10).[65] Interestingly, the 1,4-diene was generated exclusively, and in higher yields, under the thermal conditions with and without the addition of cyclohexylamine. Formation of the 1,4-diene presumably arises from β-elimination of the intermediate cobaltacycle, with elimination occurring to yield a stable enol ether (Scheme 1: **A→E→I**).

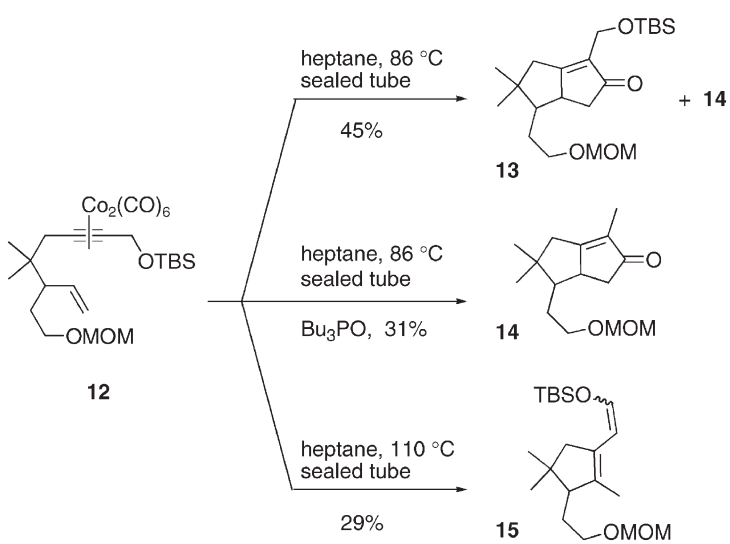


A: 0.01 M CH_2Cl_2, 6 equiv NMO, N_2, rt; **B**: 0.01 M toluene, N_2, 65 °C; **C**: 0.003 M 1,2-DCE, 10 equiv of cyclohexylamine, Ar, 85 °C.

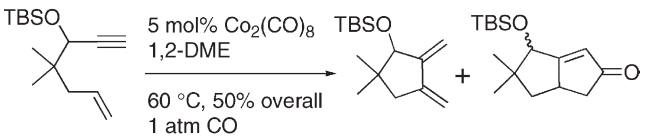
(10)

Among the reaction conditions tried for the cyclization of enyne **12**, to generate a key intermediate in the synthesis of quadrone, the classical thermal conditions led to the desired adduct **13**, albeit in only 45% yield (Scheme 5).[20] Surprisingly, under these conditions enyne **12** also yielded products of C–O bond reduction **14**, in addition to the anticipated PK adduct **13**. In the attempts to optimize the formation of adduct **13**, reaction conditions using higher temperature or promoters only led to elimination to give enol ether **15** or C–O bond reduction to yield enone **14**.

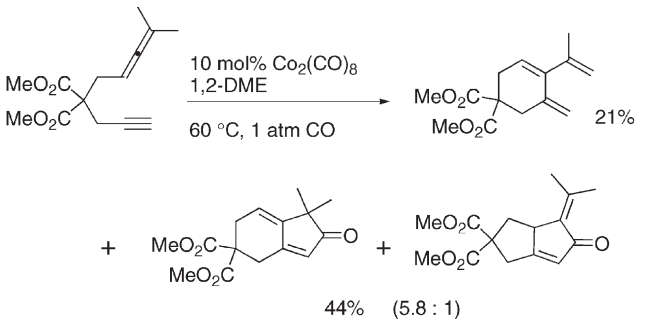
Moreover, diene formation was observed under catalytic Pauson–Khand conditions, where the formation of 1,3-dienes, in addition to the desired PK product was noted (Eq. 11).[66] Under the same catalytic conditions, however, an allenyne furnished a 1,4-diene, in addition to the PK products in a 1:2 ratio (Eq. 12).[66] Interestingly, the use of the solvent mixture, CF_3CH_2OH/1,2-DME (2:1), or an (alkylthio)alkyne moiety eliminated the problem of competing diene formation.[66]



Scheme 5.

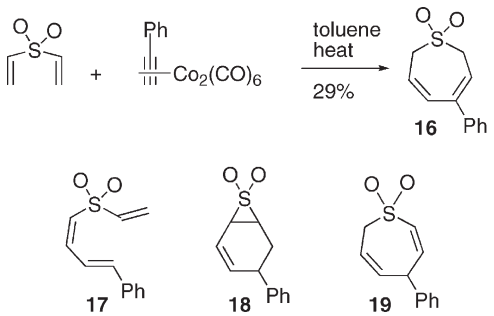


(11)



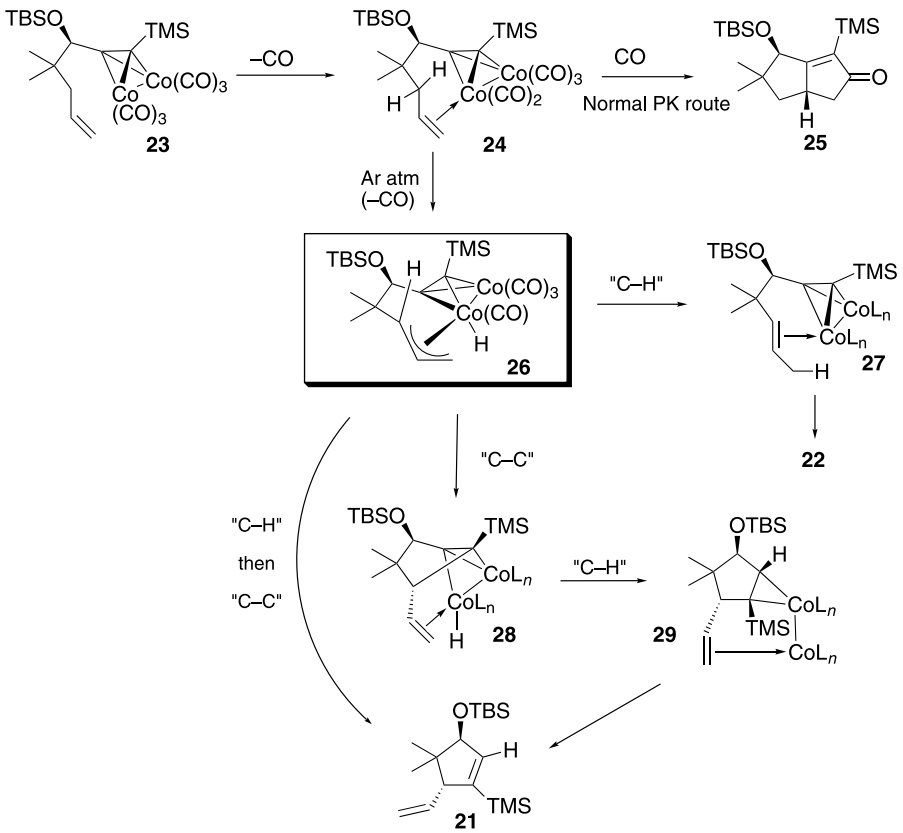
(12)

Finally, having shown that alkenes bearing electron-withdrawing groups yielded dienes, Pauson attempted to extend the reaction to the use of divinyl sulfone as an alkene partner. A 1:1 cycloadduct, cyclic sulfone **16**, was formed instead of the expected triene **17** (Eq. 13).[67] It was speculated that sulfone **16** arose from triene **17**, which underwent an intramolecular Diels–Alder cycloaddition to yield bicyclic sulfone **18**. Opening of the three-membered sulfone ring accompanied by a hydrogen shift gave **19**, which isomerized to the observed product **16**.[67]



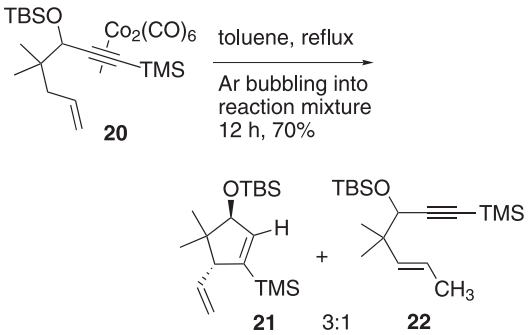
(13)

2.2.2. Alkene isomerization. Transition metals are well known to promote double bond migrations. Cobalt carbonyl complexes are no exception, where isomerizations of alkenes prior to the PKR have been observed. Thermolysis of the dicobalthexacarbonyl complex of a sterically encumbered 1,6-enyne, with argon bubbling through the reaction mixture, resulted in a remarkable cobalt-mediated allylic C–H activation followed by a formal 5-*endo-dig* cyclization to yield diene **21** as the major product (Eq. 14).[68] Double bond migration in the starting 1,6-enyne–$Co_2(CO)_6$ complex also generated a 1,5-enyne **22**, which was unreactive towards cyclization. Both alkene isomerization and the unusual rearrangement were speculated to be derived from a common intermediate **26** as shown in Scheme 6 (cf. Scheme 1, **K→L→M→N** and **K→L→O→P**, respectively). The normal PK cycloadduct arises via metallacycle formation from **24**, a process driven by CO saturation, otherwise, the sterically encumbered substrate undergoes an allylic C–H insertion generating cobalt



Scheme 6.

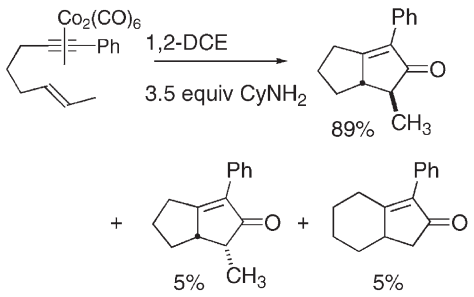
hydride **26**. Partitioning of this complex between reductive elimination to form a C–H bond (leading to **22**, Scheme 6) and migratory insertion to form a C–C bond (leading to **21**, Scheme 6) accounts for the two observed products. Deuterium labeling studies support the formation of proposed intermediate **26**.



(14)

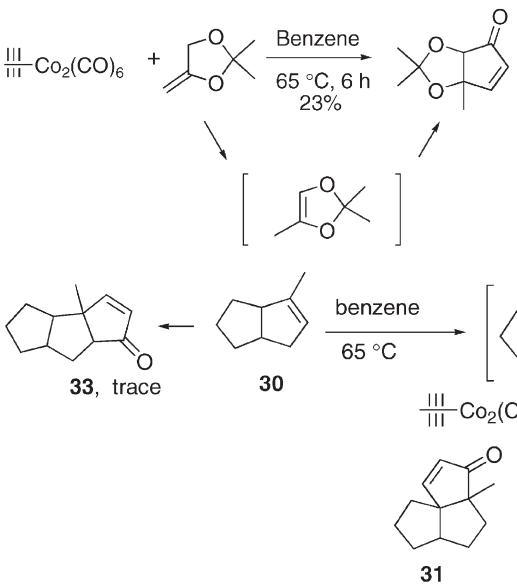
This interesting series of reactions is limited to a specific group of sterically hindered substrates as numerous bulky enynes undergo PKR's in the absence of a CO atmosphere. Internal alkynes other than trialkylsilicon- or trialkylgermanium-substituted yielded complex mixtures of products under these reaction conditions. A comparison of enynes, where the alkyne substituent was modified from carbon to silicon and to germanium, suggested that an inductive effect influencing the electron density on the cobalt is an important product-determining factor. This novel cycloisomerization was extended to the highly diastereoselective formation of 2*H*,5*H*-dihydrofurans using trimethylsilyl-substituted alkynes, with *t*-butyl hydroperoxide (TBHP) as an additive under an atmosphere of air.[69] Monocyclic alkenes were likewise generated from the thermolysis of enyne–$Co_2(CO)_6$ complexes in a non-coordinating solvent under a H_2 atmosphere (Section 2.2.4.1).

In the cyclization of a 1,6-enyne, bicyclo[3.3.0]octenone and an unexpected bicyclo[4.3.0]nonenone product were formed (Eq. 15).[28] The latter product is presumably derived from the 1,6-enyne, which had isomerized to the 1,7-enyne, although the mechanism for the isomerization prior to cyclization was not probed. Isomerization from a 1,7-enyne to a 1,6-enyne prior to cycloaddition was likewise observed.[28] In an attempt to generate a bicyclo[5.3.0] ring system from a 1,8-enyne, double bond migration occurred to generate the corresponding 1,7-enyne, which underwent a normal Pauson–Khand cyclization.[70]



(15)

Rearrangements of strained alkenes under PK reaction conditions are also common. Thermal reaction of benzvalene resulted in its rearrangement to benzene. The desired adduct was formed in 30–45% yields under promotion by amine oxides at ambient temperature.[71,72] Double bond migration to form more substituted alkenes also occurred in a number of cases. Pauson and co-workers detected a shift of an *exo* methylene double bond into a five-membered ring under PK conditions to yield the product of cycloaddition across a trisubstituted alkene (Eq. 16).[73] In triquinane syntheses via PKR, double bond migrations transforming tri- to tetrasubstituted alkenes were also observed,[73] yielding the angularly fused triquinanes **31** and **32**, instead of the desired linear isomer **33** (Eq. 17). While rearrangement to the more substituted alkene isomer is not surprising, it is rare and truly remarkable that the tetrasubstituted isomer even underwent the intermolecular Pauson–Khand cycloaddition.

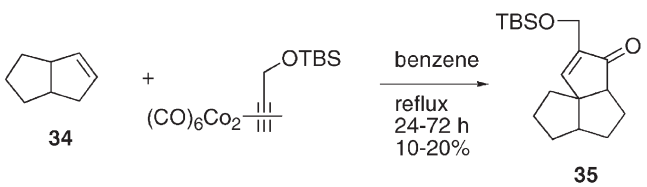


(16)

stoichiometric: excess alkene: **31** + **32**, (7%)
catalytic: CO, excess alkene, alkyne: **31** + **32**, (24%)

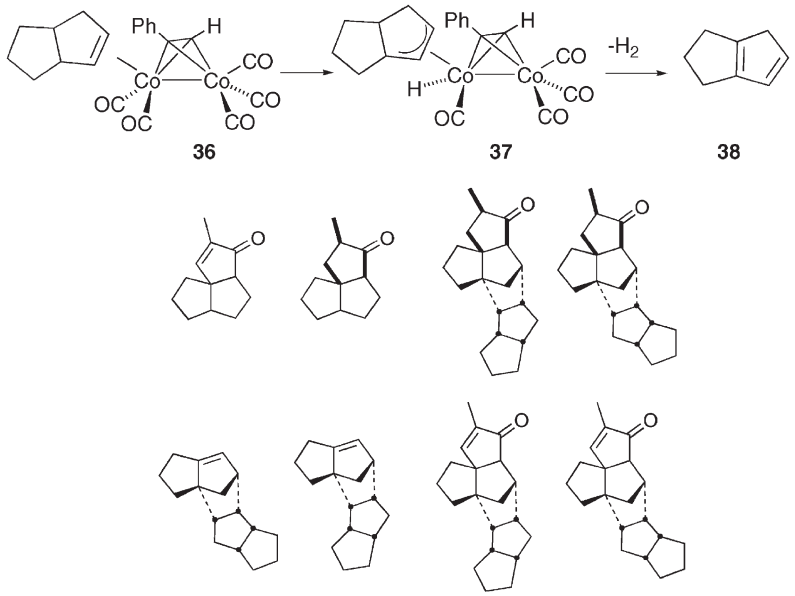
(17)

A similar migration in a less substituted diquinane homolog was also observed (Eq. 18).[74] Reaction of **34** with an excess of the alkyne cobalt complex gave rise to the angularly fused triquinane **35** as a single regioisomer. At higher reaction temperatures a multitude of other products was isolated, which were speculated to arise from diene **38**, generated from alkene isomerization via cobalt hydride **37** (Scheme 7). The organocobalt hydride species **37** was presumably generated from an allylic C–H insertion in complex **36** (Scheme 1, **K→L**). Further Diels–Alder reactions, PK processes and 1,4-reductions of the final enones account for the formation of the unexpected products (1–40% yields of each, depending on the conditions used).



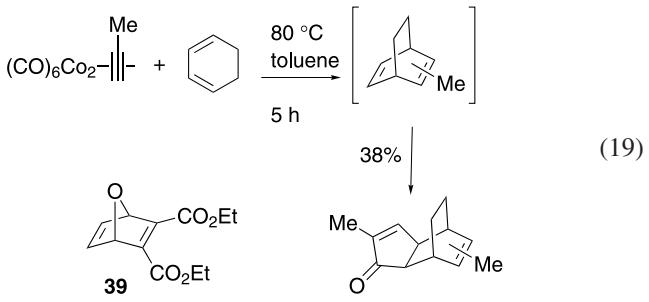
(18)

During an investigation of other types of alkenes that could undergo cycloaddition with an alkyne complex, Pauson found that cyclohexa-1,3-dienes gave tricyclic ketones in which 2 equiv. of the alkyne moiety had been incorporated



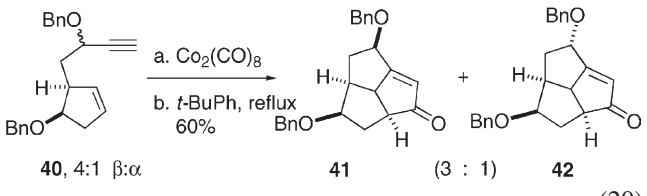
Scheme 7.

(Eq. 19).[14,75] It was speculated that a Diels–Alder reaction initially occurred giving rise to a bicyclo[2.2.2]octadiene, with the less substituted alkene undergoing an intermolecular PKR. Since cyclohexa-1,3-dienes do not undergo thermal Diels–Alder reactions under comparable conditions, the cobaltcarbonyl complex must therefore promote the initial cycloaddition. Additionally, the bicyclooctadiene was not isolable suggesting that the PK reaction was faster than the Diels–Alder reaction. In contrast, the oxygen-bridged alkene **39** did not undergo a PK reaction under these conditions, but underwent deoxygenation to yield diethylphthalate as the sole product. When subjected to the identical reaction conditions, cyclohexa-1,4-diene yielded the same tandem Diels–Alder/PK adduct. The initial cobalt carbonyl complex is also believed to promote the isomerization. 1,4-Dihydroanisole and 1,4-dihydromesitylene did not undergo isomerization under the reaction conditions.

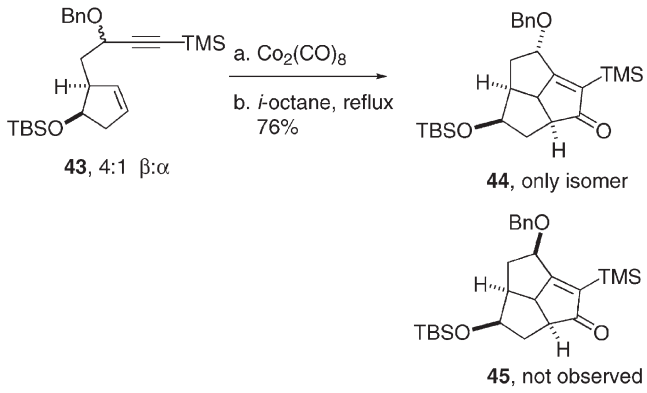


(19)

2.2.3. Ionization and hydrogenolysis of propargylic groups. Hexacarbonyldicobalt-complexed propargylic ethers are susceptible to ionization due to the stabilization of the resulting cation imparted by the cobalt-complexed alkyne moiety.[76] An unusual example of cation stabilization is associated with epimerization at the propargylic center during a PK cycloaddition.[77] Thermal reaction of a 4:1 mixture of enyne **40**, bearing a terminal acetylene, led to PK products where the initial isomer ratio at the propargylic carbon was essentially unchanged (Eq. 20). However, cyclization of a 4:1 mixture of **43**, with an internal alkyne, led to the exclusive formation of a single enone isomer **44**, in which the propargylic position was epimerized (Eq. 21). These results are best explained by considering steric strain in the transition states leading to the diastereomeric products. In the case of the disubstituted alkyne, it was speculated that there is significant steric strain in the transition state caused by the *endo*-oriented propargylic benzyl ether that inhibits the cycloaddition. This provides an opportunity for isomerization at the propargylic position providing the less hindered *exo* isomer (α), which then undergoes cycloaddition. Since steric strain is greatly reduced with the terminal alkyne, both starting isomers proceeded directly to the observed products with minimal epimerization.

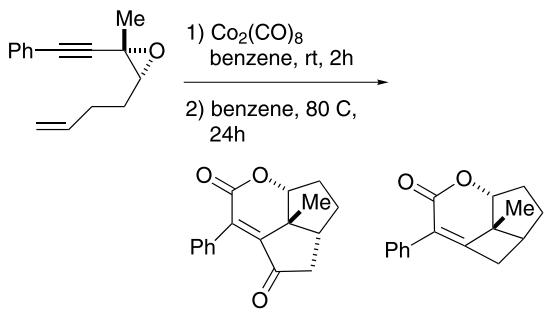


(20)



(21)

Thermolysis of a dicobalthexacarbonyl-complexed enyne bearing a *cis*-epoxide conjugated with the alkyne, under an

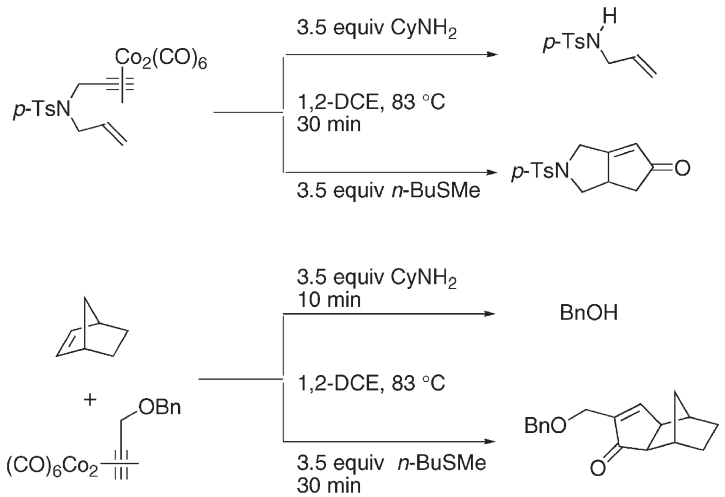


Scheme 8.

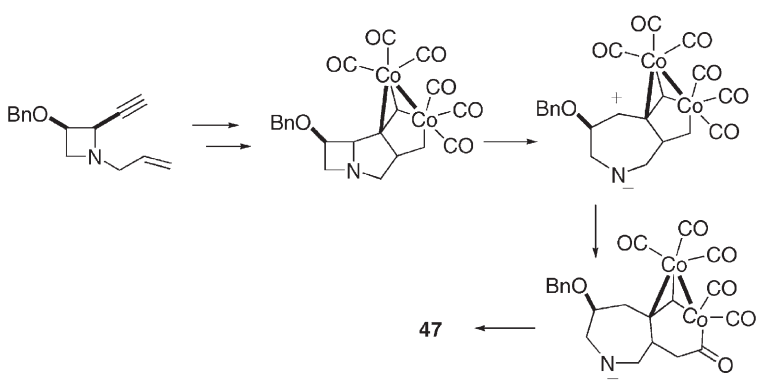
atmosphere of carbon monoxide, gave rise to a tricyclic γ-lactone via propargylic epoxide opening followed by a series of cyclizations (Scheme 8).[78] Under a blanket of N_2, CO insertion did not occur and a four-membered carbocyclic ring was incorporated into the major product. The generality of this interesting transformation has been demonstrated with a series of examples.

Hydrogenolysis of propargylic groups prior to cycloaddition occasionally occurs.[79,80] Under stoichiometric PKR conditions propargylic amides and ethers are prone to cleavage in reactions promoted by three equivalents of cyclohexylamine (Scheme 9). This problem was avoided by using *n*-BuSMe as a promoter.

Direct formation of medium-sized rings, with specific skeletal requirements, using the PKR is evident in a few isolated examples.[65,80–82] A by-product bearing a seven-membered ring, bicycle **47**, was isolated from the PKR of an *N*-allylazetidine (Eq. 22).[83] It was speculated that ionization of the propargylic C–N bond occurred at the stage of the metallacycle via a cobalt-stabilized cationic intermediate (Scheme 10).[76] To demonstrate that **46** is not a direct precursor to **47**, a mixture of **46** and **47** was resubjected to the reaction conditions, and was recovered unchanged. This cleavage could be driven by ring strain in the intermediate bicyclic heterocycle and/or by a weakened C–N bond due to coordination of the amine to a cobalt species in the reaction medium. Hydride transfer from the medium, perhaps from a cobalt hydride,[84,85] and protonation would account for the neutralization of the charges generated. Other related substrates in which the amine is non-propargylic, or is in the propargylic position but would not open the four-membered ring if C–N bond cleavage occurred, were reported to undergo the PKR. In light of known examples of seven-membered ring formation via PK reactions, it is highly unlikely that C–N bond

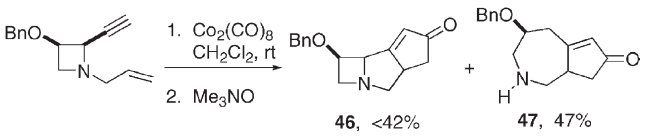


Scheme 9.



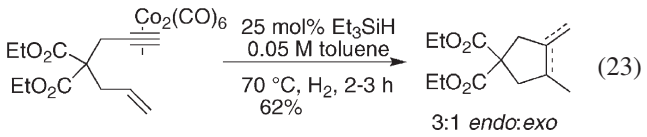
Scheme 10.

cleavage occurred before metallacycle formation. 1,8-Enynes with significant degrees of rotational freedom, as with this example, are not yet good candidates for PK cycloadditions.



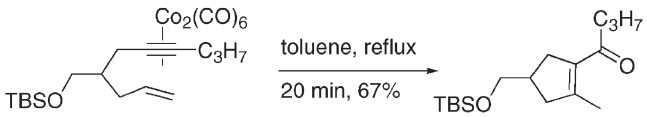
(22)

2.2.4. Formation of organic products via other pathways. 2.2.4.1. Oxidative and reductive cyclizations. Interestingly, it was observed that reaction atmospheres other than CO influence the mode of cyclization of (enyne)$Co_2(CO)_6$ complexes. For instance, when the PK cycloaddition was performed under an atmosphere of H_2, in a non-coordinating solvent, monocyclic alkenes were obtained. Optimization of the reaction conditions demonstrated that 25 mol% of $HSiEt_3$ was beneficial to promote the desired outcome of the reaction (Eq. 23). Only unsubstituted 1,6- and 1,7-enynes were susceptible to the presumed interception of the metallacyclic intermediate, providing moderate yields of monocyclic alkenes.[86]



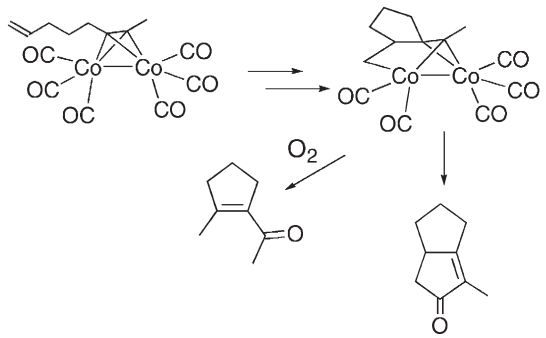
(23)

Further modification of the reaction atmosphere to a mixture of nitrogen and oxygen led to the formation of a monocyclic enone during an attempted intramolecular PKR.[26] Thermolysis of the dicobalthexacarbonyl complex of 1,6-enynes under an atmosphere of air resulted in interruption of the PK process, with concomitant oxidation of the substrate (Eq. 24). Monocyclic enones were formed in good yields with a number of different enynes.



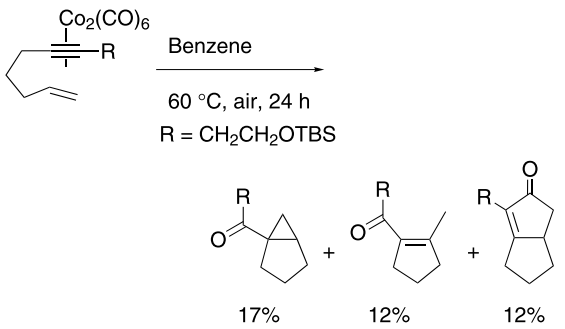
(24)

While the role of molecular oxygen in interrupting the normal Pauson–Khand manifold is unclear, a plausible explanation is that both the normal and interrupted PK products arise from a common metallacyclic intermediate (Scheme 11). Interception of the cobaltacycle by molecular oxygen, probably at the metal center initially, could account



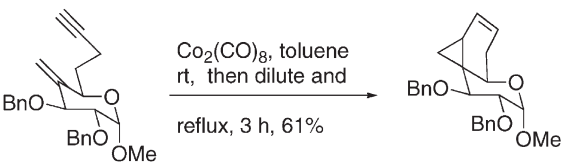
Scheme 11.

for a divergence in the reaction pathway (Scheme 1: **A→B→C**).[26] During these studies it was noted that, at lower temperatures, small amounts of a cyclopropyl ketone were also isolated, in addition to the monocyclic and bicyclic enones (Eq. 25). Thermolysis of the dicobalthexacarbonyl derivative of a 1,6-enyne, in the presence of air at 60 °C, gave rise to low yields of a mixture of the normal PK cycloadduct, interrupted PK monocyclic enone, and cyclopropyl ketone (Eq. 25).[87]

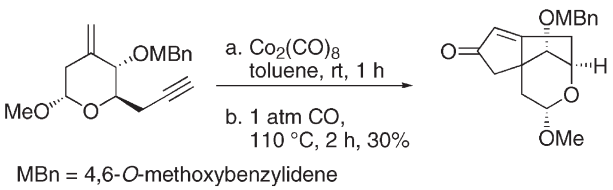


(25)

Another cyclopropyl-containing unexpected product was likewise isolated from the reaction of a 4-*exo* methylene sugar-derived enyne (Eq. 26).[88] It was believed that a metal carbene intermediate was responsible for the observed transformation.[89] On the contrary, a related 3-*exo* methylene sugar-derived enyne underwent a normal Pauson–Khand reaction smoothly (Eq. 27). These results show a pronounced dependence of substrate structure on the course of the PKR.



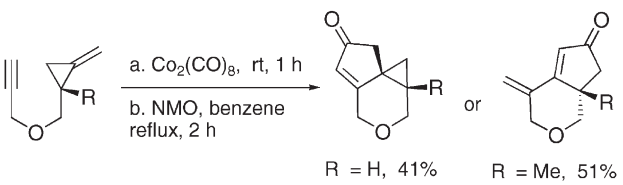
(26)



MBn = 4,6-*O*-methoxybenzylidene

(27)

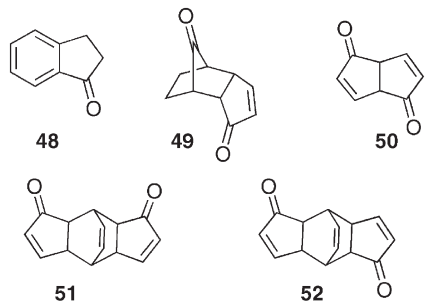
An additional interesting example of the influence of substrate structure on the outcome of the PKR is highlighted in Eq. 28. When R=H, the normal PK cycloaddition occurred, yet when R=methyl, a rearrangement with cyclopropane ring opening took place. It is notable that the alkyne carbons were not incorporated into the cyclopentenone unit of the dienone.[90] A mechanism for this unusual rearrangement was proposed.[90]



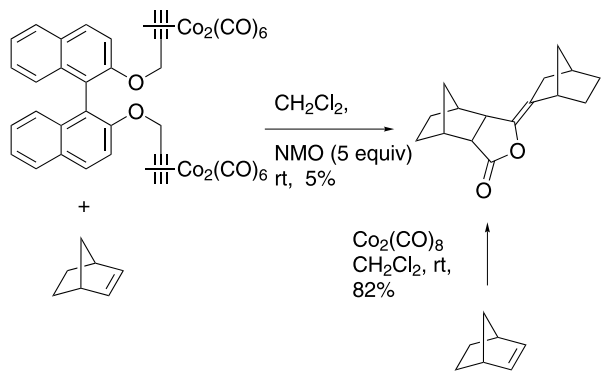
(28)

2.2.4.2. Alkyne and alkene reactions and cycloadditions, and other rearrangements. Trisubstituted alkenes

normally react slowly in intermolecular PK reactions, thereby allowing alternative reactions to occur. In a reaction of a hindered, trisubstituted alkene several organic products, derived solely from the combination of acetylene and carbon monoxide, were formed under relatively mild conditions (1,2-DME, 5 days, CO/acetylene 1:1, 65 °C).[91,92] Ketonic products **48**-**52** (≤10% yields), in addition to benzene and benzoquinone, were speculated to arise from a series of primary and secondary processes. When the active catalyst was generated by reaction of $NaBH_4$ with $Co(acac)_2$, ethylene was shown to be unreactive such that bifurandiones, derived from the cobalt-mediated reaction of alkynes with carbon monoxide, were obtained as by-products from these attempted PK reactions.[93] Bifurandiones have also been shown by Pauson to be formed from the reaction of acetylenes and carbon monoxide in the presence of $Co_2(CO)_8$.[13,94]

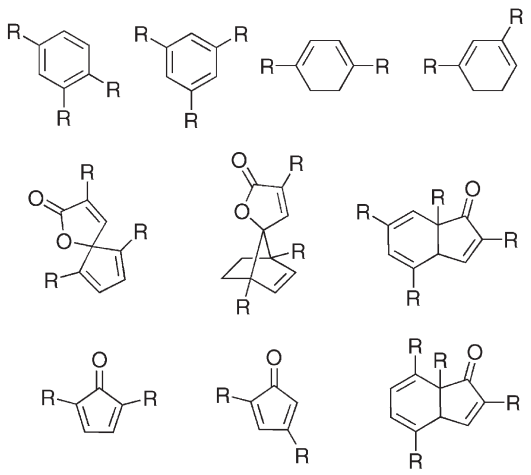


In the presence of the dicobalthexacarbonyl complex of an apparently unreactive alkyne, norbornene underwent a carbonylative dimerization to generate an enol lactone in 5% yield (Scheme 12).[95] None of the expected PK cycloadduct was observed. In the absence of the alkyne, reaction of norbornene with $Co_2(CO)_8$ gave an 82% yield of the enol lactone. While this is the first report of lactone formation under Pauson–Khand conditions, this lactone has been previously synthesized under palladium or cobalt catalysis.[96]



Scheme 12.

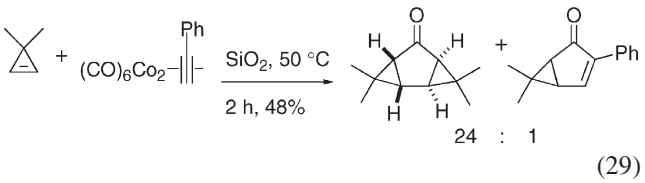
Due to the ease with which they are formed via transition metal catalysis, arenes are also very common by-products in intermolecular Pauson–Khand reactions, in particular, when di- and trisubstituted alkenes are employed. However, these unanticipated products have generally been ignored.[1,4,5,13,14,17,91,97,98] In early studies on the catalytic PKR under high pressures of carbon monoxide, acetylene and ethylene, a number of products resulting from



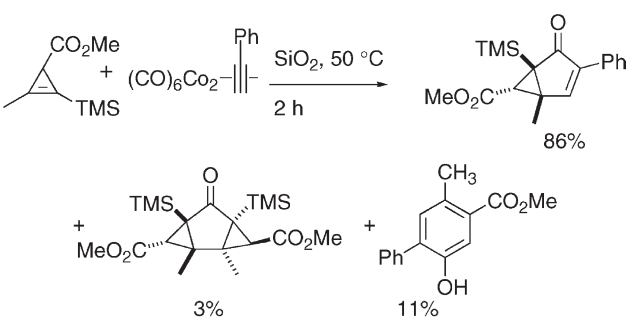
Scheme 13.

the reactants reacting in ratios other than 1:1:1, and undergoing tandem reactions were isolated (Scheme 13).[99] These products resulted from four types of prominent side reactions: cyclotrimerization, co-cyclotrimerization, spirofuran formation and cyclopentadienone formation. In addition, cyclization of 1,6-heptenyne, under thermal conditions, gave rise to small amounts of a non-ketonic product identified as 5-methoxy-3-methyl-1-pentanol.[100]

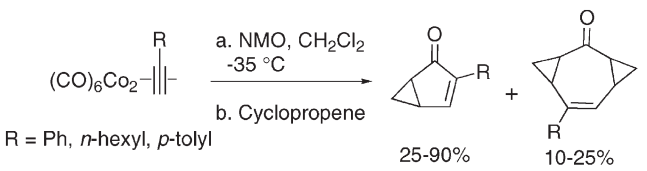
Highly reactive partners in the PKR have likewise been found to result in unexpected products. For example, cyclopropenes bearing unsubstituted alkenes were initially considered to be poor substrates for thermal Pauson–Khand reactions. They are highly reactive and participated in a cyclocarbonylation incorporating two cyclopropene molecules (Eq. 29). However, disubstitution on the alkene blocks the undesired cyclocarbonylation process, and favors the formal [2+2+1] cycloaddition using the dry state adsorption conditions (Eq. 30).[101] It has recently been discovered that cyclopropene reacts with dicobalthexacarbonyl-complexed alkynes at −35 °C using NMO to promote the reaction. Interestingly, presumably due to the high reactivity of cyclopropene, 10–25% of a product arising from insertion of 2 equiv. of cyclopropene was identified (Eq. 31).[102]



(29)

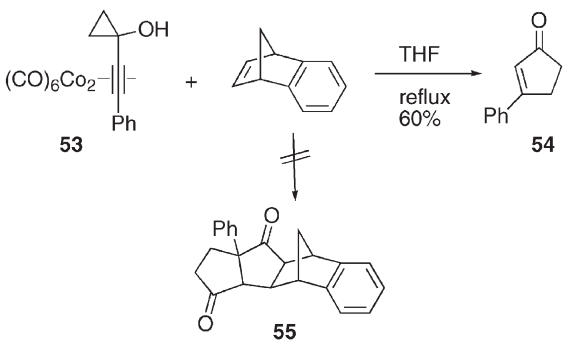


(30)

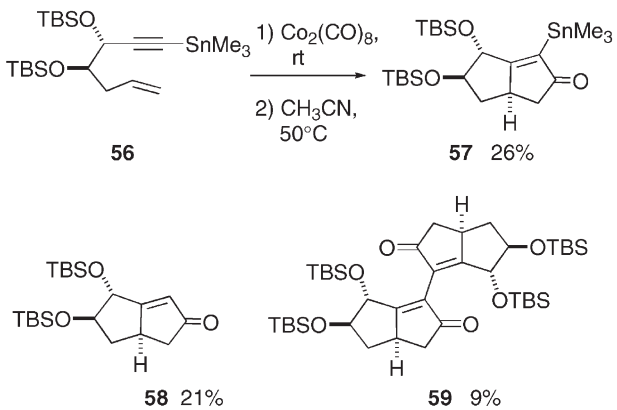


(31)

Cyclopropyl-substituted acetylene derivatives were used while investigating a sequential Pauson–Khand cycloaddition and vinyl cyclopropane-to-cyclopentene rearrangement to generate bicyclo[3.3.0]octanes.[103–105] Unexpectedly, reaction of **53** with benzonorbornadiene in refluxing THF yielded cyclopentenone **54**, with no trace of the desired product **55**. The conditions for this transformation have been optimized giving a method of general synthetic utility.

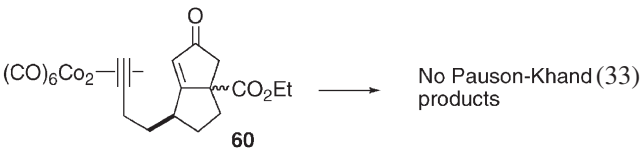


To facilitate functionalization of the 2-position of the newly formed cyclopentenone, PK reactions of trialkylstannyl- and trialkylgermyl substituted alkynes were conducted.[106] Although both substrates underwent PK cycloaddition, the latter substrate behaved better under these conditions. The trimethylstannyl group is sensitive to hydrolytic cleavage prior to cycloaddition giving rise to the destannylated enone **58** (Eq. 32). Surprisingly, dimer **59** was also isolated from this reaction.

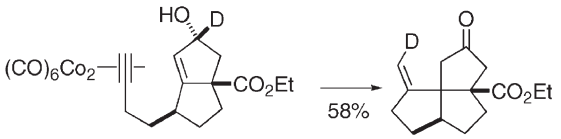


(32)

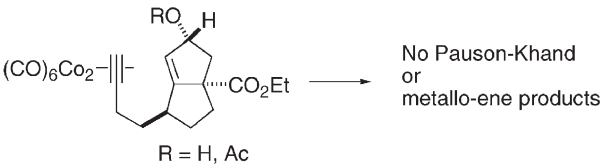
Tandem PK reactions can potentially serve as a novel and concise approach to the [5.5.5.5]fenestrane skeleton.[107,108] Although it would seem to be an ideal choice, enyne **60** failed to yield PK cycloadducts under a variety of conditions (Eq. 33). In an effort to synthesize the [5.5.5.5]fenestrane skeleton using less polarized alkenes under promotion by amine oxides, a product derived from a metallo-ene process was uncovered (Eq. 34).[108] In the cyclization of a deuterated dicobalthexacarbonyl-complexed enyne the deuterium was selectively transferred to the *cis* position on the *exo* methylene group. Neither the metallo-ene reaction, nor the PKR proceeded with closely related enynes (Eq. 35).



(33)

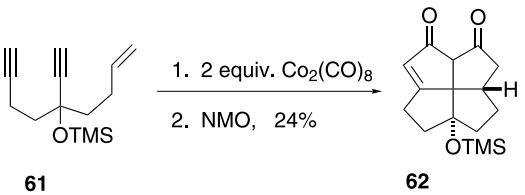


(34)



(35)

Reconsideration of the problem encountered in the PK approach to fenestrane led to a stepwise route, whereby the unfunctionalized enediyne **61** was expected to undergo sequential Pauson–Khand cycloadditions, with substrate modification between the reactions. Treatment of diyne **61** with 2 equiv. of $Co_2(CO)_8$, followed by NMO provided the [5.5.5.5]fenestrane skeleton **62** (Eq. 36). This result is remarkable in light of the failure of enone **60** to react (Eq. 33). A mechanistic explanation for this puzzling result is described in Scheme 14. It was proposed that the intermediate metallacycle undergoes cycloaddition rather than the fully decomplexed cyclopentenone, which was shown to be unreactive as a partner in the second PKR (e.g., Eq. 33). Recently, it has been demonstrated that enones participate as active partners in the synthesis of the [5.5.5.5]fenestrane skeleton using cobalt nanoparticles under 20 atm of carbon monoxide.[109]



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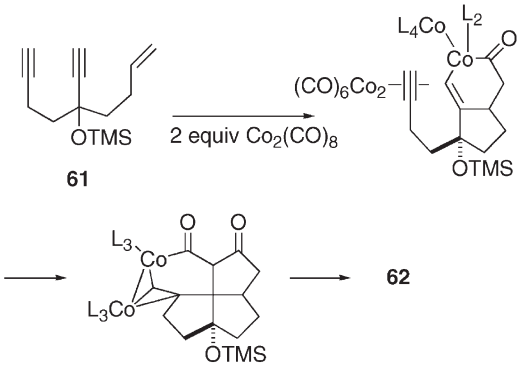
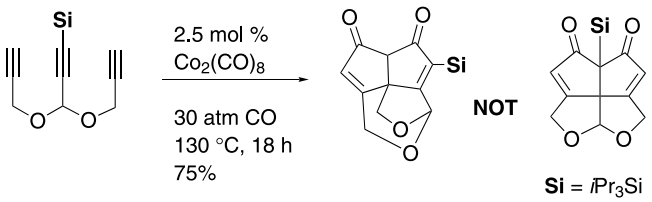


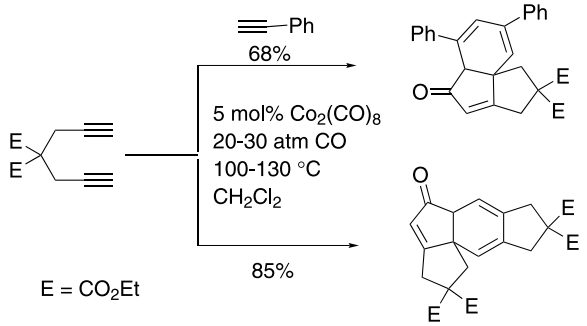
Scheme 14.

Tandem PKR cyclizations of triynes have also been exploited as a general synthetic approach to the [5.5.5.5]fenestrane skeleton. Suitably substituted triynes underwent tandem PK cycloadditions under 30 atm of carbon monoxide (Eq. 37).[110] With an internal alkyne however, cycloaddition occurred to yield a bridged rather than the expected fused tetracycle. Since stepwise PK reactions for the tandem process were not attempted, whether the second cycloaddition occurs on the metallacyclohexadienone, or the uncomplexed cyclopentadienone, is still unclear.



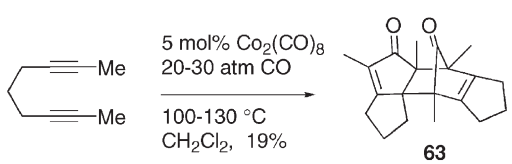
(37)

Intermolecular reactions of 1,6-diynes with mono- or bis-alkynes yielded tandem formal [2+2+1] and [2+2+2] cycloaddition products under high pressures of carbon monoxide (Scheme 15).[110] The sequential process proceeded most effectively with terminal alkynes.

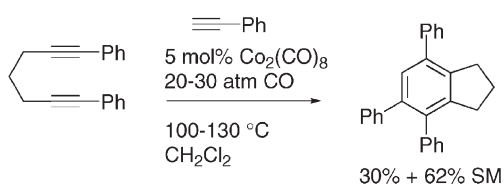


Scheme 15.

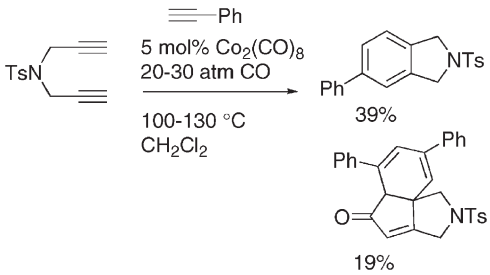
Intermolecular reaction of a diyne bearing two internal alkynes gave rise to an interesting Diels–Alder adduct **63**, which resulted from the reaction of two [2+2+1] cycloadducts (Eq. 38). With 1,7-diphenylhepta-1,6-diyne or bis(propargyl)-*p*-toluenesulfonamide, a [2+2+2] cycloaddition, to furnish a substituted arene, was more favorable than the tandem process initiated by the [2+2+1] cycloaddition (Eqs. 39 and 40).[110]



(38)

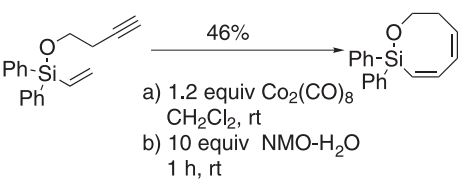


(39)



(40)

In an attempt to use silicon as a traceless tether in the PKR of a 1,7-enyne, an unusual dienylsilane was isolated in moderate yields (Eq. 41).[111] Several examples demonstrated the generality of the vinylsilane cycloisomerization with alkynes to form eight-membered rings. In the absence of silicon in the tether 1,7-enynes are expected to undergo normal PK cycloadditions. Neither the homologous 1,6- nor 1,8-enynes underwent cycloisomerization, although the latter provided very small amounts of an intramolecular carbosilylated product (Eq. 42). Substitution of carbons in the tether with heteroatoms, such as sulfur, nitrogen (e.g., Eqs. 65–67) and oxygen (e.g., Eqs. 81–84) leads to the expected PK cycloadduct.



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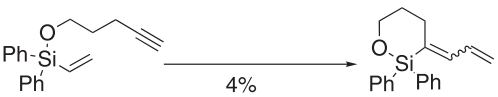
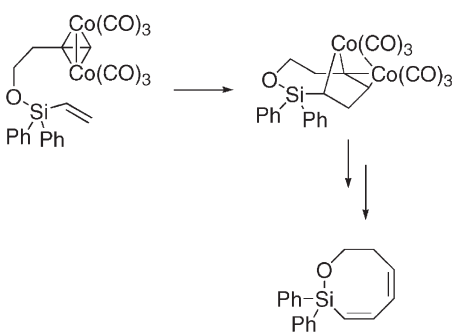


(42)

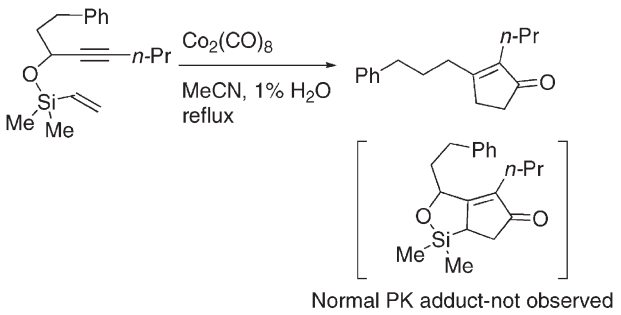
Both the mechanism of the transformation, and the reasons for the mechanistic divergence are unclear. A possible explanation involves insertion of the alkene into the distal C–Co bond, rather than the proximal bond, leading to a key intermediate that can be converted to the observed product by successive β-hydride abstraction, reductive elimination and decomplexation (Scheme 16). The regiochemistry of the insertion is most likely determined by reaction at the more electropositive terminus of the alkene as defined by the silicon functionality.[111]



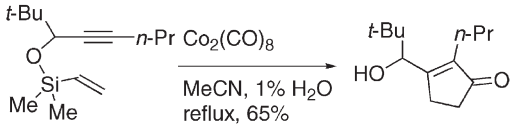
Scheme 16.

Surprisingly, vinyl silanes bearing one fewer carbon in the tether, for example, 1,6-enynes, underwent Pauson–Khand reactions to yield monocyclic enones lacking silicon (Eq. 43).[112] Several examples illustrate the generality of

the process, where the tethered vinyl silane provides a surrogate for ethylene in the PKR. The use of wet acetonitrile was key to the success of the cycloaddition. It was speculated that the expected PK adduct was formed, but it subsequently underwent secondary processes leading to a monocycle. Deuterium labeling studies suggested that the normal PK adduct loses the γ-positioned silicon to give rise to a cobalt dienolate, which undergoes a 1,5-hydride shift followed by a cobalt-mediated reduction of the resulting γ-ethereal substituent.[113] This latter process is well documented (see Section 2.6.2). Further support for the mechanistic hypothesis arises from the isolation of the desilylated hydroxy enone bearing a bulky propargylic substituent (Eq. 44).

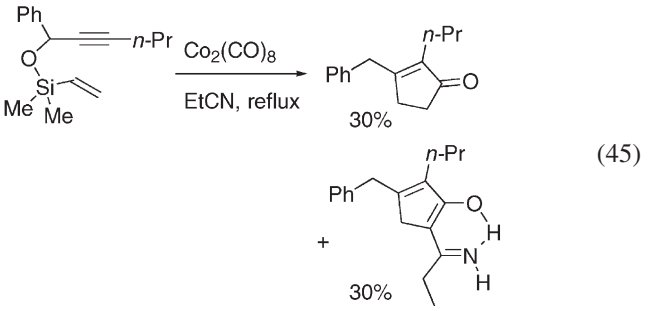


(43)

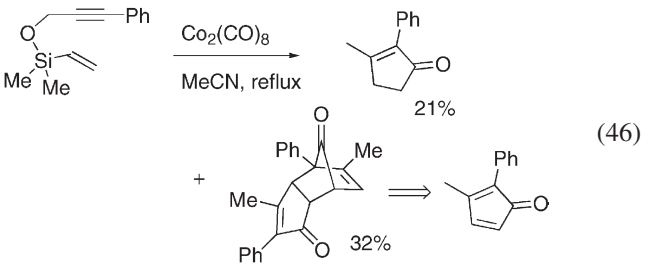


(44)

During the course of these mechanistic studies, enones that had incorporated a molecule of solvent were also isolated (Eq. 45). In anhydrous solvents, lower yields of the monocyclic PK products were observed. Additionally, a Diels–Alder adduct generated via an intermolecular [4+2] cycloaddition was obtained (Eq. 46). In many of the vinyl silane reactions performed, Diels–Alder adducts were observed, but only in minor amounts.



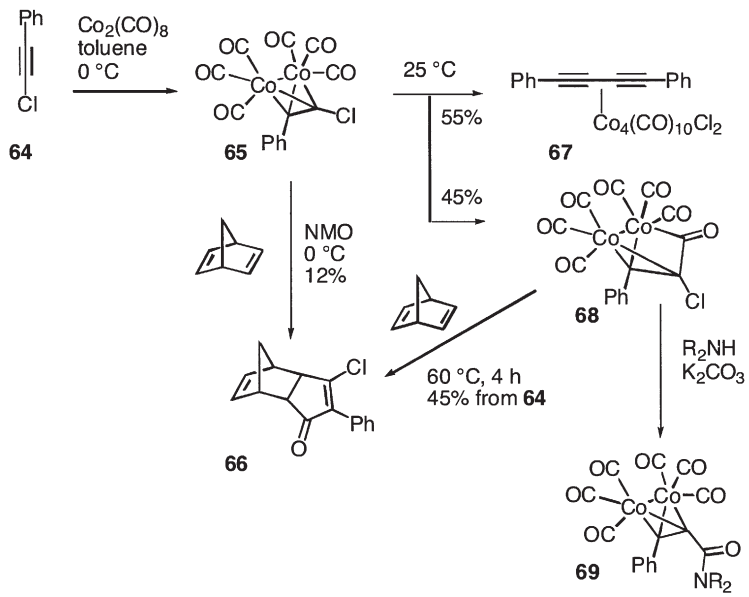
(45)



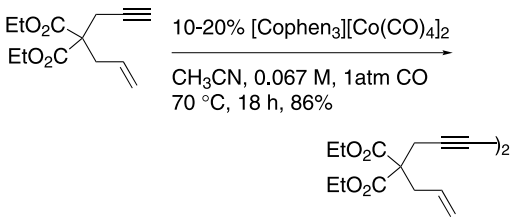
(46)

A successful series of silicon-tethered allenic Pauson–Khand-like cyclizations using alkynyl silanes has also been reported (vide infra).[114] These reactions gave high yields of hetero-bicycles where both allene double bonds underwent cyclization selectively.

Homocoupling of terminal alkynes generating 1,3-diynes has also been observed under Pauson–Khand reaction conditions. During the course of studies on the role of amines in the catalytic PKR the in situ formation of different amine-ligated cobalt carbonyl complexes and their subsequent reactions with enynes was probed.[115] Using catalytic amounts of $Co_2(CO)_8$ with 1,10-phenanthroline, alkyne homocoupling products were unexpectedly isolated instead of the PK cycloadduct (Eq. 47). Reactions of a series of alkynes demonstrated the generality of the procedure (70–88% yields).



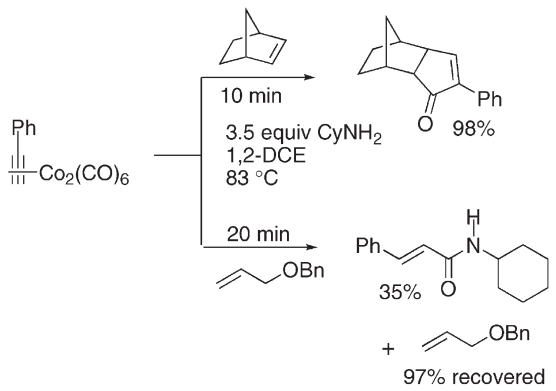
Scheme 17.



(47)

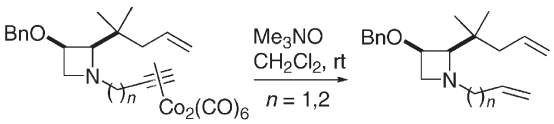
Using amine oxides to promote cycloaddition at 0 °C, 1-halo-2-phenylacetylene underwent the cobalt-mediated PKR with norbornadiene although in low yield (Scheme 17, **64→65→66**).[116] However, at ambient temperature, and in the absence of amine oxides, complex **65** gave two new cobalt complexes **67** and **68**. Complex **67** resulted from the homocoupling of the alkyne with concomitant cluster formation from the original dicobalthexacarbonyl alkyne complex **65**. Complex **68** was not isolable, but underwent the PKR with norbornadiene at 60 °C, and reacted with amines to yield aminocarbonylation products, for example, **69**. Use of an allylic amine sets the stage for a tandem aminocarbonylation-PKR in which several examples with phenyl-substituted alkynes demonstrate the generality of the unanticipated aminocarbonylation (67–99% yields from **68**).

Attempted intermolecular Pauson–Khand reactions of dicobalthexacarbonyl complexes of unactivated alkynes with unstrained alkenes, in the presence of cyclohexylamine, led to a novel hydrocarbamoylation with concomitant demetallation (Scheme 18).[117] Interestingly, whereas the reaction with the very reactive norbornene led to normal PK products the less reactive allyl benzyl ether gave a product with no alkene incorporation. The reaction conditions have been optimized to favor hydrocarbamoylation, which proceeds in 47–82% yields with a variety of alkynes and amines (refluxing toluene, 1–4 h).



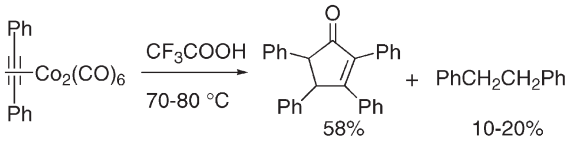
Scheme 18.

When a desired cycloaddition is slow due to ring size, or steric or electronic factors other undesired reactions might begin to surface. Reduction of an alkyne to the corresponding alkene was observed in small quantities during an attempted formation of seven- or eight-membered rings (Eq. 48).[118]



(48)

In the presence of trifluoroacetic acid, alkyne complexes underwent reduction to decomplexed alkenes, which further reacted with cobalt-complexed alkynes to give moderate yields of PK cycloadducts (Eq. 49).[119] Complete reduction of the alkyne to the alkane was observed as well. Several examples illustrate the generality of the transformation.

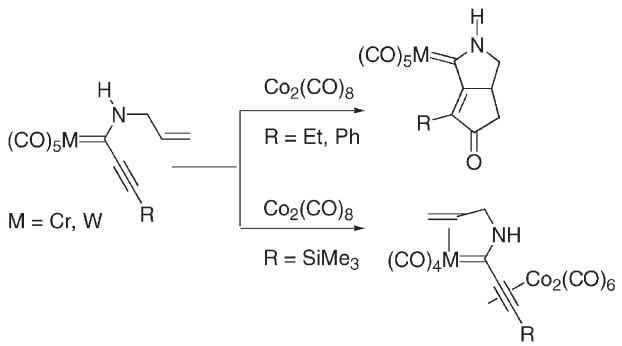


(49)

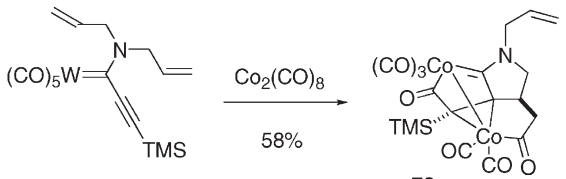
In a few isolated examples, alkenes were shown to undergo secondary processes in the absence of the alkyne. An intramolecular tandem catalytic PKR using cobalt nanoparticles on charcoal (CNC) led successfully to bicyclic ketones. However, intermolecular cycloaddition of phenylacetylene with norbornene using CNC, gave rise to modest yields of expected cyclopentanone with minor amounts of norbornene hydroformylation adducts.[120]

2.3. Organometallic compounds

2.3.1. Pauson–Khand reaction of carbene-bearing enynes. It was demonstrated that alkynyl(allylamino)carbene metal complexes undergo the Pauson–Khand reaction under very mild conditions (Scheme 19).[121] However, with a bulky substituent on the alkyne terminus (R=TMS), cycloaddition with the alkene is inhibited presumably due to its coordination with the carbene metal center. Use of the analogous (diallyl)carbene metal complex was expected to facilitate the Pauson–Khand reaction by providing an uncoordinated alkene for the desired cycloaddition. Surprisingly, none of the anticipated cyclopentenone was obtained, but rather, an interesting pentacyclic organometallic complex **70** was isolated, the structure of which was determined by X-ray diffractometry.[122–124]

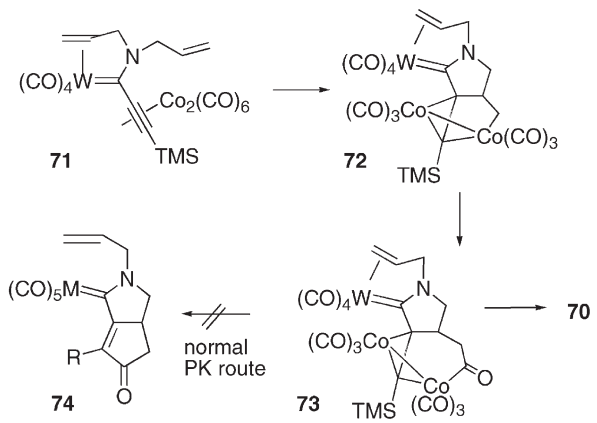


Scheme 19.



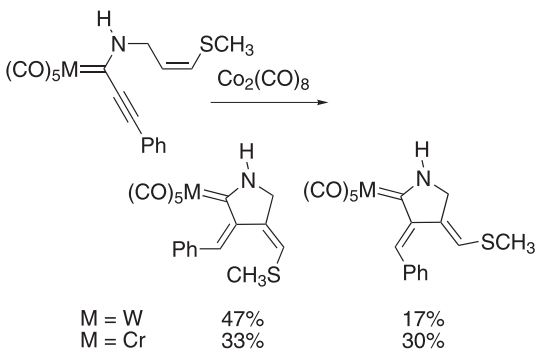
70

Mechanistically, it was envisioned that the formation of **70** is a consequence of a different evolution of the PKR after the initial metallacycle is generated (Scheme 20, cf. Scheme 1).[122] Cycloaddition of **71** gives **72**, which undergoes carbonylation generating the key organometallic complex **73**. At this point, it was speculated that the steric demands of both the trimethylsilyl and $W(CO)_4$ groups are responsible for the change in pathway to give **70**, via reductive elimination of **73**, rather than the normal PK product. Reactions of analogous complexes with alkyl- or phenyl-substituted alkynes and (allylamino)- or (diallylamino)carbene complexes all resulted in carbonylative cycloadditions.



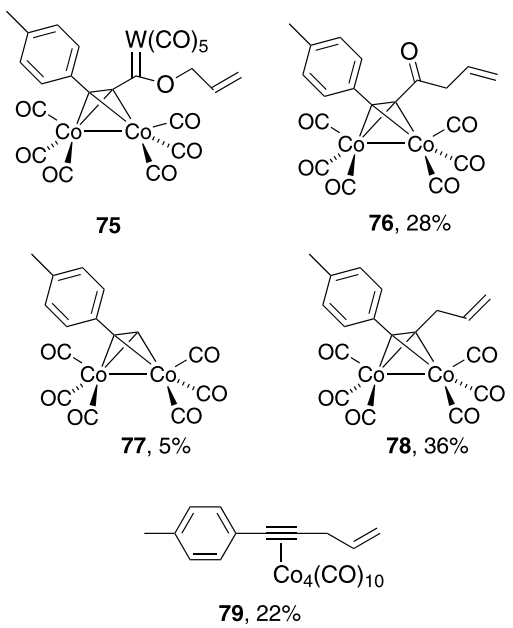
Scheme 20.

In a related study using metal carbene complexes, the effect of heteroatom-substituted alkenes in the PKR was investigated.[125] Treatment of the thio-substituted carbene complex with $Co_2(CO)_8$ in THF at ambient temperature gave two isomeric 1,2-dienes (Eq. 50). Since none of the desired PK cycloadduct was isolated, the presence of the thioether moiety at the C–M bond of the metallacyclic intermediate presumably inhibits carbonylation and allows the β-elimination to occur (cf. Scheme 1, Section 2.2.1). In contrast, incorporation of a thioether at the internal position of the alkene did not interfere with the normal PK route.

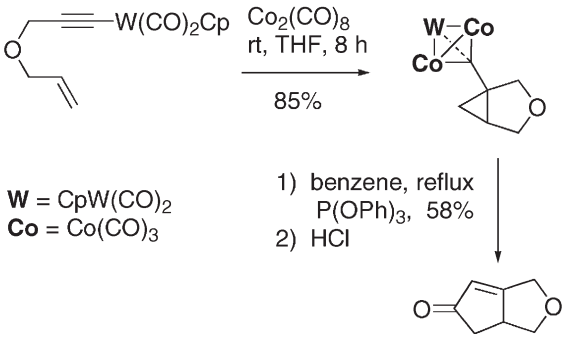


(50)

While the aminocarbene complexes containing (allylamino)-(alkynyl)carbene ligands cyclized to a cyclopentenone skeleton under extraordinarily mild conditions, the corresponding alkoxycarbene complexes proved trouble-some in the analogous PK process.[126] Stirring a toluene solution of complex **75** at ambient temperature for two to three days furnished complexes **76**-**79**, in addition to $Co_4(CO)_{12}$ and $W(CO)_6$. No products containing a cyclopentenone moiety were found. The carbene centered C–C and C–O bond cleavage that regenerates the metal hexacarbonyl and leads to predominantly cobalt-coordinated enynes can be rationalized in terms of a retro-Fischer carbene synthesis. Analogous results were obtained with the corresponding chromium carbene complex.

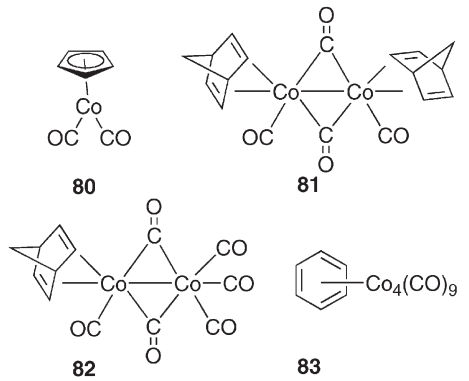


Dicobalthexacarbonyl complexes of alkynyltungsten compounds underwent the PK cycloaddition efficiently. However, proposed carbenoid intermediates were shown to lead to a bicyclic cyclopropane as an intermediate, which could be converted to the bicyclic enone upon heating in benzene (Eq. 51).[127]

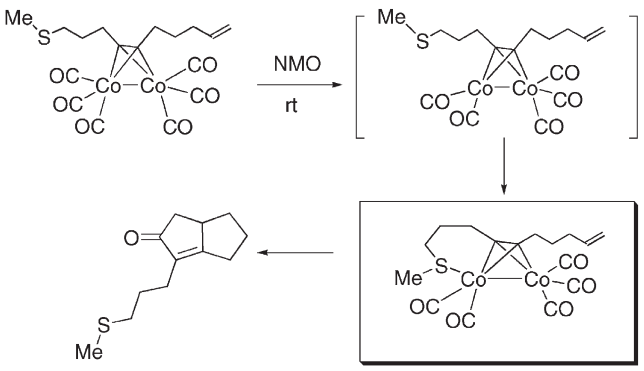


(51)

2.3.2. Formation of organometallic complexes. In some very unusual cases, metal residues remain incorporated in the unexpected product. In the seminal studies of Pauson, thermal reaction of hexacarbonyldicobalt-complexed alkynes with norbornadiene resulted in a number of other metal-containing species, for example, **80**-**83**, depending on the solvent and conditions used.[13,14,17]

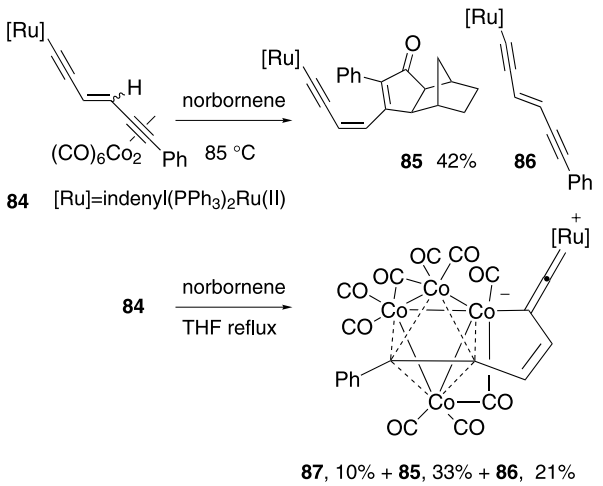


Early work on the effect of coordinating heteroatoms on the intramolecular PK cycloaddition led to a surprising result, which later formed the basis for related heteroatom-chelated cobalt carbonyl-mediated reactions.[22] A study was conducted in which the tether length between the alkyne and coordinating heteroatom was varied. It was found that, as the tether length was increased to three atoms the NMO-promoted PK reaction slowed down significantly. This rate reduction was evidently due to the formation of a stable heteroatom-complexed pentacarbonyl intermediate, which was isolated and could be slowly converted to the desired PK product (Eq. 52). This represents the first isolation of a post-alkyne complexation intermediate (**2**, Scheme 1).[22] Subsequent to this work, Pericas reported the isolation of a similarly chelated chiral intermediate.[25]



(52)

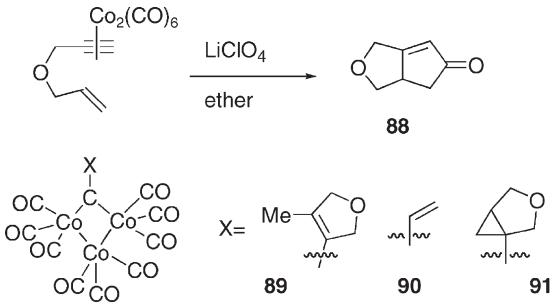
A new tetracobalt cluster was likewise isolated from the Pauson–Khand reactions of (σ-alkynyl)ruthenium complexes bearing a conjugated enediyne functionality.[128] Thermal reaction of complex **84** in norbornene yielded the expected PK cycloadduct **85**, in addition to the decomplexed *trans*-enediyne **86** (Scheme 21). On the contrary, when the reaction was carried out in refluxing THF a new cluster **87** was formed, along with **85** and **86**. It was speculated that complex **87** was formed by reaction of *Z*-**84** with the $Co_2(CO)_n$ released after the PK process occurred, which generated **85**. Complex **87** was alternatively generated directly from the reaction of enediyne complex **84** with $Co_4(CO)_{12}$ in refluxing THF (44% yield). The new vinylidene complex **87** is active in PK cycloadditions although, relative to the reaction with the original alkyne complex, it requires higher reaction temperatures and longer reaction times. This suggests that complex **87** is not an intermediate in the observed cyclocarbonylation process.



Scheme 21.

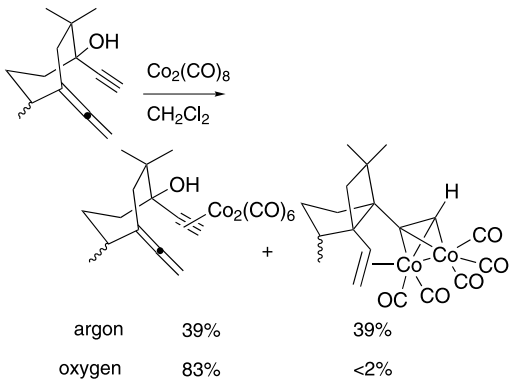
Reactions of **84** with unstrained alkenes did not lead to any cyclocarbonylated products.

When lithium perchlorate was used as a promoter for the PKR in ether, the dicobalthexacarbonyl complex of allyl(propargyl)ether furnished three unique isolable organometallic complexes **88**–**91** (5–15% yields of each), in addition to the expected PK cycloadduct (Eq. 53).[129] While the cycloaddition was promoted, the enhancement effect of lithium perchlorate was inferior to those of other promoters, such as cyclohexylamine.[27]



(53)

In an approach to the skeleton of the anti-tumor agent suberosenone, an unexpected cyclization was likewise observed during the generation of the dicobalthexacarbonyl complex of an allenyne (Eq. 54).[130,131] It was speculated that hydride addition to the central carbon of the allene generated a reactive intermediate, which underwent a C–C bond forming process at the propargylic position. Facilitation of bond formation at the propargylic carbon is expected due to the stabilization of a developing positive charge by the dicobalthexacarbonyl moiety.[76] Hydridocobaltcarbonyls have been speculated to be responsible for the reduction of C–O bonds before and after cycloaddition (vide infra). Reduction products in other reactions involving the use of dicobalthexacarbonyl-complexed alkynes have been suppressed by conducting the reaction in the presence of oxygen. Toward this end, generation of the desired alkyne cobalt complex was indeed achieved when the complexation was conducted under a blanket of oxygen.



(54)

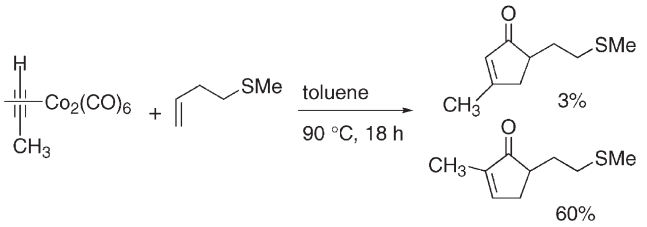
In most of the unexpected results described thus far the Pauson–Khand process has been completely diverted to other pathways. However, the reaction that generates **70** illustrates a very unusual example of trapping of a metallacyclic intermediate with concomitant inhibition of the remainder of the Pauson–Khand process, leaving an organometallic product. In several other examples of Pauson–Khand reactions the most reasonable mechanistic hypothesis, that takes into account the observed results, involves reaction of the metallacyclic intermediate in an alternate sequence with the PK cycloaddition ultimately undergoing completion to the expected enone, for example, Eqs. 22 and 36 and Scheme 3. Until these examples, reactions of Pauson–Khand metallacyclic intermediates in other pathways had not been previously considered in the mechanistic description of the PKR. All of these results were unexpected and the mechanistic proposals are indeed intriguing.

2.4. Promotion of the PKR under dry state reaction conditions

An interesting discovery that further led to the development of the dry state adsorption condition (DSAC) protocol for the PKR was reported in early studies by Smit and Caple.[132] Since the dicobalthexacarbonyl-complexed enynes are moderately stable to silica gel column chromatography, they can be prepared in situ, or isolated and purified using a short plug of silica gel. However, it was noted that a significant reduction in the expected amount of the metal-containing product after column chromatography of a dicobalthexacarbonyl-complexed enyne. Careful evaluation of the mixture revealed that, in the presence of the pendant alkene, cyclocarbonylation had occurred on the silica gel at ambient temperature.[132] Subsequent to this initial discovery, an evaluation of the different adsorbents was performed, which greatly enhanced the potential of the method.[133–135]

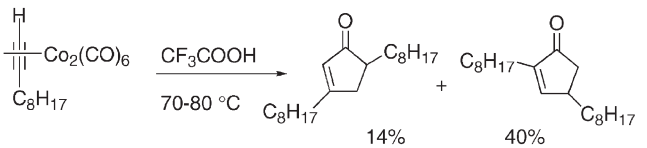
2.5. Unexpected regio- and stereochemical outcomes

2.5.1. Regiochemistry in intermolecular cycloadditions. In the mechanism of the intermolecular PK reactions it is generally accepted that the regiochemical outcome with respect to both the alkene and alkyne is determined at the metallacycle-forming step (Scheme 1, **3** to **4**). Steric crowding manifests itself strongly in the formation of the initial carbon–carbon bond (Scheme 2). Thus, terminal alkynes provide 2-substituted isomers almost exclusively. There are a few examples in which PK reactions of terminal alkynes have yielded small amounts of the 3-substituted-2-cyclopentenones. Pauson and Khand reported isolation of trace amounts of what was presumed to be the 3-substituted-2-cyclopentenones in their early evaluation of the scope of the reaction.[136] In the heteroatom-directed thermal cycloaddition the 3-substituted isomer was also formed when propyne was the alkyne partner, albeit in low yield (Eq. 55).[58]



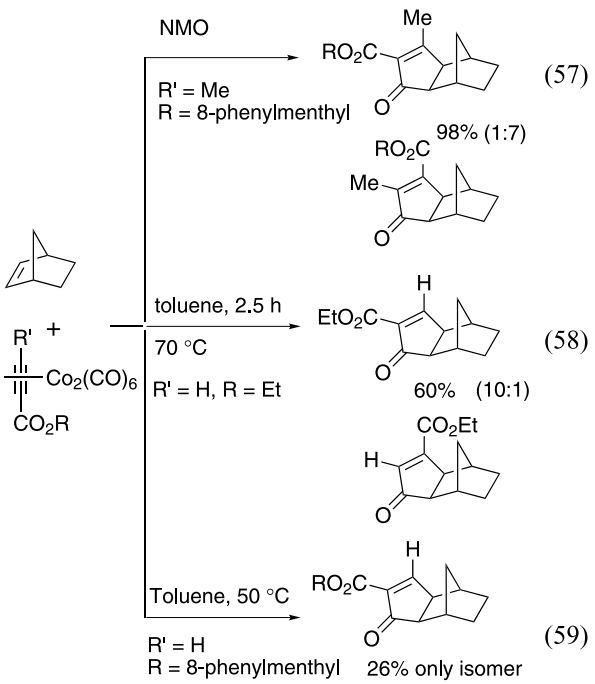
(55)

Thermolysis of (alkyne)dicobalthexacarbonyl complexes, prepared by in situ reduction of $CoBr_2$ with Zn under a CO atmosphere, in the presence of an excess of trifluoroacetic acid gave moderate yields of cyclopentenones with interesting regioselectivities. Quite surprisingly, the 3-substituted isomer was observed as a significant by-product (Eq. 56). It should be noted that the 3-substituted cyclopentenones were not formed under the analogous reaction conditions without trifluoroacetic acid. The transformation was demonstrated to be general (five examples, 50–58% yields) although, in all cases, 10–20% of the corresponding alkane was observed.



(56)

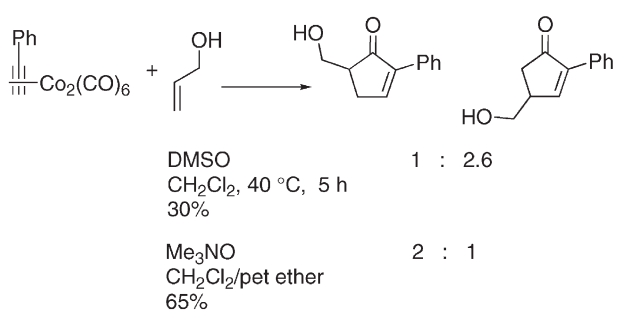
Furthermore, substitution on the alkyne with activating groups is expected to alter its reactivity and selectivity, thereby influencing the regiochemical outcome in the PKR. There are cases when there has been a delicate interplay between steric and electronic effects in the PKR. For instance, while PK reactions of internal alkynoates typically yield 1,4-dicarbonyl compounds,[137] reaction of 8-phenylmenthyl 2-butynoate gave a 1:7 ratio of the 1,3 and 1,4-keto-esters (Eq. 57).[138] Reactions with other chiral internal alkynoates led only to the 1,4-dicarbonyl isomer. With terminal alkynoates, formation of the 1,3-dicarbonyl cycloadduct predominated, and is best explained by considering a steric influence of the ester moiety over the cycloaddition (Eqs. 58 and 59, Scheme 2, R=CO_2R, **3**→**7**).[137,138]



The regiochemical outcome of reactions with polarized alkynes was recently rationalized based on a *trans* effect in the discriminant loss of a carbon monoxide ligand, as dictated by the electronic nature of the alkyne substituents.[31,34] A density functional theory study was carried out to probe these differences. Support for the electronic argument arises from the highly selective PK reaction of ethyl 4-(4-methylphenylethynyl)benzoate with norbornene providing the cyclopentenone with the electron deficient arene at the 3-position. These results also explain the differences in selectivity between PK reactions of propiolate and butynoate.

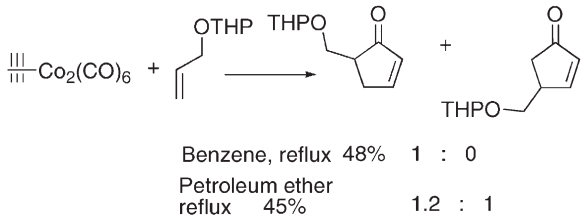
Moreover, regioselectivity from the reaction of mono- or 1,2-disubstituted alkenes in intermolecular Pauson–Khand reactions with terminal alkyne complexes is essentially random.[1–12] While 1,1-disubstituted alkenes react with terminal alkynes to yield the 2,4,4-trisubstituted isomer of the cycloadduct,[2,5,139,140] terminal alkenes react with internal alkynes to furnish predominantly the 2,3,5-tri-substituted isomer (see Scheme 2).[141,142] Several notable exceptions to these broad generalities are highlighted below.

It was found that promoters affect the regiochemical outcome of the intermolecular PKR.[143] While use of DMSO as a promoter favored the formation of the 2,4-disubstituted cyclopentenone, Me_3NO yielded the 2,5-disubstituted isomer as the major product (Scheme 22).



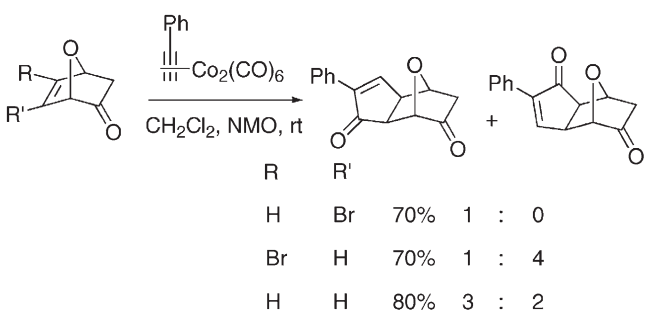
Scheme 22.

Reversal of regioselectivity was also observed in the reaction of allyl tetrahydropyranyl ether with acetylene-hexacarbonyldicobalt in different solvents.[2] Whereas the 5-substituted cyclopentenone was formed exclusively in benzene, its 4-substituted isomer was also obtained in equal amounts when the reaction was conducted in petroleum ether (Scheme 23). The reason for the loss of regioselectivity in a non-aromatic solvent is not immediately obvious. Interestingly, thermolyses of 3-arylpropenes with (acetylene)$Co_2(CO)_6$ in refluxing toluene gave the 5-substituted cyclopentenones exclusively. The reason for this unexpected selectivity is also not clear at this point.[52]



Scheme 23.

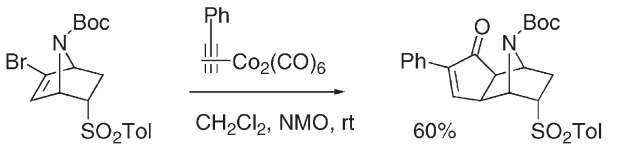
Evaluation of the PK reaction of halogenated 7-oxanorbornenes resulted in unusual regiochemical consequences,[144] where the halogen substituent on the alkene significantly influenced the regiochemical outcome of the cycloaddition (Scheme 24). As a control element for selectivity, the halogen allowed the cyclopentenones to be formed regiospecifically with the C–C bond forming on the more electropositive terminus of the alkene. Debromination was also observed and presumed to have occurred after the cycloaddition. Identical results were expected from all three oxanorbornenes if debromination occurred prior to cycloaddition.[136,145] The regiochemistry of cycloaddition is consistent with reactions of other electron-deficient alkenes from which dienes were also formed.[45] Cycloaddition appears to take place with C–C bond formation at the alkene terminus opposite the alkene electron-withdrawing group.[35] In addition, substitution of an electron-withdrawing group at the 2-position of norbornene was shown to exert a modest long-range influence on the regiochemical outcome of the cycloaddition. The effect of 2-substituted norbornenes was studied in detail demonstrating a modest



Scheme 24.

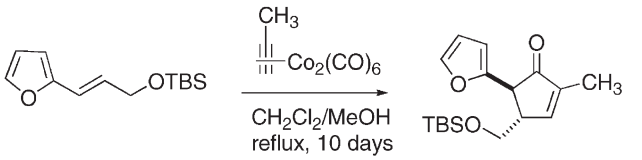
preference for C–C bond formation at the more electropositive alkene carbon.[35,146]

Analogous regiocontrol was observed with related brominated 7-azanorborn-5-enes in PK cycloadditions (Eq. 60). Interestingly, reaction of the diastereomeric *exo*-tosyl-substituted 7-azanorborn-5-ene formed the *endo* cycloadduct as a minor by-product (5%), in addition to a mixture of the expected regioisomeric enones (40%).[147]

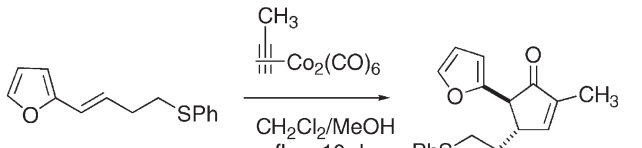


(60)

2-Vinylfurans were found to exert a powerful directing influence (Eq. 61)[148] even overwhelming the directing effect of a homoallylic thioether (Eq. 62).[58] Styrenes also exhibit similar influences over the regiochemistry of cycloaddition. No dienes were isolated from these reactions.[52]

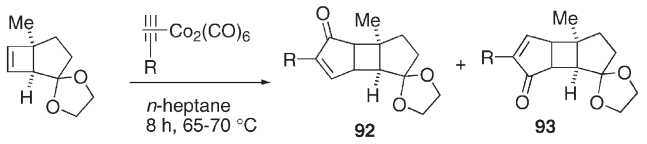


(61)



(62)

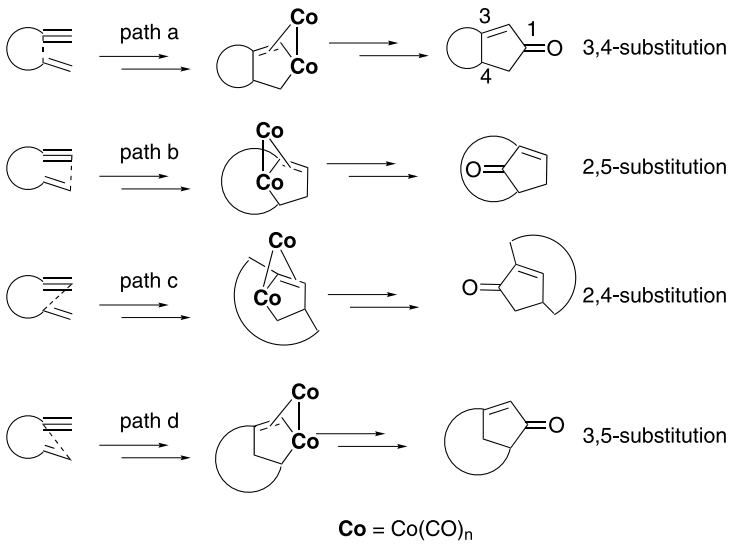
The unusual steric characteristics exhibited by substituted cyclobutenes were shown to effect regioselective intermolecular cycloadditions as a function of the alkyne substituent.[149] Based on early work by Schore, enone **93** was anticipated to be the major product from the reaction of a fused cyclobutene with a cobalt carbonyl complexed alkyne.[92] Quite unexpectedly, if the alkyne component were acetylene, enone **92** was obtained exclusively, whereas if it were trimethylsilylacetylene, only enone **93** was obtained. These results further reinforce the importance of steric interactions in the determination of the PK reaction outcome.



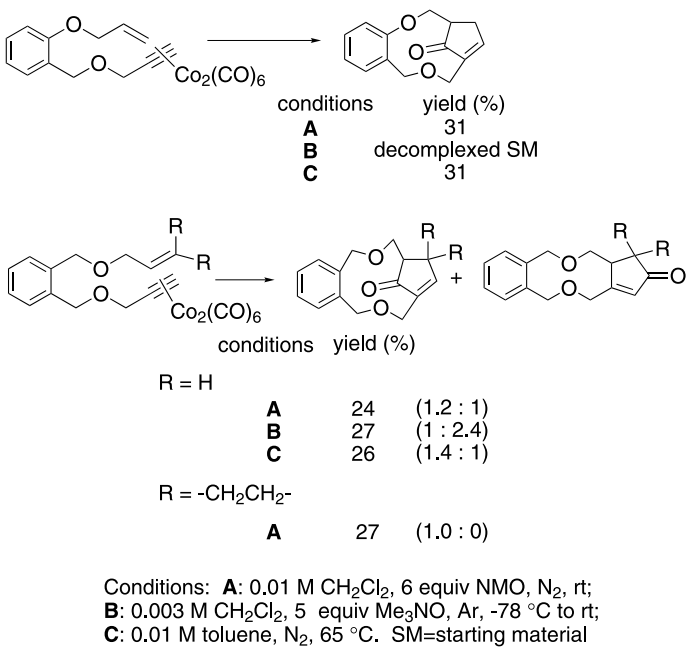
R	92	93
H	83% 1	0
n-Pr	72% 1.3	1
TMS	86% 0	1

2.5.2. Regiochemistry in intramolecular cycloadditions. When the tether length between the alkene and alkyne groups is long enough to render unrestricted conformational mobility different modes of carbon–carbon bond attachment in the insertion step are possible (Scheme 25). For instance, cyclization of terminally substituted α,ω-enynes, shown to undergo macrocyclization, afforded cyclopentenones whose substitution pattern represented two of the four possible permutations of insertion, that is, paths a and b. In these cases medium-sized rings were synthesized via the intramolecular Pauson–Khand reaction of α,ω-enynes typically on rigid aromatic templates.[65]

Enynes with short tether lengths normally undergo cycloadditions across the alkyne with opposite regioselectivity compared to the intermolecular case, that is, formation of 3,4-substituted bicyclopentenone (path a). The strain associated in the incipient metallacyclic intermediate, due to the short chain, limits carbon–carbon bond to occur only at



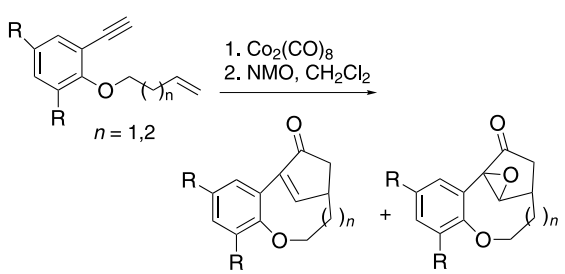
Scheme 25.



Scheme 26.

the substituted termini of both groups, as seen in numerous cases of intramolecular PKR of 1,*n*-enynes (*n*=6, 7). However, when the tether is long enough carbon–carbon bond formation can occur at the less substituted termini of both reactive groups resulting in a 2,5-disubstituted bicyclopentenone (path b). Thus, a 1,10-enyne gave the bridged macrocycle, according to path b, in which the substituted end of the alkyne resulted in position 2 of the cyclopentenone (Scheme 26). Although only the 2,5-disubstituted cyclopentenone was obtained in the reaction of a 1,11-enyne depicted in Eq. 10, the 1,11-enyne shown in Scheme 26 gave both 2,5- and 3,4-disubstituted enones. The macrocyclic diene observed in the former presumably originated from reduction of the same metallacycle as the cyclopentenone (Eq. 10). Notable exclusion of the 3,4-disubstituted adduct and sole formation of the 2,5-disubstituted bridged-macrocycle (27%) were observed with the analogous 1,11-cyclopropylidenyne. Formation of metallacycle according to path b accommodates the steric requirements imposed by the cyclopropyl moiety.

Following this report, it was shown that the use of a



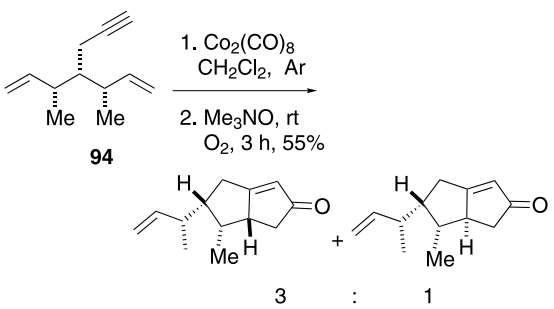
(63)

buttressing effect with aromatic templates further facilitated cyclization providing a limited synthesis of several medium-sized rings. In an attempt to generate medium-sized rings from phenyl-templated 1,8- and 1,9-enynes, reverse cycloaddition across the terminal alkyne was observed to provide eight- or nine-membered rings rather than seven- or eight-membered rings, respectively (Eq. 63).[81] None of the Pauson–Khand adduct with the expected regiochemistry from tethered reactive groups was obtained, that is, via paths a and b. The observed 2,4-disubstituted-product apparently originated from the metallacycle derived from insertion at the unsubstituted terminus of the alkyne and the substituted terminus of the alkene (path c). This is the first example of this mode of insertion. Insertion at the substituted terminus of the alkyne is less favored due to incipient steric interactions with the alkene hence, a 3,5-substituted cyclopentenone is not observed (path d; Scheme 2).

Unexpected epoxidation of the strained bridgehead cyclopentenone in the eight-membered ring formed in the PKR was also observed. Epoxide formation was presumably mediated by NMO although control experiments suggested that the oxidation was cobalt-catalyzed since direct reaction of the enone with NMO did not yield an epoxide. The homologous bicyclo[6.2.1]undecenone did not undergo the corresponding oxidation. No explanation for this unprecedented mode of cycloaddition was provided. However, steric interactions, which so powerfully direct the regiochemical outcome of intermolecular cycloadditions, can be invoked inasmuch as the increased aromatic substitution resulted in a buttressing effect. Several examples of seven-membered carbocycle formation using allene–alkyne PK and PK-like cycloadditions have also been reported.[150–152]

2.5.3. Stereochemistry. Substituents on the tether between the alkene and alkyne groups also influence the stereo-

chemical outcome of the newly forming stereogenic center at the ring fusion in intramolecular PK reactions. Since substituents on the *endo* face of the developing cobalt metallacycle are considered destabilizing, allylic and propargylic groups are preferentially oriented in the *exo* position (relative to the ring fusion hydrogen in the bicyclic transition state). Schore first observed a reversal of normal stereoselectivity in the intramolecular PKR, where cyclization of the *syn*,*syn* isomer **94** gave a 3:1 mixture of stereoisomeric cyclopentenones in which the enone bearing both substituents in the *endo* configuration was the major product (Eq. 64).[153] A computational model for rationalizing and predicting the outcome of this, and other cycloadditions of 1,6-enynes was developed, and was based on the metallacyclic intermediate rather than a pre-reaction conformational preference of the enyne.[32]

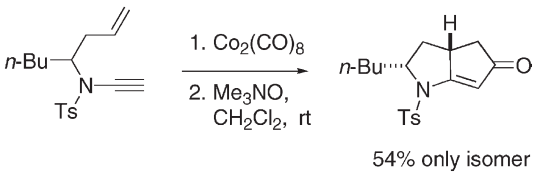


(64)

Introduction of substituents in the propargylic and homopropargylic positions, or allylic and homoallylic positions of a 1,6-enyne, similar to Schore's examples, resulted in a very modest preference for the *endo* orientation of the propargylic or allylic group. A metallacyclic model also appropriately explained these results observed by Hanoaka.[154] A recent report, using either cobalt on charcoal or $Co_2(CO)_8$ catalysis, revealed high *endo* selectivity in bicyclo[3.3.0]octenone synthesis with enynes bearing allylic and homoallylic substituents.[155] Interestingly, in the synthesis of the bicyclo[4.3.0]nonenone skeleton, incorporation of substituents at either the propargylic and homopropargylic, or allylic and homoallylic positions led to a very high selectivity for the *endo* isomer (Scheme 27).[64,156,157]

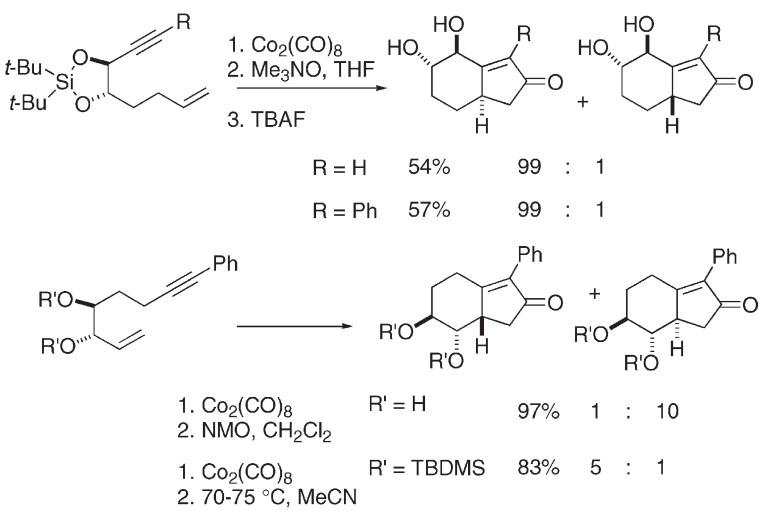
Examples of enynes with different alcohol protecting groups and alkyne substituents demonstrated the generality of the conformationally induced stereocontrolled cycloaddition. The results could not be explained satisfactorily using a metallacycle model, but could be rationalized by an analysis of steric interactions in a pre-reaction enyne conformation. Whether the enyne conformational preference model should be used to predict cyclizations of all substituted 1,7-enynes is unclear at this point due to the paucity of examples relative to the substituted 1,6-enyne systems.[158]

Despite the general assumption that electron-deficient alkynes are unsuitable substrates in PK reactions, several examples have recently emerged to demonstrate that this is not always the case. For instance, intramolecular cycloadditions of *N*-functionalized alkynylamides occurred diastereoselectively with *endo* stereoselectivity (Eq. 65). Four examples demonstrate the generality of the use of the *N*-toluenesulfonyl group as a stereodirecting group.[159] These cycloadditions were unexpectedly selective, and can be best explained using a metallacyclic intermediate model.[32] Extension of the observation to the use of chiral *N*-functionalized-*N*-(ethynyl)allylglycines led to the synthesis of bicyclic enamides with high *endo* selectivity and diastereoselectivity (>95%).[160]



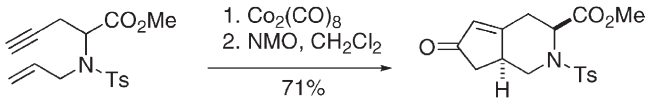
(65)

The toluenesulfonyl group also effectively directed a substituent on the tether to the *endo* orientation in a series of heterobicyclo[4.3.0]nonenones synthesized both in solution and in the solid phase.[161] An allylic sulfonamide directed a tether substituent to the *endo* position with high selectivity under both conditions (Eq. 66). However, the corresponding propargylic sulfonamide provided the *exo* isomer exclusively (Eq. 67). Similar results, demonstrated with several examples, were obtained in the solid phase (polymer attachment

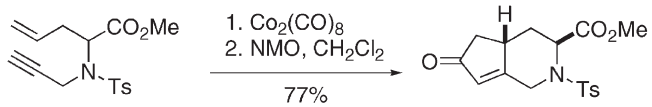


Scheme 27.

via the ester functionality). In these studies, aromatic nitro groups were also reduced to the corresponding substituted anilines, representing the first examples of in situ reduction of aromatic nitro groups under PK reaction conditions.[161]

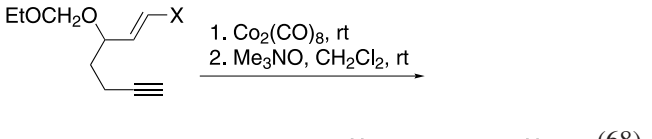


(66)



(67)

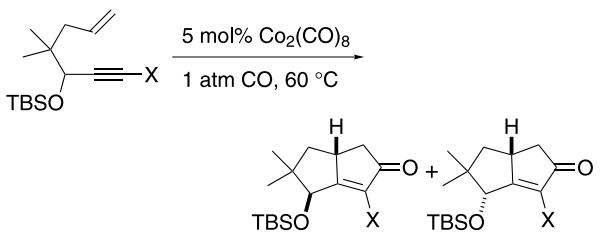
High *endo* stereoselectivity was likewise observed when an *E*-phenylsulfonyl-substituted alkene was incorporated into the substrate (Eq. 68). In the absence of the phenylsulfonyl group the *exo* isomer was the major isomer formed, although it was always generated with its *endo* isomer.[57,162] Several examples further illustrate the powerful directing effect of this group. Steric interactions in the bicyclic metallacyclic intermediates adequately explain these results.



(68)

X = H	72%	1	:	3
X = SO_2Ph	76%	40	:	1

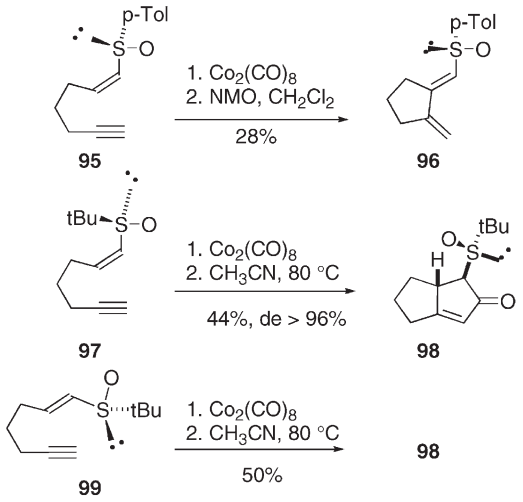
Furthermore, (alkylthio)alkynes were demonstrated to enhance the efficiency and stereoselectivity of the intramolecular PK cycloaddition (Eq. 69).[66] When an ethoxy substituted enyne was subjected to cyclization conditions the normal stereoselectivity was reversed, with the *endo* isomer being formed as the major isomer while the yield remained high. The reason for this reversal in selectivity as a function of the heteroatom is not well understood.



X = H	TFE:1,2-DME (2:1)	80%	1.6	:	1
X = SMe	1,2-DME	99%	3.9	:	1
X = OEt	1,2-DME	84%	1	:	1.4

(69)

Chiral sulfinylated enynes also yielded unexpected results in intramolecular reactions (Scheme 28).[163,164] While the *cis* aryl vinylsulfoxide **95** yielded a diene, the *cis tert*-butyl- vinylsulfoxide **97** furnished PK adduct **98** with excellent diastereoselectivity. The former product is expected from the reaction of an electron-poor alkene under PK conditions (Section 2.2.1). However, the *trans* vinylsulfoxide **99** underwent PK cycloaddition to yield the same diastereomer **98**. Not surprisingly, a mixture of the chiral *cis* and *trans* vinyl sulfoxides generated the same cyclopentenone. Two possible mechanistic scenarios have been put forth to explain the results. The



Scheme 28.

chiral *cis* vinylsulfoxide could have isomerized to the *trans* isomer prior to cycloaddition, thus providing the same product from the mixture. Alternatively, the *cis* and *trans* vinylsulfoxides might exhibit the same π-facial selectivity in the key metallacycle-forming step, but the *cis* adduct isomerized to the more stable *trans* isomer at the enone stage. Interestingly, optically active alkynyl sulfoxides underwent unexpected racemization during PK cycloadditions under thermal and oxidative conditions.[165]

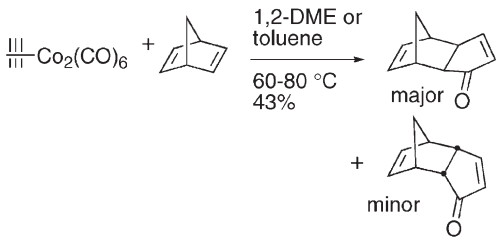
2.6. Reactions that occur after the PK reaction

Various reactions were also reported that presumably occur after the completion of the formal Pauson–Khand process. Whether or not they involve the cyclopentenone moiety, these reactions can generally be categorized as:

(a) Isomerization, for example, isomerization of *exo*- to *endo*-PK cycloadducts in norbornadienyl systems, and double bond migration in and epimerization at the α-position of the cyclopentenone products;
(b) Elimination of appropriately-situated leaving groups;
(c) Reduction, for example, hydrogenolysis of propargylic heteroatom substituents, reduction of functionalized vinyl groups, and 1,4-reduction of cyclopentenone; and
(d) Oxidation of the double bond in the enone.

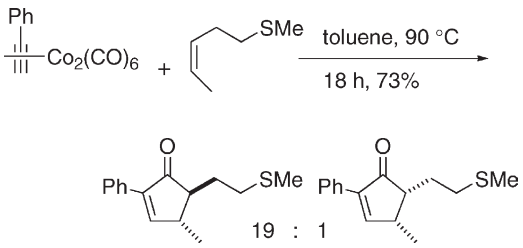
2.6.1. Isomerization, double bond migration and elimination. Not unexpectedly, the first report of one such reaction was from the Pauson laboratory.[14,75] Cycloadditions using norbornadiene as the alkene component

generally provide the *exo* cycloadduct. However, thermolysis of acetylenedicobalthexacarbonyl with norbornadiene gave a mixture of *endo* and *exo* adducts (Eq. 70). Interestingly, it was demonstrated that isomerization of the *exo* adduct to the *endo* isomer occurred during the reaction, and it was slower in toluene than in 1,2-DME. PK adducts derived from the analogous norbornene were of the *exo* configuration only, and did not undergo isomerization. In Pauson's work, substituted alkynes gave only the *exo* adducts in reactions with norbornadiene. Since this early work *endo* adducts as major isomers or as by-products, even with substituted alkynes, have been reported by others.[44,91,92,166–172]



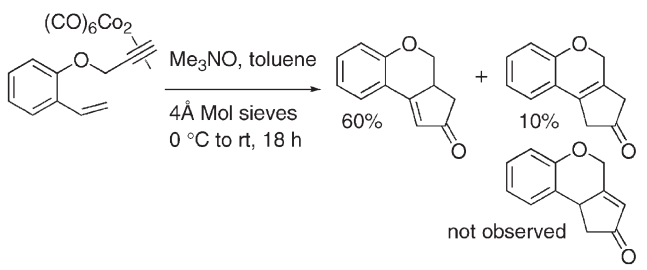
(70)

Under the classical thermal cyclization conditions epimerization α to the carbonyl of the newly formed cyclopentenone was observed (Eq. 71).[28,58,164] While the possibility of alkene isomerization prior to cycloaddition was not ruled out, it was demonstrated that epimerization can take place after cyclopentenone formation.[58] With the advent of the amine oxide-promoted reactions, where shorter reaction times and lower temperatures are possible, translation of alkene stereochemistry into the cycloadduct is generally highly efficient.



(71)

Although driven by the formation of a more stable alkene, migration of the cyclopentenone double bond occurs relatively infrequently. Prolonged reaction times or the presence of a base[151] tends to favor double bond migration and other secondary processes. Intramolecular reactions of styrene derivatives typically provide significant amounts of PK adducts with migrated double bonds (Eq. 72).[61,173] Deconjugation of an α,β-unsaturated enone to a β,γ-enone to form a tetrasubstituted alkene is uncommon, although it is



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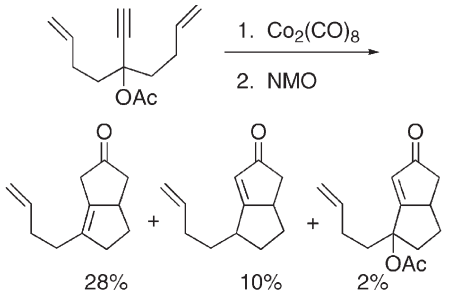
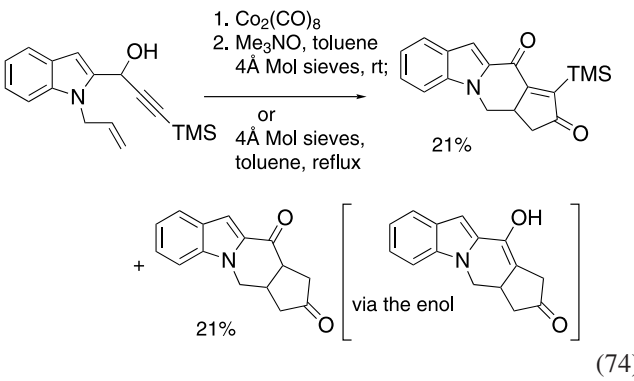
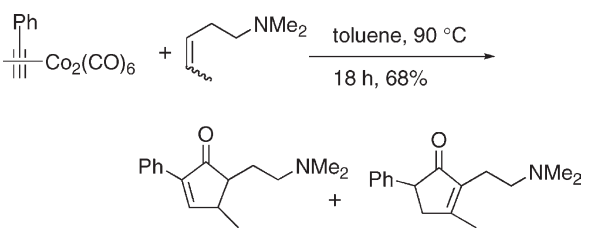


(73)

favorable in the presence of a leaving group in the allylic position (Eq. 73),[107] or when a conjugated alkene or an enol is formed (Eq. 74).[174,175] The saturated diketone in Eq. 74 was formed via the enol ether with concomitant desilylation occurring upon migration of the emerging double bond. Interestingly, in the amine-oxide-promoted reaction, the allylic alcohol resulting from the PK cycloaddition was oxidized to the ketone generating an enedione. Protection of the alcohol as the TBS ether eliminated both the oxidation and double bond migration problems. Somewhat surprisingly, in the dimethylamino-directed intermolecular PKR, double bond migration was observed with a disubstituted alkene (Eq. 75).[58]

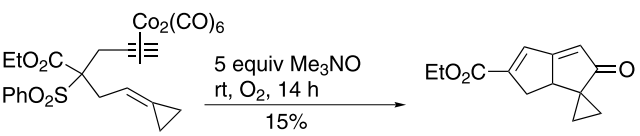


(74)

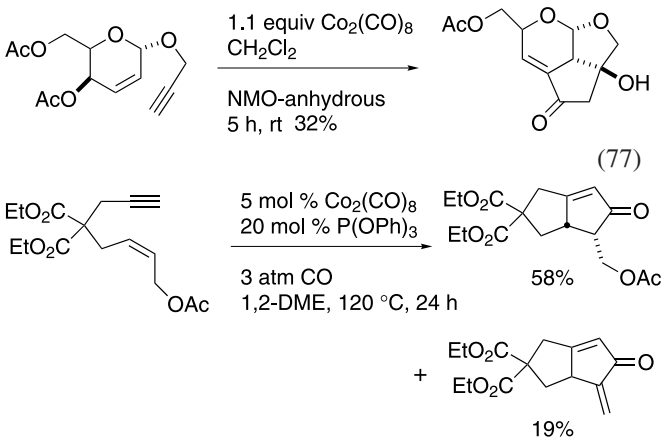


(75)

Leaving groups appropriately oriented in the cycloadduct tend to undergo 1,2-elimination to generate a conjugated system.[50,173,176–180] Elimination of sulfonyl and acetyl groups was reported to occur under either mild amine oxide-promoted reactions (Eqs. 76 and 77), or thermally- induced reactions (Eq. 78).



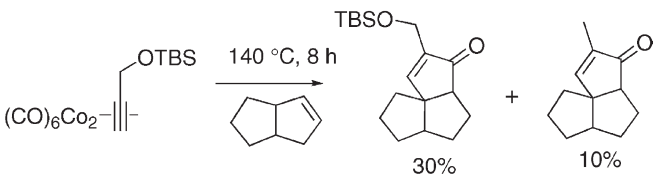
(76)



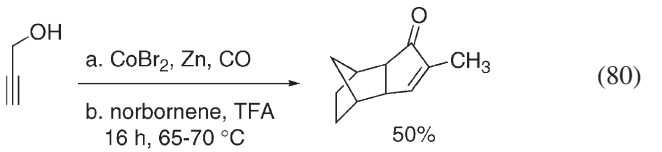
(77)

(78)

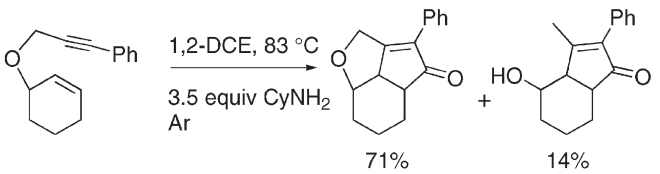
2.6.2. Hydrogenolysis of substituted cyclopentenones. Hydrogenolysis of C–O bonds present before cycloaddition as propargylic substituents, or after cycloaddition as allylic groups occurred under both amine oxide and thermal reaction conditions (Eqs. 73, 79–84; Scheme 5).[20,28,61,74,79,84,86,107,113,133,134,166,181] In some cases, prevention of the reduction process, believed to be due to the presence of cobalt hydrides, was possible by conducting the reaction under a blanket of O_2 (Eqs. 82 and 83). Consequently, regio- and diastereoselective construction of a 3-methylcyclopentenone moiety was effected by optimizing the conditions for reductive cleavage of an ethereal tether (Eq. 84).[182]



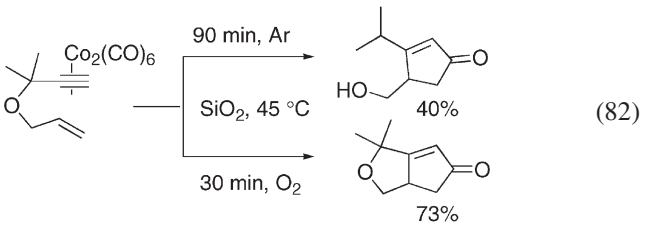
(79)



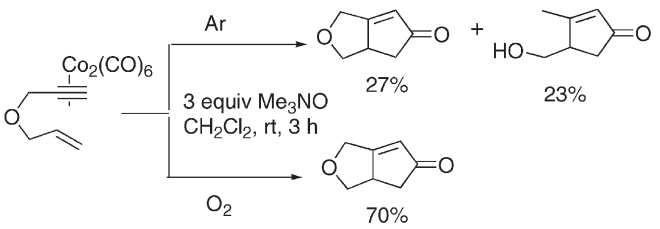
(80)



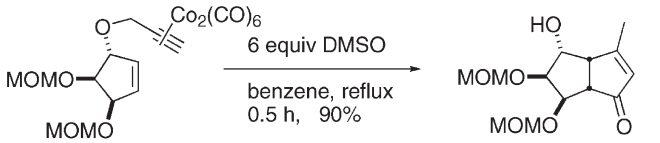
(81)



(82)



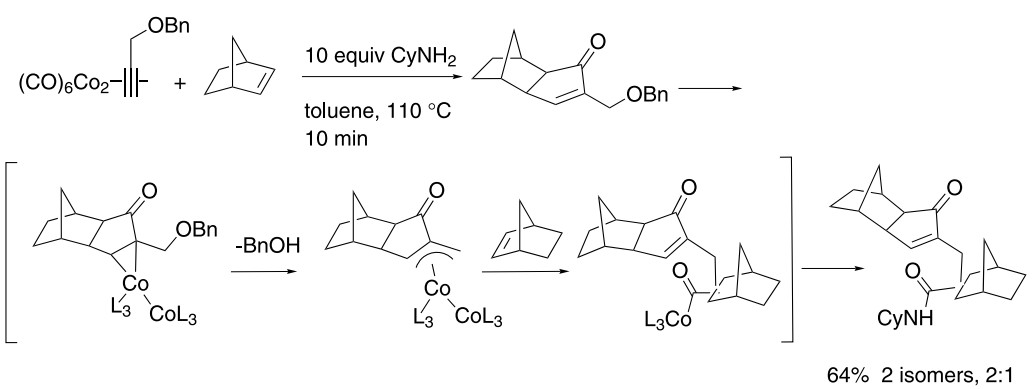
(83)



(84)

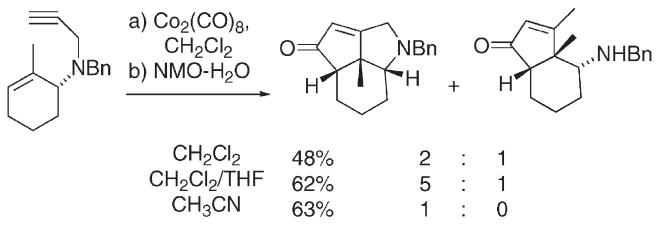
Mechanistically, when the resulting allylic group is *exo* to the newly forming ring, C–O bond cleavage could in principle have occurred either before or after the cycloaddition. Observed results do not necessarily clarify the specific reaction pathway in all cases. However, when the resulting allylic group is in the tether between the alkene and alkyne, product formation and regiochemistry strongly suggest that reduction occurred after cycloaddition. Cleavage of a propargylic group in the tether prior to cycloaddition generally results in a failure to observe the desired cycloaddition, for example, Scheme 9.[61,79]

In a synthesis of dendrobine, hydrogenolysis of the resulting allylic amino functionality was observed, and was determined to be a function of the solvent (Eq. 85).[183] Because of product dependence on solvent polarity, it was proposed



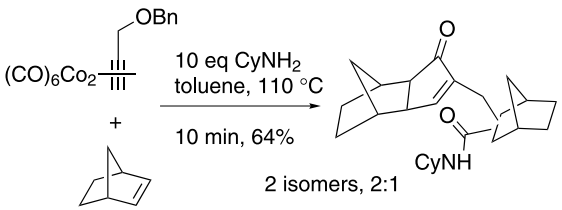
Scheme 29.

that coordination of cobalt to the amine was responsible for promoting the side reaction.



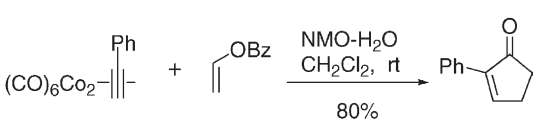
(85)

The lability of an allylic ether group under PKR conditions also rendered the possibility of initiating a cascade of subsequent transformations. Highly complex final products were derived from a novel series of transformations of norbornene and the dicobalthexacarbonyl complex of an alkyne bearing a benzylic ether, namely Pauson–Khand reaction, allylic deoxygenation, alkene insertion and carbamoylation (Eq. 86). Cobalt-mediated displacement of the allylic ether obtained from a PK cyclization generated a π-allylcobalt complex, which further reacted with norbornene to give a 2:1 adduct as a 2:1 mixture of stereoisomers (Scheme 29).[29]



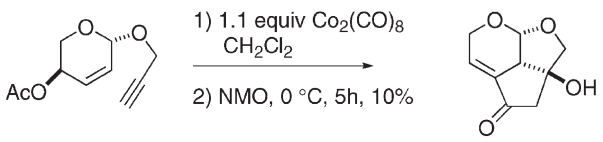
(86)

With the aim of synthesizing polyoxygenated cyclopentenones, vinyl esters were likewise investigated as olefinic substrates in the PKR.[145] Vinyl ethers, under the traditional thermal PK procedure, gave rise to mixtures of 4- and 5-alkoxycyclopentenones in low yields.[73,184] Thus, it was anticipated that use of amine oxides to promote the reaction would result in an improvement in the yield. Surprisingly, under these conditions, reaction of phenylacetylenehexacarbonyldicobalt with vinyl acetate gave only the 2-phenyl-2-cyclopentenone, the product of deoxygenation. It was speculated that low oxidation state cobalt species were responsible for the reduction. This reaction was optimized to provide a new synthetic tool, where other 'ethylene equivalents', such as vinyl bromide[136] and vinyl benzoate, have been shown to undergo effective PKR (Eq. 87).[185] It was recently noted that 1-sulfonimidoyl substituted 1,7-enynes undergo cycloaddition followed by in situ reductive cleavage of the sulfonimidoyl group.[186] Halogenated alkenes were similarly studied in the PKR using bromine as a regiochemical control element in which in situ halogen removal after cycloaddition left no trace of the directing group (Scheme 24).[144] However, fluoroalkenes undergo the Pauson–Khand reaction in moderate yield giving rise to the defluorinated enone as the only product.[44]

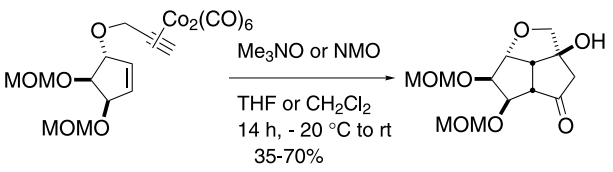


(87)

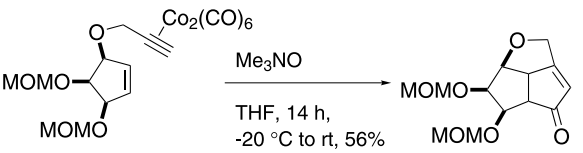
2.6.3. In situ oxidation of strained cyclopentenones. Strained enones generated from PK reactions were demonstrated to undergo subsequent processes in order to reduce inherent strain in the molecule. An epoxidation of a bridgehead alkene[81] was noted in the synthesis of medium-sized rings via the amine-oxide-promoted PKR (Eq. 63). 3-Hydroxylation of bridging enones was also observed on several occasions under oxidative cyclization conditions (Eq. 77,[177] Eq. 88,[187] and Eq. 89[182]). It is of interest that the β-anomer (Eq. 88) furnished the hydroxylation product while the corresponding α-anomer yielded the desired PK product, albeit only in low yield (10%). Hydroxylation of the ether-bridged tricycle was shown to be diastereomer dependent (Eq. 89 vs. Eq. 90). These results were rationalized by comparison of the effective angle and steric strain in both the enones and the diastereomeric hydroxylated products. The mechanisms of the epoxidation and hydroxylation reactions are not well understood at this point.



(88)



(89)



(90)

2.6.4. Formation of bicyclooctanones: reductive PKR. Formation of saturated ketones from enynes, referred to as the reductive PKR, under PK conditions has also been observed. This transformation, which has not received as much attention as the related Pauson–Khand reaction, constitutes a formal sequential cyclocarbonylation and 1,4-reduction of the intermediate bicyclooctenone. It has often been reported as a side reaction in several modified Pauson–Khand reaction procedures. This is a potentially useful reaction since in almost all of the PK cyclizations that have been applied in organic synthesis the cyclopentenones were subsequently converted to the saturated ketones.[63,183,188] Unless the enone moiety is needed for further elaboration, this transformation is conceivably quite useful in synthesis.

Table 1 summarizes accounts on cyclopentanone formation arising from alkenes and cobalt alkyne complexes. Isolation and identification of significant quantities of cyclopentanones were first accounted by Serratosa in cyclizations of (enyne)$Co_2(CO)_6$ complexes that were carried out at unusually high temperatures in aromatic solvents (entry 1).[74,189] Significant amounts of cyclopentanones were

Table 1. Accounts on reductive Pauson–Khand reactions

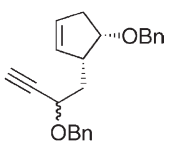
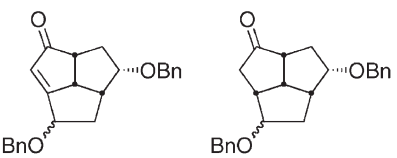
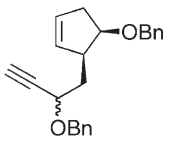
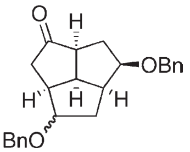
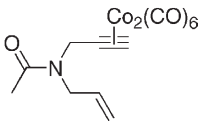
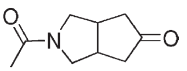
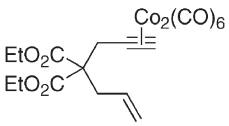
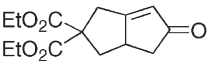
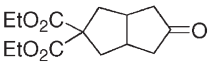
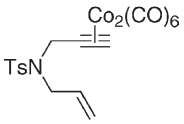
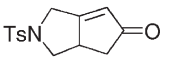
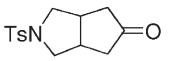
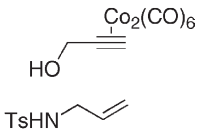
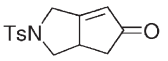
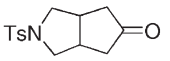
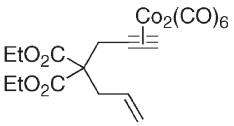
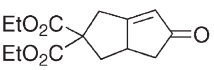
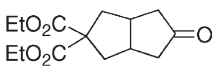
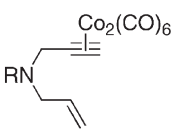
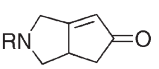
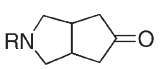
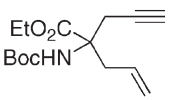
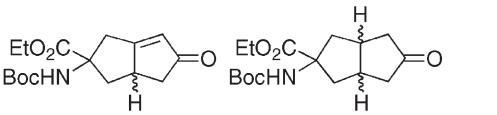
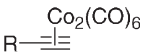
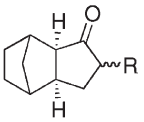
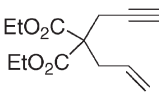
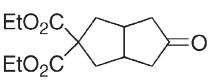
Entry	Substrate(s)	Reaction conditions	Product(s) (% yield)
1		(a) 1.4 equiv. $Co_2(CO)_8$, *t*-BuPh, N_2, rt, 6 h; (b) CO, 169 °C, 2–3 h	 60% (no ratio indicated)
2	 (4:1 dr)	(a) 1.3 equiv. $Co_2(CO)_8$, pentane, N_2, rt, 12 h; (b) 230–400 mesh ASTM silica gel; evaporate; (c) 'Buchi rotavapor' 150 °C, 6 h	 30% (3:1 dr)
3		SiO_2, 70 °C, 1.5 h	 67%
		Ultrasound, *i*-octane, 60 °C, 5 h	36%
		UV, *i*-octane, 50 °C, 20 h (300 nm/85 W)	33%
		i-Octane, 100 °C, 24 h	5%
4		CH_2Cl_2, Me_3NO, −78 °C to rt, Ar	 81%  2%
5		CH_2Cl_2, Me_3NO, −78 °C to rt	 
		Ar	82% (4:1)
		O_2	99% (1:0)
6		(a) $BF_3{\cdot}Et_2O/CH_2Cl_2$, −78 °C to rt; (b) 3–4 equiv. Me_3NO, CH_2Cl_2, rt Ar, 1 h	  80% (4:1)
7			 
		CH_2Cl_2, 40 °C, air, 36 h	25% 2%+18% RSM
		CH_2Cl_2, 3 equiv. DMSO, 40 °C, air, 4 h	83% 3%
8		Merck silica gel 60, rotary evaporator, 70 °C	 
		R=Boc N_2	94% (0:1)
		Air	79% (1:5)
		R=Bz N_2	87% (0:1)
		Air	<53% (1:0)

Table 1 (*continued*)

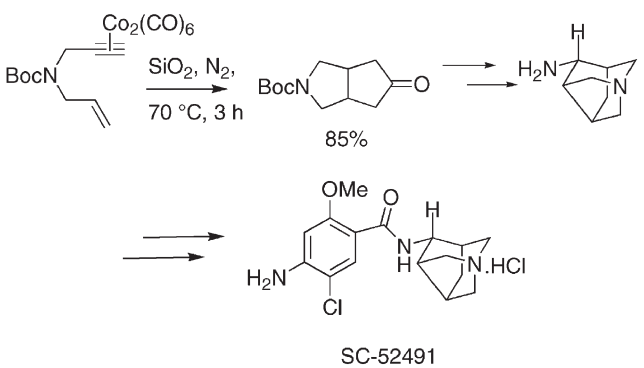
Entry	Substrate(s)	Reaction conditions	Product(s) (% yield)
9		(a) $Co_2(CO)_8$, toluene rt, 4 h; (b) Toluene, 80 °C, 3 h	 47% Minor (no yield given)
10		(a) 2 equiv. $CoBr_2$, 2.2 equiv. Zn THF, CO, 25 °C, 3 h; (b) 2 equiv. norbornene, 8 equiv. TFA, 60–70 °C, 16 h	 R=*n*-$C_{10}H_{21}$ 60% R=Ph 40%
11		1 equiv. $Co_4(CO)_{12}$, *i*-PrOH, H_2, 70 °C, 16 h	 67%

observed in cyclizations of these complexes in refluxing toluene, *tert*-butylbenzene and xylene.[85] As expected, at lower temperatures this side reaction was avoided and the desired PKR was favored.[74] In contrast, saturated ketones were also exclusively formed at a higher temperature (entry 2) using the dry state adsorption conditions (DSAC)[133–135] protocol.[190] In fact, Pauson later reported that cyclopentanones had been frequently encountered as trace by-products in their earlier cyclization studies,[191] although in their detailed study on cyclizations of *N*-acylallylpropargylamines, its exclusive formation was achieved using several protocols (entry 3).[191] 1,7-Enynes underwent the normal Pauson–Khand cyclization regardless of the reaction conditions.

Following these initial reports only occasional accounts on cyclopentanone formation as a side reaction in subsequent modified protocols for the PKR appeared. Under an argon atmosphere, saturated carbocyclic and azacyclic ketones were observed as minor products when the reaction was promoted using amine oxides, although their formation was prevented under an atmosphere of O_2 (entries 4 and 5).[166] Similar observations were noted in the studies on the one-pot sequential $BF_3{\cdot}Et_2O$-mediated reactions of dicobalthexacarbonyl complexes of propargyl alcohol with allyl amides (Nicholas reaction) and the Me_3NO-promoted Pauson–Khand reaction (entry 6).[192] Similarly, it was noted that the formation of saturated ketones was enhanced in cyclizations mediated by NMO containing 3 M equiv. of water. It was further found that in the presence of D_2O, the bridgehead position, and to a smaller extent, the methylene moiety α to the carbonyl group were deuterated.[107] In catalytic Pauson–Khand reactions using aqueous colloidal cobalt nanoparticles as catalysts under high CO pressures, the formation of saturated ketones was observed when terminal alkynes were employed.[193] The aqueous thermal Pauson–Khand reaction of substrates bearing a terminal alkyne, in which the sluggishness of the reactions in water alone was circumvented by the use of surfactants, gave rise to reduced enones when using $Co_4(CO)_{12}$ as the catalyst.[194] Bicyclooctanones were likewise obtained as minor products in cyclizations in CH_2Cl_2 under air, with or without DMSO as an additive (entry 7).[143] Interestingly, increasing the amount of DMSO in the reaction increases the efficiency of cyclopentanone formation under these reaction conditions. This observation was not pursued nor was its generality established.

A systematic study was conducted that demonstrated the exclusive formation of azabicyclic saturated ketones from enynes.[195] Pauson–Khand reactions under the DSAC protocol under an inert atmosphere provided excellent yields of azabicyclo[3.3.0]octanones from *N*-protected allylpropargylamines.[195] Standard cyclizations in air gave mixtures of ketones and enones (entry 8). The reversal of the reaction course is noteworthy in cyclizations of *N*-benzylated substrates under a N_2 atmosphere and air. This protocol was subsequently applied to the construction of the key *meso*-azabicyclo[3.3.0]octanone intermediate for the syntheses of the antagonists SC-52490 and SC-52491 via the enantiomeric azaadamantane (Scheme 30).[196] In an approach to a bicyclic non-proteinogenic α-amino acid, the in situ generated cobalt carbonyl complex of an *N*-protected homoallylamine gave the saturated bicyclic ketone in toluene at 80 °C under a nitrogen atmosphere (entry 9).[197]

In the presence of trifluoroacetic acid, cyclopentanones

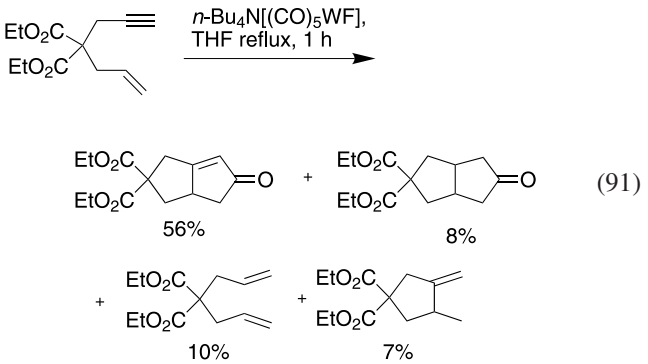


Scheme 30.

were formed from the Pauson–Khand reactions of cobalt alkyne complexes with norbornene under a CO atmosphere, although minor amounts of cyclopentenones were still observed (entry 10).[198] Under these reaction conditions, the cobalt carbonyl complex was generated in situ from the reduction of $CoBr_2$ by Zn metal, which subsequently reacted with the alkyne present in the mixture. Trifluoroacetic acid was proposed either to induce formation of $HCo(CO)_4$, which reduced the enone, or react with the reactive intermediate prior to decomplexation.

While exploring the reactivity of $Co_4(CO)_{12}$,[86,199] in particular with enynes, it was discovered that the reaction of diethyl (propargyl)allylmalonate with a stoichiometric amount of $Co_4(CO)_{12}$ in *iso*-propanol under a H_2 atmosphere provided a good yield of a cyclopentanone (entry 11).[86] A reductive Pauson–Khand cyclization of enynes has presumably occurred under these conditions although this was observed to be limited to 1,6-enynes bearing a terminal alkyne group and a mono- or disubstituted alkene moiety. 1,7-Enynes, in contrast, generated a mixture of substituted cyclohexenes in addition to the PK adduct.[86] It has long been documented that in *iso*-propanol under a CO atmosphere at rt, $Co_4(CO)_{12}$ could be transformed into $Co_2(CO)_8$ that could potentially effect the PKR of enynes.[200] It was further speculated that, via a metal hydride transfer, the PK cycloadduct underwent an in situ 1,4-reduction by $HCo(CO)_4$, that is presumably generated from the reaction of residual cobalt carbonyl complexes with an excess of *iso*-propanol. $HCo(CO)_4$ has been proposed, in early studies cited above, to reduce enones to ketones under the PKR conditions. Deuterium labeling experiments also indicated that, although a hydrogen atmosphere is beneficial to the reactions the hydroxylic hydrogen of the solvent is the hydrogen that is being transferred into the enone. When intramolecular cycloadditions of internal alkynes were conducted in 1,2-DME, in the presence of water as an additive, cyclopentanones were observed as major products.[181]

Formation of reduction products as a side reaction was also observed in the cyclization of enynes in refluxing THF using the in situ-generated *n*-$Bu_4[(CO)_5WF]$ (Eq. 91). Complete suppression of this side reaction and a similar yield of the cyclopentenone were achieved when an equivalent anhydrous system, K(DB18C6)$[(CO)_5WF]$ was used, although a longer reaction time was required.[201] Procedures for the tandem Pauson–Khand reaction followed by an in situ reduction have now been established.[120,202]

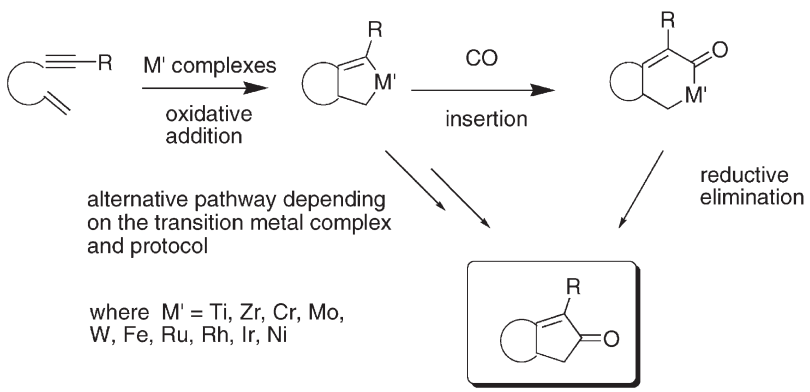


(91)

3. Pauson–Khand-type reactions

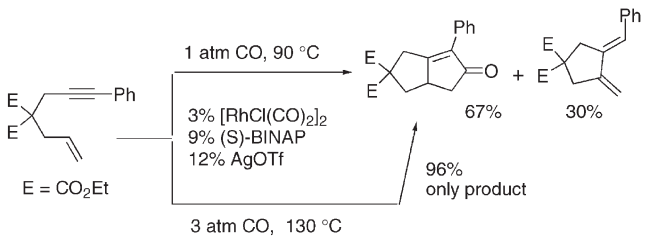
It is generally accepted that the Pauson–Khand reaction proceeds via a metallacyclopentene, which is derived from the oxidative addition of a cobalt-coordinated alkyne with an alkene (Scheme 1). Since other transition metals have been either demonstrated or speculated to generate bicyclic metallacyclopentenes from enynes, a variety of other metal complexes have consequently been demonstrated to effect Pauson–Khand-type reactions (Scheme 31). They offer alternative protocols exhibiting complementary reactivity to, or even superior selectivity than, the ones reported based on cobalt complexes. In a similar manner, alkene–alkyne co-cyclizations with CO to yield cyclopentenones using transition metal complexes other than cobaltcarbonyl complexes, the Pauson–Khand-type reactions, have also led to a number of surprising results. The most commonly formed by-products are 1,3- and 1,4-dienes and monoalkenes, although other modes of interruption of the PK-like process have also been observed.

Different types of dienes have been formed under the PK-like reaction conditions. Asymmetric Rh(I)-catalyzed intramolecular PK-type reactions proceed using $[RhCl(CO)_2]_2$ as the catalyst with (*S*)-BINAP as the chiral ligand under 1–3 atm of CO in THF (Eq. 92).[203] Of the 12



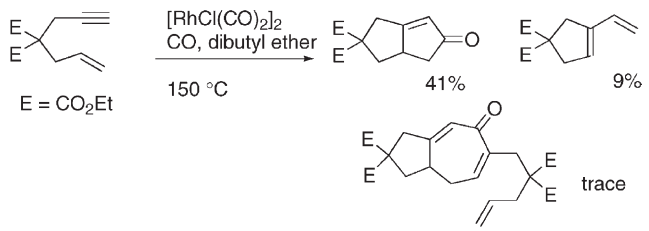
Scheme 31.

examples, only one gave rise to a 1,3-diene as a by-product. Diene formation was proposed to occur through β-elimination and reductive coupling of the corresponding rhodium metallacyclopentene intermediate (cf. Scheme 1). This route to dienes was, however, inhibited by high pressures of CO, which presumably promote CO insertion.

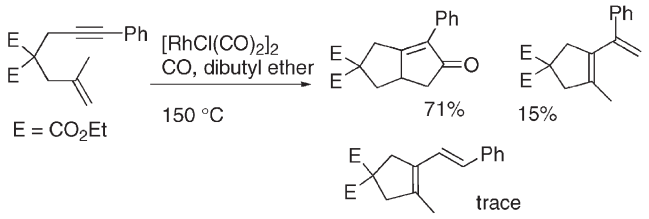


(92)

At a higher temperature and using dibutyl ether as solvent, reactions of a 1,6-enyne bearing a terminal alkyne with $[RhCl(CO)_2]_2$ yielded two by-products resulting from skeletal reorganizations and intermolecular cycloadditions of the metallacycle (Eq. 93).[204,205] Interestingly, with an internally substituted alkene and an internal alkyne two different cycloisomerized products were formed under the same reaction conditions (Eq. 94).[205] Other complexes of ruthenium[206] and platinum[207] have also been shown to effect skeletal reorganizations of 1,6-enynes in high yields.

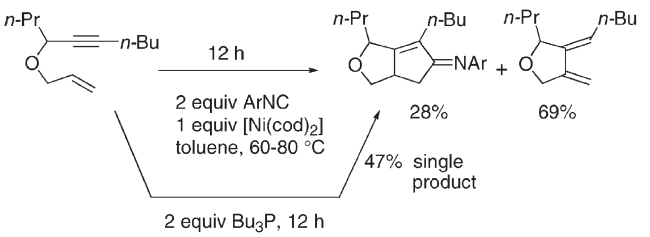


(93)

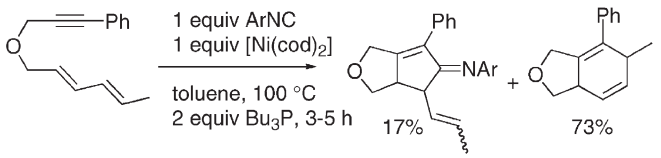


(94)

Dienes were likewise isolated in a nickel-promoted cyclocarbonylation of enynes, although the presence of a phosphine inhibited 1,3-diene formation and promoted the desired cyclocarbonylation (Eq. 95).[208] Quite unexpectedly, nickel-promoted cyclization of a 1,3-dienyne gave rise to a Diels–Alder adduct as the major product, a process favored by the presence of a terminal methyl group on the diene moiety (Eq. 96).[209]



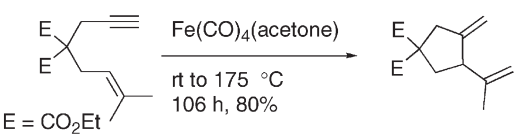
(95)



(96)

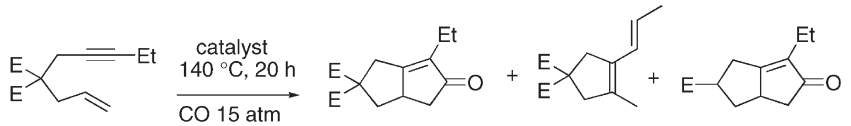
Ruthenium-catalyzed Pauson–Khand type cycloadditions also require relatively high temperatures and high pressures of carbon monoxide for successful conversion of enynes to bicyclic cyclopentenones.[210–212] It was further noted that the efficacy of the desired cycloaddition and minimization of by-product formation were determined to be a function of solvent and catalyst type (Table 2).[210] Formation of the 1,3-diene was suggested to arise from β-hydride elimination of a metallacyclic intermediate and its subsequent reductive elimination/alkene isomerization.[213] Using higher pressures of CO, $[Ru_3(CO)_{12}]$-catalyzed intermolecular reactions of alkynes with strained alkenes furnished hydroquinones.[211]

1,4-Dienes were isolated from reactions using both iron and titanium complexes. In the iron-promoted process, reaction of the trisubstituted alkene with the alkyne moiety yielded a 1,4-diene, which was presumably derived from an iron-mediated ene reaction (Eq. 97).[214,215] In Buchwald's titanium-catalyzed enyne cyclocarbonylation protocol diene formation was only observed from an enyne possessing a *trans*-disubstituted alkene (Eq. 98).[216,217] A plausible mechanistic rationale involves formation of a titanium metallacyclic intermediate followed by sequential β-hydride elimination and reductive elimination (Scheme 1).

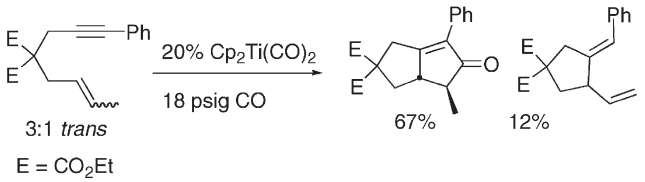


(97)

Table 2. Ruthenium-catalyzed PK-type cycloadditions: solvent and catalyst dependence

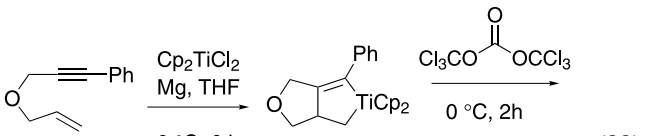


catalyst	solvent	yield (%)		
$Ru_3(CO)_{12}$	DMAC	79	trace	0
$Ru_3(CO)_{12}$	toluene	67	15	0
$[RuCl_2(CO)_3]_2$	DMAC	53	9	0
Ru(cod)(cot)	DMAC	22	trace	38

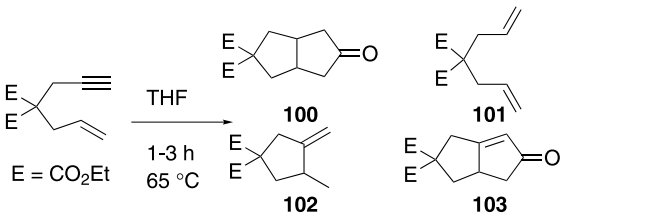


(98)

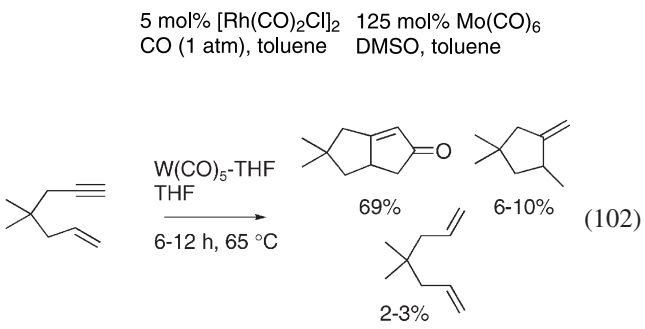
Alkenes resulting from protonolysis of a metallacyclic intermediate or from the in situ reduction of an alkyne have been observed from reactions of enynes using stoichiometric amounts of complexes of titanium (Eq. 99),[218] chromium (Eq. 100)[201] and tungsten (Eqs. 101 and 102).[201,219] The mechanistic origin of the reduction products is not clear in all cases.



(99)

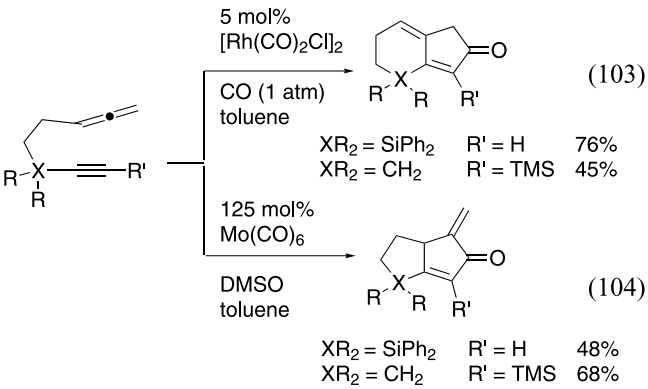


	100	101	102	103	
$Bu_4N[(CO)_5CrF]$	0	36	0	10	(100)
$Bu_4N[(CO)_5WF]$	8	10	7	56	(101)



(102)

Since initial reports on the viability of allenes as partners in the PKR,[220] allenes have been extensively studied in PK and PK-like reactions, which has led to the formation of a variety of side products.[221] Either π-bond of the allene can now be selectively incorporated into the cyclopentenone. In a silicon-tethered allenic PK-like reaction, selectivity reverses from the terminal to the internal double bond with different metal catalysts,[114,150,222] and this observation was extended to include selectivity in carbocycle synthesis (Eqs. 103 and 104). Pauson–Khand-like reactions using allenes are also subject to the formation of unexpected products via secondary processes. 1,4-Dienes were observed,[223,224] as well as conjugated dienones from eliminations of γ-substituted enones.[225] Due to their enhanced conformational rigidity, allenynes were shown to yield seven-membered carbocycles.[150,224–226]

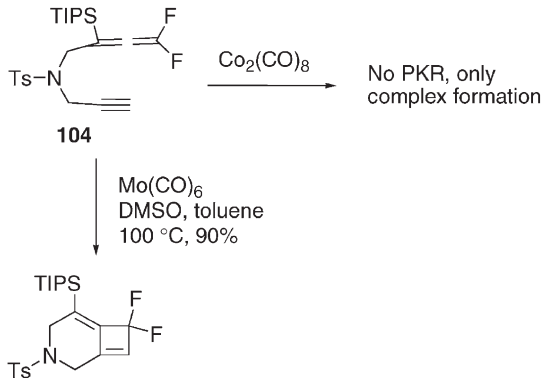


(103)

(104)

In an attempt to generate fluorinated compounds, PK cycloadditions of *gem*-difluoroallenes were investigated.[227,228] While the cyclization using standard PK conditions were unsuccessful, use of the molybdenum-based conditions gave a novel difluoro-fused cyclobutene with no trace of the other regioisomer (Scheme 32). Several examples illustrate the generality of the process. It was speculated that the putative metallacycle undergoes a reductive elimination more rapidly than a CO insertion giving rise to the [2+2] adduct.

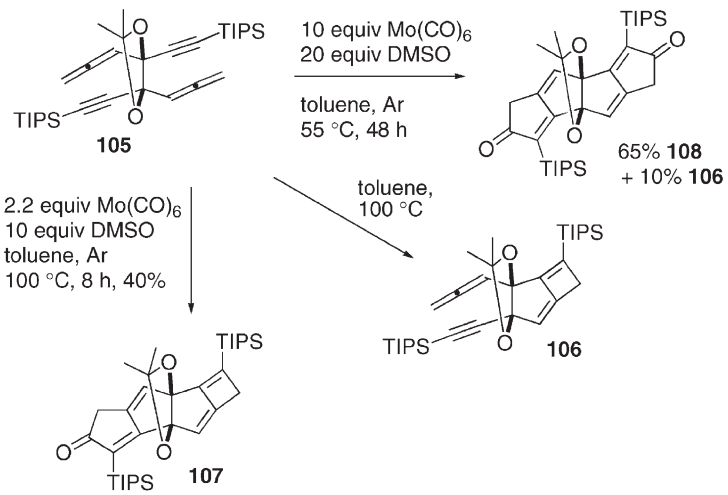
An analogous [2+2] adduct was observed in the synthesis of polyquinenes via an allenic PK-like process.[229] In the absence of a metal catalyst, a [2+2] allenic cycloaddition occurred yielding **106** (Scheme 33). In the presence of two equivalents of $Mo(CO)_6$, both PK and [2+2] cycloadditions



Scheme 32.

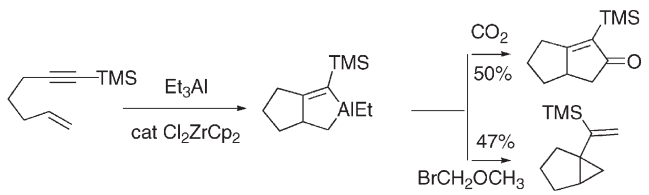
occurred giving rise to **107**. Cyclobutene formation was minimized with the use of ten equivalents of metal promoter providing the desired polycycle **108**.

Investigations of carbon–carbon bond forming reactions of aluminum metallacycles led to the unexpected formation



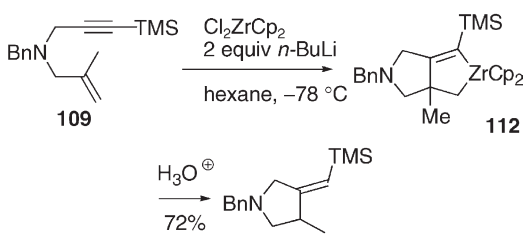
Scheme 33.

of a vinylcyclopropane (Eq. 105).[230] Several examples illustrated the generality of the cyclization.

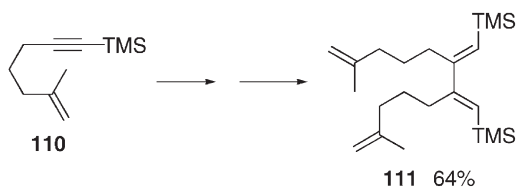


(105)

Sterically congested or conformationally mobile enynes tend to react via alternate pathways. Zirconium-mediated cycloaddition of enyne **109** led to the desired alkene product after protonolysis, although the analogous enyne **110** yielded dimer **111** as the sole product (Eq. 107).[230] Conformational mobility of enyne **110** allowed for the dimerization of the alkyne rather than the intramolecular cycloaddition, which would have been more facile in substrates bearing tether substituents that exert Thorpe-Ingold assistance.

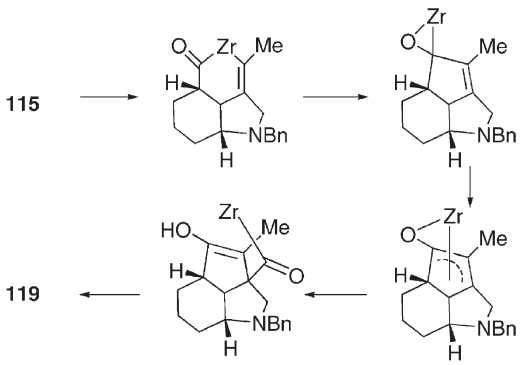


(106)

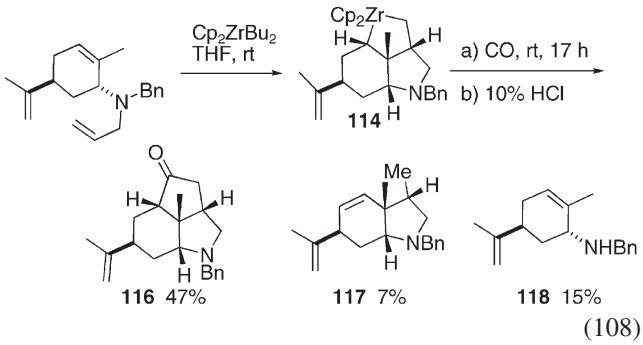


(107)

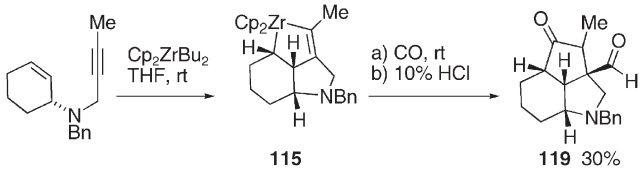
Another surprising set of results was obtained in the attempted carbonylation of zirconacycles **114** and **115** (Eqs. 108 and 109).[231,232] Reaction of zirconacycle **114** for 17 h under a blanket of carbon monoxide followed by treatment with acid yielded the desired ketone **116**, in addition to small amounts of alkenes **117** and **118**. Alkene **117** is the product of β-hydride elimination and protonolysis while monocycle **118** is a product of *N*-deallylation. Loss of the allylic amine was proposed to occur via a (π-allyl)zirconium complex. Carbonylation of zirconacycle **115** under identical conditions gave solely the doubly carbonylated adduct **119**. While the reason for the incorporation of the two carbonyl groups is unclear, a proposed mechanistic rationale is presented in Scheme 34.



Scheme 34.



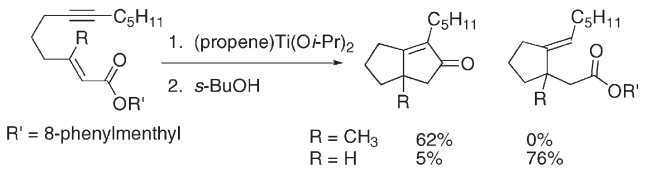
(108)



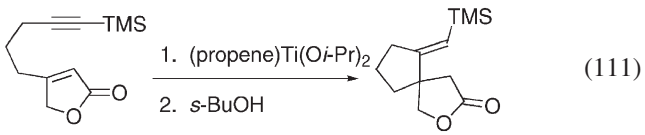
(109)

Although intramolecular molybdenum-mediated carbonylative enyne cycloadditions proceed well to give the desired cyclopentenone, the corresponding intermolecular processes yield alkyne cyclotrimerization products.[233] Ruthenium-catalyzed intermolecular cycloadditions of strained alkenes gave rise to hydroquinones instead of the anticipated adducts, thus providing a limitation of $Ru_3(CO)_{12}$-mediated PK-type processes.[234] The corresponding rhodium-catalyzed intermolecular cycloaddition of strained alkenes provided the expected cycloadducts. Reactions, however, with unstrained alkenes gave quinones in good yields, which result from the cycloaddition of 2 equiv. of an alkyne with 2 equiv. of CO.[205]

Titanium-mediated cycloadditions of enoates, which are doubly substituted at the β-position have been shown to yield bicyclooctenones efficiently.[235,236] In the absence of the second β-alkyl group monocycles were formed instead of bicycles (Eq. 110). In addition, a rigid cyclic ester failed to undergo the desired carbonylation halting the process at the stage of the monocycle (Eq. 111).



(110)



(111)

Furthermore, a few examples of unexpected regio- and stereochemical outcomes are evident in PK-type reactions. The regiochemical outcome of intermolecular PK-type cycloadditions is generally less selective than that of the cobalt-mediated counterparts, where the largest group ends up adjacent to the carbonyl of the cyclopentenone. With bis(cyclopentadienyl)tetracarbonyl–dimolybdenum complexes of terminal alkynes, mixtures of 2- and 3-substituted regioisomers were obtained in moderate yields in their reactions with norbornadiene and norbornene, forming up to 40% of the unexpected 3-substituted regioisomer.[237,238] An intermolecular cycloaddition between norbornene and 1-phenyl-1-propyne catalyzed by $[RhCl(CO)_2]_2$ gave a 1:1 mixture of both regioisomers.[205] Using the dimethyl-(2-pyridyl)silyl group as a removable directing group,[239] ruthenium-catalyzed intermolecular cycloadditions with terminal alkynes gave mixtures of 2- and 3-substituted enones.[240] The directing group was shown to control the regiochemical outcome resulting from cycloaddition across the alkene moiety.[22]

Substituents on the tether between the alkene and alkyne influence the stereochemical outcome of the newly forming stereogenic center in intramolecular processes. In PK-like processes, the stereochemical influence from groups on the tether is not well-documented as few examples are available. In some cases, mixtures of *endo* and *exo* adducts have been documented.[205,241]

Finally, in parallel with the cobalt-mediated cycloaddition, several different reactions have been reported to take place after the cyclocarbonylation. Decarbonylation of a β-keto ester under rhodium-catalyzed conditions occurred competitively,[44,205] and isomerization α to the carbonyl of the newly formed cyclopentenone took place under titanium catalysis.[216]

4. Summary and outlook

The Pauson–Khand reaction typifies the tremendous impact of transition metal complexes in modern organic transformations. The rapid development that it has seen, including the related PK-type reactions, is a result of their continued appeal, which further led to the discovery of other potentially useful side reactions. Considering the enormity of these reactions we felt that a comprehensive organization was essential, especially when some of them have already been amplified for practical use. This review is further intended to stimulate researchers to be more critical and unbiased in examining reaction outcomes, the manner in which the Pauson–Khand reaction itself was discovered. Finally, we hope that this focus on side reactions observed under the PK and PK-type reaction conditions can serve as a catalyst for research and review in other areas of chemistry.

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Tubiferal A, a backbone-rearranged triterpenoid lactone isolated from the myxomycete *Tubifera dimorphotheca*, possessing reversal of drug resistance activity

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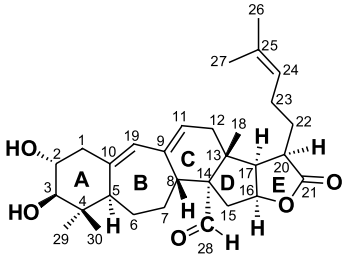
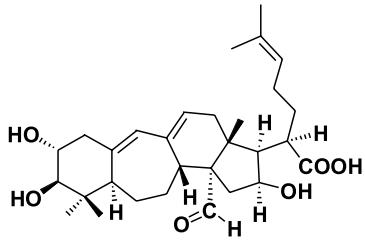
Abstract—Tubiferal A, a novel rearranged triterpenoid lactone, has been isolated from field-collected fruit bodies of the myxomycete, *Tubifera dimorphotheca*, and its structure elucidated by spectral data. Tubiferal A (**1**) possesses a 9,10-secocycloartan-16,21-olide skeleton, and this new compound exhibited a reversal effect of vincristine (VCR) resistance (more than 4-fold) against VCR-resistant KB cell lines. Tubiferal B (**2**), corresponding to the seco acid of **1** was also isolated, but showed no comparable activity.

1. Introduction

Myxomycetes (true slime molds) are an unusual group of primitive organisms that may be assigned to one of the lowest classes of eukaryotes, and chemical studies on the secondary metabolites of the myxomycetes are limited so far.[1] During a search for bioactive natural products from myxomycetes,[2,3] we recently investigated a field-collected sample of the fruit bodies of *Tubifera dimorphotheca* (Enteridiaceae). Here we describe the isolation and structure elucidation of a novel triterpenoid lactone, tubiferal A (**1**). Compound **1** was revealed to possess a reversal effect of vincristine (VCR) resistance (more than 4-fold) against VCR-resistant KB cell lines. Tubiferal B (**2**), corresponding to the seco acid of **1**, was also isolated, but showed no comparable activity.



1



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2. Results and discussion

The fruit bodies of *Tubifera dimorphotheca*, collected in Kochi Prefecture, Japan, were extracted with 90% MeOH and 90% acetone. The combined extracts were subjected to

Keywords: Myxomycete; *Tubifera dimorphotheca*; Rearranged triterpenoid; Reveasal of drug resistance.
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flash chromatography on ODS, followed by preparative HPLC on ODS eluted with 65–75% MeOH to give tubiferals A (**1**) and B (**2**) in 0.3 and 0.4% yield of the extract, respectively.

Tubiferal A (**1**), colorless amorphous solid, $[\alpha]_D^{22} = -87$ (*c* 0.12, MeOH), showed a quasi-molecular ion peak at *m/z* 483 $(M+H)^+$ in its positive ion FAB mass spectrum. The molecular formula of **1** was revealed as $C_{30}H_{42}O_5$ by the HRFABMS data [*m/z* 483.3101, $(M+H)^+$, Δ −0.9 mmu]. The UV spectrum of **1** showed absorption maxima at 239 and 246 nm, indicating the presence of conjugated system(s). The IR absorption bands at 1770 and 1715 cm^{-1} were suggestive of the presence of two carbonyl groups. The ^1H NMR spectrum of **1** in $CDCl_3$ (Table 1) showed a characteristic low-field resonance at δ_H 9.65 (1H, s), assignable to an aldehyde group. The ^1H NMR also showed signals due to three olefinic protons (δ_H 5.07, 5.78, and 6.10), three oxymethine protons (δ_H 3.13, 3.59, and 4.85), and five singlet methyls (δ_H 0.77, 1.04, 1.07, 1.60, and 1.70). These observations were also corroborated by its ^{13}C NMR spectrum (Table 1), aided by DEPT experiments, which gave thirty signals assignable to two carbonyls, six olefinic carbons (three methines and three quaternary), three oxymethines, seven sp^3 methylenes, four non-oxygenated sp^3 methines, three sp^3 quaternary carbons, and five methyl groups. Since five out of the ten unsaturation equivalents were accounted for from the ^{13}C NMR data, **1** was inferred to have five rings. The ^1H–^1H COSY spectrum of **1** showed the connectivities for five proton-networks: H_2-1/H-2/H-3, H-5/H_2-6/H_2-7/H-8, H-11/H_2-12, H_2-15/H-16/H-17/H-20/H_2-22, and H_2-23/H-24 (as shown in Figure 1). Interpretation of the HMBC spectral data of **1** led to assemblage of these five proton-networks and the remaining hydrogens and quaternary carbons to construct the whole structure of **1** consisting of four consecutive 6/7/6/5 carbocycles with a γ-lactone and a side chain as described below.

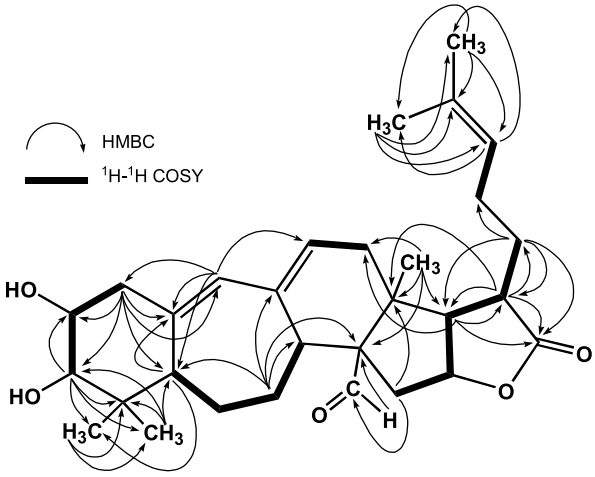


Figure 1. Key ^1H–^1H COSY and HMBC data of **1**.

Table 1. ^1H and ^{13}C NMR data of tubiferals A (**1**) and B (**2**)

Positions	**1** ($CDCl_3$)		**2** (CD_3OD)	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1	(α) 2.21 dd (13.9, 7.9) (β) 2.52 dd (13.9, 5.1)	47.2	(α) 2.13 dd (12.7, 12.0) (β) 2.44 dd (12.7, 5.4)	49.2
2	3.59 m	71.3	3.47 ddd (12.0, 9.3, 5.4)	72.2
3	3.13 d (9.2)	82.5	3.00 d (9.3)	83
4		40.8		41.9
5	2.04 m	50.1	2.04 m	51.1
6	(α) 1.25 m (β) 1.38 m	25.6	(α) 1.39 m (β) 1.73 m	26.8
7	(α) 1.25 m (β) 1.45 dd (13.4, 8.2)	29.8	(α) 1.13 dd (8.4, 3.8) (β) 2.17 m	31.1
8	2.40 br d (11.9)	45.6	2.36 m	47.7
9		137.7		138.6
10		134.8		135.1
11	5.78 br t (2.4)	129.1	5.77 s	131.8
12	(α) 2.28–2.32 m (β) 2.35 dd (19.8, 5.4)	37.8	(α) 2.28 m (β) 2.36 m	37.9
13		45		46.1
14		65.7		64
15	(α) 2.68 dd (13.8, 7.9) (β) 1.65 m	34	(α) 2.67 dd (13.2, 4.5) (β) 1.21 dd (13.2, 8.6)	38.5
16	4.85 ddd (7.9, 6.3, 3.5)	82.1	4.28 ddd (8.6, 6.6, 4.5)	71.8
17	2.31 dd (7.9, 6.3)	51	1.50 dd (8.6, 6.6)	55.1
18	1.07 s (3H)	18.9	1.15 s (3H)	18.7
19	6.10 s	130.2	6.07 s	131.1
20	2.68 m	43	2.57 m	n.o.
21		178.4		n.o.
22	1.65 m and 2.04 m	25.9	1.42 m and 1.90 m[a]	33.1[a]
23	2.14 m and 2.19 m	27.1	1.95 m and 2.04 m[a]	27.4[a]
24	5.07 br t (7.2)	123	5.13 br t (5.7)	125.9
25		133.5		131.6
26	1.70 s (3H)	25.8	1.64 s (3H)	25.7
27	1.60 s (3H)	17.9	1.58 s (3H)	17.7
28	9.65 s	208.1	9.58 s	210.3
29	1.04 s (3H)	24.7	1.00 s (3H)	25.1
30	0.77 s (3H)	14.9	0.72 s (3H)	15

[a] Signals may be reversed. n.o.: not observed (probably due to small quantity).

The HMBC correlation data, shown in Figure 1, provided evidence for the following connections: (1) two singlet methyls of H_3-29 (δ_H 1.04) and H_3-30 (δ_H 0.77) were attached to the C-4 quaternary carbon (δ_C 40.8), which was located between the two sp^3 methines C-3 (δ_C 82.5) and C-5 (δ_C 50.1); (2) two trisubstituted double bonds (δ_C 134.8, 130.2, 137.7, and 129.1; δ_H 6.10 and 5.78) were conjugated and placed at the C-10/C-19/C-9/C-11 positions to construct 6- and 7-membered rings for the A- and B-rings, respectively; (3) a tertiary methyl (δ_H 1.07 and δ_C 18.9; C-18) and the aldehyde group (δ_H 9.65 and δ_C 208.1; C-28) were attached at the C-13 and C-14 positions, respectively, to give rise to 6- and 5-membered rings for the C- and D-rings, respectively; (4) an ester (or lactone) carbonyl group (δ_C 178.4; C-21) was connected to the C-20 methine carbon, and the low-field resonance of the oxymethine proton on C-16 (δ_H 4.85) implied that the C-16 oxymethine was connected with the C-21 carbonyl group to form a γ-lactone ring, which was consistent with the fact that **1** was inferred to have five rings (vide supra); (5) A side chain consisting of a 4-methyl-3-pentenyl group (C-22–C-27) was also attached to the C-20 methine carbon.

The ^{1}H NMR chemical shifts of H-2 (δ_H 3.59) and H-3 (δ_H 3.13) implied that two hydroxyl groups were located vicinally at the C-2 and C-3 positions, and the coupling constant ($J_{2,3}$=9.2 Hz) was typical for *trans*-diaxial protons, thus indicating that both hydroxyl groups were equatorial. The stereochemical assignment of the angular hydrogens (H-5, H-8, H-16, H-17, and H-20), the angular methyl group (C-18), and the aldehyde group (C-28) were made on the basis of a NOESY spectrum as shown in Figure 2. The key correlations were: H-1α/H-3, H-1α/H-5, H-1β/H-2, H-2/H_3-30, H-3/H-5, H-3/H_3-29, H-6β/H_3-30, H-6β/H-8, H-7α/H-28, H-8/H-15β, H-8/H_3-18, H-12β/H_3-18, H-12α/H-28, H-15α/H-16, H-16/H-17, H-17/H-20, and H_2-22/H_3-18. These ring-juncture configurations of **1** were consistent with those of the cycloartane-triterpene nucleus,[4] although **1** possessed no cyclopropane moiety.

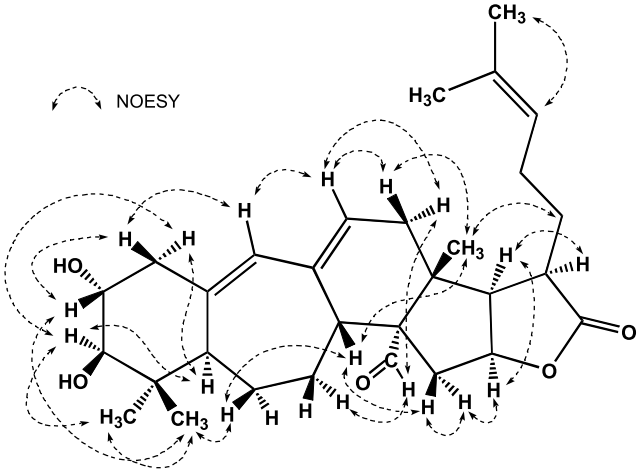
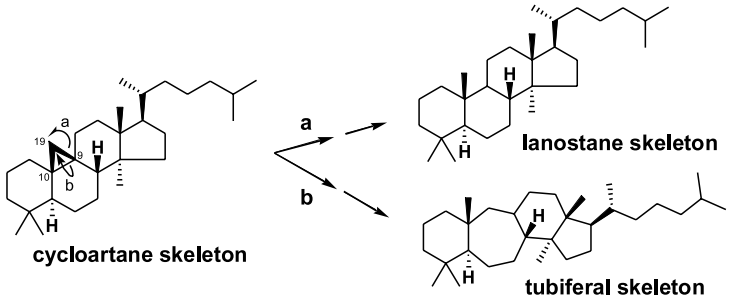


Figure 2. Key NOESY data of **1**.

The molecular formula of tubiferal B (**2**) was revealed as $C_{30}H_{44}O_6$ on the basis of HRFABMS data [*m*/*z* 501.3179, $(M+H)^+$, Δ −3.7 mmu], having one H_2O molecule more than tubiferal A (**1**). TLC examination implied that compound **2** was more polar than **1** (R_f values on ODS TLC developed with 90% MeOH; **1**: 0.39 and **2**: 0.64). The ^{1}H and ^{13}C NMR spectral data of **2** (Table 1), as well as its UV absorption, were paralleled those of compound **1**, although the oxymethine proton on C-16 and the C-17 methine proton resonated at relatively higher field for **2** (H-16, δ_H 4.28; H-17, δ_H 1.50). Thus, compound **2** was suggested to be the seco acid derivative of the γ-lactone moiety of compound **1**, which was supported by the detailed interpretation of ^{1}H–^{1}H COSY and HMBC spectra of **2**. Treatment of **1** with dilute KOH afforded **2**, which was detected on the basis of TLC examination.

The basic skeleton of tubiferal A (**1**) may be classified as a 9,10-secocycloartan-16,21-olide skeleton, which was conceived to be biogenetically produced through (i) ring opening of the cyclopropane of a cycloartane triterpene by fission of the 9,10-bond to give a 7-membered B-ring (Scheme 1), and (ii) oxidation of the C-21 methyl group to a carboxyl group. Reopening of the cyclopropane ring of cycloartane triterpene occurs by fission of the 9,19-bond in the biosynthesis of plant sterols to give the methyl group at C-10,[4] whereas cyclopropane ring-opening in a different direction may take place in the case of this myxomycete metabolite **1**. Acerinol (**3**)[5] and its related compounds are known to possess a related 3,10-epoxy-9,10-secocycloartane skeleton, which were first obtained from the hydrolysis products of the glycoside fraction of *Cimicifuga acerina*. Acerinol (**3**) was therefore artificially generated from a cycloartane-triterpene such as cimigenol (**4**) by treatment with mineral acid.[6] In case of acerinol-related compounds, the fission of cyclopropane ring is likely to be assisted by the formation of the 3,10-epoxy ring.



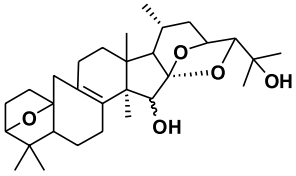
Scheme 1. Conceivable backbone rearrangements from the cycloartane skeleton.

Table 2. Cytotoxicity of tubiferals A (**1**) and B (**2**) (IC_{50} values, μg/mL)

	KB/VJ-300		LNCaP	KOB	
	VCR(+)	VCR (−)		TRAIL(+)	TRAIL (−)
1	2.7	>12.5	13.2	>6.3	>6.3
2	>12.5	>12.5	>12.5	>6.3	>6.3
Verapamil[a]	1.1	>25	—	—	—
Curcumin[a]	—	—	—	20	>25
Cisplatin[a]	—	—	1.5	—	—

Tests toward each cell line were carried out in the absence (−) and presence (+) of 100 ng/mL of VCR and 500 ng/mL of TRAIL, respectively, which did not affect the growth of the cells.

[a] Positive controls.



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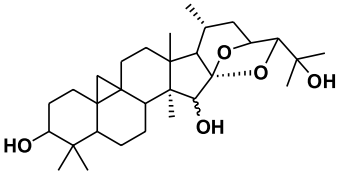

4

The cytotoxic activity of tubiferals A (**1**) and B (**2**) was examined against three human tumor cell lines, and IC_{50} value (μg/mL) data are presented in Table 2. Tubiferal A (**1**) showed weak or no cytotoxicity against these cell lines at concentrations used in this experiment. Interestingly, in the presence of 100 ng/mL of VCR in the culture of VCR-resistant KB cells,[7] compound **1** possessed cytotoxicity (IC_{50} value: 2.7 μg/mL). This finding suggests that compound **1** overcame multidrug resistance of tumor cells. On the other hand, the seco acid (**2**) was inactive against all tested cell lines. Both compounds **1** and **2** did not enhance TRAIL (TNF-related apoptosis inducing ligand) induced apoptosis in TRAIL resistant KOB (adult T cell leukemia) cells.

3. Experimental

3.1. General procedures

^1H and ^{13}C NMR spectra of **1** were recorded on a 500 MHz spectrometer. Standard pulse sequences were employed for 2D NMR experiments. HMBC spectra were recorded using a 65 ms delay time for long-range C–H coupling with *Z*-axis PFG. NOESY spectra in the phase-sensitive mode were recorded using the TPPI method with spectral widths of both dimensions of 5252 Hz, and 128 scans with 16 dummy scans were accumulated into 1K data points for each of 256 t_1 increments. The mixing time was set to 500 ms.

3.2. Organism

The fruit bodies of *Tubifera dimorphotheca* were collected and identified by Y. Y. at Ohtsu, Kochi-shi in Kochi Prefecture, Japan, in August 2001. A voucher specimen (#21625) is maintained by Y. Y. (Ohtsu-ko, Kochi).

3.3. Extraction and isolation

The air-dried fruit bodies of *Tubifera dimorphotheca* (3.7 g) were extracted with 90% MeOH (100 mL×2) and 90% acetone (100 mL×1). The combined MeOH and acetone extracts (0.31 g) were subjected to ODS flash column chromatography (column A; 2.0×20 cm) eluted with 20–100% MeOH in H_2O. The fraction (21 mg) of column A eluted with 20% MeOH was further separated by preparative HPLC (column B; Develosil ODS-HG-5, 20×250 mm; eluent, 75% MeOH; flow rate, 8.0 mL/min; detection, UV at 254 nm) to give tubiferal A (**1**, 0.8 mg, t_R=32.0 min). The fraction (9.9 mg) of column B (t_R=7.0∼11.0 min) was purified again by HPLC (Develosil ODS-HG-5, 10×250 mm; eluent, 65% MeOH; flow rate, 3.5 mL/min; detection, UV at 254 nm) to give tubiferal B (**2**, 1.2 mg, t_R=13.0 min).

3.3.1. Tubiferal A (1). Colorless amorphous solid; $[\alpha]_D^{22}=-87$ (*c* 0.12, MeOH); UV (MeOH) λ_{max} 239 (ε 18,000) and 246 nm (18,000); IR (film) ν_{max} 3390, 2930, 2860, 1770, 1715, 1560, 1455, and 1390 cm^{-1}; ^1H and ^{13}C NMR (Table 1); FABMS *m/z* 483 $(M+H)^+$; HRFABMS calcd for $C_{30}H_{43}O_5$ $(M+H)^+$ 483.3110, found *m/z* 483.3101.

3.3.2. Tubiferal B (2). Colorless amorphous solid; $[\alpha]_D^{22}=-46$ (*c* 0.20, MeOH); UV (MeOH) λ_{max} 240 (ε 20,000) and 246 nm (20,000); IR (film) ν_{max} 3420, 2925, 2850, 1710, 1560, 1450, and 1360 cm^{-1}; ^1H and ^{13}C NMR (Table 1); FABMS *m/z* 501 $(M+H)^+$ and 523 $(M+Na)^+$; HRFABMS calcd for $C_{30}H_{45}O_6$ $(M+H)^+$ 501.3216, found *m/z* 501.3179.

3.3.3. Conversion of 1 into 2. Treatment of **1** (0.1 mg) with 2N KOH (10 μL) and MeOH (50 μL) at room temperature overnight afforded **2**, which was detected on the basis of TLC examination (ODS, MeOH/H_2O, 9:1).

3.3.4. Cultured cell lines for cytotoxicity tests. VCR selected multidrug resistant variants of the human epidermoid carcinoma KB cells (KB/VJ-300)[8] were a gift from Prof. M. Kuwano (Kyushu University School of Medicine). The human prostate carcinoma LNCaP (human prostate cancer) cells were a gift from Prof. S. Egawa (Kitasato University School of Medicine). All these cells were maintained in culture flasks in MEM medium supplemented with 10% fetal calf serum (FCS) and 60 μg/mL of kanamycin. KOB cells (human adult T-cell leukemia) were a gift from Prof. T. Yamada (Graduate School, Nagasaki University), and were maintained in RPMI-1640 medium supplemented with 10% FCS and 60 μg/mL of kanamycin.

3.3.5. Measurement of cell viability. For the in vitro drug treatment experiments, tumor cells (1.1×10^4 cells/mL for KB cells, and 2×10^4 cells/mL for LNCaP cells) were seeded in 195 μL of culture medium/well in 96-well plates (Corning Glass Works), and incubated for 24 h at 37 °C in a 5% CO_2 −95% air atmosphere. The cells were treated in triplicate with 5 μL of graded concentrations of samples, and were then incubated in a CO_2 incubator at 37 °C for 72 h. Cell viability was determined by the colorimetric assay using MTT.[9] For KOB cells, 3.5×10^5 cells/mL of the cells were seeded in 95 μL of culture medium/well in 96-well plates, and were treated with 5 μL of graded concentrations of samples in the absence or presence of 0.5 μg/mL of TRAIL, and were then incubated for 42 h at 37 °C in a 5% CO_2 −95% air atmosphere. Cell viability was determined by the colorimetric assay using the alamer blue.[10]

Acknowledgements

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Gemini peptide lipids with ditopic ion-recognition site. Preparation and functions as an inducer for assembling of liposomal membranes

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Abstract—Gemini amphiphiles having two peptide lipid units and a spacer group connected at the polar heads were synthesized. A gemini peptide lipid bearing L-histidyl residues, hydrophobic double-chain segments, and a tri(oxyethylene) spacer performed as an inducer of the reversible assembling of liposomal membranes through ditopic ion recognition toward transition metal ions and alkali metal ions. The vesicular assembling behavior induced by the gemini peptide lipids was sensitive to the structural difference in the amino acid residue and the spacer group of the lipids.

1. Introduction

Liposomal membranes formed with phospholipids or bilayer-forming synthetic lipids have been widely employed as biomembrane models, drug carriers, nano-reactors, and scaffolds for supramolecular devices.[1–9] On functionalization of the liposomal membranes, the lipid assemblies have been usually handled as the uni-vesicular state, but not as the multi-vesicular assembly. In the light of the superiority of the multi-cellular organisms in biological systems as compared with the corresponding unicellular states, however, establishment of the methodology to construct the multi-vesicular assemblies as artificial tissues is of great significance. On these grounds, many kinds of approaches for assembling of the liposomal membranes have been proposed up to the present time.[10–18] In this article, we are to report a novel strategy to create reversible assembling system of the liposomal membranes by using an ion-recognizable gemini peptide lipid (**1**) as an inducer (Fig. 1).

Our molecular design of the lipid **1** was inspired by a naturally occurring gemini lipid, cardiolipin, having unique dimeric lipid structure and interesting biological functions.[19,20] Especially, we paid attention to the specific ion binding behavior of the cardiolipins toward divalent ions such as Ca^{2+} and Mg^{2+} to influence the aggregate morphology of the lipid membranes. Up to the present time, a considerable number of investigations have been reported on synthetic gemini surfactants consist of two surfactant molecules via a spacer group.[21–23] The gemini surfactants provide novel and interesting opportunities to investigate various supramolecular morphologies depending on the structural characteristics following to attractive

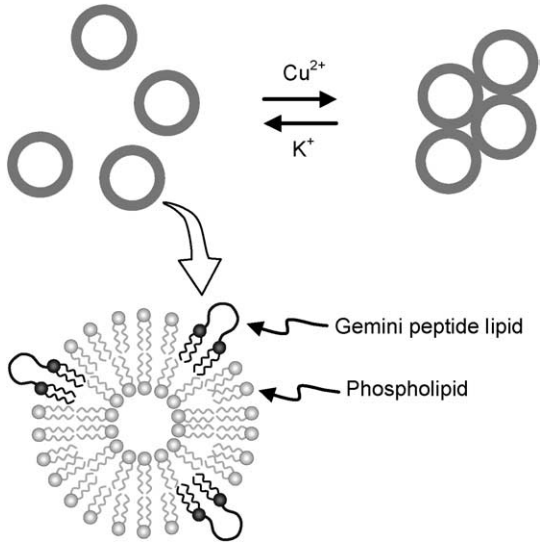

Figure 1. Schematic representation of the assembling of liposomes containing the gemini peptide lipid as triggered by specific ion recognition.

Keywords: Gemini peptide lipid; Ditopic ion-recognition; Vesicular assembling; Pseudo-crown ether; Supramolecular chemistry.
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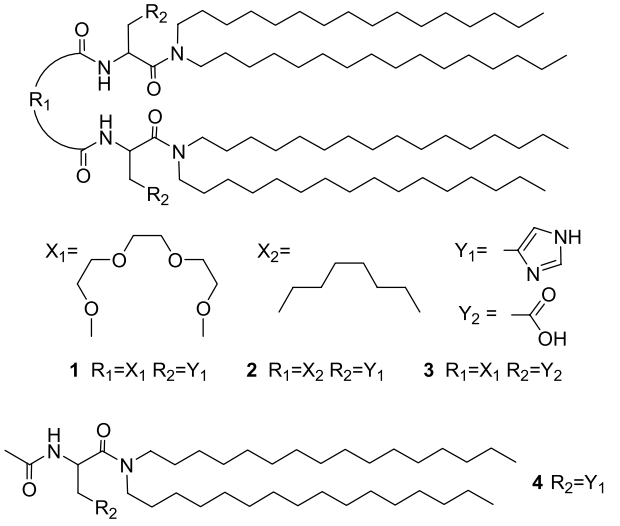
applications. Although much attention has been focused on physicochemical properties of the synthetic gemini surfactants, there are few reports on the synthetic gemini lipids composed of two double-chain segments like the cardiolipin. Thus, we prepared the gemini lipids having two double-chain units and two kinds of ion recognition sites, by extending our previous studies on the bilayer-forming synthetic peptide lipids having an amino acid moiety interposed between the polar head moiety and a hydrophobic double-chain segment.[24]



2. Results and discussion

2.1. Synthesis of the gemini peptide lipids

In order to enhance the ion-recognition ability of the synthetic gemini lipid in the liposomal membranes, we introduced two L-histidyl residues as the polar heads and a tri(oxyethylene) group as a spacer between the head moieties, expecting that the former and the latter groups act as effective binding sites for transition metal ions and alkali metal ions, respectively. The gemini peptide lipid (**1**) was synthesized through condensation of the peptide lipids with the corresponding bis(acyl chloride). As the reference lipids of **1**, we also prepared a gemini peptide lipid having a hydrocarbon spacer (**2**), a gemini peptide lipid bearing L-aspartate residues (**3**), and a non-gemini peptide lipid (**4**). The syntheses of these lipids were basically referred to the synthetic procedures of the peptide lipids.[24]

2.2. Ion recognition behavior of the gemini peptide lipids and its consequence in assembling of the liposomal membranes

The hybrid bilayer vesicles were prepared by sonication of an aqueous dispersion of dimyristoylphosphatidylcholine (DMPC) and a gemini peptide lipid in a 10:1 molar ratio with a cup-type sonicator at 30 W for 6 min. The hydrodynamic diameter (D_{hy}) of the hybrid vesicle of **1** was evaluated to be 160 nm by means of dynamic light scattering (DLS) measurements. Upon addition of Cu^{2+} ions to the hybrid vesicles at pH 9 and 30 °C, the D_{hy} value was significantly increased, suggesting the assembling of the vesicles or the followed fusion (Fig. 2). The similar behavior was also observed for the hybrid vesicles of **2**, but not for the hybrid vesicles containing the gemini lipid **3** or the non-gemini lipid **4** and the liposomes formed with DMPC alone under the comparable concentration conditions.

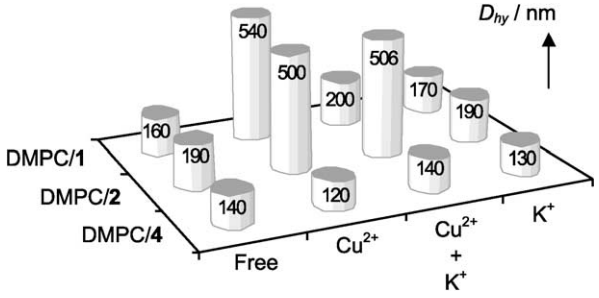


Figure 2. Effects of Cu^{2+} and K^+ ions for the vesicular assembling as evaluated by DLS at pH 9 and 30 °C. Concentrations in mmol dm^{-3}: [DMPC], 0.5; [gemini lipid], 0.05; [**4**], 0.1; [Cu^{2+}], 0.5; [K^+], 5.0.

The present hybrid vesicle of **1** showed a phase transition from gel to liquid-crystalline state with the peak maximum (T_m) at 24.3 °C and its enthalpy change (ΔH) of 4.3 kJ mol^{-1} per the matrix lipid, as evaluated by differential scanning calorimetry (DSC). Upon addition of Cu^{2+} ions to the vesicular solution, the phase transition behavior was scarcely affected, reflecting that the metal ions did not give perturbation in the packing shape of the lipid molecules in the membrane so as to change the aggregate morphology; the T_m and ΔH values were 24.3 °C and 4.0 kJ mol^{-1}, respectively, in the presence of Cu^{2+} ions in an equimolar amount to the phospholipid. In general, remarkable changes in the phase transition can be detected by DSC for the morphological transformation from small vesicles to the corresponding larger ones.[25,26] In addition, the increased D_{hy} value was immediately recovered to the original value in the metal-free system upon addition of an excess amount of EDTA. The results clearly indicate that the assembling of the hybrid vesicles formed with DMPC and **1** was triggered by Cu^{2+} ions without accompanying fusion of the vesicles as illustrated in Figure 1.

The ion binding to the surface of the lipid bilayer vesicle was qualitatively examined by ζ-potential measurements.[27] pH-Dependences of the ζ-potential for the DMPC vesicles containing the gemini peptide lipid **1** in the presence and absence of Cu^{2+} ions were shown in Figure 3. In the metal-free system, deprotonation of the imidazolyl groups in **1** caused the decrease in the ζ-potential from +40 to −20 mV. On the other hand, significant increase in the ζ-potential was observed in a pH region over 7 in the presence of Cu^{2+} ions. The results strongly suggest that Cu^{2+} ions bind to the histidyl residues of the gemini peptide lipids to induce the vesicular assembling.

Specificity of the ion recognition by the gemini peptide lipid to induce the vesicular assembling was evaluated from the extent of the increased D_{hy} values upon addition of various transition metal ions (Table 1). The ion selectivity for the hybrid vesicles composed of DMPC with **1** or **2** was well correlated to the general stability sequence of divalent

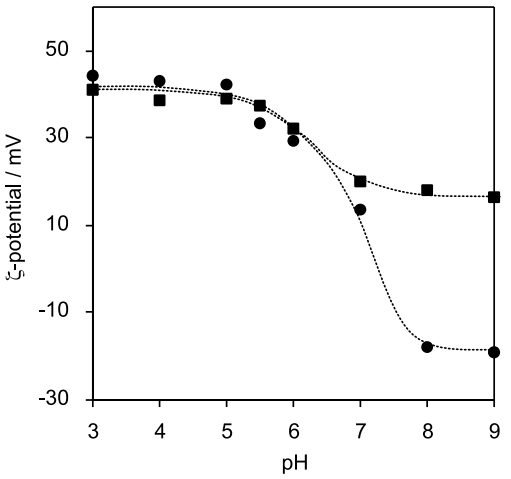


Figure 3. pH-Dependences of ζ-potential for the DMPC vesicle containing the gemini peptide lipid **1** at 30 °C in the presence (square) and absence (circle) of Cu^{2+} ions (0.5 mmol dm^{-3}). Concentrations in mmol dm^{-3}: [DMPC], 0.5; [**1**], 0.05; [Na^{+}] 0.5.

Table 1. Hydrodynamic diameters for the DMPC vesicles containing the gemini peptide lipid at pH 9.0 and 30 °C[a]

Metal ions	Hydrodynamic diameter/nm[b]	
	Lipid **1**	Lipid **2**
None	150 (20)	190 (20)
Mn^{2+}	140 (10)	190 (20)
Fe^{2+}	150 (10)	210 (20)
Co^{2+}	270 (20)	230 (30)
Ni^{2+}	320 (40)	240 (20)
Cu^{2+}	540 (20)	500 (30)
Zn^{2+}	350 (50)	360 (20)

[a] Hydrodynamic diameters were determined by DLS. Concentrations in mmol dm^{-3}: [DMPC], 0.5; [**1**] or [**2**], 0.05, [metal ions], 0.5.
[b] Standard deviation of three independent measurements is in parenthesis.

transition metal complexes, the Irving–Williams series; $Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$.[28,29] Under the similar concentration conditions, alkali and alkaline-earth metal ions did not act as the trigger for assembling of the hybrid vesicles.

In order to elucidate the stoichiometry and the binding constant for the copper complexes formed in the hybrid vesicles, circular dichroism (CD) spectra were taken in aqueous solution by monitoring the conformational changes in the chiral histidyl moieties of the lipid upon complexation.[30,31] The CD spectral changes of the gemini peptide lipid **1** embedded in the DMPC vesicle upon addition of Cu^{2+} ions are shown in Figure 4(A). The titration isotherm shown in Figure 4(B) was obtained by monitoring the CD intensity change at 214 nm ($\Delta\Delta\varepsilon_{214}$), which was applied to determine the binding constant of Cu^{2+} ions with **1**. The Job's plot analyses in the vesicular system revealed that Cu^{2+} ions bind to the imidazolyl groups in a ratio of 1:4. The binding constants for the other lipids, **2** and **4**, were also determined in the similar manner. Thus the binding constants for the 1:2 complexes of Cu^{2+} ions with the gemini lipids **1** and **2** in the DMPC vesicle were 1.6×10^{11} and 1.3×10^{11} dm^{6} mol^{-2}, respectively. These values are also represented to be 2.6×10^{22} and 1.7×10^{22} dm^{12} mol^{-4} for the lipid **1** and **2**, respectively, as apparent binding

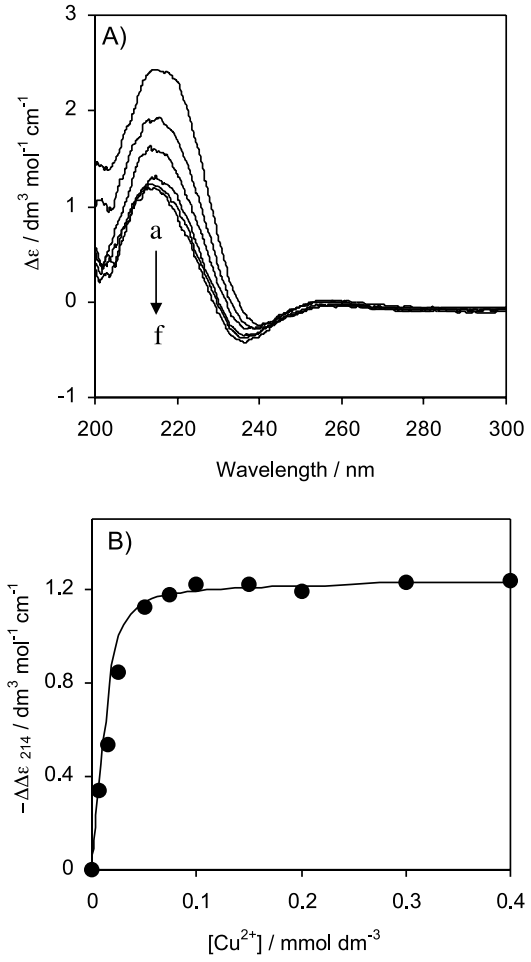


Figure 4. (A) CD spectral changes for the DMPC (0.5 mmol dm^{-3}) vesicle containing the gemini peptide lipid **1** (0.05 mmol dm^{-3}) upon addition of Cu^{2+} ions. The concentrations of Cu^{2+} ions in mmol dm^{-3}: a, 0; b, 0.015; c, 0025; d, 0.05; e, 0.2; f; 0.5. (B) Change in the molar CD at 214 nm ($\Delta\Delta\varepsilon_{214}$) upon titration of the gemini peptide lipid **1** with Cu^{2+} ions.

constants for the 4:1 complex of the imidazolyl groups in the lipid and Cu^{2+} ions. Whereas the binding constant of Cu^{2+} ions toward the non-gemini lipid **4** with one imidazolyl group per one lipid molecule was 1.5×10^{17} dm^{12} mol^{-4} for the 1:4 complex, being much weaker than those of the corresponding gemini lipids. Under the conditions in Figure 2, for example, the imidazolyl groups of the gemini lipid **1** completely form the copper complex, whereas only 75% of the histidyl residue of **4** binds Cu^{2+} ions and 25% of the imidazolyl group is free from the metal coordination.

Thus, we can image the mechanism for the Cu^{2+}-triggered assembling of the liposomal membranes containing the gemini peptide lipid as follows. In order to keep two lipid bilayer surfaces at separation less than about 2 nm in aqueous media, some attractive force which overcomes the repulsive hydration force observed on the surface of the hydrated lipid membranes[32,33] would be necessary. Thus, our observation that the DMPC liposomes containing the non-gemini lipid **4** did not form the vesicular assembly in the presence of Cu^{2+} ions indicates that the intra-vesicular 1:4 complex of the metal ions with the imidazolyl groups is

thermodynamically more stable than the corresponding inter-vesicular complex under the present conditions, presumably owing to the repulsive hydration force. On the other hand, the gemini peptide lipids with two imidazolyl groups can stabilize the inter-vesicular complex reinforced with the linkage of the spacer unit, as shown in Figure 5. Although the corresponding intra-vesicular complex may be also formed in the hybrid liposome of the gemini peptide lipid, the inter-vesicular complex would play pivotal role as the membrane junction to induce the vesicular assembling. We also observed that the assembling of the hybrid vesicles was triggered by Cu^{2+} ions in the liquid crystalline state above the T_m of the lipid membrane, but not below the T_m at which the inter-vesicular complex would be hardly formed in the rigid gel matrix with highly restricted molecular motion. This observation strongly support that the inter-vesicular complex shown in Figure 5 is a key species for the vesicular assembling in this study.

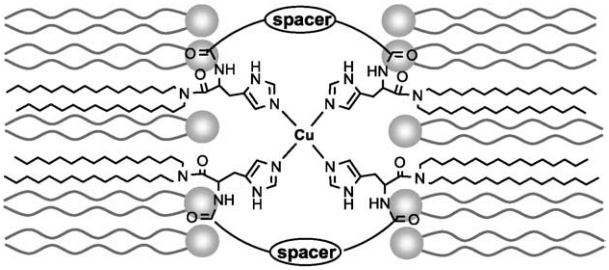


Figure 5. Plausible key species of the copper complex of the gemini peptide lipid having L-histidyl residues which stabilizes the vesicular assembly by forming the membrane junction.

2.3. Heteroditopic ion-recognition by the gemini peptide lipid and its consequence in disassembling of the liposomal membranes

The gemini peptide lipid **1** has a pseudo-crown ether moiety at the spacer unit, and is expected to behave as a ditopic ion receptor. As shown in Figure 2, the hydrodynamic diameter of the assembled vesicles in the presence of Cu^{2+} ions was decreased from 540 to 200 nm upon further addition of K^+ ions (5.0 mmol dm^{-3}). On the other hand, there was no significant change of the vesicular size upon addition of K^+ ions in the absence of Cu^{2+} ions. The results clearly indicate that the assembling of the liposomal membranes is reversibly controlled by ditopic ion recognition of **1** with Cu^{2+} and K^+ ions. Since the disassembling of the vesicles was not observed for the hybrid vesicles of DMPC and the gemini peptide lipid lacking the pseudo-crown ether moiety **2** upon addition of K^+ ions after the Cu^{2+}-triggered vesicular assembling. Thus the disassembling behavior of the hybrid vesicles of DMPC and **1** was interpreted by replacement of the Cu^{2+}-binding to the imidazolyl groups with the K^+-binding to the pseudo-crown ether moiety to breakdown the inter-vesicular copper complex.

In addition, marked selectivity for alkali metal ions was observed in the vesicular disassembling behavior (Fig. 6). Tendency of the disassembling effect seems to be correlated with the binding affinity of alkali metal ions to the pseudo-crown ether moiety;[34,35] $K^+ > Na^+ > Li^+ > Rb^+ \approx Cs^+$. Our present results would bring up possibilities to extend the interesting ditopic ion-recognition systems in solutions[36–38] to those in the lipid membrane systems as the biomembrane models.

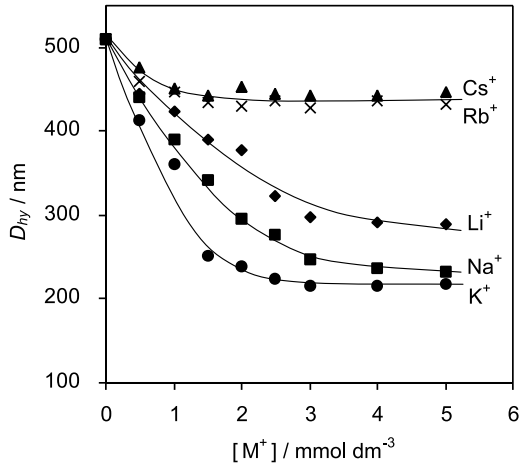


Figure 6. Effect of alkali metal ions (M^+) on hydrodynamic diameter (D_{hy}) of the DMPC vesicles containing gemini peptide lipid (**1**) in the presence of Cu^{2+} ion at 30 °C and pH 9. Concentrations in mmol dm^{-3}: [DMPC], 0.5; [**1**], 0.05; [Cu^{2+}], 0.5.

3. Conclusion

We have shown here that the transformation between the assembling and disassembling of the liposomal membranes can be reversibly controlled as a response of heteroditopic ion recognition by the gemini peptide lipid embedded in the vesicles. We believe our results revealed a new function of the gemini surfactants and propose a guidepost to design supramolecular assemblies exhibiting ditopic molecular recognition and its response.

4. Experimental

4.1. General

Organic solvents were purified, dried by standard procedures and kept over a drying agent before use. Unless otherwise mentioned, reagents were commercially available as a guaranteed grade and used without further purification. Thin layer chromatography (TLC) was performed on a silica gel 70 FM plate-Wako (Wako Pure Chemical Industries) with fluorescence detection under UV light. Liquid chromatography was performed using a silica gel column (Wako-gel C-300) and/or high performance liquid chromatography (HPLC) using a JAI Model instrument (Japan Analytical Instruments) equipped with JAIGEL−1H and -2H columns. ^{1}H NMR spectra were taken on a JEOL JNM-LA400 spectrometer. HR-MS (FAB+) was recorded with a JEOL JMS-700 MStation mass spectrometer.

4.2. Synthesis

4.2.1. *N*,*N*-Dihexadecyl-N^2-*t*-butoxycarbonyl-N^τ-tosyl-L-histidinamide [Boc-His(Tos)2C_{16}]. N^2-*t*-Butoxycarbonyl-N^τ-tosyl-L-histidine (3.00 g, 7.33 mmol) was added to a solution of dihexadecylamine (2.85 g, 6.11 mmol) and

triethylamine (0.74 g, 7.33 mmol) in dry dichloromethane (20 dm^{-3}) at 0 °C with stirring for 15 min. Diethylcyano phosphate (1.20 g, 7.33 mmol) was added to the solution and stirred for 30 min at 0 °C and then for 1 h at 25 °C. The solution was evaporated in vacuo to give a solid. The crude product was purified by liquid chromatography on a column of silica gel (Wako-gel C-300) with chloroform–methanol (99.5:0.5 v/v) as eluent giving a white solid, yield 5.18 g (99%); mp 52.6–53.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.88 (6H, t, J=6.7 Hz, $(CH_2)_{13}CH_3$), 1.24 (52H, m, $NCH_2(CH_2)_{13}CH_3$), 1.35 (9H, s, $(CH_3)_3CO$), 1.43 (4H, m, $NCH_2CH_2(CH_2)_{13}CH_3$), 2.42 (3H, s, $C_6H_4CH_3$), 2.80 (2H, m, $CHCH_2Im$), 2.99–3.42 (4H, m, $NCH_2CH_2(CH_2)_{13}CH_3$), 4.81 (1H, m, $CHCH_2Im$), 5.27 (1H, d, J=8.3 Hz, CONH), 7.09 (1H, s, Im-5H), 7.33 (2H, d, J=8.4 Hz, o-C_6H_4), 7.79 (2H, d, J=8.4 Hz, m-C_6H_4), 7.89 (1H, s, Im-2H). Anal. calcd for $C_{50}H_{88}N_4O_5S$: C, 70.05; H, 10.35; N 6.54%. Found: C, 70.21; H, 10.62; N, 6.55%.

4.2.2. N^2,$N^{2'}$-2,5,8,11-Tetraoxadodecanedioyl-bis(*N*,*N*-dihexadecyl-N^{τ}-tosyl-L-histidinamide) [Teo-Bis(His(Tos)2C_{16})].

Trifluoroacetic acid (8.90 g, 78.0 mmol) was added to a solution of Boc-His(Tos)2C_{16} (3.34 g, 3.90 mmol) in dry dichloromethane (10 dm^{-3}) at 25 °C with stirring for 2 h. The solvent was evaporated in vacuo, and the residue and triethylamine (3.95 g, 39.0 mmol) was dissolved in dry dichloromethane at 0 °C. 2,5,8,11-Tetraoxadodecanedioyl dichloride (0.536 g, 1.95 mmol) dissolved in dichloromethane (10 dm^{-3}) was added to the solution for 20 min. The mixture was stirred for 1 h at 25 °C and washed with brine. The solvent was evaporated in vacuo, and the crude product was purified by liquid chromatography on a column of silica gel (Wako-gel C-300) with chloroform–methanol (99:1 v/v) as eluent and then HPLC with chloroform as eluent to give a colorless oil, yield 0.75 g (22%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.88 (12H, t, J=6.7 Hz, $(CH_2)_{13}CH_3$), 1.26 (104H, m, $(CH_2)_{13}CH_3$), 1.41 (8H, m, $NCH_2CH_2(CH_2)_{13}CH_3$), 2.42 (6H, s, $C_6H_4CH_3$), 2.84 (4H, m, $CHCH_2Im$), 2.93–3.42 (8H, m, $NCH_2CH_2(CH_2)_{13}CH_3$), 3.62 (4H, s, $CH_2CH_2O(CH_2)_2OCH_2CH_2$), 3.65 (4H, m, $CH_2CH_2OCH_2CH_2OCH_2CH_2$), 4.12–4.32 (4H, m, $CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2$), 4.81 (2H, m, $CHCH_2Im$), 5.73 (2H, d, J=8.3 Hz, CONH), 7.09 (2H, s, Im-5H), 7.33 (4H, d, J=8.4 Hz, o-C_6H_4), 7.79 (4H, d, J=8.4 Hz, m-C_6H_4), 7.89 (2H, s, Im-2H). Anal. calcd for $C_{98}H_{170}N_8O_{12}S_2\cdot 5H_2O$: C, 65.15; H, 10.04; N, 6.20%. Found: C, 65.15; H, 9.67; N, 6.12%.

4.2.3. N^2,$N^{2'}$-2,5,8,11-Tetraoxadodecanedioyl-bis(*N*,*N*-dihexadecyl-L-histidinamide) (1).

Aqueous NaOH (1.0 mol dm^{-3}, 10 dm^{-3}) was added to Teo-Bis(His(Tos)2C_{16}) (0.43 g, 0.28 mmol) in methanol (100 dm^{-3}) with stirring for 1 h at 0 °C. The solvent was removed in vacuo, and the residue was purified by liquid chromatography on a column of silica gel (Wako-gel C-300) with chloroform–methanol (97:3 v/v) to give a colorless oil, yield 0.145 g (41%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.88 (12H, t, J=6.7 Hz, $(CH_2)_{13}CH_3$), 1.26 (104H, m, $(CH_2)_{13}CH_3$), 1.47 (8H, m, $NCH_2CH_2(CH_2)_{13}CH_3$), 3.02 (4H, m, $CHCH_2Im$), 3.22–3.39 (8H, m, $NCH_2CH_2(CH_2)_{13}CH_3$), 3.64 (4H, s, $CH_2CH_2OCH_2CH_2OCH_2CH_2$), 3.67 (4H, m, $CH_2CH_2OCH_2CH_2OCH_2CH_2$), 4.12–4.32 (4H, m, $CH_2CH_2OCH_2CH_2OCH_2CH_2$), 4.81 (2H, m, $CHCH_2Im$), 6.41 (2H, br, CONH), 6.88 (2H, s, Im-5H), 7.51 (2H, s, Im-2H). Anal. calcd for $C_{84}H_{158}N_8O_8$: C, 71.64; H, 11.31; N, 7.96%. Found: C, 71.30; H, 11.53; N, 7.68%. HR-MS (FAB$^+$): exact mass calcd for $C_{84}H_{159}N_8O_8$ $[M+H]^+$ 1408.2281, found 1408.2275.

4.2.4. *N*,*N*-Dihexadecyl-N^2-*t*-butoxycarbonyl-N^{τ}-benzyloxymethyl-L-histidinamide [Boc-His(Bom)2C_{16}].

N^2-*t*-Butoxycarbonyl-N^{τ}-benzyloxymethyl-L-histidine (6.76 g, 18 mmol) was added to a solution of 1-hydroxybenzotiazole (2.43 g, 18.0 mmol) in dry dichloromethane (20 dm^{-3}) at 0 °C with stirring for 5 min. Then *N*,*N*′-dicyclohexylcarbodiimide (2.97 g, 14.4 mmol) was added to the solution and stirred at 0 °C. After 15 min, dihexadecylamine (5.74 g, 12.0 mmol) was added to the solution and stirred for 3 h at 0 °C and then for 42 h at room temperature. The precipitation was removed by filtration and the solvent was removed in vacuo. The residue dissolved in ethyl acetate (300 dm^{-3}) was washed sequentially with 10% aqueous citric acid, 5% aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. After being dried, the solution was evaporated in vacuo to give a yellow oil. The crude product was purified by liquid chromatography on a column of silica gel (Wako-gel C-300) with chloroform–methanol (99.5:0.5 v/v) as eluent giving a white solid, yield 3.02 g (31%); mp 49.8–50.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.88 (6H, t, J=6.7 Hz, $(CH_2)_{13}CH_3$), 1.26 (52H, m, $(CH_2)_{13}CH_3$), 1.39 (9H, s, $(CH_3)_3CO$), 1.47 (4H, m, $NCH_2CH_2(CH_2)_{13}CH_3$), 2.92 (2H, m, $CHCH_2Im$), 3.00–3.44 (4H, m, $NCH_2CH_2(CH_2)_{13}CH_3$), 4.45 (1H, d, J=11.9 Hz, $ImCH_2OCHHC_6H_5$), 4.51 (1H, d, J=11.9 Hz, $ImCH_2OCHHC_6H_5$), 4.79 (1H, m, $CHCH_2Im$), 5.29 (1H, d, J=11.0 Hz, $ImCHHOCH_2C_6H_5$), 5.32 (1H, d, J=8.5 Hz, CONH), 5.41 (1H, J=11.0 Hz, $ImCHHOCH_2C_6H_5$), 6.89 (1H, s, Im-5H), 7.32 (5H, m, $OCH_2C_6H_5$), 7.46 (1H, s, Im-2H). Anal. calcd for $C_{51}H_{90}N_4O_4$: C, 74.40; H, 11.02; N 6.81%. Found: C, 74.27; H, 10.91; N, 6.87%.

4.2.5. N^2,$N^{2'}$-Octanedioyl-bis(*N*,*N*-dihexadecyl-N^{τ}-benzyloxymethyl-L-histidinamide) [C_6-Bis(His(Bom)2C_{16})].

Trifluoroacetic acid (8.16 g, 71.6 mmol) was added to a solution of Boc-His(Bom)2C_{16} (2.95 g, 3.58 mmol) in dry dichloromethane (40 dm^{-3}) at room temperature with stirring for 2 h. The solvent was evaporated in vacuo, and the residue and triethylamine (2.95 g, 28.6 mmol) was dissolved in dry dichloromethane (40 dm^{-3}) at 0 °C. Octanedioyl dichloride (0.61 g, 2.86 mmol) dissolved in dichloromethane (7 dm^{-3}) was added to the solution for 1 h. The mixture was stirred for 4 h at 25 °C and the solvent was removed in vacuo. The residue dissolved in dichloromethane (200 dm^{-3}) was washed sequentially with 10% aqueous citric acid, 5% aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. After being dried, the solution was evaporated in vacuo to give a yellow oil. The crude product was purified by liquid chromatography on a column of silica gel (Wako-gel C-300) with chloroform–methanol (99:1 v/v) as eluent giving a colorless oil, yield 2.42 g (85%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.88 (12H, t, J=6.7 Hz, $(CH_2)_{13}CH_3$), 1.26 (108H, m, $(CH_2)_{13}CH_3$, $CO(CH_2)_2(CH_2)_2(CH_2)_2CO$), 1.47 (8H, m, $NCH_2CH_2(CH_2)_{13}CH_3$), 1.58 (4H, m, $COCH_2CH_2(CH_2)_2CH_2CH_2CO$), 2.12 (4H, m, $COCH_2(CH_2)_4CH_2CO$), 3.02 (4H, m, $CHCH_2Im$), 3.11–3.43 (8H, m, $NCH_2CH_2(CH_2)_{13}CH_3$),

4.42 (2H, d, $J=11.9$ Hz, ImCH$_2$OC*H*HC$_6$H$_5$), 4.54 (2H, d, $J=11.9$ Hz, ImCH$_2$OCH*H*C$_6$H$_5$), 5.17 (2H, m, C*H*CH$_2$Im), 5.31 (2H, d, $J=11.0$ Hz, ImC*H*HOCH$_2$C$_6$H$_5$), 5.41 (2H, $J=11.0$ Hz, ImCH*H*OCH$_2$C$_6$H$_5$), 6.89 (2H, s, Im-5H), 7.22 (2H, d, $J=8.5$ Hz, CON*H*), 7.32 (10H, m, OCH$_2$C$_6$*H*$_5$), 7.51 (2H, s, Im-2H). Anal. calcd for $C_{100}H_{174}N_8O_7\cdot 1H_2O$: C, 74.95; H, 11.07; N, 6.99%. Found: C, 74.87; H, 10.90; N, 6.92%.

4.2.6. N^2,$N^{2'}$-Octanedioyl-bis(*N*,*N*-dihexadecyl-L-histidinamide) (2). Pd-C 10% (0.36 g) was added to C_6-Bis(His(Bom)2C_{16}) (1.13 g, 0.69 mmol) dissolved in 80% aqueous acetic acid (20 dm^{-3}). The mixture was placed under hydrogen at atomospheric pressure and room temperature for 15 h with stirring. The mixture was filtered on celite and the filtrate was concentrated under reduced pressure. The crude product was purified by liquid chromatography on a column of silica gel (Wako-gel C-300) with chloroform–methanol (97:3 v/v) as eluent giving a white solid, yield 72.1 mg (17%); mp 95.4–96.1 °C. ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ 0.88 (12H, t, $J=6.7$ Hz, (CH$_2$)$_{13}$C*H*$_3$), 1.26 (108H, m, (C*H*$_2$)$_{13}$CH$_3$, CO(CH$_2$)$_2$(C*H*$_2$)$_2$(CH$_2$)$_2$CO), 1.58 (4H, m, COCH$_2$C*H*$_2$(CH$_2$)$_2$C*H*$_2$CH$_2$CO), 2.12 (4H, m, COC*H*$_2$(CH$_2$)$_4$C*H*$_2$CO), 3.02 (4H, m, CHC*H*$_2$Im), 3.13–3.39 (8H, m, NC*H*$_2$CH$_2$(CH$_2$)$_{13}$CH$_3$), 5.17 (2H, m, C*H*CH$_2$Im), 6.83 (2H, s, Im-5H), 7.22 (2H, d, $J=8.5$ Hz, CON*H*), 7.63 (s, 2H, Im-2H). Anal. calcd for $C_{84}H_{158}N_8O_4\cdot 2CH_3CO_2H$: C, 72.18; H, 11.43; N, 7.65%. Found: C, 72.45; H, 11.47; N, 7.72%. HR-MS (FAB$^+$): exact mass calcd for $C_{84}H_{159}N_8O_4$ [M+H]$^+$ 1344.2484, found 1344.2483.

4.2.7. N^2-Acetyl-*N*,*N*-dihexadecyl-N^τ-benzyloxymethyl-L-histidinamide [Ac-His(Bom)2C_{16}]. Trifluoroacetic acid (7.04 g, 61.8 mmol) was added to a solution of Boc-His(Bom)2C_{16} (2.54 g, 3.08 mmol) in dry dichloromethane (10 dm^{-3}) at room temperature with stirring for 2 h. The solvent was evaporated in vacuo, and the residue and triethylamine (3.13 g, 30.1 mmol) was dissolved in dry dichloromethane (10 dm^{-3}) at 0 °C. Acetic anhydride (0.921 g, 9.02 mmol) was added to the solution for 1 h. The mixture was stirred for 8 h at room temperature and the solvent was removed in vacuo. The residue dissolved in dichloromethane (100 dm^{-3}) was washed sequentially with 10% aqueous citric acid, 5% aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. After being dried, the solution was evaporated in vacuo to give a yellow oil. The crude product was purified by liquid chromatography on a column of silica gel (Wako-gel C-300) with chloroform–methanol (99:1 v/v) as eluent giving a colorless oil, yield 1.13 g (49%). ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ 0.88 (6H, t, $J=6.7$ Hz, (CH$_2$)$_{13}$C*H*$_3$), 1.26 (52H, m, (C*H*$_2$)$_{13}$CH$_3$), 1.47 (4H, m, NCH$_2$C*H*$_2$(CH$_2$)$_{13}$CH$_3$), 2.00 (3H, s, C*H*$_3$CO), 2.98 (2H, m, CHC*H*$_2$Im), 3.01–3.50 (4H, m, NC*H*$_2$CH$_2$(CH$_2$)$_{13}$CH$_3$), 4.46 (1H, d, $J=11.7$ Hz, ImCH$_2$OC*H*HC$_6$H$_5$), 4.58 (1H, d, $J=11.7$ Hz, ImCH$_2$OCH*H*C$_6$H$_5$), 5.11 (1H, m, C*H*CH$_2$Im), 5.31 (1H, d, $J=11.0$ Hz, ImC*H*HOCH$_2$C$_6$H$_5$), 5.41 (1H, $J=11.0$ Hz, ImCH*H*OCH$_2$C$_6$H$_5$), 6.36 (1H, d, $J=8.3$ Hz, CON*H*), 6.83 (1H, s, Im-5H), 7.32 (5H, m, OCH$_2$C$_6$*H*$_5$), 7.46 (1H, s, Im-2H). Anal. calcd for $C_{48}H_{84}N_4O_3$: C, 75.34; H, 11.06; N, 7.32%. Found: C, 74.97; H, 11.18; N, 7.27%.

4.2.8. N^2-Acetyl-*N*,*N*-dihexadecyl-L-histidinamide (4). Pd-C 10% (0.223 g) was added to Ac-His(Bom)2C_{16} (0.893 g, 1.16 mmol) dissolved in 80% aqueous acetic acid (20 dm^{-3}). The mixture was placed under hydrogen at atomospheric pressure and room temperature for 24 h with stirring. The mixture was filtered on celite and the filtrate was concentrated under reduced pressure. The crude product was purified by liquid chromatography on a column of silica gel (Wako-gel C-300) with chloroform–methanol (97:3 v/v) as eluent giving a white solid, yield 0.254 g (33%); mp 60.7–61.5 °C. ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ 0.88 (6H, t, $J=6.7$ Hz, (CH$_2$)$_{13}$C*H*$_3$), 1.26 (52H, m, (C*H*$_2$)$_{13}$CH$_3$), 1.47 (4H, m, NCH$_2$C*H*$_2$(CH$_2$)$_{13}$CH$_3$), 2.00 (3H, s, C*H*$_3$CO), 2.98 (2H, m, CHC*H*$_2$Im), 3.01–3.50 (4H, m, NC*H*$_2$CH$_2$(CH$_2$)$_{13}$CH$_3$), 5.03 (1H, m, C*H*CH$_2$Im), 6.57 (1H, d, $J=8.5$ Hz, CON*H*), 6.83 (1H, s, Im-5H), 7.57 (1H, s, Im-2H). Anal. calcd for $C_{40}H_{76}N_4O_2\cdot 0.5H_2O$: C, 73.45; H, 11.87; N, 8.57%. Found: C, 73.35; H, 11.83; N, 8.39%. HR-MS (FAB$^+$): exact mass calcd for $C_{40}H_{77}N_4O_2$ [M+H]$^+$ 645.6047, found 645.6041.

4.2.9. N^2,$N^{2'}$-2,5,8,11-Tetraoxadodecanedioyl-bis(*N*,*N*-dihexadecyl-L-aspartic 1-amide) (3). The gemini peptide lipid having aspartate residues (**3**) was prepared in a manner analogous to that for the synthesis of **1** by using N^2-*t*-butoxycarbonyl-O^4-benzyl-L-aspartic acid instead of N^2-*t*-butoxycarbonyl-N^τ-tosyl-L-histidine. In the final step, the benzyl groups were removed by the Pd-C catalyzed hydrogenation. A colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ 0.88 (12H, t, $J=6.7$ Hz, (CH$_2$)$_{13}$C*H*$_3$), 1.26 (104H, m, (C*H*$_2$)$_{13}$CH$_3$), 1.58 (8H, m, NCH$_2$C*H*$_2$(CH$_2$)$_{13}$CH$_3$), 2.65 (2H, m, CHC*H*$_2$COOH), 3.21–3.43 (8H, m, NC*H*$_2$CH$_2$(CH$_2$)$_{13}$CH$_3$), 3.67 (4H, s, CH$_2$CH$_2$OC*H*$_2$C*H*$_2$OCH$_2$CH$_2$), 3.69 (4H, m, CH$_2$C*H*$_2$OCH$_2$CH$_2$OC*H*$_2$CH$_2$), 4.14–4.33 (4H, m, C*H*$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$C*H*$_2$), 4.97 (2H, m, C*H*CH$_2$COOH), 6.89 (2H, br, CONH). Anal. calcd for $C_{80}H_{154}N_4O_{12}\cdot 0.5H_2O$: C, C, 69.98; H, 11.38; N, 4.08%. Found: C, 69.98; H, 11.50; N, 4.16%. HR-MS (FAB$^+$): exact mass calcd for $C_{80}H_{155}N_4O_{12}$ [M+H]$^+$ 1364.1642, found 1364.1649.

4.3. Preparation of hybrid vesicles

Hybrid liposomes employed in this study were generally prepared according to established protocol[1] as follows. Appropriate amounts of synthetic lipid and dimyristoylphosphatidylcholine (DMPC) were dissolved in chloroform. The solvent was evaporated under nitrogen gas flow and the residual trace solvent was completely removed in vacuo. Hydration of the thin film thus obtained on the wall of a vial was performed at 40 °C with an appropriate amount of water. Multi-walled bilayer vesicles were formed upon vortex mixing of the aqueous dispersion. The corresponding single-walled vesicles were prepared by sonication of the dispersion sample with a cup-type sonicator above the phase transition temperature for 5 min.

4.4. Measurements

4.4.1. Differential scanning calorimetry (DSC). The phase transition behavior of the lipid bilayer vesicles was measured with a differential scanning calorimeter (VP-DSC, MicroCal). The measurements were performed

between 10 and 50 °C with a 0.5 °C/min heating rate. Phase transition temperature (T_m), its enthalpy change (ΔH) was evaluated.

4.4.2. Dynamic light scattering (DLS) measurement. Hydrodynamic diameter of the lipid bilayer vesicles was measured by a dynamic light scattering spectrometer equipped with 633 nm He–Ne laser (DLS-6000, Otsuka electronics) at 30 °C. Time course of the light scattering from the sample was analyzed by the Cumulant method at an angle of 90° from the incident light.

4.4.3. ζ-Potential measurement. Binding of metal ions to the vesicular surface was evaluated from change in the ζ-potential value by using an electrophoretic light scattering apparatus by a laser doppler system (ELS-6000, Otsuka Electronics) at 30 °C. Latex beads of polystyrene with a 200 nm diameter were employed as a standard. The vesicular solution was mixed with NaCl as an electroryte and its pH was adjusted by aqueous HCl or NaOH.

4.4.4. Circular dichroism spectroscopy. In order to evaluate the Cu^{2+}-binding to the gemini peptide lipid, circular dichroism (CD) measurements were carried out by a spectropolarimeter (J-820, JASCO). The CD spectra of the peptide lipid embedded in the DMPC liposome were measured at pH 9.0 and 30 °C by changing the Cu^{2+} concentrations. Titration isotherms were obtained from the changes in CD intensity, and the data were fitted to an appropriate binding model. An iterative curve-fitting method yielded the binding constant and the maximum change in CD intensity. The binding constants mentioned in the text are the average of three independent measurements. Job's method was used to determine the stoichiometry of the complex of the lipid with Cu^{2+} ions.

Acknowledgements

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Nucleophilic chain substitution on perfluoroketene dithioacetals by ethyl 2-trimethysilyl acetate. Application to the synthesis of 2-trifluoromethyl succinic acid derivatives☆

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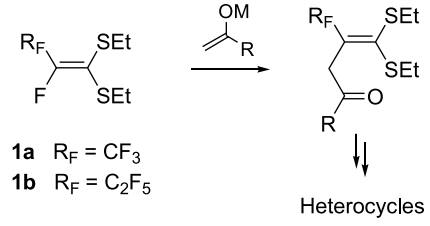
Abstract—A highly efficient substitution of the vinyl fluoride of perfluoroketene dithioacetals was achieved using trimethylsilylacetate to give 2-perfluoroalkyl succinic acid derivatives and 2-trifluoromethyl succinimides. This chain process was initiated by a catalytic amount of fluoride salt, whereas reaction failed with the corresponding lithium enolate.

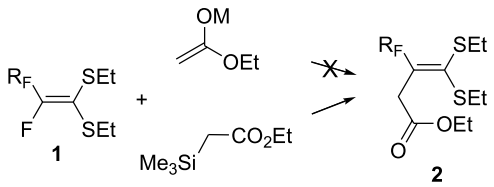
1. Introduction

Within the framework of our studies on new methods for the synthesis of multifunctional organofluorine compounds, we have developed perfluoroketene dithiocetals **1** as versatile building blocks. Compounds **1** are synthetic equivalents of 2-hydroperfluorocarboxylic derivatives.[1] Their umpolung reactivity, associated to the vinyl fluorine substitution, significantly extends their applications. The substitution by alkoxide or simple organometallic reagents has previously been observed for the difluoromethylene analogues.[2] The reaction of **1** with functionalized nucleophiles offers a greater potential because of possible subsequent heterocyclization (Scheme 1). We have reported applications in the synthesis of trifluoromethyl lactones,[3] lactams,[4] pyridazines,[5] furanes and pyrroles.[6] The first step in all these syntheses consists of the reaction of **1** with a ketone enolate.



Scheme 1.

To diversify the synthetic applications of **1**, we wished to extend these reactions to other nucleophilic species, in particular ester enolates. Surprisingly, in contrast to lithium enediolates,[7] various attempts with lithium ethyl acetate enolate (from AcOEt and LDA) failed whatever the reaction conditions (Scheme 2). Instead of the expected product **2**, the only isolated product resulted from the displacement of the vinyl fluoride by the ethoxide group, the latter being produced by a Claisen condensation which eventually occurred after a long reaction time. We wish to describe a chain reaction with ethyl 2-trimethylsilyl acetate which enabled us to overcome this failure and to apply our synthetic method to the synthesis of 2-trifluoromethylsuccinic acid derivatives.



Scheme 2.

2. Results and discussion

Silylated nucleophiles often behave differently than their metallated analogues, due to their stabilized nature. Several

☆ Perfluoroketene dithioacetals. Part 12. For part 11, see Ref. 7

Keywords: Vinyl fluorine substitution; Silyl nucleophile; Succinic acid derivatives; Trifluoromethyl succinimides.
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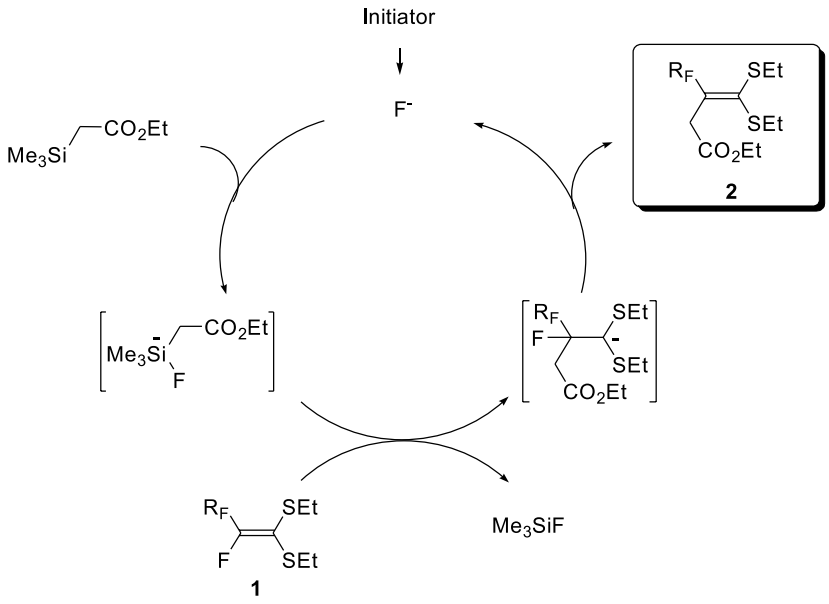


Scheme 3.

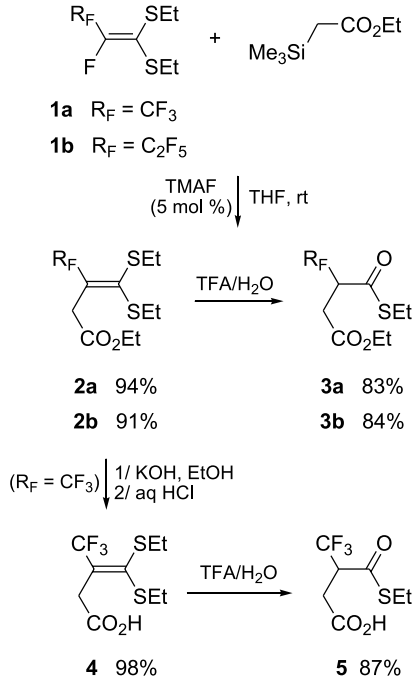
significant examples can be cited: trifluoromethytrimethylsilane is a nucleophilic trifluoromethylating reagent of choice whereas main metal analogues decompose into difluorocarbenes.[8] 2-Trimethylsilyldithiolane acts, under fluoride activation, as an efficient nucleophile whereas the 2-lithio analogue decomposes via ethylene elimination.[9]

A stabilized hypervalent intermediate is the key form of nucleophile donor. If the nucleophilic reaction releases a silicophilic nucleofugal group, the transformation can proceed by a mild chain mechanism. The chain transfer step is often a silicon transfer to an alkoxide, as in the case of nucleophilic additions on carbonyl compounds. Owing to the strength of the Si–F bond, the chain transfer is particularly efficient in reactions involving fluoride elimination, as shown in the conversion of acylsilane into difluoroenol silyl ethers using trifluoromethyl–trimethylsilane.[10] This led us to consider the substitution reaction of the vinyl fluoride of **1** with ethyl 2-trimethylsilyl acetate following the chain reaction depicted in Scheme 3.

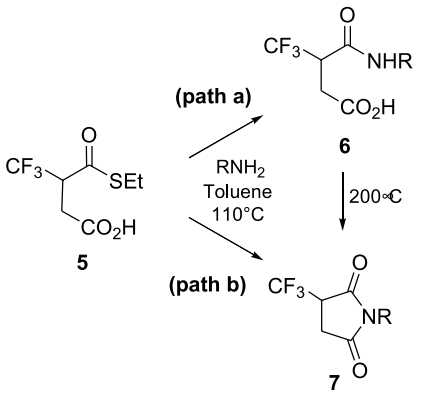
Reaction conditions were optimized regarding the fluoride initiator and the solvent used. With cesium fluoride in DME or the usual tetrabutylammonium fluoride in THF, difficulties were encountered in reaching a total conversion and interesting yields. Tetramethylammonium fluoride (TMAF) in THF proved to be the best initiator. This fluoride salt is easily dehydrated by simple heating under vacuum without the decomposition encountered with TBAF. Unfortunately the very clean reaction observed was initially counterbalanced by an incomplete conversion. As in any chain process, the efficiency of the chain transfer step is crucial in bringing the reaction to completion. Finally, a total conversion with excellent yields of products **2** was achieved using 5% of TMAF in THF, provided that the initiator was added portionwise (see Experimental). The dithioacetal moiety was hydrolyzed under the usual conditions to give the 2-perfluoroalkyl dicarboxylic derivatives **3**, bearing two differentiated carboxyl functions (Scheme 4).

Compound **3a** was initially chosen as a model to explore the reactivity of the dicarboxylic derivatives. A high chemical resistance of the ester moiety was observed in the reaction of **3a** with methylhydrazine which gave the monocondensation product with the thiolester group instead of the expected dihydropyridazinedione. On the other hand, **2a** was easily saponified to give the intermediate ketenedithioacetal **4** in almost quantitative yield. This product was then converted in high yield to the acid thiolester **5** by a stronger acid treatment (Scheme 4). Compound **4** was also prepared in one step by reacting **1a** with the lithium dianion of acetic acid.[7]

In contrast to **3a**, **5** behaved as a bis(electrophilic) species,



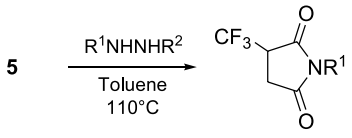
Scheme 4.



R	Path	Product	(%)
Bn	**a**	**7a**	73
nC_5H_{11}	**a**	**7b**	71
*i*Pr	**a**	**7c**	56
$PhCH(CH_3)$	**a**	**7d**	76
Ph	**b**	**7e**	81
pMeOPh	**b**	**7f**	81
2-Pyridyl	**b**	**7g**	31
NH_2	**b**	**7h**	45
NHMe	**b**	**7i**	47

Scheme 5.

giving some unexpected results. Reaction with aliphatic primary amines under standard conditions first gave the opened acid-amide **6a–d** (Scheme 5, path a). Cyclodehydration then gave 2-trifluoromethyl succinimides **7a–d** by heating the corresponding **6a–d** to 200 °C (Scheme 5). The reaction of **5** with aromatic primary amines directly provided the corresponding *N*-aryl succinimides **7e–g** (Scheme 5, path b). Hydrazine and methylhydrazine reacted similarly giving the corresponding *N*-aminosuccinimides **7h**,**7i** in moderate yields. In contrast phenylhydrazine gave **7e**, a condensation product with the loss of one nitrogen. Similar cleavage of the nitrogen–nitrogen bond has already been observed.[11] In the same way, reaction with *N*,*N*′-dimethylhydrazine gave *N*-methyl-2-trifluoromethyl succinimide **7j** (Scheme 6).



R^1	R^2	Product (yield %)
Ph	H	**7e** (38 %)
Me	Me	**7j** (30 %)

Scheme 6.

Succinimides constitute an important class of organic compounds, both as synthetic intermediates and for their biological properties.[12] The introduction of fluorine and in particular of a trifluoromethyl substituent greatly modifies the physico-chemical and biological properties of organic substrates.[13] 2-Trifluoromethyl succinimides, and more generally 2-trifluoromethyl succinic acid derivatives are undoubtedly very interesting building blocks open to a wide range of potential transformations. Several compounds comprising the 2-trifluoromethyl succinic or succinimide framework have been described,[14,15] most of them being obtained from 2-trifluoromethylmaleimide or maleic acid.[15] To our knowledge, there is one report on the direct synthesis of 2-trifluoromethyl succinimides, and this in poor yield.[16] The reaction sequence presented here is thus the first general preparation of *N*-alkyl or *N*-aryl 2-trifluoromethyl succinimides of practical value and transposable to a multigram scale.

3. Conclusions

In summary, we have developed a preparative access to 2-trifluoromethyl and 2-pentafluoroethyl succinic acid derivatives in various forms, particularly in the 2-trifluoromethyl imide series. This is the result of the combination of the starting perfluoroketene dithioacetal functionality and the specific behavior of the silylated precursor of ethyl acetate enolate. Applications in the pentafluoroethyl series are under investigation and will be reported in due course.

4. Experimental

4.1. Materials and general methods

Melting points are uncorrected FT-IR spectra were recorded on a MIDAC Corporation Spectrafile IR apparatus. ^1H, ^{13}C and ^{19}F spectra were recorded on a Bruker AC-250 or AC-500 spectrometer with $CDCl_3$ as the solvent. Tetramethylsilane ($\delta=0.00$ ppm) or $CHCl_3$ ($\delta=7.27$ ppm) were used as internal standards for ^1H, $CDCl_3$ ($\delta=77.23$ ppm) for ^{13}C NMR spectra, and $CFCl_3$ ($\delta=0.0$ ppm) for ^{19}F NMR spectra. GCMS spectra were obtained on Trace MS Thermoquest apparatus (70 eV) in electron impact mode. Elemental analyses were performed with a Perkin–Elmer CHN 2400 apparatus. High Resolution Mass Spectra (HRMS) were performed on Q-TOF Micromass in positive ESI mode (CV=30 V). All reactions were monitored by TLC (Merck F 254 silica gel) or by ^{19}F NMR. All anhydrous reactions were carried out under dry argon. THF was dried and distilled from sodium/benzophenone. Ethyl 2-trimethylsilyl acetate was distillated before use. Tetramethylammonium fluoride (TMAF) was dried by heating at 200 °C, under reduced pressure, during 4–5 h. Perfluoroketene dithioacetals **1a**,**b** were prepared according to our reported method.[1] Products were separated by chromatography on silica gel using a mixture of petroleum ether and ethyl acetate.

4.2. Typical procedure for the preparation of compounds (2a,b) (Scheme 4)

To a suspension of TMAF (100 mg, 1.0 mmol, 0.025 equiv) in dry THF (100 mL), under argon atmosphere, was added **1a** (10.1 g, 43.0 mmol, 1 equiv). Ethyl 2-trimethylsilyl acetate (9.4 mL, 51.0 mmol, 1.2 equiv) was then added

dropwise to the resulting suspension. The mixture was stirred at room temperature under argon (4–5 h). Each hour a new portion of TMAF (50 mg, 0.5 mmol) was added until total conversion of the starting dithioacetal **1a** (4–5×). The crude mixture was washed with brine (60 mL). After separation, the aqueous phase was extracted twice with ether (2×50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel using a mixture of petroleum ether–EtOAc (99/1) to give the ketene dithioacetal **2a** (12.2 g, 94%).

4.2.1. Ethyl 4,4-bis(ethylsulfanyl)-3-trifluoromethylbut-3-enoate (2a). Yield: 94%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23 (t, $^3J_{H,H}$=7.3 Hz, 3H, SCH_2CH_3), 1.25 (t, $^3J_{H,H}$=7.1 Hz, 3H, OCH_2CH_3), 1.27 (t, $^3J_{H,H}$=7.3 Hz, 3H, SCH_2CH_3), 2.84 (q, $^3J_{H,H}$=7.3 Hz, 2H, SCH_2CH_3), 2.86 (q, $^3J_{H,H}$=7.3 Hz, 2H, SCH_2CH_3), 3.74 (s, 2H, H-2), 4.16 (q, $^3J_{H,H}$=7.1 Hz, 2H, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0 (s, OCH_2CH_3), 14.6 and 15.0 (s, 2× SCH_2CH_3), 27.9 and 28.8 (s, 2×SCH_2CH_3), 37.5 (q, $^3J_{C,F}$=2.8 Hz, C-2), 61.2 (s, OCH_2CH_3), 122.7 (q, $^1J_{C,F}$=275.6 Hz, CF_3), 130.2 (q, $^2J_{C,F}$=29.0 Hz, C-3), 146.0 (q, $^3J_{C,F}$=3.1 Hz, C-4), 169.3 (s, C-1); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −57.0 (s); IR (film) 2981, 2930, 1740, 1302, 1159, 1132 cm^{-1}; GCMS (EI) *m/e* (%) 302 (M^+), 274, 253, 229, 139 (100), 75. Anal. Calcd for $C_{11}H_{17}F_3O_2S_2$: C, 43.69; H, 5.67. Found: C, 43.37; H, 5.95.

4.2.2. Ethyl 4,4-bis(ethylsulfanyl)-3-pentafluoroethylbut-3-enoate (2b). Yield: 91%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 and 1.25 and 1.26 (t, $^3J_{H,H}$=7.2 Hz, 9H, 2× SCH_2CH_3+OCH_2CH_3), 2.84 and 2.86 (q, $^3J_{H,H}$=7.2 Hz, 4H, 2×SCH_2CH_3), 3.66 (s, 2H, H-2), 4.15 (q, $^3J_{H,H}$=7.2 Hz, 2H, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0 and 14.6 and 14.8 (s, 2×SCH_2CH_3+OCH_2CH_3), 28.3 and 29.3 (s, 2×SCH_2CH_3), 38.1 (t, $^3J_{C,F}$=4.3 Hz, C-2), 61.2 (s, OCH_2CH_3), 113.3 (tq, $^1J_{C,F}$=257.4, $^2J_{C,F}$=39.0 Hz, CF_2), 119.2 (qt, $^1J_{C,F}$=288.0, $^2J_{C,F}$=39.0 Hz, CF_3), 127.2 (t, $^2J_{C,F}$=20.7 Hz, C-3), 148.8 (t, $^3J_{C,F}$=3.2 Hz, C-4), 169.3 (s, C-1); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −107.1 (m, 2F, CF_2), −83.3 (m, 3F, CF_3); IR (film) 2982, 2931, 1741, 1197, 1130 cm^{-1}; GCMS (EI) *m/e* (%) 352 (M^+), 323, 303, 279 (100), 189, 75.

4.3. Typical procedure for acid hydrolysis of compounds (2a,b and 4) (Scheme 4)

To a solution of ketene dithioacetal **2a** (6.64 g, 22.0 mmol, 1 equiv) in trifluoroacetic acid (15 mL, 0.2 mol, 9 equiv) was added water (1.2 mL, 66.0 mmol, 3 equiv). The mixture was refluxed until complete conversion of **2a** (10 h). After cooling, water (30 mL) was added and the medium was basified using a saturated aqueous solution of $NaHCO_3$ (20 mL). The resulting aqueous phase was extracted twice with CH_2Cl_2 (2×40 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel using a mixture of petroleum ether–EtOAC (95/5) to give the compound **3a** (4.71 g, 83%).

4.3.1. Ethyl 3-(ethylsulfanylcarbonyl)-4,4,4-trifluorobutyrate (3a). Yield: 83%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (t, $^3J_{H,H}$=7.1 Hz, 3H, OCH_2CH_3), 1.27 (t, $^3J_{H,H}$=7.4 Hz, 3H, SCH_2CH_3), 2.73 (dd, $^2J_{H,H}$=17.2, $^3J_{H,H}$=4.0 Hz, 1H, H-2), 2.97 (qd, $^3J_{H,H}$=7.4, J=1.5 Hz, 2H, SCH_2CH_3), 3.08 (dd, $^2J_{H,H}$=17.2, $^3J_{H,H}$=10.3 Hz, 1H, H-2), 3.82 (dqd, $^3J_{H,H}$=10.3, $^3J_{H,F}$=8.5, $^3J_{H,H}$=4.0 Hz, 1H, H-3), 4.15 (q, $^3J_{H,H}$=7.1 Hz, 2H, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0 (s, SCH_2CH_3 or OCH_2CH_3), 14.1 (s, SCH_2CH_3 or OCH_2CH_3), 24.2 (s, SCH_2CH_3), 31.0 (q, $^3J_{C,F}$=2.5 Hz, C-2), 52.7 (q, $^2J_{C,F}$=27.0 Hz, C-3), 61.4 (s, OCH_2CH_3), 123.6 (q, $^1J_{C,F}$=280.8 Hz, CF_3), 169.4 (s, C-1), 192.4 (q, $^3J_{C,F}$=2.1 Hz, *C*OS); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −68.2 (d, $^3J_{F,H}$=8.5 Hz); IR (film) 2984, 2937, 1742, 1686, 1306, 1259, 1170, 1123 cm^{-1}; GCMS (EI) *m/e* (%) 259 (M+1), 213, 197 (100), 169, 149, 121, 101. Anal. Calcd for $C_9H_{13}F_3O_3S$: C, 41.86; H, 5.07. Found: C, 42.06; H, 5.08.

4.3.2. Ethyl 3-(ethylsulfanylcarbonyl)-4,4,5,5,5-pentafluoropentanoate (3b). Yield: 84%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.26 (t, $^3J_{H,H}$=7.1 Hz, 3H, OCH_2CH_3 or SCH_2CH_3), 1.27 (t, $^3J_{H,H}$=7.4 Hz, 3H, OCH_2CH_3 or SCH_2CH_3), 2.80 (dd, $^2J_{H,H}$=17.2, $^3J_{H,H}$=3.6 Hz, 1H, H-2), 2.9–3.2 (m, 3H, SCH_2CH_3 and H-2), 3.84 (m, 1H, H-3), 4.17 (q, $^3J_{H,H}$=7.1 Hz, 2H, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.87 and 13.92 (s, SCH_2CH_3 and OCH_2CH_3), 24.2 (s, SCH_2CH_3), 30.7 (m, C-2), 50.5 (t, $^2J_{C,F}$=20.7 Hz, C-3), 61.4 (s, OCH_2CH_3), 113.1 (tq, $^1J_{C,F}$=257.5, $^2J_{C,F}$=37.9 Hz, CF_2), 118.5 (qt, $^1J_{C,F}$=287.1, $^2J_{C,F}$=37.8 Hz, CF_3), 169.3 (s, C-1), 192.4 (m, *C*OS); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −82.6 (m, 3F, CF_3), −115.6 (dd, $^2J_{F,F}$=274.1, $^3J_{F,H}$=13.8 Hz, 1F, CF_2), −117.5 (dd, $^2J_{F,F}$=274.1, $^3J_{F,H}$=13.8 Hz, 1F, CF_2); IR (film) 2983, 2936, 1743, 1686, 1276, 1210 cm^{-1}; GCMS (EI) *m/e* (%) 309 (M+1), 263, 247, 219, 199 (100), 151, 77.

4.3.3. 3-(Ethylsulfanylcarbonyl)-4,4,4-trifluorobutanoic acid (5). Yield: 87%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (t, $^3J_{H,H}$=7.4 Hz, 3H, SCH_2CH_3), 2.80 (dd, $^2J_{H,H}$=17.8, $^3J_{H,H}$=3.9 Hz, 1H, H-2), 2.97 (q, $^3J_{H,H}$=7.4 Hz, 2H, SCH_2CH_3), 3.16 (dd, $^2J_{H,H}$=17.8, $^3J_{H,H}$=10.1 Hz, 1H, H-2), 3.80 (m, 1H, H-3), 11.3 (brs, 1H, OH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0 (s, SCH_2CH_3), 24.3 (s, SCH_2CH_3), 30.7 (q, $^3J_{C,F}$=2.0 Hz, C-2), 52.4 (q, $^2J_{C,F}$=27.4 Hz, C-3), 123.5 (q, $^1J_{C,F}$=280.8 Hz, CF_3), 175.8 (s, C-1), 192.2 (q, $^3J_{C,F}$=1.5 Hz, *C*OS); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −68.1 (d, $^3J_{F,H}$=8.6 Hz); IR (film) 3053, 2971, 2937, 1720, 1684, 1260, 1171, 1124 cm^{-1}; GCMS (EI) *m/e* (%) 231 (M+1), 169, 149, 121, 101, 95, 62 (100); HRMS (ESI) calcd for $C_7H_9F_3O_3NaS$ *m/e*=253.0122; found 253.0122.

4.4. Preparation of compound (4) (Scheme 4)

To a solution of compound **2a** (9.97 g, 33.0 mmol) in EtOH (50 mL) was added an aqueous solution of KOH 3 M (50 mL). The mixture was heated at 80 °C for 3 h. After cooling at 0 °C and acidification with hydrochloric acid 1 M (30 mL) until pH=1, the mixture was extracted with ether (3×100 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was recrystallized using a mixture of petroleum ether–EtOAc to give the compound **4** (8.9 g, 98%).

4.4.1. 4,4-Bis(ethylsulfanyl)-3-trifluoromethylbut-3-enoic acid (4). Solid: mp 79–80 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23 (t, $^3J_{H,H}$=7.2 Hz, 3H, SCH_2CH_3), 1.26 (t, $^3J_{H,H}$=7.2 Hz, 3H, SCH_2CH_3), 2.84 (q, $^3J_{H,H}$=7.2 Hz, 2H, SCH_2CH_3), 2.87 (q, $^3J_{H,H}$=7.2 Hz, 2H, SCH_2CH_3), 3.79 (s, 2H, H-2), 11.5 (s, 1H, OH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.6 and 14.9 (s, 2×SCH_2CH_3), 28.0 and 28.9 (s, SCH_2CH_3), 37.3 (m, C-2), 122.7 (q, $^1J_{C,F}$=275.6 Hz, CF_3), 129.1 (q, $^2J_{C,F}$=29.4 Hz, C-3), 147.0 (m, C-4), 176.2 (s, C-1); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −57.0 (s); IR (KBr) 3100, 2965, 1697, 1570, 1411 cm^{-1}; HRMS (ESI) calcd for $C_9H_{14}F_3O_2S_2$ *m/e*=275.0387; found 275.0374.

4.5. Typical procedure for preparation of succinimides (7a–d) (Scheme 5, path a)

To a solution of γ-carboxy-thioester **5** (0.23 g, 1.00 mmol, 1.00 equiv) in toluene (6 mL) was added benzylamine (0.11 g, 1.04 mmol, 1.05 equiv). The mixture was heated first at 110 °C for 2 h (formation of intermediate **6a**). After evaporation of toluene, the residue was heated to 200 °C for 1–3 h. After cooling, the crude mixture was diluted with ether (8 mL) and washed with brine (5 mL). After separation, the aqueous phase was extracted with ether (3×5 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel using a mixture of petroleum ether/EtOAc (85/15) to give the succinimide **7a** (0.19 g, 73%).

4.5.1. 3-Benzylcarbamoyl-4,4,4-trifluoro-butanoic acid (6a). Yield: 68%; Solid: mp 167–169 °C; ^{1}H NMR (250 MHz, CD_3OD) δ 2.75 (dd, $^2J_{H,H}$=17.2, $^3J_{H,H}$=3.4 Hz, 1H, H-2), 3.09 (dd, $^2J_{H,H}$=17.2, $^3J_{H,H}$=11.1 Hz, 1H, H-2), 3.7 (m, 1H, H-3), 4.4 (m, 2H, $NHCH_2$), 7.3 (m, 5H, Ph), NH and OH not visible; ^{13}C NMR (62.9 MHz, CD_3OD) δ 31.1 (m, C-2), 44.4 (s, $NHCH_2$), 47.7 (q, $^2J_{C,F}$=26.7 Hz, C-3), 126.5 (q, $^1J_{C,F}$=279.2 Hz, CF_3), 128.2 (s, CH Ph), 128.4 (s, 2×CH Ph), 129.5 (s, 2×CH Ph), 139.3 (s, C_q Ph), 167.6 (m, *C*ON), 173.2 (s, C-1); ^{19}F NMR (235.4 MHz, CD_3OD) δ −68.2 (d, $^3J_{F,H}$=8.6 Hz); IR (KBr) 3297, 3098, 2971, 2941, 1710, 1656, 1242, 1169 cm^{-1}; MS (ESI) *m/e* (%) 314 $(M+K)^+$, 298 $(M+Na)^+$, 276 $((M+H)^+$, 100). Anal. Calcd for $C_{12}H_{12}F_3NO_3$: C, 52.37; H, 4.39; N, 5.09. Found: C, 51.82; H, 4.24; N, 4.94.

4.5.2. 1-Benzyl-3-trifluoromethyl-pyrrolidine-2,5-dione (7a). Yield: 73%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.86 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=5.4 Hz, 1H, H-4), 2.99 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=9.4 Hz, 1H, H-4), 3.6 (m, 1H, H-3), 4.68 (d, $^2J_{H,H}$=17.2 Hz, 1H, NCH_2), 4.73 (d, $^2J_{H,H}$=17.2 Hz, 1H, NCH_2), 7.3 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.4 (q, $^3J_{C,F}$=1.7 Hz, C-4), 43.1 (s, NCH_2), 44.4 (q, $^2J_{C,F}$=30.0 Hz, C-3), 123.7 (q, $^1J_{C,F}$=278.5 Hz, CF_3), 128.3 (s, CH Ph), 128.7 (s, 2×CH Ph), 128.8 (s, 2×CH Ph), 134.8 (s, C_q Ph), 169.3 (q, $^3J_{C,F}$=2.6 Hz, C-2), 173.0 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.3 (d, $^3J_{F,H}$=9.5 Hz); IR (film) 3036, 2954, 1789, 1716, 1456, 1402 cm^{-1}; GCMS (EI) *m/e* (%) 258 (M+1), 257 (M^+), 160, 104, 95, 77 (100), 51; HRMS (ESI) calcd for $C_{12}H_{11}F_3NO_2$ *m/e*=258.0742; found 258.0736.

4.5.3. 1-(*n*-Pentyl)-3-trifluoromethyl-pyrrolidine-2,5-dione (7b). Yield: 71%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, $^3J_{H,H}$=6.9 Hz, 3H, CH_3), 1.3 (m, 4H, 2×CH_2), 1.6 (m, 2H, NCH_2CH_2), 2.83 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=5.2 Hz, 1H, H-4), 2.98 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=9.4 Hz, 1H, H-4), 3.54 (t, $^3J_{H,H}$=7.4 Hz, 2H, NCH_2), 3.5–3.6 (m, 1H, H-3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.8 (s, CH_3), 22.1 (s, CH_2), 27.0 (s, CH_2), 28.7 (s, CH_2), 29.4 (m, C-4), 39.5 (s, NCH_2), 44.3 (q, $^2J_{C,F}$=29.9 Hz, C-3), 123.7 (q, $^1J_{C,F}$=278.5 Hz, CF_3), 169.6 (q, $^3J_{C,F}$=3.0 Hz, C-2), 173.4 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.4 (d, $^3J_{F,H}$=8.6 Hz); IR (film) 2960, 2874, 1716, 1405, 1353, 1256, 1186 cm^{-1}; GCMS (EI) *m/e* (%) 238 (M+1), 237 (M^+), 181, 168 (100), 41; HRMS (ESI) calcd for $C_{10}H_{15}F_3NO_2$ *m/e*=238.1055; found 238.1064.

4.5.4. 1-Isopropyl-3-trifluoromethyl-pyrrolidine-2,5-dione (7c). Yield: 56%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.38 (d, $^3J_{H,H}$=6.9 Hz, 6H, CH_3), 2.78 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=5.1 Hz, 1H, H-4), 2.93 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=9.5 Hz, 1H, H-4), 3.5 (m, 1H, H-3), 4.40 (sept, $^3J_{H,H}$=6.9 Hz, 1H, NC*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 18.9 (s, CH_3), 29.3 (q, $^3J_{C,F}$=1.8 Hz, C-4), 44.0 (q, $^2J_{C,F}$=29.5 Hz, C-3), 44.7 (s, NCH), 123.8 (q, $^1J_{C,F}$=278.7 Hz, CF_3), 169.5 (m, C-2), 173.4 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.6 (d, $^3J_{F,H}$=9.5 Hz); IR (film) 2982, 1785, 1716, 1404, 1369 cm^{-1}; GCMS (EI) *m/e* (%) 210 (M+1), 209 (M^+), 194, 168 (100), 123, 95, 44; HRMS (ESI) calcd for $C_8H_{11}F_3NO_2$ *m/e*=210.0742; found 210.0740.

4.5.5. 1-(1′-Phenylethyl)-3-trifluoromethyl-pyrrolidine-2,5-dione (7d). Yield: 76%; mixture (50/50) of diastereomers; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.82 (d, $^3J_{H,H}$=7.3 Hz, 3H+3H, CH_3), 2.78 and 2.79 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=5.0 Hz, 1H+1H, H-4), 2.90 and 2.92 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=9.5 Hz, 1H+1H, H-4), 3.5 (m, 1H+1H, H-3), 5.45 and 5.46 (q, $^3J_{H,H}$=7.3 Hz, 1H+1H, NC*H*), 7.2–7.5 (m, 5H+5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.1 and 16.4 (s, CH_3), 29.3 (m, C-4), 44.0 (q, $^2J_{C,F}$=29.9 Hz, C-3), 51.0 and 51.2 (s, NCH), 123.7 and 123.8 (q, $^1J_{C,F}$=278.8 Hz, CF_3), 127.3 and 127.5 (s, 2×CH Ph), 128.0 and 128.1 (s, CH Ph), 128.5 (s, 2×CH Ph), 138.5 and 138.7 (s, C_q Ph), 169.3 (m, C-2), 173.1 and 173.2 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.5 and −69.4 (d, $^3J_{F,H}$=9.5 Hz); IR (film) 2981, 1713, 1606, 1505, 1455, 1385 cm^{-1}.

4.6. General procedure for preparation of succinimides (7e–i) (Scheme 5, path b)

The same procedure as described for path a (Scheme 5), except that the mixture was heated at 110 °C for 2 h, gave after work-up and purification by silica gel chromatography (mixture of petroleum ether–ethyl acetate) the succinimides **7e–i**.

4.6.1. 1-Phenyl-3-trifluoromethyl-pyrrolidine-2,5-dione (7e). Yield: 81%; solid: mp 117 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.86 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=5.5 Hz, 1H, H-4), 2.99 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=9.5 Hz, 1H, H-4), 3.6 (m, 1H, H-3), 7.1 (dm, $^3J_{H,H}$=7.5 Hz, 2H, 2×CH Ph), 7.4 (m, 3H, 3×CH Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.4 (q, $^3J_{C,F}$=2.0 Hz, C-4), 44.4 (q, $^2J_{C,F}$=29.9 Hz, C-3), 123.7 (q, $^1J_{C,F}$=278.5 Hz, CF_3), 126.3 (s, 2×CH Ph), 129.2 (s, CH

Ph), 129.3 (s, 2×CH Ph), 131.0 (s, C_q Ph), 168.7 (q, $^3J_{C,F}$= 2.7 Hz, C-2), 172.5 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.2 (d, $^3J_{F,H}$=9.5 Hz); IR (KBr) 3074, 2960, 1717, 1406, 1212 cm^{-1}; GCMS (EI) *m/e* (%) 243 (M^+), 174, 120, 95, 91 (100), 77. Anal. Calcd for $C_{11}H_8F_3NO_2$: C, 54.33; H, 3.32; N, 5.76. Found: C, 54.56; H, 3.13; N, 5.72.

4.6.2. 1-(*p*-Methoxyphenyl)-3-trifluoromethyl-pyrrolidine-2,5-dione (7f). Yield: 81%; solid: mp 148–150 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.95 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=5.3 Hz, 1H, H-4), 3.09 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$= 9.6 Hz, 1H, H-4), 3.6 (m, 1H, H-3), 3.82 (s, 3H, CH_3), 6.98 (d, $^3J_{H,H}$=8.6 Hz, 2H, 2×CH Ar), 7.15 (d, $^3J_{H,H}$=8.6 Hz, 2H, 2×CH Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.4 (q, $^3J_{C,F}$=2.0 Hz, C-4), 44.3 (q, $^2J_{C,F}$=30.1 Hz, C-3), 55.4 (s, CH_3), 114.5 (s, 2×CH Ar), 123.5 (s, NC_q Ar), 123.7 (q, $^1J_{C,F}$=279.1 Hz, CF_3), 127.5 (s, 2×CH Ar), 159.8 (s, OC_q Ar), 169.0 (q, $^3J_{C,F}$=3.2 Hz, C-2), 172.8 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.3 (d, $^3J_{F,H}$=8.6); IR (KBr) 3020, 2955, 1714, 1609, 1445, 1411 cm^{-1}; GCMS (EI) *m/e* (%) 273 (M^+, 100), 204, 122. Anal. Calcd for $C_{12}H_{10}F_3NO_3$: C, 52.75; H, 3.69; N, 5.13. Found: C, 52.89; H, 3.63; N, 4.80.

4.6.3. 1-(Pyridin-2-yl)-3-trifluoromethyl-pyrrolidine-2,5-dione (7g). Yield: 31%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.04 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=5.4 Hz, 1H, H-4), 3.20 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=9.7 Hz, 1H, H-4), 3.8 (m, 1H, H-3), 7.30 (dd, $^3J_{H,H}$=7.9, $^4J_{H,H}$=0.9 Hz, 1H, CH Ar), 7.41 (ddd, $^3J_{H,H}$=7.9, $^3J_{H,H}$=4.9, $^4J_{H,H}$=0.9 Hz, 1H, CH Ar), 7.89 (ddd, $^3J_{H,H}$=7.9, $^3J_{H,H}$=7.9, $^4J_{H,H}$=1.8 Hz, 1H, CH Ar), 8.65 (dm, $^3J_{H,H}$=4.9 Hz, 1H, CH Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.8 (m, C-4), 44.7 (q, $^2J_{C,F}$= 30.1 Hz, C-3), 122.2 (s, CH Ar), 123.7 (q, $^1J_{C,F}$=278.8 Hz, CF_3), 124.6 (s, CH Ar), 138.7 (s, CH Ar), 145.3 (s, C_q Ar), 149.9 (s, CH Ar), 168.2 (m, C-2), 171.9 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.0 (d, $^3J_{F,H}$=9.5 Hz); IR (film) 3064, 2930, 1798, 1736, 1594, 1472, 1439, 1387 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_8F_3N_2O_2$ *m/e*=245.0538; found 245.0534.

4.6.4. 1-Amino-3-trifluoromethyl-pyrrolidine-2,5-dione (7h). Yield: 45%; oil; ^{1}H NMR (250 MHz, CD_3OD) δ 2.86 (dd, $^2J_{H,H}$=18.3, $^3J_{H,H}$=4.8 Hz, 1H, H-4), 3.09 (dd, $^2J_{H,H}$=18.3, $^3J_{H,H}$=9.5 Hz, 1H, H-4), 3.97 (qdd, $^3J_{H,F}$= 9.5, $^3J_{H,H}$=9.5, $^3J_{H,H}$=4.8 Hz, 1H, H-3), NH_2 not visible; ^{13}C NMR (62.9 MHz, CD_3OD) δ 29.5 (q, $^3J_{C,F}$=2.1 Hz, C-4), 44.8 (q, $^2J_{C,F}$=29.9 Hz, C-3), 126.5 (q, $^1J_{C,F}$= 277.4 Hz, CF_3), 170.8 (q, $^3J_{C,F}$=3.2 Hz, C-2), 174.7 (s, C-5); ^{19}F NMR (235.4 MHz, CD_3OD) δ −68.7 (d, $^3J_{F,H}$= 9.5 Hz); GCMS (EI) *m/e* (%) 183 (M+1), 156, 123, 95 (100), 77, 69; HRMS (ESI) calcd for $C_5H_6F_3N_2O_2$ *m/e*= 183.0381; found 183.0376.

4.6.5. 1-Methylamino-3-trifluoromethyl-pyrrolidine-2,5-dione (7i). Yield: 47%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.71 (d, $^3J_{H,H}$=5.2 Hz, 3H, CH_3), 2.83 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=4.8 Hz, 1H, H-4), 3.00 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$= 9.5 Hz, 1H, H-4), 3.6 (m, 1H, H-3), 4.73 (q, $^3J_{H,H}$=5.2 Hz, 1H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 27.8 (q, $^3J_{C,F}$= 2.1 Hz, C-4), 37.5 (s, CH_3), 42.7 (q, $^2J_{C,F}$=30.1 Hz, C-3), 123.5 (q, $^1J_{C,F}$=279.0 Hz, CF_3), 167.0 (q, $^3J_{C,F}$=3.2 Hz, C-2), 170.9 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.5 (d, $^3J_{F,H}$=9.5 Hz); IR (film) 3497, 3303, 2944, 1717, 1361, 1259, 1178 cm^{-1}; GCMS (EI) *m/e* (%) 197 (M+1), 168, 95, 77, 69 (100); HRMS (ESI) calcd for $C_6H_8F_3N_2O_2$ *m/e*=197.0538; found 197.0543.

4.7. Preparation of the succinimide (7j) (Scheme 6)

To a suspension of sodium ethoxide (68 mg, 1.00 mmol, 2.00 equiv) in dry toluene (3 mL) was added *N*,*N*′-dimethylhydrazine dihydrochloride (69 mg, 0.52 mmol, 1.05 equiv). The mixture was stirred at room temperature for 1 h. The γ-carboxy thioester **5** (0.12 g, 0.50 mmol, 1.00 equiv) was then added. The resulting mixture was heated at 110 °C for 2 h and gave after work-up and purification by silica gel chromatography (mixture of petroleum ether–EtOAc (80/20)) the succinimide **7j** (27 mg, 30%).

4.7.1. 1-Methyl-3-trifluoromethyl-pyrrolidine-2,5-dione (7j). Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.87 (dd, $^2J_{H,H}$= 18.5, $^3J_{H,H}$=5.3 Hz, 1H, H-4), 3.01 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=9.5 Hz, 1H, H-4), 3.07 (s, 3H, NCH_3), 3.6 (m, 1H, H-3); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.3 (d, $^3J_{F,H}$= 8.6 Hz); GCMS (EI) *m/e* (%) 182 (M+1), 181 (M^+), 124, 96 (100).

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A novel synthetic method for 2-arylmethyl substituted imidazolines and imidazoles from 2-aryl-1,1-dibromoethenes

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Abstract—Various 2-arylmethylimidazolines were prepared by treating readily available 2-aryl-1,1-dibromoethenes with ethylenediamine under mild conditions and further converted into the corresponding imidazoles smoothly with Swern oxidation.

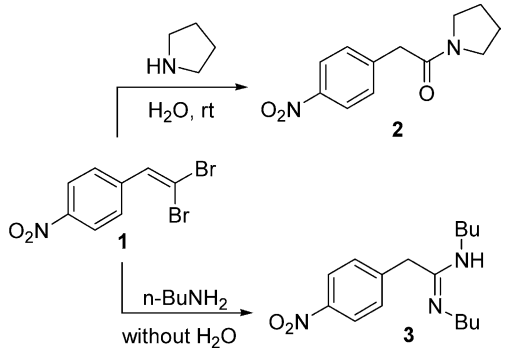
1. Introduction

1,1-Dihaloalkenes, efficiently prepared from the corresponding aldehydes are useful intermediates in organic synthesis. They have been used as alkynyl precursors,[1] monomers of AB_2 type polymers,[2] and for the synthesis of conjugated dienes or enynes.[3] They also have been effective intermediates for the stereoselective formation of either *E*- or *Z*-alkenes via transition metal-catalyzed coupling reactions.[4] Recently, we and others have found that 2-aryl-1,1-dibromoethenes reacted with secondary or primary amines under mild conditions to give the substitution products such as **2** (Scheme 1).[3c,5] We have also shown that the reaction of 2-(4-nitrophenyl)-1,1-dibromoethene **1** with $BuNH_2$ gave amidine **3** quantitatively in the absence of water and the reaction with ethylenediamine gave a good yield of the corresponding imidazoline.[5a]

There has been considerable attention on the synthesis of imidazolines and imidazoles[6] because of their diverse biological and pharmacological activities.[7] A novel and efficient methodology for the preparation of imidazoline[8] and imidazole derivatives[9] would provide synthetic chemists with a valuable tool and versatility. Although several synthetic methods have been developed for 2-substituted imidazolines and imidazoles, there is still a need for a method employing mild reaction conditions and readily available reagents. Because the reaction of 2-aryl-1,1-dibromoethenes with ethylenediamine can provide another mild and efficient alternative to the known synthetic methods of 2-arylmethyl substituted imidazolines and imidazoles, we have systematically investigated the reactions of various 2-aryl-1,1-dibromoethenes and report the results as follows.

2. Results and discussion

First, the formation of imidazolines from aryl dibromoethenes with ethylenediamine as a reaction solvent was examined at room temperature (Table 1). The required aryl dibromoethenes were efficiently prepared from the corresponding aryl aldehydes with different substituents in 73–99% yield as described in the previous work.[5a] Both the rate and the yield of the imidazoline formation reactions depend much on the electronic properties of the substituents on the aryl group. Aryl dibromoethenes with an electron-withdrawing substituent produced the corresponding imidazolines at a faster rate and in better yield than those with an electron-donating group. To our satisfaction, the



Scheme 1. The substitution reactions of 2-(4-nitrophenyl)-1,1-dibromoethene **1** with amines.[5a]

Keywords: Aryl-1,1-dibromoethene; Imidazoline; Swern oxidation; Imidazole.

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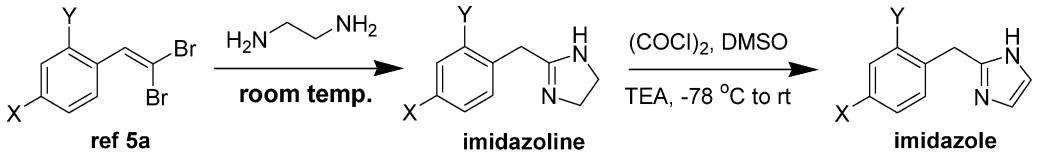
Table 1. Synthesis of 2-arylmethyl substituted imidazolines and imidazoles from 2-aryl-1,1-dibromoethenes



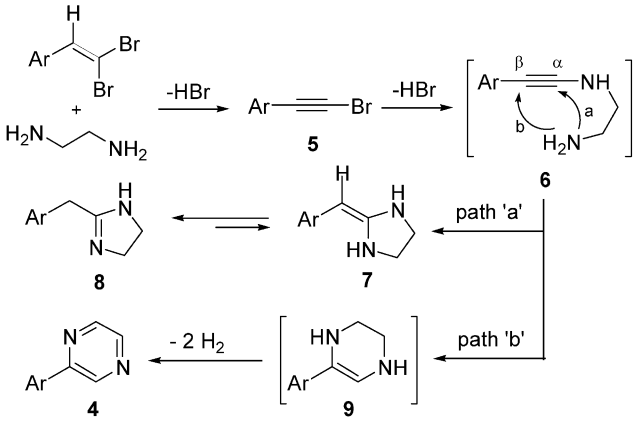
Entry	X	Y	Imidazoline		Imidazole	
			Time (h)	Yield[a] (%)	Time (h)	Yield[a] (%)
1	NO_2	H	0.5	81	2.5	75
2	H	NO_2	0.5	90	2.5	73
3	CN	H	1	93	2.5	66
4	CF_3	H	1	95	2.5	58
5	H	CF_3	5	93	2.5	74
6	Cl	H	3	95	2.5	58
7	H	Cl	6	95	2.5	68
8	H	H	15	75	2.5	84
9	Me	H	36	63[b]	2.5	89
10	H	Me	48	92	2.5	67
11	MeO	H	80	70[b,c]	2.5	53
12	H	MeO	84	55	2.5	75

[a] Isolated yield.
[b] Corresponding pyrazines **4** were obtained additionally in 13–15% yield (Scheme 2).
[c] The crude yield.

reaction of *o*-nitrophenyl dibromoethene with ethylenediamine gave a high yield of the corresponding imidazoline (entry 2). Its reaction with pyrrolidine in the previous report gave a poor yield (20%) of 2-(*o*-nitrophenyl)acetamide because of other unknown side products.[5a] Although the *p*-cyano group is tolerated under the reaction conditions (entry 3), the *o*-cyano group seemed to react to give the unidentified side products and no desired product was isolated (not shown). For the slow-reacting aryl dibromoethenes, the reaction rate could be increased by raising the reaction temperature up to 50 °C and the reactions were finished less than 30 min. However, the yields of the corresponding imidazolines were not improved. It is also notable that the reaction rate of aryl dibromoethenes with an *ortho* substituent is slower compared to that with a *para* substituent probably because of the steric hindrance from the *ortho* substituent. It was interesting to find that aryl dibromoethenes with a *para* electron-donating substituent on the aryl group produced the corresponding pyrazines **4** (Scheme 2) in 15% (Ar=4-methylphenyl) and 13% (Ar=4-methoxyphenyl) yield, respectively, in addition to the expected imidazolines (entries 9 and 11).[10] Only trace amount of the corresponding pyrazines was detected with aryl dibromoethenes having an electron-donating group at an *ortho* position, probably because of the steric hindrance in the reaction intermediate. The same reactions with alkyl dibromoethenes prepared from octanal and cyclohexane carboxaldehyde were very slow. No reaction occurred after 24 h and undesired products were noticeable after 40 h with no expected imidazoline detected. The reaction of **1** with *N*-methylethylenediamine yielded the corresponding *N*-methyl imidazoline in 65% yield together with a small amount of unknown by-products.[11]

Next, we have tested several oxidation methods to convert imidazoline into imidazole with dehydrogenation catalysts or reagents such as Pd, DDQ or MnO_2[12–15] and found that the Swern oxidation reaction[16] gave a reasonable yield of the desired imidazoles (Table 1). For entry 11, the crude imidazoline product was not purified and used directly for the dehydrogenation reaction because a significant decrease in the yield was observed after unsuccessful purification of the crude imidazoline with silica gel column chromatography. Thus, a better yield of the imidazole product was obtained using the crude imidazoline in the Swern oxidation. An oxidation reaction of 2-(4-nitrophenyl)methylimidazole with MnO_2 resulted in the further oxidation at the benzylic position to give 2-(4-nitrobenzoyl)imidazoline in about 20% yield and other unidentified products (not shown). No dehydrogenation reaction was successful with Pd catalyst or DDQ at room temperature.

A plausible explanation for the reaction results of aryl dibromoethenes with ethylenediamine is shown in Scheme 2. The dehydrobromination reaction occurs to give alkynyl bromide **5** under the reaction conditions. A similar dehydrobromination mechanism for the formation of



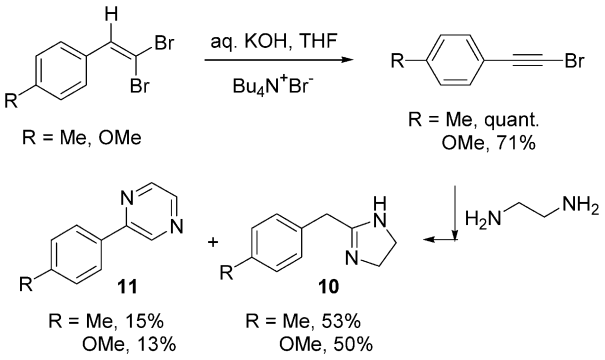
Scheme 2. A probable mechanism for the formation of imidazoline and pyrazine.

alkynyl halide was proposed with quaternary ammonium hydroxide.[17] A substitution reaction of **5** with ethylenediamine would result in ynamine **6**[18] that can undergo an addition reaction to the triple bond in either way, path 'a' or 'b'. A 6-*endo* mode of cyclization via path 'b' yields tetrahydropyrazine **9** while a 5-*exo* type of ring closure via path 'a' produces imidazoline **8** after equilibration with the initial addition intermediate **7**.[19] A similar ynamine intermediate was suggested for the formation of imidazolines from the reaction of ynamine of aziridine with primary amines.[8a] In situ air oxidation of **9** would give the more stable product, pyrazine **4**.

We have tested the possible involvement of alkynyl bromide as a reaction intermediate by an independent reaction of alkynyl bromide with ethylenediamine (Scheme 3). The required alkynyl bromides were prepared separately according to the literature.[20] Treatment of alkynyl bromides having an electron-donating group with ethylenediamine gave a mixture of imidazoline **10** and pyrazine **11** as products. Heating the reaction mixture to 50 °C or under reflux increased the yield of each product by about 5%. It was worthy to note that no significant amount of pyrazine was detected from alkynyl bromides with an electron-withdrawing group or an *ortho* substituent (not shown). Presumably, the electron-withdrawing group makes the α-carbon attached to the amine more electrophilic to the incoming amine and the *ortho* substituent seems to increase steric hindrance for the nucleophilic attack at the β-carbon by the amine (Scheme 2). Another thing to note is the facile oxidation of partially saturated pyrazine **9** to fully unsaturated pyrazine **4**. We could not isolate or even detect **9** in the reaction mixture at all. In contrast, no autoxidation product of partially saturated imidazole **7** or **8** was observed in either reaction, that is, one-step or two-step reaction (Schemes 2 or 3).

3. Conclusion

We have established that a novel transformation of aryl dibromoethenes into the corresponding 2-arylmethyl substituted imidazolines can be done efficiently under mild conditions and the selective oxidation of the imidazoline ring is possible to give the corresponding imidazole with the Swern oxidation in the presence of the reactive benzylic group. The methods described in the present study would be a good and mild way to prepare pharmaceutically important imidazoline and imidazole derivatives.



Scheme 3. Independent synthesis of imidazoline and pyrazine from alkynyl bromide.

4. Experimental

4.1. General

Materials were obtained from commercial suppliers and used without further purification. For anhydrous solvents, dichloromethane was distilled from calcium hydride immediately prior to use. THF and 1,4-dioxane were distilled from sodium/benzophenone ketyl. All glassware, syringes, needles, and magnetic bars used in moisture-sensitive reactions were oven-dried at 120 °C for at least 4 h and stored in desiccators until use. Upon workup, solvent was removed with a rotary evaporator and then with a high vacuum pump. Reactions were monitored with TLC. Commercially available TLC plates (silica gel, 5–25 μm) were visualized under UV light (254 or 365 nm) and then with a molybdophosphoric acid or ninhydrin stain. The R_f values of aryl dibromoethenes and imidazolines were measured with hexane/EtOAc (4:1) and CH_2Cl_2/MeOH (4:1), respectively. For pyrazines and imidazoles, pure EtOAc was used for measurement of the R_f value, unless stated otherwise. Flash column chromatography was carried out on Kieselgel 60 (Merck). ^1H and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, in $CDCl_3$ unless stated otherwise and data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm); chemical shift (multiplicity, integration, coupling constant (J) in Hz).

4.2. General procedure for synthesis of 2-arylmethylimidazoline

To a solution of ethylenediamine (5 mL) was added aryl dibromoethene (0.50 mmol) at room temperature. After stirring for the indicated time in Table 1, the resulting mixture was concentrated under reduced pressure to remove excess ethylenediamine. An aq ammonia (20 mL) solution was added to the residue and the resulting mixture was extracted with chloroform (3×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give the crude residue. The crude product was chromatographed on silica gel and elution with ethyl acetate afforded the corresponding pyrazine, if any. Further elution with a solution of dichloromethane, ethanol and triethylamine (7:2:1) yielded the corresponding pure imidazoline.

4.2.1. 2-(4-Nitrophenyl)methylimidazoline. Yield (83 mg, 81%); violet solid; mp 135–137 °C; R_f 0.49; ^1H NMR δ 3.62 (s, 4H), 3.69 (s, 2H), 7.47 (d, 2H, J=8.7 Hz), 8.19 (d, 2H, J=8.7 Hz); ^{13}C NMR δ 36.3, 50.5 (br), 124.3, 130.2, 144.3, 147.4, 165.0; HRMS (CI) calcd for $C_{10}H_{12}N_3O_2$ 206.0929 (M^++1), found 206.0925.

4.2.2. 2-(2-Nitrophenyl)methylimidazoline. Yield (92 mg, 90%); pale yellowish solid; mp 118–120 °C; R_f 0.48; ^1H NMR δ 3.58 (s, 4H), 3.86 (s, 2H), 4.54 (br s, 1H), 7.44 (ddd, 1H, J=8.3, 7.3, 1.1 Hz), 7.52 (dd, 1H, J=8.3, 1.1 Hz), 7.60 (ddd, 1H, J=8.3, 7.3, 1.1 Hz), 8.01 (dd, 1H, J=8.3, 1.1 Hz); ^{13}C NMR δ 33.4, 49.9 (br), 125.0, 128.2, 131.5,

132.8, 133.5, 148.9, 165.0; HRMS (EI) calcd for $C_{10}H_{11}N_3O_2$ 205.0851, found 205.0854. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.52; H, 5.50; N, 20.48.

4.2.3. 2-(4-Cyanophenyl)methylimidazoline. Yield (86 mg, 93%); pale yellowish solid; mp 172–174 °C; R_f 0.48; ^{1}H NMR δ 3.61 (br s, 4H), 3.64 (s, 2H), 7.41 (d, 2H, J=8.3 Hz), 7.63 (d, 2H, J=8.3 Hz); ^{13}C NMR δ 33.5, 47.4 (br), 108.3, 116.1, 127.1, 129.9, 139.1, 162.3; HRMS (CI) calcd for $C_{11}H_{12}N_3$ 186.1031 (M^++1), found 186.1034.

4.2.4. 2-(4-Trifluoromethylphenyl)methylimidazoline. Yield (108 mg, 95%); pale yellowish solid; mp 100–102 °C; R_f 0.48; ^{1}H NMR δ 3.61 (br s, 4H), 3.66 (s, 2H), 7.41 (d, 2H, J=8.2 Hz), 7.60 (d, 2H, J=8.2 Hz); ^{13}C NMR 35.7, 49.7, 124.0 (q, J=270.0 Hz), 125.5 (q, J=3.8 Hz), 129.1, 129.2 (q, J=32.1 Hz), 140.1 (q, J=1.2 Hz), 165.4; HRMS (CI) calcd for $C_{11}H_{12}N_2F_3$ 229.0952 (M^++1), found 229.0952.

4.2.5. 2-(2-Trifluoromethylphenyl)methylimidazoline. Yield (106 mg, 93%); pale yellowish solid; mp 87–89 °C; R_f 0.48; ^{1}H NMR δ 3.59 (br s, 4H), 3.77 (s, 2H), 7.36–7.39 (m, 1H), 7.51–7.53 (m, 2H), 7.66 (d, 1H, J=7.7 Hz); ^{13}C NMR δ 32.3, 49.7 (br), 124.2 (q, J=271.4 Hz), 125.7 (q, J=5.6 Hz), 126.9, 128.3 (q, J=29.6 Hz), 131.2, 131.9, 134.6 (q, J=1.2 Hz), 165.1; HRMS (CI) calcd for $C_{11}H_{12}N_2F_3$ 229.0952 (M^++1), found 229.0957. Anal. Calcd for $C_{11}H_{11}N_2F_3$: C, 57.89; H, 4.86; N, 12.28. Found: C, 57.82; H, 4.97; N, 11.95.

4.2.6. 2-(4-Chlorophenyl)methylimidazoline. Yield (92 mg, 95%); pale yellowish solid; mp 138–140 °C; R_f 0.47; ^{1}H NMR δ 3.60 (s, 6H), 7.22 (d, 2H, J=8.3 Hz), 7.30 (d, 2H, J=8.3 Hz); ^{13}C NMR (acetone-d_6) δ 35.6, 50.6 (br), 129.0, 131.5, 132.5, 137.2, 167.2; HRMS (CI) calcd for $C_{10}H_{12}N_2Cl$ 195.0689 (M^++1), found 195.0690. Anal. Calcd for $C_{10}H_{11}N_2Cl$: C, 61.70; H, 5.70; N, 14.39. Found: C, 61.76; H, 5.77; N, 14.17.

4.2.7. 2-(2-Chlorophenyl)methylimidazoline. Yield (92 mg, 95%); yellowish solid; mp 132–134 °C; R_f 0.48; ^{1}H NMR δ 3.59 (br s, 4H), 3.75 (s, 2H), 7.19–7.25 (m, 2H), 7.35–7.40 (m, 2H); ^{13}C NMR δ 33.7, 49.9 (br), 127.2, 128.5, 129.5, 131.0, 134.0, 134.2, 165.3; HRMS (CI) calcd for $C_{10}H_{12}N_2Cl$ 195.0689 (M^++1), found 195.0689. Anal. Calcd for $C_{10}H_{11}N_2Cl$: C, 61.70; H, 5.70; N, 14.39. Found: C, 62.00; H, 5.78; N, 14.40.

4.2.8. 2-Benzylimidazoline. Yield (59 mg, 75%); light brown oil; R_f 0.49; ^{1}H NMR δ 3.59 (br s, 4H), 3.71 (s, 2H), 6.73 (br s, 1H), 7.22–7.37 (m, 5H); ^{13}C NMR δ 35.0, 48.3, 127.1, 128.7, 128.9, 135.1, 167.3; HRMS (CI) calcd for $C_{10}H_{13}N_2$ 161.1079 (M^++1), found 161.1079.

4.2.9. 2-(4-Methylphenyl)methylimidazoline. Yield (55 mg, 63%); pale yellowish solid; mp 172–174 °C; R_f 0.52; ^{1}H NMR δ 2.34 (s, 3H), 3.96 (br s, 4H), 4.18 (s, 2H), 7.18 (d, 2H, J=8.2 Hz), 7.29 (d, 2H, J=8.2 Hz); ^{13}C NMR 21.1, 32.0, 44.6, 128.9, 129.6, 129.9, 138.0, 170.8; HRMS (CI) calcd for $C_{11}H_{15}N_2$ 175.1235 (M^++1), found 175.1236.

4.2.10. 2-(2-Methylphenyl)methylimidazoline. Yield (80 mg, 92%); yellowish solid; mp 77–79 °C; R_f 0.53; ^{1}H NMR δ 2.33 (s, 3H), 3.58 (br s, 4H), 3.63 (s, 2H), 7.18–7.19 (m, 4H); ^{13}C NMR δ 19.4, 34.1, 49.8, 126.2, 127.3, 130.0, 130.4, 134.4, 137.0, 166.0; HRMS (CI) calcd for $C_{11}H_{15}N_2$ 175.1235 (M^++1), found 175.1236. Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.80. Found: C, 75.43; H, 8.13; N, 16.23.

4.2.11. 2-(2-Methoxyphenyl)methylimidazoline. Yield (52 mg, 55%); pale yellowish oil; R_f 0.51; ^{1}H NMR δ 3.46 (br s, 1H), 3.55 (br s, 4H), 3.62 (s, 2H), 3.87 (s, 3H), 6.88–6.96 (m, 2H), 7.23–7.28 (m, 2H); ^{13}C NMR δ 30.5, 50.1 (br), 55.4, 110.5, 120.9, 124.6, 128.3, 130.7, 157.0, 166.9; HRMS (CI) calcd for $C_{11}H_{15}N_2O$ 191.1184 (M^++1), found 191.1183.

4.2.12. 2-(4-Methylphenyl)pyrazine. Yield (13 mg, 15%); yellow solid; mp 125–127 °C; R_f 0.54; ^{1}H NMR δ 2.43 (s, 3H), 7.33 (d, 2H, J=8.0 Hz), 7.92 (d, 2H, J=8.0 Hz), 8.48 (d, 1H, J=2.6 Hz), 8.61 (dd, 1H, J=2.6, 1.6 Hz), 9.01 (d, 1H, J=1.6 Hz); ^{13}C NMR δ 21.4, 126.8, 129.8, 133.6, 140.1, 142.0, 142.6, 144.1, 152.9; HRMS (CI) calcd for $C_{11}H_{11}N_2$ 171.0922 (M^++1), found 171.0923. Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 78.00; H, 6.11; N, 16.35.

4.2.13. 2-(4-Methoxyphenyl)pyrazine. Yield (12 mg, 13%); pale yellowish solid; mp 104–105 °C; R_f 0.50; ^{1}H NMR δ 3.88 (s, 3H), 7.04 (d, 2H, J=8.6 Hz), 7.99 (d, 2H, J=8.6 Hz), 8.44 (d, 1H, J=2.6 Hz), 8.59 (m, 1H), 8.98 (m, 1H); ^{13}C NMR δ 55.4, 114.5, 128.3, 128.9, 141.6, 142.1, 144.0, 152.5, 161.2; HRMS (CI) calcd for $C_{11}H_{11}N_2O$ 187.0871 (M^++1), found 187.0873. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.07; H, 5.51; N, 15.02.

4.3. General procedure for synthesis of 2-arylmethylimidazole

To a solution of CH_2Cl_2 (20 mL) and DMSO (0.17 mL, 1.25 mmol) was added oxalyl chloride (1.25 mL of 2 M solution in CH_2Cl_2, 1.25 mmol) at −78 °C under N_2 atmosphere. After stirring for 20 min, a solution of the purified or crude imidazoline (0.50 mmol) in CH_2Cl_2 (15 mL) was added to the reaction mixture. After stirring for 50 min, TEA (0.71 mL, 2.5 mmol) was added and then the reaction mixture was warmed to room temperature. After stirring for 50 min, an aq ammonia solution (20 mL) was added and the resulting mixture was extracted with $CHCl_3$ (3×10 mL). The combined organic layers were washed with brine (2×20 mL), dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was eluted with ethyl acetate only to give the corresponding imidazoles with silica gel column chromatography.

4.3.1. 2-(4-Nitrophenyl)methylimidazole. Yield (62 mg, 75%); pale yellowish solid; mp 190 °C; R_f 0.11; ^{1}H NMR δ 4.23 (s, 2H), 7.02 (s, 2H), 7.42 (d, 2H, J=8.8 Hz), 8.19 (d, 2H, J=8.8 Hz); ^{13}C NMR (methanol-d_4) δ 32.6, 120.7, 122.5, 128.5, 144.6, 144.7, 146.1; HRMS (CI) calcd for $C_{10}H_{10}N_3O_2$ 204.0773 (M^++1), found 204.0773.

4.3.2. 2-(2-Nitrophenyl)methylimidazole. Yield (67 mg, 73%); pale yellowish solid; mp 125–126 °C; R_f 0.13; ^{1}H NMR δ 4.35 (s, 2H), 6.97 (br s, 2H), 7.39–7.44 (m, 1H), 7.58–7.60 (m, 2H), 7.97 (d, 1H, J=7.9 Hz); ^{13}C NMR (methanol-d_4) δ 29.7, 120.0, 123.1, 126.5, 130.5, 131.0, 131.7, 143.4, 147.3; HRMS (EI) calcd for $C_{10}H_9N_3O_2$ 203.0695, found 203.0697. Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.25; H, 4.50; N, 20.70.

4.3.3. 2-(4-Cyanophenyl)methylimidazole. Yield (56 mg, 66%); white solid; mp 150–151 °C; R_f 0.10; ^{1}H NMR (acetone-d_6) δ 4.16 (s, 2H), 6.96 (s, 2H), 7.48 (d, 2H, J=8.2 Hz), 7.69 (d, 2H, J=8.2 Hz); ^{13}C NMR δ (acetone-d_6) δ 35.2, 111.0, 119.4, 130.5, 133.0, 145.4, 146.0; HRMS (CI) calcd for $C_{11}H_{10}N_3$ 184.0875 ($M^+ + 1$), found 184.0879. Anal. Calcd for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.01; H, 5.07; N, 22.55.

4.3.4. 2-(4-Trifluoromethylphenyl)methylimidazole. Yield (62 mg, 58%); white solid; mp 124–125 °C; R_f 0.11; ^{1}H NMR δ 4.19 (s, 2H), 7.00 (s, 2H), 7.37 (d, 2H, J=8.1 Hz), 7.59 (d, 2H, J=8.1 Hz); ^{13}C NMR (acetone-d_6) δ 35.0, 125.4 (q, J=270.0 Hz), 126.0 (q, J=3.8 Hz), 128.9 (q, J=32.3 Hz), 130.1 (br), 144.4, 146.5; HRMS (CI) calcd for $C_{11}H_{10}N_2F_3$ 227.0796 ($M^+ + 1$), found 227.0794.

4.3.5. 2-(2-Trifluoromethylphenyl)methylimidazole. Yield (78 mg, 74%); white solid; mp 148–149 °C; R_f 0.15; ^{1}H NMR δ 4.26 (s, 2H), 6.95 (s, 2H), 7.34 (t, 1H, J=7.9 Hz), 7.35 (d, 1H, J=7.9 Hz), 7.47 (t, 1H, J=7.9 Hz), 7.65 (d, 1H, J=7.9 Hz); ^{13}C NMR δ 31.2, 121.9 (br), 124.4 (q, J=272.0 Hz), 125.9 (q, J=5.6 Hz), 126.8, 128.2 (q, J=29.6 Hz), 131.2, 132.1, 136.2, 145.6; HRMS (CI) calcd for $C_{11}H_{10}N_2F_3$ 227.0796 ($M^+ + 1$), found 227.0800.

4.3.6. 2-(4-Chlorophenyl)methylimidazole. Yield (53 mg, 58%); light yellowish solid; mp 158–159 °C; R_f 0.11; ^{1}H NMR δ 4.10 (s, 2H), 7.00 (br s, 2H), 7.19 (d, 2H, J=8.5 Hz), 7.31 (d, 2H, J=8.5 Hz); ^{13}C NMR (methanol-d_4) δ 31.7, 119.9, 126.9, 128.4, 130.7, 135.2, 145.0; HRMS (CI) calcd for $C_{10}H_{10}N_2Cl$ 193.0532 ($M^+ + 1$), found 193.0534. Anal. Calcd for $C_{10}H_9N_2Cl$: C, 62.35; H, 4.71; N, 14.54. Found: C, 62.26; H, 4.81; N, 14.11.

4.3.7. 2-(2-Chlorophenyl)methylimidazole. Yield (62 mg, 68%); light yellowish solid; mp 123–124 °C; R_f 0.13; ^{1}H NMR δ 4.24 (s, 2H), 6.96 (br s, 2H), 7.19–7.24 (m, 2H), 7.30–7.33 (m, 1H), 7.37–7.41 (m, 1H); ^{13}C NMR δ 32.6, 121.8, 127.2, 128.3, 129.5, 130.8, 133.7, 135.5, 145.7; HRMS (EI) calcd for $C_{10}H_9N_2Cl$ 192.0454, found 192.0454. Anal. Calcd for $C_{10}H_9N_2Cl$: C, 62.35; H, 4.71; N, 14.54. Found: C, 62.59; H, 4.84; N, 14.52.

4.3.8. 2-Benzylimidazole. Yield (50 mg, 84%); brown solid; mp 120–121 °C; R_f 0.13; ^{1}H NMR (methanol-d_4) δ 4.06 (s, 2H), 6.97 (br s, 2H), 7.20–7.31 (m, 5H); ^{13}C NMR (methanol-d_4) δ 33.0, 120.4, 125.8, 127.6, 127.8, 137.0, 146.5; HRMS (CI) calcd for $C_{10}H_{11}N_2$ 159.0922 ($M^+ + 1$), found 159.0919. Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.29; H, 6.73; N, 17.29.

4.3.9. 2-(4-Methylphenyl)methylimidazole. Yield (70 mg, 89%); pale yellowish solid; mp 106–107 °C; R_f 0.10; ^{1}H NMR δ 2.34 (s, 3H), 4.09 (s, 2H), 6.95 (br s, 2H), 7.14 (br s, 4H); ^{13}C NMR (methanol-d_4) δ 21.0, 34.6, 122.3, 129.4, 130.2, 135.9, 137.4, 148.5; HRMS (CI) calcd for $C_{11}H_{13}N_2$ 173.1079 ($M^+ + 1$), found 173.1079. Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.76; H, 7.11; N, 16.23.

4.3.10. 2-(2-Methylphenyl)methylimidazole. Yield (53 mg, 67%); brown solid; mp 146–147 °C; R_f 0.11; ^{1}H NMR δ 2.23 (s, 3H), 4.13 (s, 2H), 6.95 (br s, 2H), 7.20 (br s, 4H); ^{13}C NMR (methanol-d_4) δ 17.5, 31.1, 120.3 (br), 125.1, 125.9, 128.2, 129.2, 135.1, 135.5, 145.9; HRMS (CI) calcd for $C_{11}H_{13}N_2$ 173.1079 ($M^+ + 1$), found 173.1078. Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.68; H, 7.10; N, 16.29.

4.3.11. 2-(4-Methoxyphenyl)methylimidazole. Yield (35 mg, 53%); brown solid; mp 124–125 °C; R_f 0.13; ^{1}H NMR (acetone-d_6) δ 3.74 (s, 3H), 3.95 (s, 2H), 6.82 (d, 2H, J=8.8 Hz), 6.89 (br s, 2H), 7.16 (d, 2H, J=8.8 Hz); ^{13}C NMR (methanol-d_4) δ 34.3, 55.7, 115.0, 122.4 (br), 130.5, 131.1, 148.8, 160.0; HRMS (CI) calcd for $C_{11}H_{13}N_2O$ 189.1028 ($M^+ + 1$), found 189.1029. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.11; H, 6.67; N, 14.66.

4.3.12. 2-(2-Methoxyphenyl)methylimidazole. Yield (39 mg, 75%); white solid; mp 122–124 °C; R_f 0.11; ^{1}H NMR (methanol-d_4) δ 3.78 (s, 3H), 4.03 (s, 2H), 6.84 (ddd, 1H, J=8.7, 7.5, 1.1 Hz), 6.91 (dd, 1H, J=7.5, 1.1 Hz), 7.04 (dd, 1H, J=7.5, 1.7 Hz), 7.19 (ddd, 1H, J=8.7, 7.5, 1.7 Hz); ^{13}C NMR δ 29.6, 55.8, 111.5, 121.6, 122.2, 127.1, 129.3, 130.9, 148.2, 158.5; HRMS (CI) calcd for $C_{11}H_{13}N_2O$ 189.1028 ($M^+ + 1$), found 189.1030. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.35; H, 6.50; N, 15.00.

Acknowledgements

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11. The reaction was much cleaner in a mixed solvent system (4:1 CH_2Cl_2:*N*-methylethylenediamine) to give the desired product: sticky violet oil; R_f 0.55 (17:2:1 CH_2Cl_2:EtOH:TEA); ^{1}H NMR δ 2.73 (s, 3H), 3.31 (t, 2H, J=9.4 Hz), 3.69 (s, 2H), 3.71 (t, 2H, J=9.4 Hz), 7.46 (d, 2H, J=8.7 Hz), 8.19 (d, 2H, J=8.7 Hz); ^{13}C NMR δ 33.9, 41.1 52.2, 53.0, 123.5, 129.5, 143.6, 147.6, 165.0; MS (EI) *m*/*z* (%): 219 (M^+, 56) 218 (100), 172 (30), 136 (18), 83 (6).
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Photochromic properties of diarylethene derivatives having chryso[*b*]thiophene rings

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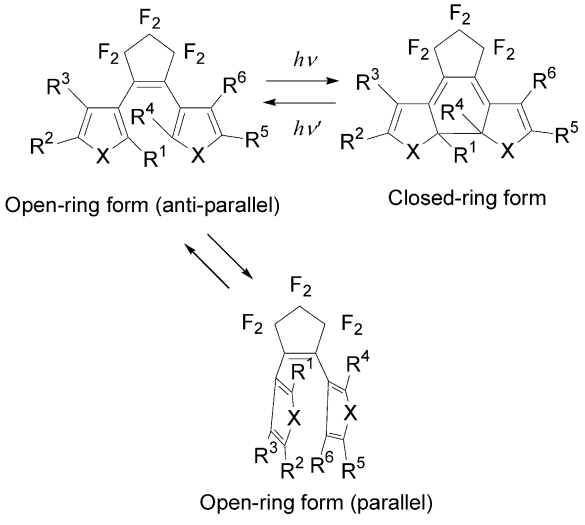
Abstract—Diarylethene derivatives having one or two chryso[*b*]thiophene ring(s) have been synthesized. In solution the derivatives underwent photochromism and the derivative with one chryso[*b*]thiophene ring exhibited photochromism even in the single crystalline phase. The color of the UV irradiated single crystal changed from blue to green by rotation the sample under polarized light.

1. Introduction

Various types of photochromic compounds have been so far synthesized in an attempt to apply the compounds to optoelectronic devices.[1–4] Among the compounds diarylethene derivatives are the most promising candidates for the applications because of their fatigue resistant and thermally irreversible properties.[2] The diarylethene derivatives undergo cyclization/cycloreversion photochromic reactions upon photoirradiation. The open-ring form has two conformations, anti-parallel and parallel ones, and only the anti-parallel conformers undergo the photocyclization reaction (Scheme 1).

The absorption maxima of the closed-ring isomers of diarylethenes are known to depend on the π-conjugate length of the aryl groups. Introduction of long π-conjugated systems increases the absorption coefficients of the closed-ring isomers and shifts the absorption bands to larger wavelengths. The absorption maximum of the closed-ring isomer of 1,2-bis(2,4-dimethylthiophen-3-yl)hexafluorocyclopentene is located at 530 nm in hexane and shows red color.[5] When phenyl groups are substituted at 5,5′-positions of the thiophene rings, the closed-ring isomer of 1,2-bis(2,4-dimethyl-5-phenylthiophen-3-yl)hexafluorocyclopentene changed to blue (λ_{max}= 562 nm).[6] The closed-ring form of 1,2-bis(5-cyano-2,4-dimethyl-5,2′:5′2-terthiophen-3-yl)hexafluorocyclopentene, which has terthiophenes as the aryl groups, shows the maximum at 653 nm.[7] The absorption maximum is further shifted to 682 nm by extending the π-conjugation length, such as 1,2-bis(2-methyl-5-(β-carotenyl)thiophen-3-yl)hexafluorocyclopentene.[8] Another approach to shift the absorption maximum is to introduce large condensed aromatic rings. In this paper, we report on diarylethene derivatives having one or two chryso[*b*]thiophene rings. The photochromic



Scheme 1.

Keywords: Photochromism; Diarylethene; Chryso[*b*]thiophene; Single crystal.
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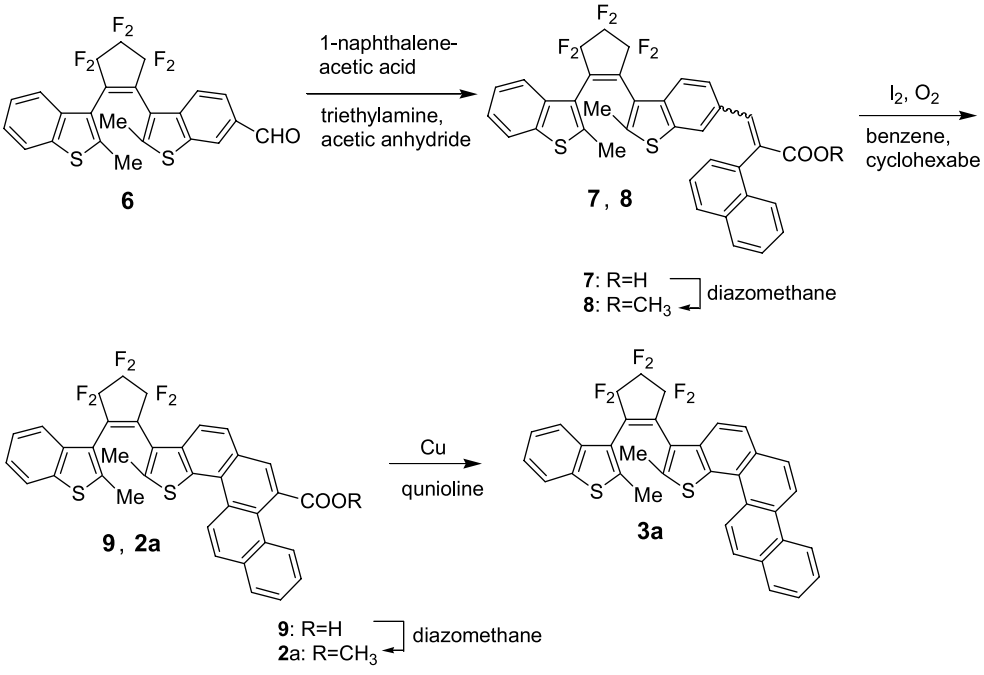
properties of these derivatives were studied in solution as well as in the single crystalline phase.

2. Results and discussion

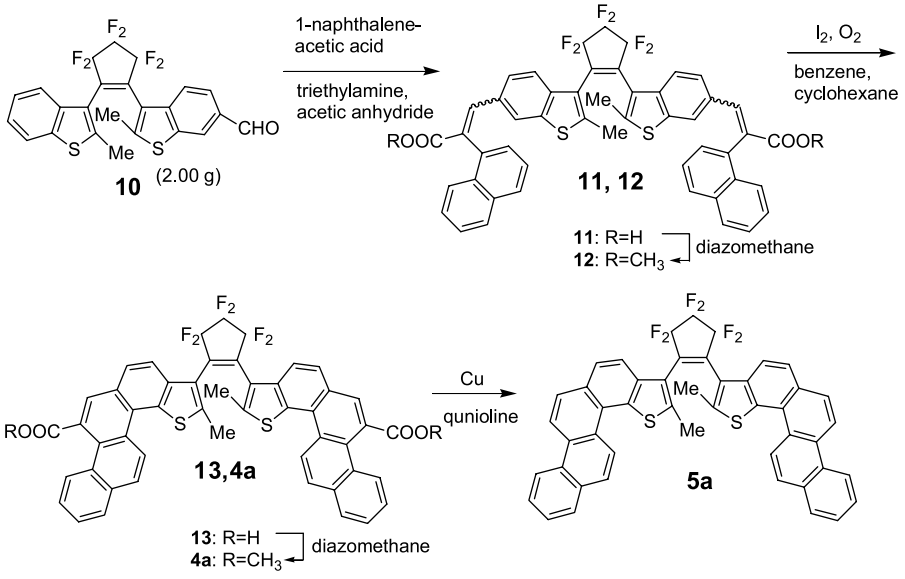
2.1. Synthesis of the diarylethene derivatives

Diarylethene **2a** was synthesized by cyclization of the naphtylethene substituent according to the procedure described in Scheme 2. Compound **2a** was converted into **3a** by heating the crude product with copper powder in quinoline in 14% yield. The diarylethene derivatives **4a** and **5a** which have two chryso[*b*]thiophene moieties were synthesized from bis-aldehyde derivatives by the same procedure as those used for **2a** and **3a** (Scheme 3). The structures of diarylethene **2a**–**5a** were determined by NMR spectroscopy, mass spectrum and elemental analysis (Chart 1). The structure of **2a** was determined by X-ray crystallographic analysis.

A single crystal of **2a** was obtained by recrystallization from chloroform. The ORTEP drawing of the diarylethene **2a** is shown in Figure 1.[9] **2a** single crystal adopted a monoclinic space group $P2_1/c$. The ORTEP drawing of **2a** indicates that **2a** has the two aryl moieties, one is a benzo[*b*]thiophene ring and the other is a chryso[*b*]thiophene ring. The distance of C(1)–C(10), which are reactive carbon atoms, was



Scheme 2.



Scheme 3.

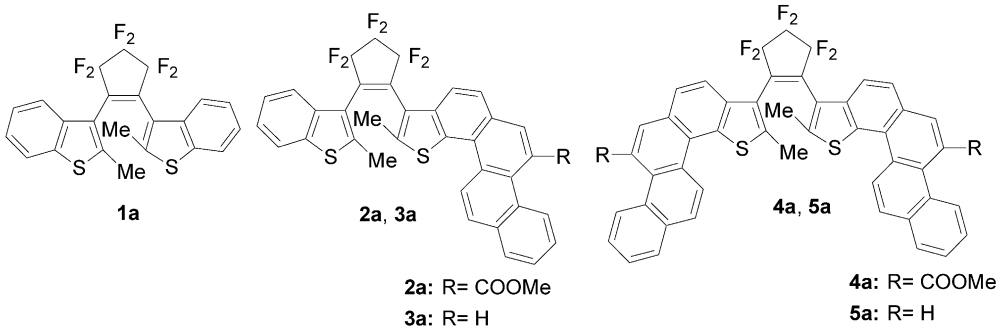


Chart 1.

0.370 nm, which is short enough for the reaction to take place in the crystalline phase.[10–17]

^{1}H NMR spectrum of **2a** in $CDCl_3$ (400 MHz) showed that the open-ring form diarylethene had two atrope conformers. One conformer has two aromatic rings in mirror symmetry (in parallel orientation) and the other in *C*2 symmetry (in anti-parallel orientation). The methyl signals of anti-parallel conformer were observed at 2.26 and 2.42 as two singlet signals. The signal at 2.26 ppm is due to methyl protons attached to the benzo[*b*]thiophene ring and the signal at 2.42 ppm due to the methyl protons of the chryso[*b*]thiophene ring. The methyl signals of the parallel conformer of **2a** were observed at 2.49 and 2.69 ppm, which are the methyl protons attached to the benzo[*b*]thiophene and chryso[*b*]thiophene rings, respectively. The intensity ratio of the two signals indicated that the relative population of anti-parallel and parallel conformers was 62:38 at room temperature.

^{1}H NMR of **4a** also showed the presence of two conformers. The methyl signals of anti-parallel and parallel conformers were observed at 2.48 and 2.70 ppm, respectively. The intensity rate of the two signals indicated that the relative population of anti-parallel and parallel conformers was 58:42.

2.2. Photochromism of the diarylethene derivatives

Compound **2a**, **3a** and **4a** underwent photochromism in solution. Figure 2(a) shows the absorption spectral change of **2a** in ethyl acetate by irradiation with 254 nm light. **2a** has the absorption maxima at 295 nm (ε, $7.8\times10^4\ M^{-1}\ cm^{-1}$). Upon irradiation with 254 nm light, the colorless solution

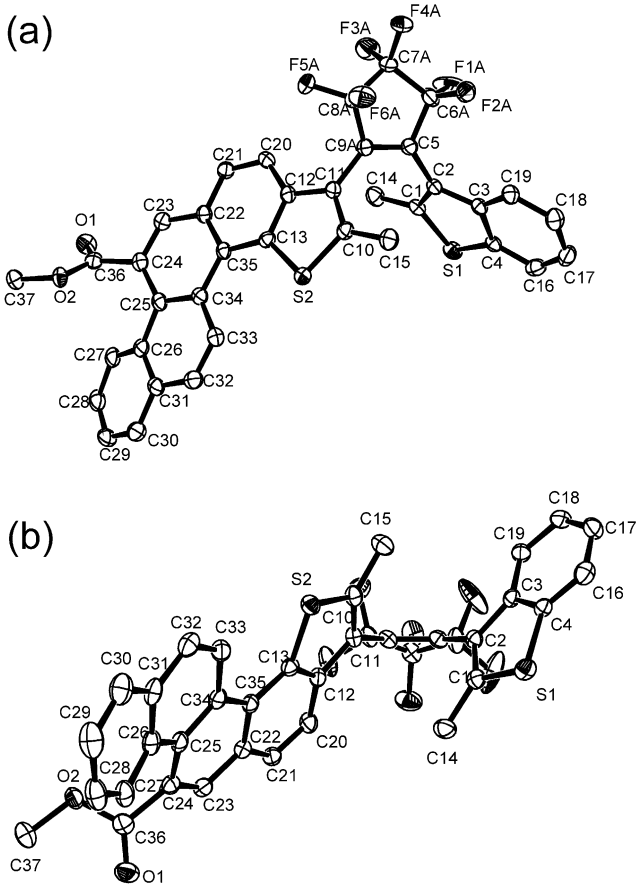


Figure 1. ORTEP drawings of top(a) and side(b) views of **2a**, showing 50% probability displacement ellipsoids.

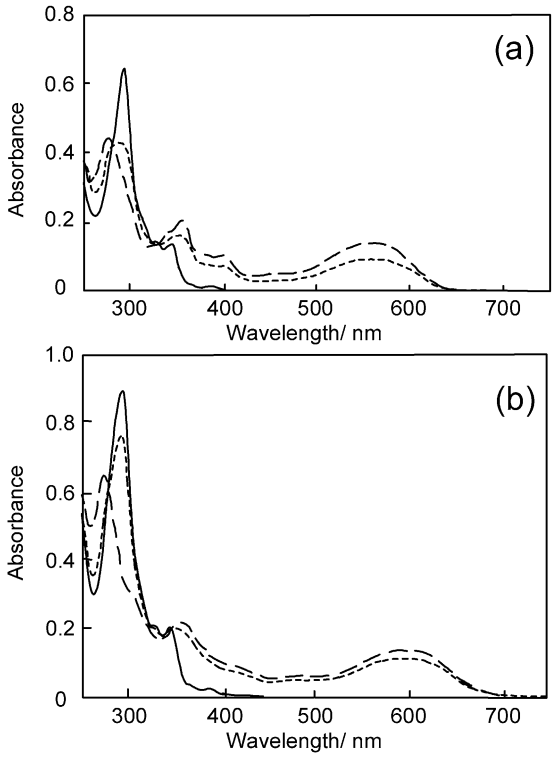


Figure 2. (a) Absorption spectra of **2a** (8.2×10^{-6} mol/l) (—), **2b** (- - - -), and the photostatonary state (– – – –) under irradiation with 254 nm light in ethyl acetate. (b) Absorption spectra of **4a** (8.1×10^{-6} mol/l) (—), **4b** (- - - -), and the photostatonary state (– – – –) under irradiation with 254 nm light.

Table 1. Absorption maxima and their coefficients of the open- and closed-ring forms of **1–5** and quantum yields of cyclization and cycloreversion reactions in ethyl acetate solution

Compound	$\varepsilon/10^4\ M^{-1}\ cm^{-1}$		Quantum yield	
	a	**b**	Cyclization	Ring-opening
1	1.4 (258 nm)	0.91 (517 nm)	0.31	0.28
2	7.8 (295 nm)	1.7 (565 nm)	0.56	0.12
3	8.4 (288 nm)	1.7 (559 nm)	0.31	0.092
4	11 (293 nm)	1.7 (598 nm)	0.36	0.040
5	11 (287 nm)	—	—	—

of **2a** turned violet, in which a visible absorption band was observed at 565 nm. The violet color is due to the closed-ring form. The conversion from **2a** to **2b** in the photostationary state under irradiation with 313 nm light was 70%. The color disappeared by irradiation with visible light ($\lambda>480$ nm). The colored isomer was isolated by HPLC, and the absorption characteristic was examined. The absorption coefficient of **2b** at 565 nm was $1.7\times10^4\ M^{-1}\ cm^{-1}$, as shown in Table 1. The absorption characteristics of **3a** and **3b** were similar to **2a** and **2b**, respectively.

Figure 2(b) shows the absorption spectral change of **4a** in ethyl acetate by irradiation with 254 nm light. **4a** has the absorption maxima at 293 nm (ε, $1.1\times10^5\ M^{-1}\ cm^{-1}$). Upon irradiation with 254 nm light, the colorless solution of **4a** turned blue, in which a visible absorption band was observed at 598 nm. The conversion from **4a** to **4b** in the photostationary state under irradiation was 78%. The color disappeared by irradiation with visible light ($\lambda>480$ nm).

Diarylethene **5a** did not show any reversible photochromism in ethyl acetate. The open-ring form **5a** has the absorption maximum at 287 nm (ε, $1.1\times10^5\ M^{-1}\ cm^{-1}$). Although the colored isomer was produced upon irradiation with 313 nm light, the isomer was unstable and decomposed in ethyl acetate. The decomposition process is an oxidation reaction of the closed-ring isomer. The degradation product has a peak at 330 (m/z) by mass spectroscopy. The mass number means the decomposed product, which is the *endo*-per oxide of 2-methylcryso[*b*]thiophene.[2]

Table 1 summarizes the absorption maxima and the absorption coefficients of open- and closed-ring isomers in ethyl acetate. The cyclization and cycroreversion quantum yields were also measured and included in Table 1. The compound **1b** showed the absorption maximum at 523 nm. The maximum shifted to 578 nm for **2b**. The longest absorption maximum of 598 nm was observed for **4b**. The absorption maximum of the colored isomers shifted to longer wavelengths by increasing the π-conjugation length. Any noticeable difference was not observed between **2b** and **3b**.

Systematic correlation between the cyclization quantum yield and the π-conjugation length was not observed. The cyclization quantum yield of **2a** ($\Phi=0.56$) was larger than that of **1a** ($\Phi=0.31$),[18] while that of **4a** ($\Phi=0.36$) was smaller than that of **2a**. The asymmetric aryl substitution increased the cyclization quantum yield. The cycloreversion quantum yields was found to decrease by extending the π-conjugation length of the aryl groups, as observed for the dithienylethenes having polyene substituents.[8] The cycloreversion quantum yield of **2b** ($\Phi=0.12$) was smaller than that of **1b** ($\Phi=0.28$),[18] and it further decreased to 0.040 for **4b**. The low cycloreversion quantum yield of **4b** indicates that the closed-ring isomer **4b** is stable. The large π conjugation throughout the molecule is considered to stabilize the closed-ring isomer.

2.3. Photochromic reaction in the single crystalline phases

Compound **2a** underwent a photochromic reaction even in the single crystalline phase. Upon irradiation with 334 nm light, the single crystals turned blue and the blue color disappeared by irradiation with visible light ($\lambda>480$ nm).

The absorption spectral change of **2a** single crystal was observed under polarized light. Figure 3 shows the photos of the color changes. Figure 3(a) and (b) are the crystal before UV irradiation. The crystals are colorless. Upon irradiation with 334 nm light, the crystal turned blue (Fig. 3(c)). When the crystal was rotated as much as 90°, the color of the crystal changed to green (Fig. 3(d)).

Figure 4 shows the polarized absorption spectra of the colored crystal. By rotating the crystal sample under polarized light, the absorption intensity ratio at 600 and

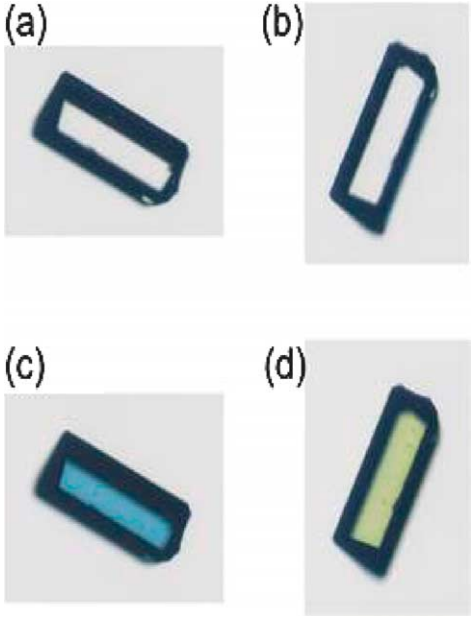


Figure 3. Photographs of single crystal **2a** under polarized light before (a, $\theta=0°$; b, $\theta=90°$) and after (c, $\theta=0°$; d, $\theta=90°$) irradiation with 313 nm light. θ is a rotation angle of the crystal.

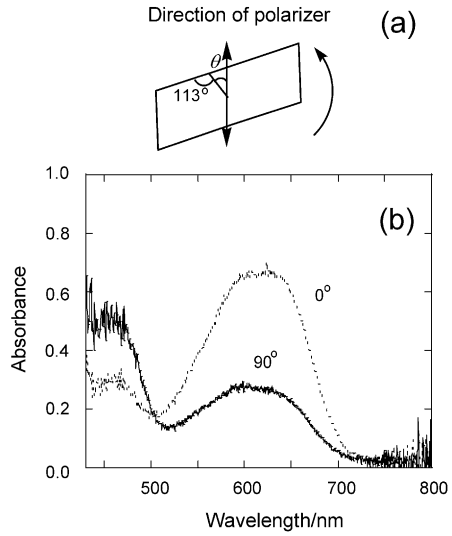


Figure 4. Polarized absorption spectra of the colored crystal **2b** (a) direction of polarizer, (b) polarized absorption spectra.

460 nm changed. The change of the color from blue to green by rotating the crystal sample indicates that the closed-ring isomer regularity orientated in the crystal.

Figure 5(a) shows the packing diagram of the surface (001). The crystal plane of (001) corresponds to the crystal surface of the single crystal. The arrow indicates the direction of the transition moment at 600 nm. Figure 5(b) shows the polarized absorption spectra at 600 nm. The absorption anisotropy indicates the direction of its electronic transition

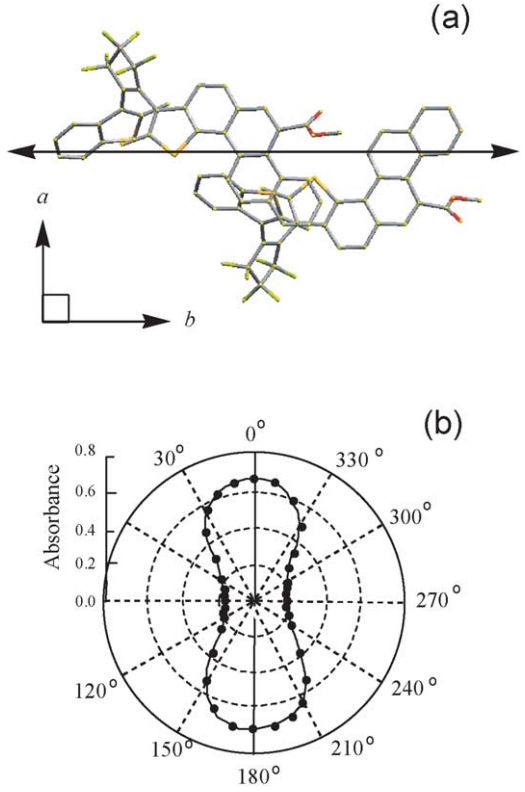


Figure 5. (a) Packing diagram of **2a** and (b) polar plots of the absorbance of **2b** at 600 nm of the surface (001).

moment of the closed-ring form in the crystal. These results confirm that the photoreaction takes place in the crystal.

The compound **3a**, **4a** and **5a** did not show any photochromism in the single crystalline phase. The reactivity is strongly dependent on the molecular structure and the conformation of the molecules. X-ray crystallographic analysis of the crystals of **3a** and **5a** revealed that the distance between the reactive carbons are too long (0.392 and 0.501 nm, respectively) for the reaction to take place.

In conclusion, we have synthesized diarylethene derivatives having chryso[*b*]thiophene rings. The derivatives having one or two chryso[*b*]thiophene aryl groups, **2a**, **3a** and **4a**, underwent photochromism in ethyl acetate, but the closed-ring form **5b** was unstable in the solvent. The derivative having one chryso[*b*]thiophene group **2a** was found to undergo photochromism in the single crystalline phase. Color change of the UV irradiated crystal from blue to green by rotating the sample was observed under polarized light.

3. Experimental

3.1. General

^{1}H NMR spectra were recorded on a JEOL-GX 270 and a JEOL-Lambda 400 spectrophotometer with $CDCl_3$ as a solvent and tetramethylsilane as an internal standard and chemical shifts are reported in ppm (δ) and J value are in Hz. Elemental analysis was performed by YANACO MT-3 CHN corder. Mass spectrometer was taken with a Finnigan MAT TSQ-70 mass spectrometer. The absorption spectra were measured using a Shimadzu UV-3100 spectrophotometer. Solvents used were spectrograde and purified by distillation before use. Absorption spectra in the single-crystalline phases were measured using a Leica DMLP polarizing microscope connected with a Hamamatsu PMA-11 detector. The samples were not degassed. Photoirradiation was carried out using an Ushio 500 W high-pressure mercury lamp. Light with appropriate wavelength was isolated by passing the light through a monochrometer or through a Toshiba cut-off filter (Y-48). The quantum yields of the diarylethene derivatives were measured in ethyl acetate against 1,2-bis(2-methylbenzo[*b*]thiophen-3-yl)hexafluorocyclopentene in *n*-hexane as a reference. HPLC was carried out on a Shimadzu LC-10AD liquid chromatography coupled with a Shimadzu SPD-10AV spectrophotomeric detector. A silicagel column (Wako Wakosil-5SIL) was used to analyze diarylethene isomers.

3.2. Synthesis

3.2.1. Preparation of 1-(2-methylbenzo[*b*]thiophen-3-yl)-2-(2-methyl-6-(1-carboxy-1-(1-naphthyl)ethen-2-yl)benzo[*b*]thiophen-3-yl)hexafluorocyclopentene (7). A solution of 1-naphthaleneacetic acid (0.271 g 1.46 mmol), 1-(2-methylbenzo[*b*]thiophen-3-yl)-2-(2-methyl-6-formylbenzo[*b*]thiophen-3-yl)hexafluorocyclopentene **6** (1.08 g, 2.18 mmol), acetic anhydride (4 ml) and triethylamine (2 ml) was refluxed for 6 h. The reaction mixture was poured into 10% hydrochloric acid (30 ml) and the mixture

was stirred at room temperature for 1 h. The resultant mixture was extracted with 100 ml of chloroform. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was evaporated. The crude product **7** was used for following cyclization reaction without further purification.

Compound **7**. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.93–2.47 (m, 6H, CH_3), 6.66–6.88 (m, 1H, vinyl H), 7.04–7.92 (m, 13H, aromatic H), 8.15–8.23 (m, 1H, aromatic H).

3.2.2. Preparation of 1-(2-methylbenzo[*b*]thiophen-3-yl)-2-(2-methyl-6-(1-methoxy-carbonyl-1-(1-naphthyl) ethen-2-yl)benzo[*b*]thiophen-3-yl)hexafluorocyclopentene (8). Compound **7** was converted to methyl ester compound **8** by treating with a diazomethane–ether solution. The solution was stirred for 10 min. The solvent was evaporated, and the product was purified with thin-layer chromatography (eluent: hexane/ethylacetate = 10:1) to give the methyl ester compound **8** in 27% yield (from **6**).

Compound **8**. Colorless crystals: mp 75–76 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.94 (s, 3H, (a-p)-*trans*), 2.06 (s, 3H, (a-p)-*trans*), 2.12 (s, 3H, (a-p)-*cis*), 2.20–2.25 (m, 3H, (p)-*cis*), 2.36–2.53 (m, 3H, (p)-*trans*), 3.70–3.72 (m, 3H, Me), 6.62–6.69 (m, 1H, vinyl H (p)), 6.77–6.85 (m, 1H, vimyl H (a-p)), 7.04–8.08 (m, 12H (a-p) + 13H (p), aromatic H), 8.17 (s, 1H (a-p), aromatic H). IR (KBr) 1712vs, 1435s, 1340s, 1275vs and 1250vs cm^{-1}. MS (*m*/*z*) 662.08 (M^+). Found: C 65.18, H 3.75%. Calcd for $C_{37}H_{24}F_6O_2S_2$: 65.38, H 3.56%.

3.2.3. Preparation of 1-(2-methylbenzo[*b*]thiophen-3-yl)-2-(7-carboxy-2-methyl-chryso[4,3-*b*]thiophen-3-yl)hexafluorocyclopentene (9). A mixture of the crude product **7** (0.394 g, 0.594 mol), iodine (20 mg), benzene (100 ml) and cyclohexane (100 ml) was irradiated with 100 W medium pressure mercury lamp for 12 h. During the course of the reaction, a slow stream of air was passed through the solution. The 10% sodium thiosulfate solution (70 ml) was added to the solution, and the resultant mixture was extracted with 100 ml of chloroform. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was evaporated to give crude compound **9**. The crude product **9** was used for following decarboxyl reaction without further purification.

Compound **9**. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.19 (s, 3H, (a-p)), 2.32 (s, 3H, (a-p)), 2.41 (s, 3H, (p)), 2.59 (s, 3H, (p)), 7.16–7.91 (m, 10H), 8.15–8.39 (m, 2H), 8.70–8.78 (m, 1H).

3.2.4. Preparation of 1-(2-methylbenzo[*b*]thiophen-3-yl)-2-(7-methoxycarbonyl-2-methylchryso[4,3-*b*]thiophen-3-yl)hexafluorocyclopentene (2a). Compound **9** was converted to methyl ester compound **2a** by treating with a diazomethane–ether solution.[19] The crude product **9** was added to diazomethane ether solution, the solution was stirred for 10 min. The solvent was evaporated and the residue was purified by thin-layer chromatography on silica gel (hexane/ethyl acetate = 1:1) to give 0.320 g of **2a** in 26% yield (from **6**).

Compound **2a**. Colorless crystals, mp 252–253 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H, (a-p)), 2.42 (s, 3H, (a-p)), 2.49 (s, 3H, (p)), 2.69 (s, 3H, (p)), 3.93 (s, 3H, (p)), 3.97 (s, 3H, (a-p)), 7.16 (t, J = 7.6 Hz, 1H, (p)), 7.22 (t, J = 7.8 Hz, 1H, (p)), 7.31 (t, J = 7.8 Hz, 1H, (a-p)), 7.39 (t, J = 7.6 Hz, 1H, (a-p)), 7.51–7.74 (m, 4H (a-p) + 4H (p)), 7.78 (d, J = 8.8 Hz, 1H, (a-p)), 7.81 (d, J = 8.4 Hz, 1H, (a-p)), 7.91 (dd, J = 8 Hz, 2Hz, 1H, (p)), 7.98–8.01 (m, 2H (a-p) + 1H (p)), 8.13 (d, J = 24 Hz, 1H, (p)), 8.15 (d, J = 28.8 Hz, 1H, (a-p)), 8.16–8.22 (m, 1H (a-p) + 2H (p)), 8.33 (s, 1H, (a-p)), 8.97–9.01 (m, 1H (p) + 1H (a-p)). IR (KBr) 1724vs, 1434s, 1340s and 1271vs cm^{-1}. Ms *m*/*z* 676.69 (M^+). Found: C 65.67, H 3.26%. Calcd for $C_{37}H_{22}F_6O_2S_2$: C 65.67, H 3.28%.

3.2.5. Preparation of 1-(2-methylbenzo[*b*]thiophen-3-yl)-2-(7-methoxycarbonyl-2-methylchryso[4,3-*b*]thiophen-3-yl)hexafluorocyclopentene (3a). A solution of the diarylethene **9** (about 0.330 g), copper (0.20 g, 0.0031 mmol) and quinoline (3 ml) was heated at 160 °C for 1 h.[17] 2 M Hydrochloric acid (30 ml) was added to the solution, and the resultant mixture was extracted with diethylether. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was evaporated. The residue was purified by thin-layer chromatography on silica gel (hexane/ethyl acetate = 3:1) to give 0.080 g of **3a** in 14% yield (from **6**).

Compound **3a**. Colorless crystals, mp 228–229 °C. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.30 (s, 3H, (a-p)), 2.39 (s, 3H (a-p)), 2.52 (s, 3H, (p)), 2.58 (s, 3H, (p)), 7.15 (t, J = 7.8 Hz, 1H, (p)), 7.24–7.31 (m, 1H (p) + 1H (a-p)), 7.39 (t, J = 7.8 Hz, 2H, (a-p)), 7.52–7.96 (m, 9H (a-p) + 9H (p)), 8.48 (d, J = 8.4 Hz, 1H, (a-p)), 8.59–8.69 (m, 2H (a-p) + 1H (p)), 8.79 (d, J = 9.2 Hz, 1H, (p)), 8.85 (d, J = 9.2 Hz, 1H, (a-p)). IR (KBr) 1432s, 1335vs and 1193s cm^{-1}. Ms (*m*/*z*) 618.09 (M^+). Found: C 67.61, H 3.56%. Calcd for $C_{35}H_{20}F_6S_2$: C 67.95, H 3.26%.

3.2.6. Preparation of 1,2-bis(2-methyl-6-(1-carboxy-1-(1-naphthyl)ethen-2-yl)-benzo[*b*]thiophen-3-yl)hexafluorocyclopentene (11). 1,2-Bis(2-methyl-6-(1-carboxy-1-(1-naphthyl)ethen-2-yl)benzo[*b*]thiophen-3-yl)hexafluorocyclopentene (**11**) was synthesized from 1,2-bis(2-methyl-6-formyl-benzo[*b*]thiophen-3-yl)hexafluorocyclopentene (**10**) (2.04 g, 3.881 mmol), 1-naphthaleneacetic acid (0.271 g 1.46 mmol), acetic anhydride (4 ml) and triethylamine (2 ml) by the same procedure as that used for **7**. The crude product **11** was used for following cyclization reaction without further purification.

Compound **11**. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.99–2.36 (m, 6H, CH_3), 6.52–6.82 (m, 2H, vinyl H), 6.98–7.93 (m, 18H, aromatic H), 8.15–8.24 (m, 2H, aromatic H).

3.2.7. Preparation of 1,2-bis(2-methyl-6-(1-methoxycarbonyl-1-(1-naphthyl)ethen-2-yl)benzo[*b*]thiophen-3-yl) hexafluorocyclopentene (12). 1,2-Bis(2-methyl-6-(1-methoxycarbonyl-1-(1-naphthyl)ethen-2-yl)benzo[*b*]-thiophen-3-yl)hexafluorocyclopentene (**12**) was synthyesized by the same procedure as that used for **8**. The crude product was purified by recrystallization from methanol to give 1.17 g of **12** in 35% yield (from **10**).

Compound **12**. Colorless crystals, mp 146–147 °C; ^{1}H NMR

($CDCl_3$, 270 MHz) δ 1.86 (s, 6H, (a-p)-(*trans*,*trans*)-methyl), 1.99 (s, 6H, (a-p)-(*trans-cis*)-methyl), 2.31–2.17 (m, 6H, (p)-(*trans-cis*)-methyl), 2.28–2.40 (m, 6H, (p)-(*trans-trans*)-methyl), 3.68–3.73 (s, 6H, (p)), 6.48–6.53 (m, 2H, (p)-vinyl), 6.71–6.81 (m, 2H, (a-p)-vinyl), 6.94–8.19 (m, 20H, aromatic H). IR (KBr) 1713vs, 1435s, 1340s, 1275vs and 1247vs cm^{-1}. Ms (*m/z*) 856.12 (M^+). Calcd for $C_{51}H_{34}F_6O_4S_2$: C 68.91, H 3.86%. Found: C 69.06, H 4.02%.

3.2.8. Preparation of 1,2-bis(7-methoxycarbonyl-2-methylchryso[4,3-*b*]thiophen-3-yl)hexafluorocyclopentene (4a). 1,2-Bis(7-methoxycarbonyl-2-methylcryso[4,3-*b*]thiophen-3-yl)hexafluorocyclopentene (**4a**) was synthesized from **11** (about 3.08 g) by the same procedure as that used for **3a**. The product **13** was treating with a diazomethane–ether solution. The crude product was purified by recrystallization from diethylether to give 0.480 g of **4a** in 14% yield (from **10**).

Compound **4a**. Colorless crystals, mp 135–136 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.48 (s, 6H (a-p)), 2.70 (s, 6H (p)), 3.89 (s, 6H (p)), 3.96 (s, 6H (a-p)), 7.51–7.64 (m, 4H (p)+4H (a-p)), 7.78 (d, J=8.8 Hz, 2H, (a-p)), 7.91 (d, J=9.2 Hz, 2H, (a-p)), 7.94–8.06 (m, 6H (p)+2H (a-p)), 8.12 (d, J=8.8 Hz, 2H, (p)), 8.18 (s, 2H, (p)), 8.19 (d, J=9.6 Hz, 2H, (a-p)), 8.33 (m, 2H, (a-p)) 8.91 (d, J=8.8 Hz, 2H, (p)), 8.94 (d, J=8.8 Hz, 2H, (a-p)). IR (KBr) 1722vs, 1341s and 1268vs cm^{-1}. Ms (*m/z*) 884.90 (M^+). Found: C 69.01, H 4.43%. Calcd for $C_{51}H_{30}F_6O_4S_2+C_4H_{10}O$: C 68.88, H 4.30%.

3.2.9. Preparation of 1,2-bis(2-methylchryso[4,3-*b*]thiophen-3-yl)hexafluoro-cyclopentene (5a). 1,2-Bis(2-methylchryso[4,3-*b*]thiophen-3-yl)hexafluorocyclopentene (**5a**) was synthesized from **13** (about 2.00 g) by the same procedure as that used for **3a**. The crude product was purified by recrystallization from diethylether to give **5a** in 12% yield (from **10**).

Compound **5a**. Colorless crystals, mp 362–363 °C (dec.); ^1H NMR ($CDCl_3$, 270 MHz) δ 2.48 (s, 6H, (a-p)), 2.69 (s, 6H, (p)), 7.50–8.04 (m, 12H, aromatic H), 8.48–8.92 (m, 4H, aromatic H). IR (KBr) 1334s, 1267vs and 1137vs cm^{-1}. Ms (*m/z*) 768.14 (M^+). Calcd for $C_{47}H_{26}F_6S_2$: C 73.42, H 3.41%. Found: C 73.61, H 3.30%.

Crystallographic data (compound **2a**, **3a** and **5a**) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 248683, CCDC 248684 and CCDC 248685. Copies of data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Synthesis and spectroscopic properties of 1,3,5-tris(arylalkynyl)-2,4,6-trimethoxybenzenes

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Abstract—A number of C_3-symetric 1,3,5-tris(arylalkynyl)-2,4,6-trimethoxybenzenes which carry electron withdrawing aryl substituents at the acetylenic periphery and donating methoxy groups on the central benzene ring are prepared via Sonogashira coupling. The utility of two different synthetic routes is evaluated as well as the effect of the nature of the aryl and ethynyl starting compounds in the coupling reaction. Finally, a correlation between the substitution pattern of the alkynyl compounds and their UV–vis and fluorescence spectroscopic properties is established.

1. Introduction

The phenyleneethnynyl moiety is frequently found as the key building unit in molecular electronic and photonic devices,[1] wires and switches,[2] fluorescent sensors,[3] and molecular rotors.[4] With efficient electronic communication along the linearly conjugated π-system alkynylbenzenes perfectly fulfill the prime requirement for an electro-optic device. The overall conjugation is virtually independent from the relative orientation of the aromatic planes of the adjacent aryl groups due to the almost frictionless rotation around the triple bond and the cylindrical symmetry of the latter.[5] Furthermore, the desired macroscopic properties of the respective system can be tuned systematically via appropriate substitution of the benzene fragments.

Linear diphenylacetylenes have been extensively studied relating their structural with the respective optical properties.[6] C_3-symmetric octopolar ethynylbenzenes are a logical continuation of the work done on diphenylacetylenes and have recently gained particular attention due to their potential in nonlinear optics.[7] In many regards they parallel the structure-activity-relationship (SAR) of their linear tolane analogues and can be easily accessed using the same well established synthetic methodology.[8] The key step in the synthesis of functional acteylenes most often consists of a Pd-catalyzed cross-coupling reaction. In spite of existing work on persubstituted alkynyl benzenes employing various coupling conditions, it has to be pointed out that such compounds with an electron rich benzene core have not been synthesized so far.

Three decades after the first report of the cross-coupling reaction between arylhalide and terminal acetylene compounds,[9] the Sonogashira reaction has turned out to be the most powerful and most frequently applied Palladium-catalyzed carbon–carbon bond formation ($sp–sp^2$) method and continues to be the topic of intense research.[10] Owing to the reaction mechanism, electron poor aryl iodides in combination with electron rich alkynes are supposed to give the best results in the cross-coupling reaction.[11] With respect to its methodology, a large number of recent studies deals with adjusting the reaction conditions for less favorable starting materials such as deactivated arylbromides, chlorides, or tosylates,[12] while steric hindrance in the substrate remains an issue. New ligand systems,[13] copper-free methods,[14] and solid phase supported synthesis[15] are among the main advances in improving reaction yields, lowering catalyst loading and avoiding the formation of undesired side-products.

2. Results and discussion

In this contribution, the synthesis of a set of persubstituted 1,3,5-trisethynyl-2,4,6-trimetoxybenzene compounds via Sonogashira-reaction using different synthetic routes is described. The C_3-symmetric systems contain an electron rich benzene core and an electronically varied periphery,

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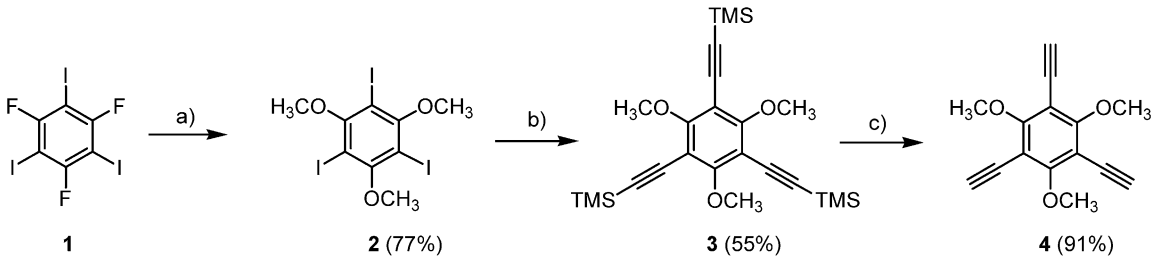


Scheme 1. Reagents and conditions: (a) $NaOCH_3$, DMI, rt, 6 h; (b) TMS–≡–H, $Pd(PPh_3)_2Cl_2$/CuI, *i*-Pr_2NH, 70 °C, 48 h; (c) K_2CO_3 (aq), MeOH, rt, 18 h.

depending on the terminal ethynylaryl substituents. The effect of the substitution pattern is studied by UV–vis and fluorescence spectroscopy, as is the variation of the overall conjugation length in the case of a buta-1,4-diyne analogue with D_2-symmetry.

2.1. Synthesis

The focus of attention concerning the synthesis of alternatingly persubstituted tris-(arylethynyl)benzenes is directed towards the possible combination of the central trisiodo- or triethynylbenzene unit with the respective periferic arylethynyl or haloaryl fragments, respectively. The trimethoxybenzene core is formed in an efficient manner by the nucleophilic aromatic substitution of the fluoride substituents of **1**[16] with sodium methoxide in 1,3-dimethyl-2-imidazolidinone (DMI) as aprotic, polar solvent.[7d] A conventional ethynylation-deprotection sequence leads to the symmetric trisethynyl derivative **4** in good yield (Scheme 1).

With the appropriate starting materials **2** and **4** in hands, two possible strategies apply for the synthesis of the desired target compounds: either installation of functional aryl substituents in the actetylenic periphery coupling compound **2** with terminal arylethynyls, or reacting easily available aryl halides with the trisethynyl derivative **4**. The latter route is more recommendable in the case of arylethynyls that are expensive or involve cumbersome procedures to be obtained.[17]

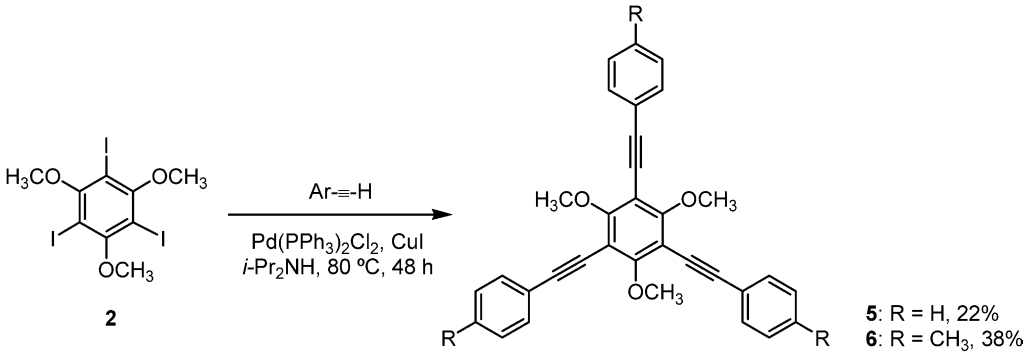
The first route, i.e. reacting 1,3,5-triiodo-2,4,6-trimethoxyenzene (**1**) with terminal alkynes, leads to 1,3,5-arylethynylbenzenes in moderate yields as shown in the case of commercially available, inexpensive phenyl- and 4-tolylacetylene (Scheme 2). The alkynes are employed in slight excess, here 1.6 equiv per halide.

Alternatively, threefold coupling of 1,3,5-trisethynyl-2,4,6-trimethoxybenzene (**4**) with activated aryliodides gives tris-(4-nitrophenyl)ethynyl and tris-(4-ethoxycarbonyl)ethynyl compounds **7** and **8** in high yields. Again, this states a good example for optimum combination of employing an electron rich alkyne derivative, albeit sterically demanding, with an electron poor aryl iodide in the Sonogashira reaction (Scheme 3).

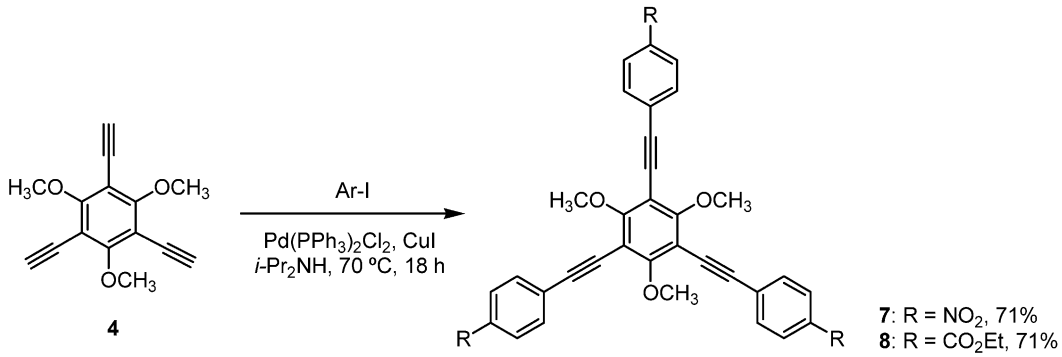
In contrast, applying a less reactive aryl fragment such as naphthylbromide changes the outcome of the reaction drastically. The expected compound **9** is isolated in poor yield (7%) together with unreacted 1-bromonaphthalene. From the same mixture compound **10** is obtained, which formally constitutes the homocoupling product of 2 equiv of 1,3-bis-(1-naphthylethynyl)-5-ethynyl-2,4,6-trimethoxybenzene (Scheme 4). The diyne is unambiguously identified by NMR and mass spectroscopy with the molecular ion at *m/z* 982. As the most characteristic features, the compound shows four sp-carbon peaks in the ^{13}C NMR spectrum and two different methoxy signals in the ^{1}H NMR spectrum owing to its reduced symmetry with respect to the C_3-symetric **9**. It can be speculated that after the twofold arylation of **4**, the remaining monoethynyl substrate is substantially deactivated to favor the competing alkyne–alkyne coupling over a third Sonogashira reaction, hence competing with the formation of **9**. This Glaser-type reaction, the copper-catalyzed coupling of terminal alkynes,[18] is a common side reaction competing with the desired hetero-coupling of the halide and the alkyne fragment. Although diyne **10** is obtained as unexpected side product, it is considered as an interesting candidate for the SAR studies.

2.2. UV–vis and fluorescence spectra

The UV–vis spectra of compounds **6–10** are shown in



Scheme 2.



Scheme 3.

Figure 1. All trimethoxybenzenes display intense low energy absorption between 250 and 400 nm. The spectral positions are typical for intramolecular charge transfer (ICT) transitions overlapping with high energy π–π^*-transitions of the diphenylacetylene units, as observed in their linear counterparts. Direct comparison of **7**, which shows a broad, unstructured absorption at 348 nm, and 4-methoxy-4′-nitrotolan ($\lambda_{max}=350$ nm in dioxane)[19] reveals the strong resemblance of the octopolar tris-(ethynylaryl)-benzenes with their dipolar diphenylacetylene analogues regarding their spectroscopic behavior. With increasing acceptor strength on the acetylenic periphery ($H{=}CH_3<CO_2Et<Naph<NO_2$),[20] the CT-band is successively red-shifted from 310 to 348 nm. The observed fine structuring in the spectra of all compounds, except for **7**, is also a common feature of diphenylacetylenes. It results from vibrational transitions in the ground state which often cannot be assigned to specific motional modes.[21] As expected from studies employing donor–acceptor substituted diphenylacetylenes,[6b] the change of the conjugation length from ethynyl in **9** to buta-1,4-diynyl in **10** does hardly affect their absorbances. Only slightly diminished intensities of the bands at 348 and 231 nm, an additional strong absorption which corresponds to the naphthyl fragments is observed in the case of the butadiyne **10**.

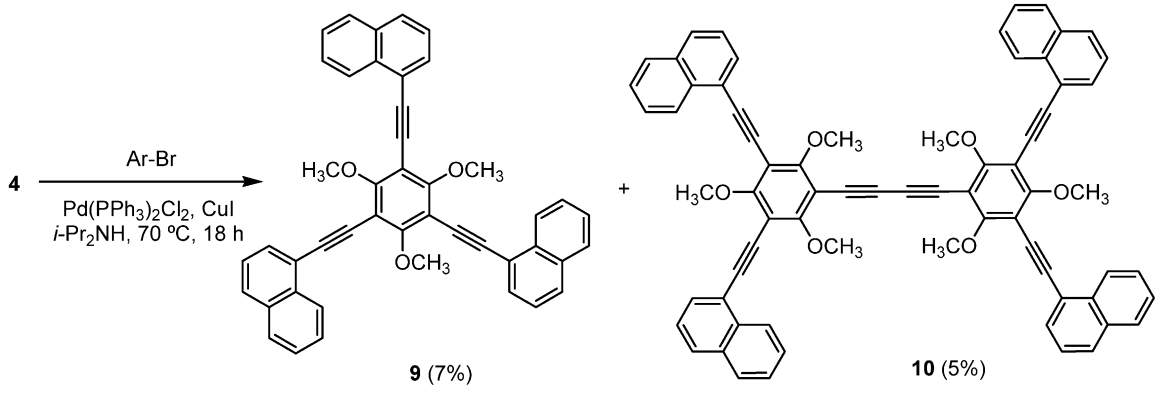
In contrast, the emission spectrum of butadiyne **10** shows a significant redshift compared to **9** (Fig. 2). The fluorescent quantum yield of **10** (0.11) drops to less than a third of the value of **9** (0.36), supposably because of the loss of excitation energy, which is efficiently converted into rotation around the central dyine-axis. It is not surprising that the conjugation-length alteration effects the spectral position of the emission spectrum while the absorption maxima of **9** and **10** remain unaffected. In contrast to the absorption, the relative orientation of the π-system fragments in the highly polar excited state strongly alters the energetic situation, and therefore the fluorescence, depending on the acetylene torsion angle.[5b]

Table 1. Spectroscopic data for compounds **5**–**10**, measured in acetonitrile

	λ_{max}^{abs} [nm] (log ε)	λ_{max}^{em} [nm]	Φ
5	293 (4.90), 310 (4.85)	373	0.26
6	296 (5.01), 314 (4.97)	373	0.53
7	347 (4.68)	422	>0.01
8	314 (4.85), 325 (4.84)	401	0.21
9	332 (4.90), 348 (4.86)	390	0.36
10	333 (4.83), 348 (4.77)	400	0.11

Excitation at 310 nm for **5** and **6**, at 350 nm for **7**–**10**. Quantum yields Φ were determined using quinine sulfate ($c=0.1$ mol L^{-1} in H_2SO_4) as standard.[24]

Compounds **5**, **6**, and **8**–**10** display similar fluorescence spectra with a structureless band in the 400 nm region, quantum yields between 0.11 and 0.53, and stokes shifts bigger than 50 nm (Table 1). The emission properties of the trinitro-compound **7** differs from this general behavior: due to the pronounced CT-character, the fluorescence maximum is shifted to 420 nm, while the quantum yield is drastically diminished (>0.01). Low-lying n–π^*-orbitals in aromatic nitro-compounds often lead to enhanced intersystem crossing, which also in the case of **7** is assumed to be the mayor pathway for fluorescence quenching.[22]



Scheme 4.

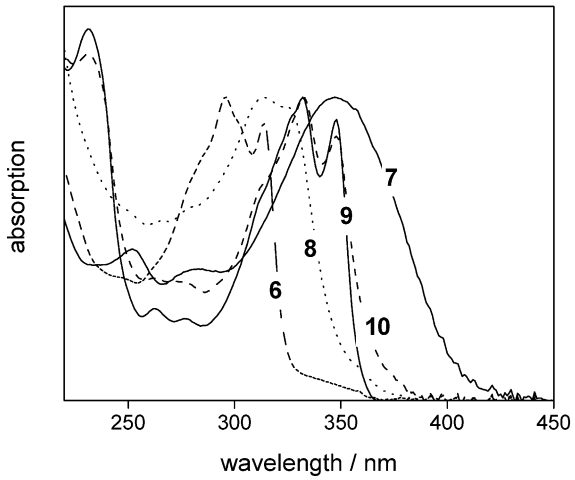


Figure 1. Normalized absorption of **6**–**10** in acetonitrile, $c=10^{-6}$ mol L^{-1}. Absorption of **5** is superimposable to that of **6** and therefore not shown.

All fluorescent measurements were carried out in sufficiently dilute solutions (0.5 μM) to exclude concentration effects such as aggregation induced spectral shifts.[23]

3. Conclusions

Different 1,3,5-trimethoxy-2,4,6-(arylethynyl) benzenes have been synthesized successfully via Sonogashira-coupling. The installation of three triple bonds on the 1,3,5-trimethoxybenzene core is either achieved in the starting material (**4**) or as final step, reacting ethynylbenzenes with the triiodo compound **2**. In accordance with theoretical mechanistic considerations, the electronic and steric nature of the halogen as well as the alkyne starting materials have a significant influence on the reaction outcome. Alkyne–alkyne homocoupling, a common side-reaction in the Sonogashira reaction leads to the diyne **10**. The spectroscopic studies reveal the target compounds to be highly fluorescent with exception of **7**. The trisethynylbenzenes displays efficient charge transfer from the electron rich central core to the acetylenic periphery. This property is the more pronounced the more electron withdrawing is the nature of the ethynylaryl substituent. This work is considered to be beneficial in the design of molecular devices and materials in two ways, conceptionally and synthetically.

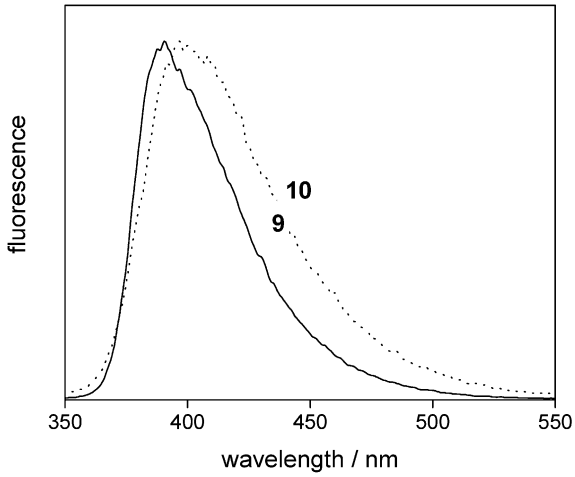


Figure 2. Normalized fluorescence spectra of **9** and **10** in acetonitrile, $c=5\times10^{-7}$ mol L^{-1}.

4. Experimental

4.1. General

All solvents and reagents were used as purchased. Ethynyl aryls were purchased from ALDRICH and used without further purification. Thin layer chromatography was performed on Alugram Sil G/UV254-coated aluminum sheets (Macherey–Nagel) with UV-detection at 254/365 nm. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AC-200 (^{1}H) and Bruker AC-300 (^{13}C) spectrometers in deuterated chloroform (deuteration grade > 99.80%) with the solvent signal serving as internal standard. Mass spectra (FAB, EI) were recorded on a HP1100MSD spectrometer. Elemental analyses were performed on a LECO CHNS 932 micro-analyzer. Spectroscopic measurements were performed using HPLC-quality solvents, and are solvent corrected. UV–vis spectra were measured on a HP 8453 (Hewlett Packard) spectrophotometer. A Perkin–Elmer LS50B luminescence spectrometer was employed for the fluorescence studies, in a foursided quartz cell at room temperature in a right angle geometry and are corrected for the spectral response for the detection system.

4.2. Materials

4.2.1. 1,3,5-Tris-[(trimethylsilyl)ethynyl]-2,4,6-trimetoxybenzene (3). General procedure for compounds **3**, **5**, and **6**: 1,3,5-triiodo-2,4,6-trimethoxybenzene (509 mg, 1.0 mmol) was stirred together with $Pd(PPh_3)_2Cl_2$ (53 mg, 0.075 mmol) and CuI (14 mg, 0.075 mmol) in degassed diisopropyamine (10 mL) for 30 min at room temperature before the acetylene compound (6.0 mmol, 0.84 mL) was added. For the synthesis of **3**, trimethylsilylacetylene was used. The mixture was heated at 70 °C for 48 h. The solvent was removed, the remaining solid was suspended in water (100 mL) and extracted with ethylacetate (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting crude product was purified by column chromatography (20:1 EtOAc–Et_2O) and final recrystallization from EtOH to give pure **3** as colorless crystals. Yield: 251 mg; 55%; mp: 84–85 °C. ^{1}H NMR: $\delta=$ 0.24 (s, 27H, CH_3), 4.01 (s, 9H, OCH_3); ^{13}C NMR: $\delta=-0.20$ (CH_3), 61.07 (OCH_3), 95.91, 103.19, ($C\equiv C$), 107.37, 164.60 (Ar); FAB$^+$-MS m/z (%): 457 (50, $[M+H]^+$). Calcd for $C_{24}H_{36}O_3Si_3$: C, 63.16; H, 7.89%. Found: C, 63.30, H, 7.86%.

4.2.2. 1,3,5-Trisethynyl-2,4,6-trimetoxybenzene (4). Compound **3** (456 mg, 1.0 mmol) was stirred in methanol (10 mL) with aqueous potassium carbonate (1 mL, saturated solution) at room temperature for 18 h. After the removal of the organic solvent, CH_2Cl_2-extraction (3×10 mL), drying of the combined organic phases ($MgSO_4$), and final removal of the solvent in vacuo, pure **4** was obtained upon

recrystallization of the remaining solid from MeOH as pale orange crystals. Yield: 218 mg; 91%; mp: 98–99 °C. ^{1}H NMR: δ=3.46 (s, 3H, C*H*), 4.04 (s, 9H, OC*H*$_3$); ^{13}C NMR: δ=61.52 (O*C*H$_3$), 74.57, 85.73 (C≡*C*), 106.64, 165.43 (Ar); FAB$^+$-MS *m/z* (%): 240 (77, M$^+$), 154 (100). Calcd for $C_{15}H_{12}O_3$: C, 75.00; H, 5.00%. Found: C, 74.62, H, 5.15%.

For synthesis and characterization of compound **5** see Ref. 7d.

4.2.3. 1,3,5-Tris-(4-methylphenylethynyl)-2,4,6-trimetoxybenzene (6). 4-Ethynyltoluene was employed following the same procedure as described for **3**. The resulting crude product was purified by column chromatography (20:1 Hex–EtOAc) and final recrystallization from *i*-PrOH to give pure **6** as off-white needles. Yield: 194 mg; 38%; mp: 137–139 °C. ^{1}H NMR: δ=2.38 (s, 9H, C*H*$_3$), 4.16 (s, 9H, OC*H*$_3$), 7.17 (AB, *J*=7.8 Hz; 6H, Ar*H*), 7.46 (AB, *J*=7.8 Hz; 6H, Ar*H*); ^{13}C NMR: δ=21.50 (*C*H$_3$), 61.44 (O*C*H$_3$), 80.21, 97.55, (C≡*C*), 107.98, 120.45, 129.09, 131.33, 138.52, 163.06 (Ar); FAB$^+$-MS *m/z* 510 (100, M$^+$). Calcd for $C_{36}H_{30}O_3$: C, 84.71; H, 5.88%. Found: C, 84.44; H, 5.99%.

4.3. General procedure for the synthesis of compounds 7–10

Halobenzene (5.0 mmol) was stirred together with $Pd(PPh_3)_2Cl_2$ (106 mg, 0.15 mmol) and CuI (28 mg, 0.15 mmol) in degassed diisopropylamine (10 mL) for 30 min at room temperature before **4** (1.0 mmol, 240 mg) was added. The mixture was heated at 70 °C for 18 h. The solvent was removed, the remaining solid was suspended in water (100 mL) and extracted with ethylacetate (3× 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the resulting crude product, which was purified as described below.

4.3.1. 1,3,5-Tris-(4-nitrophenylethynyl)-2,4,6-trimetoxybenzene (7). Halobenzene: 4-bromo-nitrobenzene. The remaining solid was recrystallized from CH_3NO_2 to give pure **7** as bright yellow crystals. Yield: 428 mg; 71%; mp: 142–144 °C. ^{1}H NMR: δ=4.20 (s, 9H, OC*H*$_3$), 7.70 (AB, *J*=8.6 Hz; 6H, Ar*H*), 8.26 (AB, *J*=8.6 Hz; 6H, Ar*H*); ^{13}C NMR: δ=61.91 (O*C*H$_3$), 85.70, 95.99 (C≡*C*), 123.77, 124.83, 129.91, 132.08, 138.67, 147.23, 164.77 (Ar); FAB$^+$-MS *m/z* 603 (31, M$^+$), 460 (100). Calcd for $C_{33}H_{21}O_3N_3$: C, 65.67; H; 3.48; N, 6.97%. Found: C, 65.84; H, 3.76; N, 6.64%.

4.3.2. 1,3,5-Tris-(4-ethoxycarbonylphenylethynyl)-2,4,6-trimetoxybenzene (8). Halobenzene: 4-iodo-ethoxycarbonylenzene. Pure **8** was obtained upon recrystallization from *i*-PrOH as pale yellow solid. Yield: 428 mg; 71%; mp: 59–62 °C. ^{1}H NMR: δ=1.41 (t, *J*=7.0 Hz, 9H, C*H*$_3$), 4.22 (s, 9H, OC*H*$_3$), 4.40 (q, *J*=7.0 Hz, 6H, C*H*$_2$), 7.61 (AB, *J*=8.6 Hz; 6H, Ar*H*), 8.05 (AB, *J*=8.6 Hz; 6H, Ar*H*); ^{13}C NMR: δ=14.28 (*C*H$_3$), 61.19 (*C*H2), 61.72 (O*C*H$_3$), 83.50, 96.94, (C≡*C*), 107.29, 127.76, 129.52, 130.02, 131.22, 164.04 (Ar), 166.00 (*C*=O); MALDI-HRMS found: 684.2354; calcd for $C_{42}H_{36}O_9$: 684.2358. R_f=0.36 (5:1 Hex–EtOAc).

4.3.3. 1,3,5-Tris-(1-naphthyl)-2,4,6-trimetoxybenzene (9) and bis-[1,3-(1-naphthylethynyl)-2,4,6-trimethoxybenz-5-yl]-buta-1,4-diyne (10). Halobenzene: 1-bromonaphthalene. Pure **9** was obtained upon column chromatography (first 20: 1, then 5:1 Hex–EtOAc) as light yellow solid, **10** as colorless solid. **9**. Yield: 44 mg; 7%; mp: 152–154 °C. ^{1}H NMR: δ=4.34 (s, 9H, OC*H*$_3$), 7.47–7.67 (m, 9H, Naph*H*), 7.79–7.82 (m, 9H, Naph*H*), 8.65 (d, *J*=8.6 Hz; 3H, Naph*H*(8)); ^{13}C NMR: δ=61.88 (O*C*H$_3$), 108.49, 121.12, 125.28, 126.31, 126.50, 126.97, 128.29, 128.96, 130.16, 133.23, 133.34, 163.49 (Ar, Naph), 95.99, 85.70 (C≡*C*); MALDI-HRMS found: 616.2191; calcd for $C_{45}H_{30}O_3$: 618.2190. R_f=0.23 (10:1 Hex–EtOAc).

Compound **10**. Yield: 12 mg; 5%; mp: 127–130 °C. ^{1}H NMR: δ=4.31 (s, 12H, OC*H*$_3$), 4.34 (s, 12H, OC*H*$_3$), 7.46–7.67 (m, 12H, Naph*H*), 7.84–7.91 (m, 12H, Naph*H*), 8.62 (d, *J*=8.6 Hz; 4H, Naph*H*(8)); ^{13}C NMR: δ=62.08 (O*C*H$_3$), 74.49 (C≡*C*–*C*≡*C*), 81.85, 85.45, 96.24 (C≡*C*-Ar), 108.12, 120.98, 125.28, 126.23, 126.53, 127.01, 128.32, 129.01, 130.13, 133.28, 155.84, 164.13, 164.88 (Ar, Naph); MALDI-HRMS found: 982.3289; calcd for $C_{70}H_{46}O_6$: 982.3294. R_f=0.44 (5:1 Hex–EtOAc).

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Optically active bisbibenzyls from *Bazzania trilobata*: isolation and stereochemical analysis by chromatographic, chiroptical, and computational methods

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Dedicated to Professor Dr. Axel Zeeck on the occasion of his 65th birthday

Abstract—Bazzanin S, a new chlorinated bisbibenzyl of the isoplagiochin D type, as well as isoplagiochin D itself were isolated from the liverwort *Bazzania trilobata*. The structure of bazzanin S was elucidated based on extensive NMR spectral evidence and by mass spectrometry. Both macrocyclic compounds, bazzanin S and isoplagiochin D, as well as previously reported bazzanins exhibit optical activity, but are not enantiopure in nature. The enantiomeric ratios of a broad array of different cyclic bisbibenzyls, isoplagiochin D, bazzanins A–C and F–J, and bazzanin S, were determined by HPLC on a chiral phase. Exemplarily for the halogen-free parent compound isoplagiochin D, elucidation of the absolute configuration was achieved by quantum chemical CD calculations.

1. Introduction

Since 1997 chlorinated metabolites derived from the cyclic bisbibenzyls isoplagiochin D (**1**) or isoplagiochin C (**4**) (both previously isolated from *Plagiochila fruticosa*[1]) have been isolated from different bryophytes (liverworts), namely from *Plagiochila deflexa*,[2] *Bazzania trilobata*,[3] *Lepidozia incurvata*,[4] *Herbertus sakuraii*,[5] *Mastigophora diclados*,[5] and *Plagiochila peculiaris*.[6]

By MALDI-TOF mass spectrometry investigations[7,8] on crude *B. trilobata* plant extracts, it has been demonstrated that these chlorinated compounds are not artefacts of an incidental occurrence or of the sample preparation, e.g. treatment with chlorinated solvents,[5] but constitute genuine natural products. Furthermore, a chloroperoxidase was detected for the first time in *B. trilobata* using the monochlorodimedone assay[9] and some of the halogenated bisbibenzyls were synthesized.[10]

Optical rotations have been reported for isoplagiochins C and D, but the $[\alpha]_D$ data varied even for the same compound depending on the plant source and the isolation protocol.[1,5] The existence of atropisomers was first discussed by Asakawa et al.[5,11] and prompted us to perform detailed studies on the chirality of the isoplagiochin C framework including HPLC-CD experiments. By experimental and quantum chemical CD (circular dichroism) investigations, the absolute configuration of the first natural compound of this type, isoplagiochin C from *P. deflexa*, was established and the energy of racemization was measured to be 102 kJ/mol, approximately.[12] The experiments showed that a decrease of the enantiomeric purity can occur during standard isolation procedures that involve temperatures higher than 50 °C.[12]

In continuation of our studies on the secondary metabolites of liverworts, we now report on a new chlorinated phenolic compound, bazzanin S from *B. trilobata*, and on the analytical separation of the enantiomers of its halogen-free parent compound, isoplagiochin D, of bazzanins A–C, F–J, and of bazzanin S, by HPLC on a chiral phase.

Keywords: *Bazzania trilobata*; Bisbibenzyls; Structural elucidation; Circular dichroism (CD); Quantum chemical CD calculations.
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Furthermore, the assignment of the absolute configuration of isoplagiochin D is described, by quantum chemical calculation of its circular dichroism (CD) spectrum using molecular dynamics (MD) simulations.

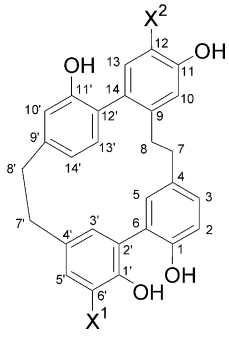
2. Results and discussion

2.1. Bazzanin S

Dried plant material of *B. trilobata* was extracted with dichloromethane and then with methanol. The dichloromethane extract was chromatographed on Sephadex LH-20 and the resulting fractions were further purified by VLC and HPLC. This led to the isolation of isoplagiochin D (**1**) and its new chlorinated derivative 6′-chloroisoplagiochin D (**2**), which, following the series of the related other bazzanins,[3,4] we named bazzanin S, along with the previously detected[3] dichloro compound, bazzanin J (**3**). Isoplagiochin D (**1**) was detected in the genus *Bazzania* for the first time (Fig. 1).

Compound **2** was obtained as a white powder; its molecular formula, $C_{28}H_{23}ClO_4$, was established by EI mass spectrometry. Its [M^+] peak in the mass spectrum showed an isotope pattern (458.2:460.2=100:38.2) typical of one chlorine atom in the molecule. The IR data indicated the presence of phenolic hydroxy groups (1285 and 1416 cm^{-1}) and a benzene ring (3336 and 1605 cm^{-1}). The ^1H and ^{13}C NMR spectra of **2** (Table 1) displayed four benzylic methylenes and 24 benzene ring carbons, including eleven aromatic protons. The NMR spectra of **2** were very close to those of **1**, except for the lacking resonance of H-6′. This proton was replaced by a chlorine substituent, which was concluded from the multiplicity and chemical shift of the corresponding carbon atom (δ_C 123.1, s). The location of the chlorine atom at C-6′ and the whole structure were deduced from the 2D NMR spectra including ^1H–^1H COSY, HMBC (Fig. 2), HSQC and NOESY data.

This is the first report on bazzanin S (**2**) as a natural product. We have recently described **2** as a derivative obtained in the total synthesis of bazzanin A and have published its NMR data in CD_3OD.[10] Both, the synthetic and the natural one now isolated, showed the same NMR spectra, but the published data proved to be partially incorrect. The revised NMR data are given in Table 1.



	X^1	X^2	
1	H	H	Isoplagiochin D
2	Cl	H	Bazzanin S
3	Cl	Cl	Bazzanin J

Figure 1. Isoplagiochin D type bisbibenzyls from *B. trilobata*.

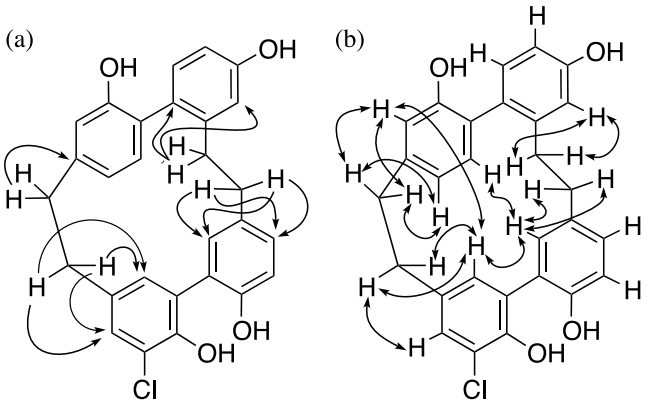
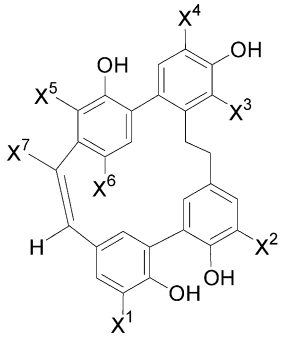


Figure 2. Key HMBC (a) and NOESY (b) couplings for bazzanin S (**2**) indicative of the bisbibenzylic structure.

2.2. Optically active bisbibenzyls

Cyclic bisbibenzyls like bazzanins or isoplagiochins C (**4**) and D (**1**) isolated from different liverworts look achiral at first sight because they are not equipped with any seemingly stable stereogenic element—and yet, optical rotatory powers have been reported for some of them.[4,5] More recently, we have performed extensive quantum chemical calculations on isoplagiochin C and have shown that one of the two biaryl axes, the one between C-12′ and C-14, is stable at room temperature and thus determines the overall chiroptical behavior of the molecule.[12] We have likewise developed an HPLC protocol for the separation of the enantiomers of isoplagiochin C on a chiral phase.[12] We could now show that this method allows us to resolve the



	X^1	X^2	X^3	X^4	X^5	X^6	X^7
Isoplagiochin C (**4**)[a]	H	H	H	H	H	H	H
Bazzanin A	Cl	H	H	H	H	H	H
Bazzanin B	Cl	H	H	H	H	H	Cl
Bazzanin C	Cl	H	H	Cl	H	H	Cl
Bazzanin D	Cl	H	H	H	Cl	H	Cl
Bazzanin E	Cl	H	H	Cl	Cl	H	Cl
Bazzanin F	Cl	H	Cl	H	H	Cl	Cl
Bazzanin G	Cl	Cl	Cl	H	Cl	H	Cl
Bazzanin H	Cl	H	Cl	H	Cl	Cl	Cl
Bazzanin I	Cl	Cl	H	Cl	Cl	Cl	Cl

[a] Not isolated from *B. trilobata*.

Figure 3. Isoplagiochin C type bisbibenzyls from *B. trilobata*.

Table 1. ^{13}C and ^{1}H NMR data for **2** (as isolated from *B. trilobata*) in CD_3OD

No.	δ_C		δ_H	m (*J* Hz)	No.	δ_C		δ_H	m (*J* Hz)
1	151.7	s	—		1′	149.1	s	—	
2	115.9	d	6.72	d (8.0)	2′	132.9	s	—	
3	129.0	d	6.98	dd (8.0, 2.2)	3′	132.9	d	6.37	d (2.2)
4	137.1	s	—		4′	135.4	s	—	
5	135.2	d	6.32	d (2.2)	5′	129.9	d	7.22	d (2.2)
6	127.4	s	—		6′	123.1	s	—	
7	38.0	t	2.47	m	7′	36.9	t	2.70	m
			2.60	m				2.91	m
8	39.9	t	2.68	m (2H)	8′	39.2	t	2.98	m (2H)
9	144.6	s	—		9′	143.0	s	—	
10	116.5	d	6.76	d (2.2)	10′	118.0	d	6.62	d (2.2)
11	157.8	s	—		11′	155.7	s	—	
12	113.8	d	6.66	dd (8.0, 2.2)	12′	128.3	s	—	
13	132.8	d	6.95	d (8.0)	13′	132.8	d	7.02	d (8.0)
14	130.7	s	—		14′	122.0	d	6.73	dd (8.0, 2.2)

enantiomers of almost all bisbibenzyls from *B. trilobata*. The structures of these compounds can be seen in Figure 3 and the naturally occurring enantiomeric ratios (e.r.) thus measured are shown in Table 2.

A direct stereochemical online analysis of the peaks by LC-CD coupling,[13,14] as exemplified for **1**, showed opposite CD curves clearly revealing that the separated substances are indeed enantiomers (see Fig. 4).

The assignment of these two peaks to the respective enantiomers was achieved by quantum chemical CD calculations using a molecular dynamics (MD) based approach.[15] As already shown in the case of the related bisbibenzyl isoplagiochin C,[12] the calculations for isoplagiochin D (**1**) proved the 'upper' axis (joining C-12′ and C-14) to be configurationally more stable at room temperature as compared to the 'bottom' one (connecting C-2′ and C-6). Arbitrarily starting with the *M*-configured stable biaryl axis of **1**, the MD simulation was carried out at a virtual temperature of 1300 K using the TRIPOS force field.[16] The computations were performed for a total time period of 500 ps, recording the structure every 0.5 ps. For the 1000 structures thus obtained, the single CD spectra were calculated and averaged arithmetically to give the overall theoretical spectrum of **1**. As shown in Figure 5, the CD spectrum calculated for the *M*-configured stable axis of **1** matches very well with the experimental one of the more

Table 2. Enantiomeric ratios of bisbibenzyls from *B. trilobata*

Compound	Enantiomeric ratio[a] (e.r.)	$[\alpha]_D$ (in MeOH)
Isoplagiochin C (**4**)[b]	15:85	−49.0 (*c* 0.75)[12]
	—[c]	±0.0 (*c* 1.0)[1]
Bazzanin A	34:66	+53.3 (*c* 0.3)[d]
Bazzanin B	37:63	+66.0 (*c* 1.0)[d]
Bazzanin C	23:77	+61.1 (*c* 1.0)[d]
Bazzanin D	—[c]	+74.4 (*c* 0.8)[d]
Bazzanin E	15:85	+190.0 (*c* 1.0)[d]
Bazzanin F	52:48	+125.0 (*c* 0.2)[d]
Bazzanin G	74:26	+40.0 (*c* 0.6)[d]
Bazzanin H	67:33	+130.0 (*c* 0.2)[d]
Bazzanin I	67:33	+60.0 (*c* 0.2)[d]
Bazzanin J (**3**)	38:62	+1.0 (*c* 0.4)
Bazzanin S (**2**)	53:47	+1.1 (*c* 0.1)
Isoplagiochin D (**1**)	48:52	−3.0 (*c* 0.2)
	—[c]	±0.0 (*c* 1.0)[1]

[a] Defined as the ratio {eluting enantiomer: more slowly eluting enantiomer}.
[b] Not isolated from *B. trilobata*.
[c] No sample available.
[d] Taken from lit.[3]

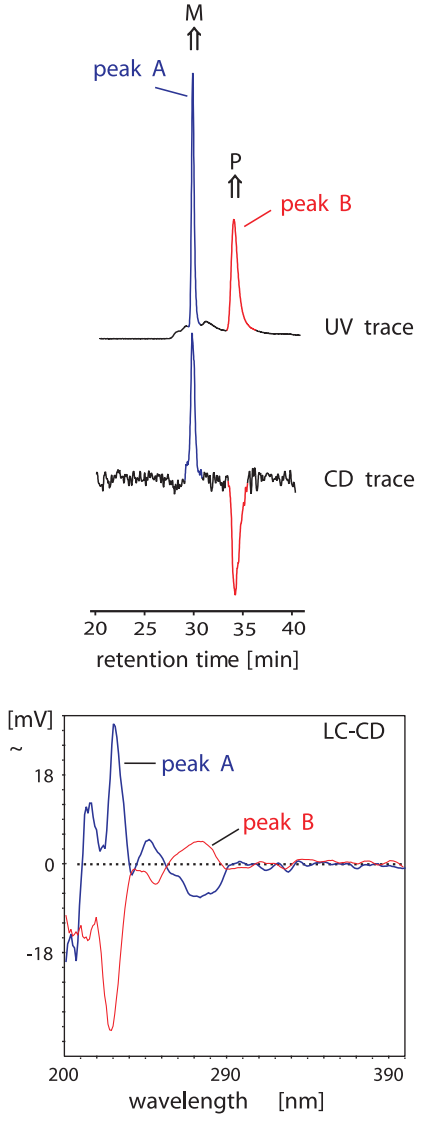


Figure 4. LC-UV and LC-CD chromatograms and full online LC-CD spectra of natural **1** from *B. trilobata*.

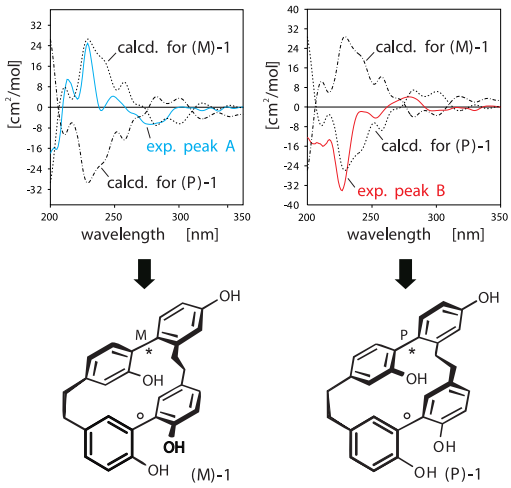
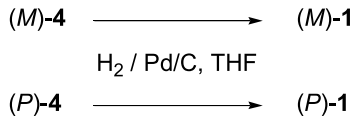


Figure 5. Assignment of the absolute configuration of isoplagiochin D (**1**) by comparison of the computational MD-based CD spectra calculated for both, (*M*)-**1** and (*P*)-**1**, with the experimental ones (in MeOH).

rapidly eluting peak **A**, while the experimental CD curve of the slower peak **B** is in a good agreement with the one calculated for *P*, clearly indicating peak **A** to correspond to (*M*)-**1** and peak **B** to (*P*)-**1** (see Fig. 5).

Although the CD spectra of isoplagiochin D (**1**) and the related (but additionally dehydrogenated) compound isoplagiochin C (**4**) are quite different experimentally, this difference is reproduced (and thus predicted) by the quantum chemical calculations. Moreover, the above assignment is in agreement with the HPLC behavior (see Fig. 4): in both cases, the more rapidly eluting peak is the respective *M*-enantiomer, and the more slowly eluting one is *P*-configured. This stereochemical correlation of isoplagiochin D (**1**) and isoplagiochin C (**4**) was also confirmed experimentally by hydrogenolysis of enantiopure samples of (*M*)-**4** and (*P*)-**4** to give (*M*)-**1** and (*P*)-**1**, respectively, without any racemization (Scheme 1).



Scheme 1. Stereochemical correlation of isoplagiochin D (**1**) by hydrogenolytic partial synthesis from isoplagiochin C (**4**).

3. Conclusion

The results presented in this paper show that, exemplarily for isoplagiochin D (**1**), the quantum chemical calculation of CD spectra is presently the method of choice to assign absolute stereostructures of cyclic bisbibenzyls. In a similar way, the stereochemical analysis of such compounds by enantiomeric resolution on a chiral HPLC phase with online measurement of the CD spectra delivers rapid information on the occurrence of the respective enantiomers in nature, as exemplified for no less than 12 bisbibenzyls, including a new one, bazzanin S (**2**). The results reveal that cyclic bisbibenzyls have now become stereochemically thrilling molecules—and that nature does not prepare them enantiomerically pure.

4. Experimental

4.1. General

IR spectra were measured on a Perkin–Elmer model 781 spectrometer with KBr pellets. The DCI MS spectra were recorded on a Finnigan MAT 90 spectrometer. The ^{1}H and ^{13}C NMR data (including 2D spectra: DEPT, HSQC, HMBC, and ^{1}H–^{1}H COSY spectra) were measured on a Bruker DRX-500 (^{1}H NMR: 500 MHz, ^{13}C NMR: 125 MHz). NMR spectra were obtained in CD_3OD relative to MeOH-d_4 at δ_H 3.30, δ_C 49.0. The optical rotatory powers were taken on a Perkin–Elmer model 241 polarimeter in MeOH. Silica gel 60 H 15 μm (Merck), silica gel 40–63 μm (Merck) were used for vacuum liquid chromatography (VLC), while thin layer chromatography was performed on silica gel (Silica gel 60 F_{254}, Merck).

4.2. Plant material

Bazzania trilobata (L.) S.F. Gray was collected in Rinnthal, Rheinland-Pfalz, Germany, in June 1999. A voucher specimen has been deposited at the General Herbarium SAAR, Saarbrücken (No. 6329).

4.3. Extraction and isolation

The extraction scheme followed the standard procedure of our group.[17] Air dried powdered plant material (900 g) of *B. trilobata* was sequentially extracted with CH_2Cl_2 and MeOH. The CH_2Cl_2 extract was evaporated in vacuo to give a green oil (37.6 g). The extract was chromatographed on Sephadex LH-20 using MeOH/CH_2Cl_2 (1:1) as the eluent to yield two fractions. Fraction 2 (18.0 g) was chromatographed on silica gel by VLC using an *n*-hexane/EtOAc gradient (10% steps, 100 mL each), to yield nine fractions. Further separation of fraction 2.9 on diol-modified silica gel by VLC using an *n*-hexane/EtOAc gradient (10% steps, 100 mL each) resulted in four fractions (2.9.1-4). Subsequent purification of fraction 2.9.4 on silica gel HPLC (Lichrospher 60 Si, 5 μm, 250×4 mm, mobile phase 1.5 mL/min *n*-hexane/EtOAc, 60:40) afforded two fractions 2.9.4.1/2. The two main compounds in fraction 2.9.4.2, **1** (7 mg) and **2** (24 mg), were separated by HPLC using a cyano stationary phase (LiChrosorb CN, 5 μm, 250×4 mm, mobile phase *n*-hexane/EtOAc, 60:40).

4.3.1. Isoplagiochin D (1). The data matched those reported in the literature.[18]

4.3.2. Bazzanin S (2). ^{1}H and ^{13}C NMR data: Table 1; IR (KBr): ν_{max} 3336, 3025, 2932, 2705, 2596, 1889, 1605, 1578, 1492, 1416, 1341, 1285, 1162, 1008, 958, 866, 817 cm^{-1}; $[\alpha]_D^{20} = +1.1$ (*c*0.1, MeOH); MS (EI): *m/z* 458.2 (M^+, 100%), 459.2 (35.3), 460.2 (38.2). Anal. calcd for $C_{28}H_{23}ClO_4$ (458.94): C, 73.28; H, 5.05. Found C, 73.18; H, 5.14.

4.4. Analytical HPLC on a chiral phase

The analytical separation was performed on a Waters 600 E multisolvent delivery system, Merck-Hitachi L-4000 UV detector, Varian 4290 integrator equipped with a Daicel

Chiralcel OD-H column (4.6×250 mm, 5 μm) and with an isopropanol/*n*-hexane gradient under the following conditions: flow 0.5 mL/min^{-1}; 0–10 min: isopropanol/*n*-hexane 10:90, 10–30 min: isopropanol/*n*-hexane 50:50, 30–40 min: isopropanol/*n*-hexane 95:5.

4.5. CD measured in hyphenation with HPLC

Online CD investigations were performed on a J-715 spectropolarimeter (Jasco) with a 5 mm standard flow cell at 254 nm. Full CD spectra were recorded in the stop-flow mode at a scan speed of 500 nm min^{-1}, with a response time of 0.5 s and a band width of 0.5 nm.

4.6. Computational

The molecular dynamics simulation was performed at a virtual temperature of 1300 K on a SCI Octane (R10000) workstation using the TRIPOS force field as implemented in the molecular modeling package Sybyl 6.4,[16] by using a time step of 0.5 fs. The wave functions for the calculation of the rotational strengths for the electronic transitions from the ground state to the excited states were obtained by CNDO/S-CI[19] calculations. The calculations were carried out with LinuX Pentium III workstations by the use of the BDZDO/MCDSPD program package.[20] For a better visualization, the rotational strengths were transformed into $\Delta\varepsilon$ values and superimposed with a Gaussian band shape function.

4.7. Stereochemical correlation of isoplagiochin D (1) by hydrogenolytic partial synthesis from isoplagiochin C (4)

Enantiopure samples of (*M*)-**4** and (*P*)-**4** were obtained by repeated semi-preparative HPLC resolution on a Daicel Chiralcel OD-H column (see Section 4.4 and Lit.[12]). Both enantiomers were hydrogenated (3.0 bar H_2, room temperature, 30 min) on a 0.02 mg (0.048 μmol) scale in THF (50 mL) containing a trace of 5% Pd/C. After filtration the hydrogenation products were concentrated (room temperature) and analyzed by HPLC using a Merck-Hitachi L-6000 HPLC pump, an L-4000 UV-detector, a Varian 4290 integrator, and a Nucleosil 100-5 C18 column (4.6× 250 mm, 5 μm) with MeOH/1% HCOOH 70:30 (1.0 mL/min), and on a Daicel Chiralcel OD-H column (see Section 4.4), clearly indicating the formation of (*M*)-**1** from (*M*)-**4** and of (*P*)-**1** from (*P*)-**4**, without any racemization (see Supporting Information).

5. Supporting information available

NMR spectra of bazzanin S (**2**): ^{1}H, ^{13}C, H,H-COSY, HSQC, HMBC, NOESY, and HPLC spectra of the stereochemical correlation of isoplagiochin D by hydrogenolytic partial synthesis from isoplagiochin C.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.08.037.

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A convenient method for the synthesis of 2-amino substituted aza-heterocycles from *N*,*N*′-disubstituted thioureas using TsCl/NaOH

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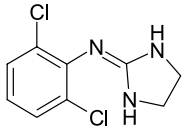
Abstract—*p*-Toluenesulfonyl chloride (TsCl)/NaOH has been introduced as reagent combination for the synthesis of 2-amino-oxa- or 2-amino-thiazolidines from *N*-(2-hydroxyethyl)-thioureas, but its general application in heterocycle synthesis has not been investigated. In this paper the convenient and efficient synthesis of a variety of 2-amino-substituted 1-aza 3-(aza, oxo or thio) heterocycles of different substitution and ring sizes is described. The application of polymer-supported TsCl facilitates work-up and renders the reaction conditions very suitable for parallel or robot synthesis.

1. Introduction

As part of our research programme to identify new inhibitors of the sodium–hydrogen exchanger (NHE) we intended to synthesise a series of clonidine analogues. Clonidine itself is known as an alpha2-adrenergic receptor agonist and an I_1 imidazoline receptor ligand with antihypertensive potential, but it also weakly inhibits rat NHEs (IC_{50} rNHE1: 210 μM, rNHE2: 42 μM, rNHE3: 620 μM).[1]



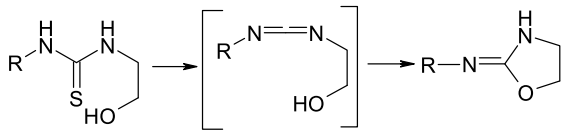
clonidine

When looking for the best approach to synthesise clonidine analogues possessing variations in ring size, substitution and ring heteroatoms in parallel fashion we identified thioureas as easily accessible precursors since they are conveniently prepared from isocyanates and amines which are commercially available in large number.

In the literature a number of reagents have been described to achieve the ring closure of thioureas to 2-amino-2-aza heterocycles. But mercury salts,[2] methyl iodode,[3] and potassium hyperoxide,[4] especially in larger scale, are not favourable due to their toxic or hazardous potential. *N*,*N*′-Dicyclohexylcarbodiimide[5] forms a thiourea during the reaction which sometimes renders product isolation difficult. Aqueous hydrochloric acid[2] requires usually reflux conditions that are not tolerated by many functional groups.

In 2001 Kim et al.[6] published the use of TsCl/NaOH for the ring closure of *N*-(2-hydroxyethyl)-thioureas to 2-amino-oxazolidines followed by an additional publication regarding the mechanism of the reaction.[7] Surprisingly, to the best of our knowledge up to date these reaction conditions were never applied to other starting materials than *N*-(2-hydroxyethyl)-thioureas.

The proposed mechanism of the ring closure step involves the formation of a carbodiimide intermediate (Scheme 1).[7] Therefore, it was interesting to study whether other ring sizes as well as alternatives to oxygen as the intramolecular



Scheme 1.

Keywords: TsCl/NaOH; Heterocycle synthesis; Thiourea; Ring closure; Cyclodesulfurisation.
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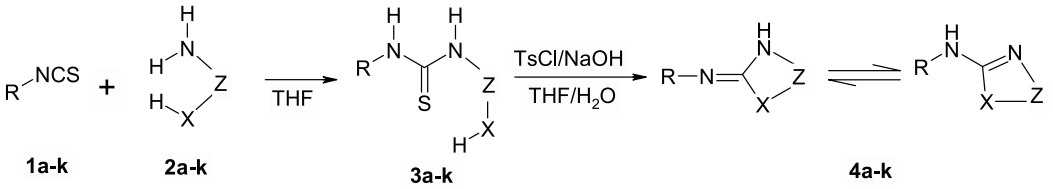
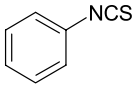
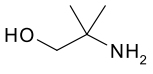
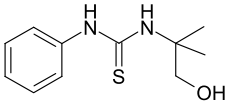
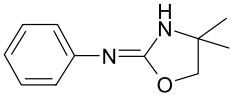
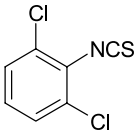
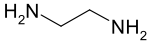
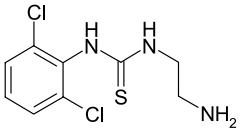
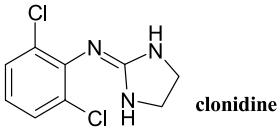
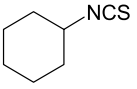
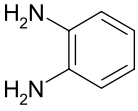
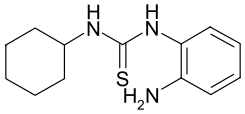
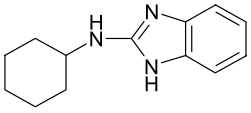
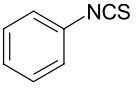
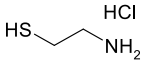
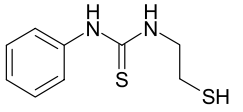
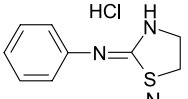
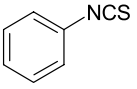
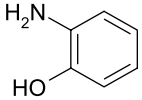
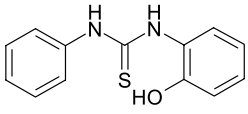
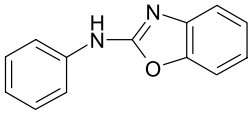
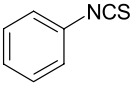
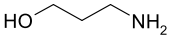
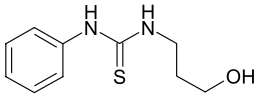
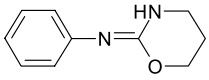
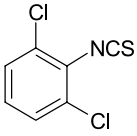
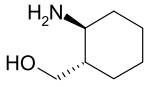
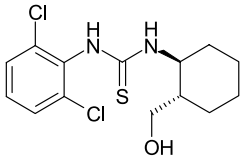
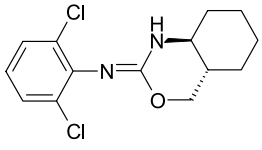
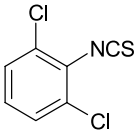
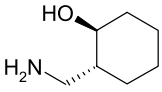
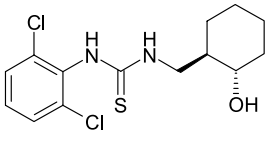
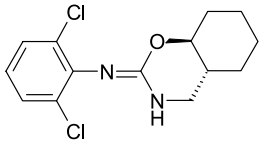
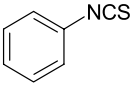
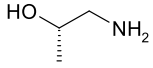
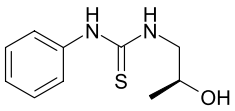
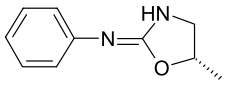
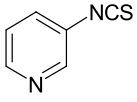
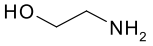
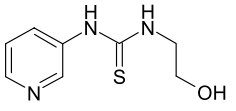


Scheme 2. Schematic approach towards 2-amino-aza heterocycles.

Table 1. Heterocycles synthesised by the TsCl/NaOH method[a]

Example	Isothiocyanate **1**	Amine **2**	Thiourea **3**	Heterocycle **4**	Yield **3** to **4**[b]	Lit.[c]
a					94% (from **1a**)	6
b				 **clonidine**	60%[d]	9
c					31%[d]	10
d					32%	11
e					72%[d,e] (from **1e**)	12
f					65%	13
g					94% (from **1g**)	—
h					47% (from **1h**)	—
i					64% (from **1i**)	—
j					52% (from **1j**)	—
k					93% (from **1k**)	—

[a] All compounds showed satisfactory analytical and spectroscopic data.
[b] Isolated yield.
[c] Known compounds were confirmed by their ^{1}H and/or ^{13}C NMR data from the literature.
[d] Using polymer-bound TsCl.
[e] One-pot procedure.

nucleophile X would be feasible. Nitrogen or sulfur could also be suitable nucleophiles as long as they react slower with tosyl chloride than the sulfur of the thiourea part. The thiourea sulfur is supposed to react fast with sulfonyl chlorides. When treating mono- or diaryl thioureas with methane- or ethanesulfonyl chloride in the presence of a base carbodiimide formation is complete at rt within 5 min.[8]

Since the reaction conditions for NaOH/TsCl mediated ring closure are convenient (stirring at ambient temperature), the reagents are cheap and the work-up seemed quite simple they were envisaged for the modification of the clonidine scaffold by parallel or robot synthesis techniques. To evaluate the scope and limitations of the TsCl/NaOH desulfurisation ring closure a series of reactions was investigated that are reported here (Scheme 2, Table 1).

2. Results and discussion

Typically, the desired cyclisation was achieved by dissolving the thiourea **3** in THF, adding 2.5 equiv of a 0.5–2 M sodium hydroxide solution under stirring followed by 1–1.4 equiv TsCl dissolved in THF. None of the new reactions in Table 1 is optimised. The yields for some of the products might be further increased under optimised conditions.

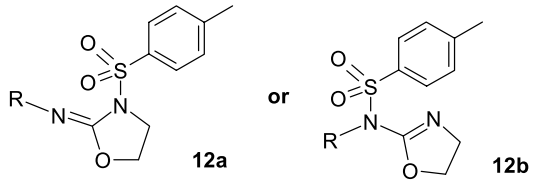
Before starting our investigations regarding substitution, ring size and intramolecular nucleophile X the 2-amino-oxazolidine formation described in the literature was repeated and confirmed (example **a**).[6]

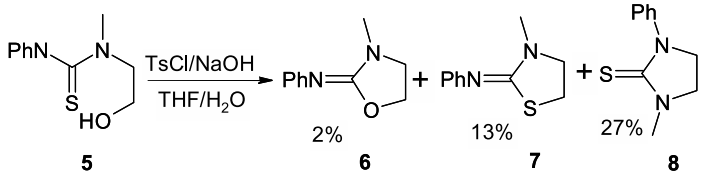
The suitability of nitrogen as nucleophile X is shown in examples **b** and **c** in Table 1. Clonidine **4b** was obtained in 60% yield from thiourea **3b** with a primary aliphatic amine as nucleophile X. Benzimidazole **4c** is obtained by the reaction of an aniline nitrogen as nucleophile X. In example **d** sulfur proofed its general suitability as nucleophile although giving the expected thiazolidine **4d** in low yield. Ring closure with phenolic oxygen is shown in example **e**. Benzoxazole **4e** was obtained in good yield. That the ring size is not limited to 5 membered rings is shown in the examples **f**, **g** and **h**, in which the [1,3]oxazinanes **4f**, **4g** and **4h** were formed in acceptable to excellent yields. Furthermore, ring-closure is not restricted to primary alcohols. Secondary alcohols react as well as shown in examples **4h** and **4i**. Heteroaromatic moieties like pyridine are also accepted under these ring closure conditions as shown in example **4j** and **4k**.

If the thiourea has more than one substituent on each nitrogen the ring closure becomes unselective.[6] *N*,*N*,*N*′-trisubstituted thiourea **5** does not selectively cyclise towards the 2-amino-oxazolidine **6**. Formation of **6** was only observed to a minor extent (2% yield). Instead thiazolidine **7** and thiourea **8** are the main products though in low isolated yields (Scheme 3).

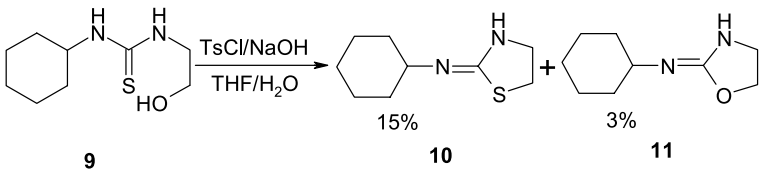
Similar observations are made if both substituents on the *N*,*N*′-disubstituted thiourea are aliphatic. The selectivity for the oxazolidine formation is lost. In the case of thiourea **9** a mixture of O and S ring closure besides starting material was obtained that was difficult to separate. Due to the separation issue isolated yields for **10** and **11** were quite low after purification (Scheme 4). In case of *N*-[(1,1-dimethyl-2-hydroxy) ethyl]-*N*-methylthio-urea selectivity towards S ring closure to the corresponding 2-thiazolamine was observed in the literature.[14]

Besides the group X the product formed during the reaction possesses also nucleophilic potential and is competing for the TsCl. In some reactions smaller amounts of a more lipophilic by-product **12a** or **12b** possessing the molecular weight of a compound resulting from the reaction of the desired product **4** with TsCl were detected by LC UV/MS. In the reaction of **3j** to **4j** the formation of two more lipohilic by-products both possessing the molecular weight of the tosylated product **4j** was observed. These by-products were not observed in the reaction of **3k** to **4k** suggesting that substitution alpha to the nitrogen disfavours the tosylation of the product nitrogen and might explain the higher yields in the case of the alpha substitution (examples **4a**, **4g** and **4k**).





Scheme 3.



Scheme 4.

Formation of **12a** or **12b** is critical, since the TsCl used for its synthesis does not react with the starting material. Further addition of TsCl to achieve complete conversion of the starting material might reduce the amount of product **4** leading to the increased formation of by-product **12** and has to be monitored carefully.

When working on small scale in parallel fashion the use of polymer-supported TsCl (ps-TsCl) facilitates work-up. Examples **4b** and **4e** were synthesised using this method.

In many cases the synthesis of thiourea **3** does not require a purification step. Thioureas **3a**, **3e**, and **3g–k** were of suitable purity after work-up (>90% by LCUV) and were directly used in the next step without further purification. Since tosylated by-products **12a/b** will be polymer bound if TsCl on solid support is used, a one-pot procedure seemed feasible starting from isothiocyanate **1** and yielding heterocylces **4** without a purification step. This one-pot procedure was applied in example **4e**. The sodium hydroxide solution and ps-TsCl in THF were directly added to the crude thiourea solution. After work-up benzoxazole **4e** was obtained in good yield (72%) and high purity (>95% by NMR and LCUV).

3. Conclusion

In summary, the successful application of the reagent combination TsCl/NaOH in ring closure reactions of *N*,*N*′-disubstituted thioureas to a variety of 2-amino-3-aza heterocycles was achieved. The reaction conditions represent a substantial extension to the existing methodology. Since they are convenient and the reagents are cheap they seem also promising for the application in large-scale synthesis. For small scale robot or parallel syntheses the one-pot procedure using ps-TsCl offers a simple and convenient method towards heterocycles **4** avoiding lengthy purification steps.

Based on this reaction conditions a series of 2-amino substituted aza-heterocyles was synthesised possessing NHE inhibitory activity. The results of this work will be reported in due course.

4. Experimental

Solvents and other reagents were used as received without further purification. ps-TsCl was purchased from Novabiochem. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane. LC UV/MS data were recorded with an Agilent series 1100 system linked to an Agilent series 1100 MSD (column: YMC J'sphere ODS H80, 20×2.1 mm, 4 μ; flow: 1 mL/min, eluent: water+0.05% TFA/acetonitril (ACN); gradient: from 4% ACN at 0 min to 95% ACN at 2.0 min, then for 0.4 min at 95% ACN; high resolution mass spectroscopy (HRMS) data were recorded on a 7T-Apex III FTICR mass spectrometer (Bruker Daltonics, Bremen) equipped with an external electrospray source. The sample was diluted in water/ACN (50/50) and admitted to the MS by flow injection (flow: 3 μL/min). Preparative reverse phase HPLC was performed on an Abimed/Gilson system (column: purospher 250×25 mm (10 μM) RP 18e; flow: 25 mL/min, eluent: water+0.05% TFA/acetonitril (ACN); gradient: from 10% ACN at 0 min to 90% ACN at 40 min). DCM/methanol gradients were used for column chromatography on silica gel. Purity and characterisation of compounds were established by a combination of LC UV, HRMS, and NMR analytical techniques. Identity of known compounds from the literature was confirmed by ^{1}H and ^{13}C NMR.

4.1. General procedure for the synthesis of compounds 3

At rt **2** (4 mmol) was dissolved in THF (10 mL) and isothiocyanate **1** (4 mmol) dissolved in THF (10 mL) was added with stirring. Reaction time 0.5–24 h. Completion of the reaction was determined by LC UV/MS. After completion of the reaction the solvent was removed and the residue was twice co-evaporated with toluene. At this stage thioureas **3a**, **3e**, and **3g–k** showed acceptable purity and were directly used in the next step. For work-up of **3b–d** and **3f** see at the respective experimental description of the respective heterocycle **4**.

4.2. General procedure for the synthesis of compounds 4

At rt **3** (1 mmol) was dissolved in THF (4 mL) and a sodium hydroxide/water solution (2.5 equiv, 0.5–2 M) was added with stirring. Then a mixture of TsCl (1–1.1 equiv) in THF (4 mL) was slowly added and the mixture was stirred for 30 min to 2 h. If there was some starting material left (LC UV/MS) further TsCl (0.1–0.3 equiv) in THF was added. When the reaction was complete the solvent was evaporated and ethyl acetate and brine were added to the residue. The layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered and evaporated. If purity was >90% by ^{1}H NMR and LCUV no purification step was performed. If the crude was less pure chromatography on silica gel or reverse phase followed.

4.2.1. (2,6-Dichloro-phenyl)-imidazolidin-2-ylidene-amine (clonidine) 4b.[9] 1-(2-Amino-ethyl)-3-(2,6-dichloro-phenyl)-thiourea **3b**: 25 equiv ethylendiamine were used. When the reaction was complete (LC UV/MS) 10% HCl solution was added. After washing with ethyl acetate (3×) saturated potassium carbonate solution was added and again extracted with ethyl acetate (3×). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was twice co-evaporated with toluene. (2,6-Dichloro-phenyl)-imidazolidin-2-ylidene-amine **4b**: **3b** (200 mg, 0.757 mmol) was dissolved in THF (4 mL) and a sodium hydroxide solution (76 mg/1.89 mmol NaOH in 2 mL water) was added followed by ps-TsCl (522 mg, 0.804 mmol, loading: 1.54 mmol/g) suspended in THF (6 mL). The mixture was stirred for 1 h. Since there was still some starting material left (LC UV/MS) additional ps-TsCl (124 mg, 0.191 mmol) was added to achieve complete conversion. After standing over night the resin was filtered off and washed twice with dichloromethane (DCM, 10 mL). The combined organic layers were evaporated and the residue dissolved in a mixture of water (10 mL) and DCM (10 mL). The layers were separated and

the aqueous layer was extracted three times with DCM (10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to yield clonidine (104 mg, 60%) as a white product.

4.2.2. (1H-Benzoimidazol-2-yl)-cyclohexyl-amine 4c.[10] 1-(2-Amino-phenyl)-3-cyclohexyl-thiourea **3c**: after stirring for 2 h at rt stirring was continued for 2 h at 50 °C. After completion of the reaction the crude was purified by revers phase HPLC. (1H-Benzoimidazol-2-yl)-cyclohexyl-amine **4c**: (**3c**: 100 mg, 0.401 mmol) no additional ps-TsCl was added to avoid product tosylation. After work up the desired product was separated from the starting material by revers phase HPLC. 26 mg white solid (31%) besides 16 mg (16%) of starting material were obtained after lyophilisation.

4.2.3. Phenyl-thiazolidin-2-ylidene-amine × HCl 4d.[11] 1-(2-Mercapto-ethyl)-3-phenyl-thiourea **3d**: 1 equiv of triethylamine was added to deprotonate cysteamine hydrochloride. The crude was treated with a mixture of ether/DMF and the insoluble residue separated by filtration. After removal of the ether in vaccuo the DMF solution was used directly for purification by reverse phase HPLC. Phenyl-thiazolidin-2-ylidene-amine×HCl **4d**: (**3d**: 1,12 mmol, reverse phase HPLC, lyophylisation in presence of HCl). Yield: 76 mg, (32%).

4.2.4. Benzoxazol-2-yl-phenyl-amine 4e.[12] (One-pot, polymer-bound TsCl): preparation of benzoxazol-2-yl-phenyl-amine **3e**: 2-aminophenol **2e** (202 mg, 1.85 mmol) was dissolved in THF (2 mL) and phenyl isothiocyanate **1e** (250 mg, 1.85 mmol) dissolved in THF (2 mL) was added with stirring. After standing overnight the reaction was complete (LC UV/MS). Sodium hydroxide solution (242 mg/6.05 mmol NaOH in 4.8 mL water) was added followed by ps-bound TsCl (1.245 g, 1.92 mmol, loading: 1.54 mmol/g) suspended in THF (11 mL). The mixture was stirred for 30 min. Since there was still starting material left (LCMS) additional ps-bound TsCl (223 mg, 0.343 mmol) was added to achieve complete conversion. Then the resin was filtered off and washed twice with dichloromethane (DCM). The combined organic layers were evaporated and the residue dissolved in a mixture of water and DCM. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to yield 278 mg (72%) of a white solid; LCMS: rt 1.42 min; MS (ESI) *m/z* 211.1 (100%, $M+H^+$); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.06 (bs, 1H), 7.61 (m, 2H), 7.49 (m, 1H), 7.32–7.44 (m, 3H), 7.24 (m, 1H), 7.08–7.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.3, 147.9, 142.2, 137.9, 129.4, 124.3, 123.4, 121.9, 118.5, 117.1, 109.1; HRMS calcd for $C_{13}H_{11}N_2O$ ($M+H^+$): 211.0866, found: 211.0867.

4.2.5. [1,3]Oxazinan-2-ylidene-phenyl-amine 4f.[13] 1-(3-Hydroxy-propyl)-3-phenyl-thiourea **3f**: The crude was purified by reverse phase HPLC. [1,3]Oxazinan-2-ylidene-phenyl-amine **4f**: (**3f**: 0.238 mmol, chromatography on silica gel (DCM/MeOH 50/1 to 0/100). Yield: 27.4 mg (64%).

4.2.6. (2,6-Dichloro-phenyl)-(octahydro-benzo[d][1,3]oxazin-2-ylidene)-amine 4g. (**3g**: 0.900 mmol, no chromatography). Yield: 261 mg (97%) of a white solid; LCMS: rt 1.00 min; MS (ESI) *m/z* 299.0 (100%, $M+H^+$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24 (d, 8.0 Hz, 2H), 6.82 (t, 8.0 Hz, 1H), 5.7 (bs, 1H), 4.11 (dd, 11.0, 4.5 Hz, 1H), 3.84 (t, 11.0 Hz, 1H), 3.01 (td, 10.5, 4.0 Hz, 1H), 1.61–1.86 (m, 5H), 1.20–1.41 (m, 3H), 0.89–1.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.6, 143.3, 129.7, 127.8, 122.5, 71.5, 54.7, 38.2, 31.9, 25.5, 25.0, 23.9; HRMS calcd for $C_{14}H_{17}Cl_2N_2O$ ($M+H^+$): 299.0712, found: 299.0719.

4.2.7. (2,6-Dichloro-phenyl)-(octahydro-benzo[e][1,3]oxazin-2-ylidene)-amine 4h. (**3h**: 0.900 mmol, chromatography ethyl acetate/DCM 1/1). Yield: 137 mg (51%); LCMS: rt 1.07 min; MS (ESI) *m/z* 299.4 (100%, $M+H^+$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, 8.0 Hz, 2H), 6.80 (t, 8.0 Hz, 1H), 6.10 (sb, ~1H), 3.85 (td, 10.5, 4.5 Hz, 1H), 3.31 (dd, 11.0, 5.5 Hz, 1H), 2.94 (t, 11.0 Hz, 1H), 1.95–2.09 (m, 1H), 1.63–1.88 (m, 4H), 1.18–1.44 (m, 3H), 0.94–1.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.7, 143.4, 129.7, 127.8, 122.3, 79.1, 45.0, 36.6, 31.2, 28.4, 24.6, 23.9; HRMS calcd for $C_{14}H_{17}Cl_2N_2O$ ($M+H^+$): 299.0712, found: 299.0717.

4.2.8. (*S*)-(5-Methyl-oxazolidin-2-ylidene)-phenyl-amine 4i. (**3i**: 3.72 mmol, chromatography on reverse phase). Yield: 417 mg (64%) of a white solid; LCMS: rt 0.71 min; MS (ESI) *m/z* 177.1 (100%, $M+H^+$); ^1H NMR (DMSO-d_6, 400 MHz): δ 8.76 (bs, ~1H), 7.46 (m, 1H), 7.20 (m, 1H), 6.86 (m, 1H), 4.66 (m, 1H), 3.83 (dd, $J=12.0$, 8.5 Hz, 1H), 3.28 (dd, $J=12.0$, 7.0 Hz, 1H), 1.30 (d, $J=6.5$ Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 155.5, 141.6, 128,4, 120,7, 118.0, 74.1, 57.6, 20.4; HRMS calcd for $C_{10}H_{13}N_2O$: ($M+H^+$) 177.1022, found: 177.1024.

4.2.9. Oxazolidin-2-ylidene-pyridin-3-yl-amine 4j. (**3j**: 1.16 mmol, chromatography DCM/MeOH 100/0 to 80/20, lyophilisation from water/acetonitrile). Yield: 99 mg (52%) of an off-white solid; LCMS: rt 0.14 min; MS (ESI) *m/z* 164.1 (100%, $M+H^+$); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.38 (d, 2.0 Hz, 1H), 8.21 (dd, 4.5, 1.5 Hz, 1H), 7.64 (bs, 1H), 7.18 (dd, 8.0, 4.5 Hz, 1H), 4.46 (t, 8.0 Hz, 2H), 3.76 (t, 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.6, 143.5, 143.3, 140.7, 128.2, 123.4, 67.8, 45.8; HRMS calcd for $C_8H_{10}N_3O$: ($M+H^+$) 164.0818, found: 164.0822.

4.2.10. (4,4-Dimethyl-oxazolidin-2-ylidene)-pyridin-3-yl-amine 4k. (**3k**: 1.10 mmol, chromatography DCM/MeOH 100/0 to 90/10, lyophilisation from water/acetonitrile). Yield: 194 mg (92%) of a white solid; LCMS: rt 0.23 min; MS (ESI) *m/z* 192.1 (100%, $M+H^+$); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.38 (bs, 1H), 8.20 (dd, 4.5, 1.5 Hz, 1H), 7.55 (bs, 1H), 7.17 (dd, 8.0, 4.5 Hz, 1H), 4.10 (s, 2H), 1.36 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 144.1, 141.5, 143.3, 128.9, 123.4, 78.9, 58.8, 27.5; HRMS calcd for $C_{10}H_{14}N_3O$ ($M+H^+$): 192.1131, found: 191.1135.

4.2.11. (3-Methyl-oxazolidin-2-ylidene)-phenyl-amine 6, (3-methyl-thiazolidin-2-ylidene)-phenyl-amine 7, and 1-methyl-3-phenyl-imidazolidine-2-thione 8. MS and ^1H NMR data were in accordance with the literature.[6,15]

4.2.12. Cyclohexyl-thiazolidin-2-ylidene-amine hydrochloride 10 and cyclohexyl-oxazolidin-2-ylidene-amine 11. Compound **10** was isolated as its hydrochloride salt. ^1H

NMR data for (**10**×HCl) were in accordance with the literature.[16] **11** could not be isolated in pure form. But identification was possible from an enriched mitxure (2:1) of **11** in the presence of **10** by LCMS and comparison of ^{1}H NMR data of the mixture with the literature.[17]

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Application of a catalytic palladium biaryl synthesis reaction, via C–H functionalization, to the total synthesis of Amaryllidaceae alkaloids

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Abstract—The total synthesis of the Amaryllidaceae alkaloids dehydroanhydrolycorine, hippadine, pratosine, anhydrolycorine, assoanine, anhydrolycorin-7-one and oxoassoanine was achieved from the appropriate *N*-benzylisatin precursors using an intramolecular, palladium catalyzed, dehydrohalogenation, biaryl synthesis reaction to establish the carbon skeleton of the natural products. In order to avoid the formation of regioisomers in the cyclization reactions it was found necessary to incorporate the halogen on the benzyl group. Borane reduction of the 7*H*-pyrrolo[3,2,1-*de*]phenanthridine-4,5-dione derivatives gave 7*H*-pyrrolo[3,2,1-*de*]- and 4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]-phenanthridines (dehydroanhydrolycorine, dehydroassoanine, anhydrolycorine and assoanine). The former were readily reduced to the latter with $NaCNBH_3$ to give anhydrolycorine and assoanine. These compounds were then oxidized to anhydrolycorin-7-one and oxoassoanine whilst the same mixtures of borane reduction products could be oxidized to give hippadine and pratosine.

1. Introduction

The Amaryllidaceae alkaloids constitute a structurally diverse group of almost 200 alkaloids isolated from the majority of the genera of the family Amaryllidaceae.[1] The structures have been classified into mainly seven groups. Many of these alkaloids possess significant biological activity and this has in many ways, as well as the structural diversity, stimulated synthetic efforts and the pursuit of new synthetic methodologies. A sub-group of the lycorine structure is represented in Figure 1. This sub-group has either a pyrrolo[3,2,1-*de*]phenanthridine (**1**) or a dihydropyrrolo[3,2,1-*de*]phenanthridine (**2**) skeleton where R_{1-4} may be a hydroxy, methoxy or a fused methylenedioxy ring (R_2/R_3). Positively charged quaternary nitrogen (X=H: vasconine and tortuesine) and neutral zwitterionic ($R_1=O^-$, X=H: ungeremine, criasbetaine and zeflabetaine) compounds have also been isolated.[1]

The use of palladium, in catalytic or stoichiometric quantities, has become an indispensable tool for the synthesis of heterocyclic compounds.[2] The synthetic strategies that have been developed for the synthesis of the pyrrolophenanthridine alkaloids are no exception. All of these strategies, that use palladium, have in common the synthesis of the biaryl linkage between a phenyl group and an indole or indoline derivative. Suzuki aryl–aryl cross couplings have been employed for the synthesis of ungeramine, hippadine (**1b**), anhydrolycorinone (**2b**) and oxoassoanine (**2d**).[3] Stille cross couplings using a 7-stannylindoline derivative were investigated by Iwao and Watanabe for the synthesis of **1b**, **2b**, **2d** and pratosine (**1d**).[4] These authors also transformed anhydrolycorine (**2a**) into kalbretorine (**1g**) via a directed *ortho* lithiation followed by boration and oxidation. Grigg and co-workers used a $Pd(OAc)_2/(Me_3Sn)_2$ system to prepare **1b** in a cyclization between two aryl iodides.[5]

A few examples of the use of palladium for the cyclization of *N*-benzoylindole derivatives are known. These cyclizations are dependant upon the structure of the substrate. Itahara observed that the $Pd(OAc)_2$ oxidative cyclization occurred at C-2 of the indole resulting in the formation of isoindolo[2,1-*a*]indole derivatives.[6] Black and co-workers obtained similar results for the oxidative cyclization of *N*-piperonylindole and methoxybenzoylindole derivatives

Keywords: Amaryllidaceae alkaloids; Pyrrolophenanthridine; Biaryl synthesis; Palladium catalysis; Dehydrohalogenation; C–H activation; C–H functionalization; Indoledione.
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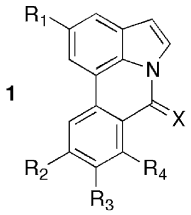
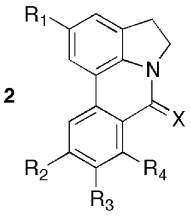


a $R_1 = R_4 = H$; $R_2/R_3 = -OCH_2O-$; X = 2H; Dehydroanhydrolycorine
b $R_1 = R_4 = H$; $R_2/R_3 = -OCH_2O-$; X = O; Hippadine
c $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$; X = 2H; Dehydroassoanine
d $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$; X = O; Pratosine
e $R_1 = R_4 = H$; $R_2 = OCH_3$; $R_3 = OH$; X = O; Pratorinine
f $R_1 = R_4 = H$; $R_2 = OH$; $R_3 = OCH_3$; X = O; Pratorimine
g $R_1 = H$; $R_2/R_3 = -OCH_2O-$; $R_4 = OH$; X = O; Kalbretorine
h $R_1 = H$; $R_2/R_3 = -OCH_2O-$; $R_4 = OCH_3$; X = O; *O*-Methylkalbretorine



a $R_1 = R_4 = H$; $R_2/R_3 = -OCH_2O-$; X = 2H; Anhydrolycorine
b $R_1 = R_4 = H$; $R_2/R_3 = -OCH_2O-$; X = O; Anhydrolycorin-7-one
c $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$; X = 2H; Assoanine
d $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$; X = O; Oxoassoanine

Figure 1. Generalized structures for pyrrolo[3,2,1-*de*]phenanthridine (**1**) and dihydropyrrolo[3,2,1-*de*]phenanthridine (**2**) alkaloids (**1c** is unknown as a natural product).

using stoichiometric quantities of $Pd(OAc)_2$.[7] Later these workers anticipated that activation of the benzo-ring of the indole nucleus with methoxy groups (4,6-disubstituted) would allow regioselective C-7 cyclization to occur in preference to C-2 cyclization. In addition, it was shown that the desired C-7 regioselectivity could be guaranteed by oxidative cyclization of *N*-benzoylindolines and subsequent oxidation to the pyrrolophenanthridinone.[8] Grigg and co-workers favoured the investigation of catalytic methods and observed that the Heck reaction[9] of *N*-(2-iodobenzoyl)-indole, and the 3-methylindole derivative, resulted in cyclization at C-2 of the indole nucleus when they used 10 mol% $Pd(OAc)_2$ and 20 mol% PPh_3, in the presence of K_2CO_3 and Et_4NCl, in refluxing acetonitrile.[10] Other investigations have also revealed the preference for cyclization at C-2 when the halogen was bonded to the *N*-benzoyl or *N*-benzyl fragment of the indole substrate.[11]

Harayama and co-workers have recently investigated the palladium catalyzed cyclizations of *N*-2-halobenzylindolines. They found that these reactions gave mixtures of the cyclized dihydropyrrolophenanthridine and oxidized dihydropyrrolophenanthridinone as well as the reduced benzylindoline and oxidized benzylindole.[12] Knölker has reported the palladium catalyzed cyclization of *N*-2-iodo-3,4-methylenedioxybenzyltetrahydroindole under air to give **2b** in 29% yield.[13]

Nucleophilic substitution of either *ortho*-methoxy or *ortho*-iodo aromatic substituents in aryloxazolines or benzaldimines, respectively, have been investigated as a means for the construction of the biaryl linkage. In the former case, Hutchings and Meyers required 5 steps to obtain **2d** in moderate overall yield by coupling a bromoindoline Grignard reagent with the appropriate oxazoline followed by subsequent transformations.[14] Similar procedures were later applied to the synthesis of **2b** and dihydrokalbretorine, DDQ oxidation of these compounds yielded **1b**, **1d** and **1g**.[15] In the latter case, Flippin and co-workers prepared vasconine by coupling an indolinylcopper reagent with the appropriate *ortho*-iodobenzaldimine in an Ullmann type biaryl synthesis. Vasconine was then transformed into assoanine (**2c**) and **2d**.[16] A similar methodology was applied later to the synthesis of the pyrrolophenanthridinium alkaloids tortuosine, criasbetaine, and ungeremine.[17] Harrowven and co-workers have made use of an intramolecular Ullmann type coupling reaction to give **1a** which was then oxidized to **1b**.[18]

Other notable methods for the synthesis of these alkaloids include radical cyclizations[19] and intramolecular cycloaddition reactions.[20]

2. Results and discussion

Our approach to the synthesis of the natural products **1** and **2** was based upon the early construction of the entire carbon framework. It was envisaged that benzylation of isatin and subsequent palladium catalyzed synthesis of the biaryl linkage would result in the obtention of the appropriate carbon skeleton.[21] Subsequent reduction and oxidation reactions would be utilized to finish the syntheses of the natural products **1**(**a**, **b** and **d**), **2**(**a**–**d**) as well as the unknown **1c** and analogous derivatives (Fig. 2).

In previous studies of the reactivity of isatin (**3**),[22] we have demonstrated that these compounds may be considered as masked indoles. The reduction of **3** and its' derivatives to indoles in high yields by THF solutions of $BH_3 \cdot THF$ has some distinct advantages over the use of other hydride reagents,[23] though, as of yet, has been rarely exploited for natural product synthesis.[23c,24] Therefore, the synthetic approach for the formation of the biaryl bond using an *N*-benzyl isatin derivative followed by $BH_3 \cdot THF$ reduction of the dioxindole nucleus guarantees the construction of the pyrrolo[3,2,1-*de*]phenanthridine skeleton (**1**) and avoids the problem of regioselective cyclization at C-7 of the indole nucleus.[6–8,10,11]

The *N*-benzylisatin derivatives (**5**) used in this study were readily prepared from the appropriate **3** and benzyl chloride (**4**) in the presence of K_2CO_3 and NaI in DMF or by the use of CaH_2 and DMF (Table 1) (Scheme 1).[25,26]

A previous study had revealed the necessity to transform the keto-carbonyl group of **5** into the *spiro*-dioxolane **6** to facilitate formation of the biaryl linkage by palladium catalysis.[26,27] The dioxolanes **6** were prepared by acid

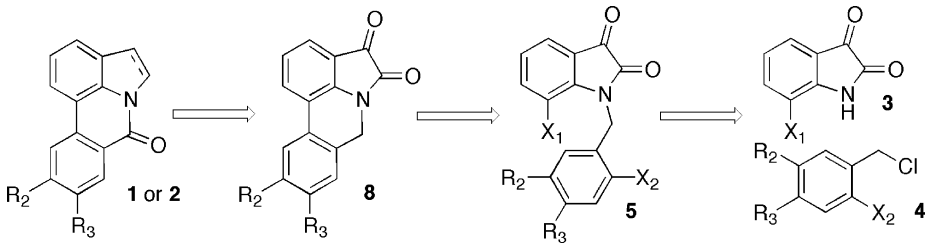
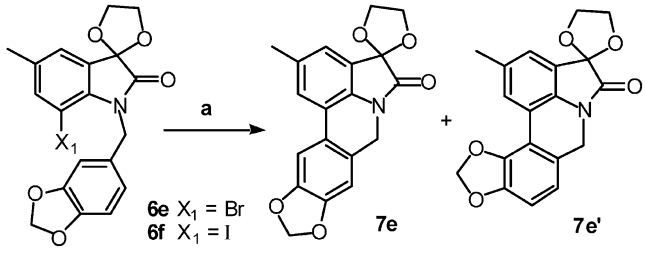


Figure 2. Retroanalysis for the synthesis of pyrrolo- and dihydropyrrolo-[3,2,1-*de*]phenanthridinones: R_2/R_3=H or –OCH_3 or –OCH_2O–; when X_1=I or Br, X_2=H; when X_1=H, X_2=I or Br.

catalysis with azeotropic removal of water using ethylene glycol and toluene. With the appropriate substrates in hand, previously determined conditions for the palladium catalyzed synthesis of the biaryl linkage were applied.[26] The substrate (0.1 M in DMF) was heated in the presence of 10 mol% $Pd(OAc)_2$, 1.0 mol equiv of Bu_4NBr, and 5 mol equiv of KOAc (oil bath temperature 100 °C). No particular precautions, such as an inert atmosphere, or anhydrous DMF, were required and the cyclizations were routinely performed exposed to the atmosphere. The oxopyrrolophenanthridine derivatives (**7**) were obtained in greater than 85% yield from the respective iodide substrates (**6a**, **c**, and **d**) after workup and purification. The bromide **6b** required a considerably longer reaction time and gave a less satisfactory yield (Table 2).

When compounds **6e** and **6f** were treated under the aforementioned palladium catalyzed reaction conditions, two regioisomeric products were obtained as a more or less 1:3 mixture (Eq. 1). The principal isomer was separated by repeated crystallization from MeOH and identified as **7e**′. Subjection of **6g** to the biaryl forming reaction gave a good yield (43%) of **7e** at 46% conversion of the substrate. Thus with an unambiguous method for the regiospecific synthesis of **7e** and the purification of **7e**′ from the mixture it was possible to assign all the signals in the ^1H and ^{13}C NMR spectra of the mixtures of **7e** and **7e**′. It is interesting to note that the regioselectivity of these reactions is opposite to that previously observed by Black and co-workers,[8] and is consistent with that recently reported by Harayama and colleagues in similar palladium catalyzed biaryl forming reactions.[28]

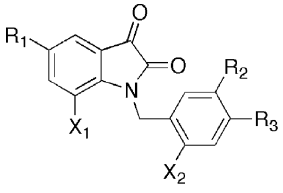


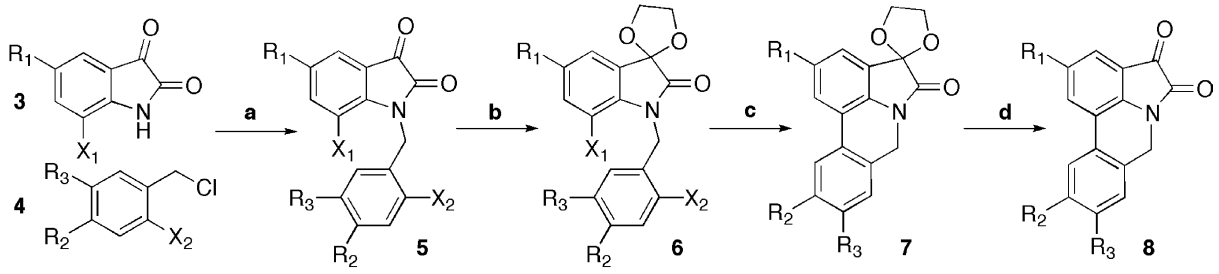
(1)

a 10 mol% $Pd(OAc)_2$, Bu_4NBr, KOAc, DMF.

The reaction mechanism for formation of the biaryl bond is presently debatable and it is possible to envisage a number of scenarios (Fig. 3).[29] Initial oxidative addition of an in situ generated anionic Pd(0) species to the aryl halide would give $ArPd(II)OAcS_2$ (where S is a solvent molecule).[30] This Pd(II) complex could evolve giving rise to the formation of an η^2-arene complex by loss of one of the ligating solvent molecules.[31] Such an η^2-arene complex can be envisioned as a precursor to any of the proposed scenarios (Fig. 3) that

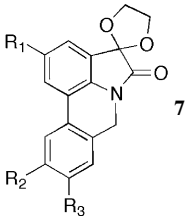
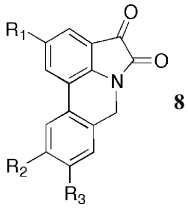
Table 1. Substrates used in this study

Compound		R_2/R_3	R_1	X_1	X_2
	**5a**	H	CH_3	I	H
	5b	–OCH_2O–	H	H	Br
	5c	–OCH_2O–	H	H	I
	5d	OCH_3	H	H	I
	5e	–OCH_2O–	CH_3	Br	H
	5f	–OCH_2O–	CH_3	I	H
	5g	–OCH_2O–	CH_3	H	Br



Scheme 1. For identification of the substituents see Table 1: (a) DMF, K_2CO_3, NaI; (b) $(CH_2OH)_2$, toluene, H_2SO_4; (c) sub. 0.1 M in DMF, 10 mol% $Pd(OAc)_2$, 1 equiv Bu_4NBr, 5 equiv KOAc, 100 °C; (d) 6 N HCl/THF (1:1, v/v) reflux.

Table 2. Cyclization and dioxolane hydrolysis reaction products

Product		R_2/R_3	R_1	Yield (%), [Reac. Time, hrs] mp (°C)	Product		Yield mp (°C)
 **7**	**6a→7a**	H	CH_3	98 [3], 191–3	 **8**	**8a**	96, 237–8
	6b→7b	$-OCH_2O-$	H	69 [24]		**8b**	92, 235–7
	6c→7b	$-OCH_2O-$	H	95 [5], 226–8			
	6d→7d	OCH_3	H	87 [10], 188–190		**8d**	87, 240–2
	6e→7e/7e′	$-OCH_2O-$	CH_3	42[a] [16]			
	6f→7e/7e′	$-OCH_2O-$	CH_3	97[b] [6]			
	6g→7e	$-OCH_2O-$	CH_3	43 [29][c], 243–5			

[a] A mixture of two regioisomers (1:3.2) as determined by ^1H NMR.
[b] A mixture of two regioisomers (1:3.0) as determined by ^1H NMR, mp of **7e′** is 217–9 °C.
[c] 20 mol% PPh_3 in place of the Bu_4NBr.

result in C–H functionalization.[32] Alternatively, the formation of an η^1-arene complex, as an intermediate, may precede the formation of the palladacycle.[33] In the first scenario, the η^2-arene complex (or the η^1-arene complex) would evolve by addition of the σ-Pd–C aryl bond to the aromatic ring in a Heck type reaction giving rise to a *trans* disposed arrangement of the Pd and hydrogen to be eliminated. In Heck reactions such eliminations occur in a *syn* manner. In order to regenerate Pd(0) it would be necessary for a base to abstract the proton, resulting in aromatization of the benzoid ring and the elimination of Pd(0) or for stereomutation of the π-allyl palladium to occur resulting in a *cis* relationship with respect to the hydrogen to be eliminated.[10,34] The second scenario proposes that the reaction mechanism passes via a classical aromatic electrophilic substitution to give a *cis*-diarylpalladium species that would eliminate Pd(0) forming the biaryl bond. Such a mechanism may or may not include a σ-complex intermediate of finite lifetime and is expected to show a normal aryl-substituent effect where electron releasing groups increase the rate of reaction.[35] However, such substituent effects have been called into question.[36] The third scenario is that an η^2-arene (or an η^1-arene) aryl-Pd complex precedes an agostic interaction between the palladium and the carbon–hydrogen bond.[37] An agostic effect may possibly represent a transition state for C–H activation which ultimately results in the formation of the *cis*-diarylpalladium (II) species.[33,36,38]

The dioxolane products **7**(**a**, **b** and **d**) were hydrolyzed in refluxing 50% aqueous 6 N HCl/THF for 5 h. Evaporation of the THF resulted in the precipitation of the dark red/purple compounds **8** in greater than 85% yield. Rigby and Mateo reported an alternative method for what was claimed to be the synthesis of compound **8b**.[39] Both the physical and the spectroscopic properties detailed for compound **8b** as prepared by Rigby and Mateo are inconsistent with those obtained in this study.

With compounds **8** in hand, attention was turned to

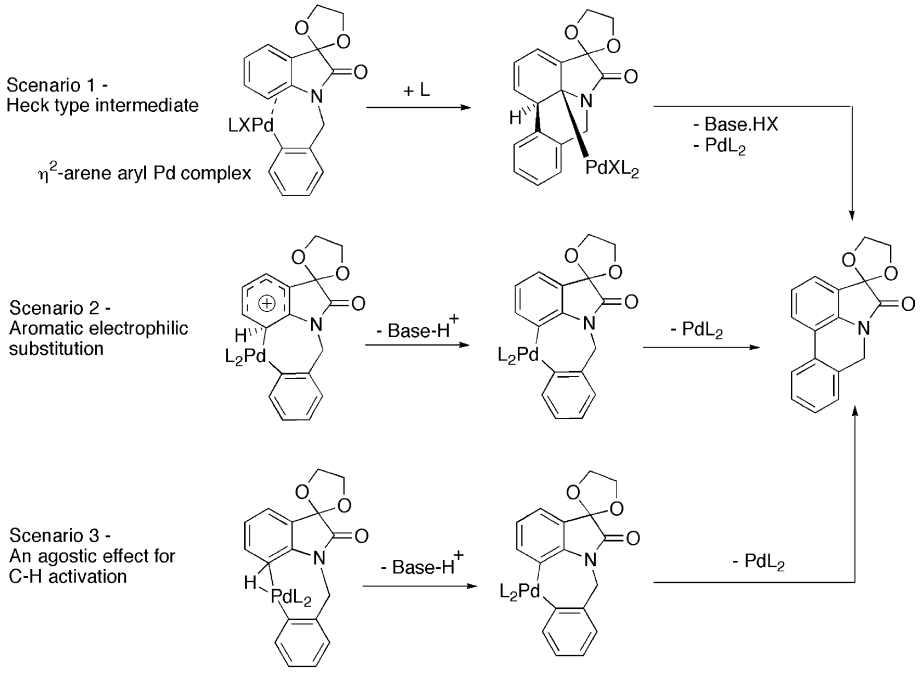
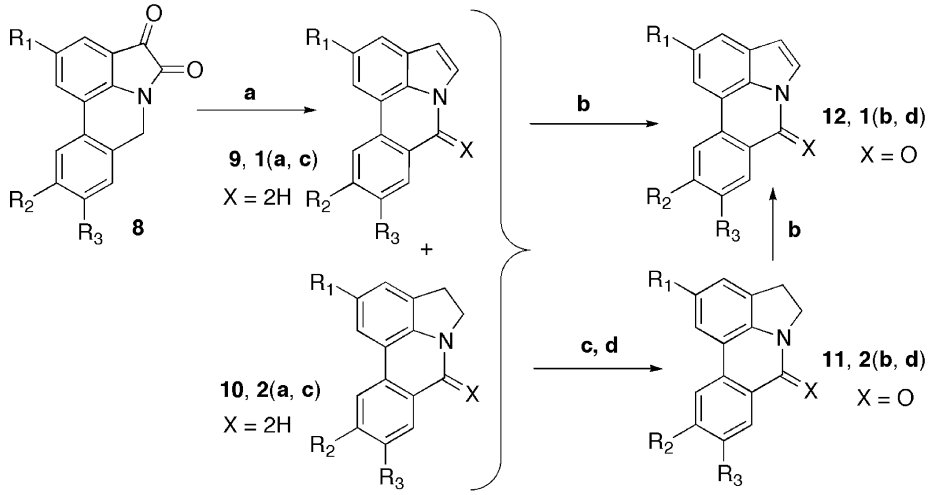


Figure 3. Reaction mechanism scenarios. In all three cases equivalent scenarios may be envisioned where the halogen would have initially been bonded to the oxindole system. No distinction is implied by the ligand (L) as to whether it is an anionic or neutral ligand and indeed L_2 could be a combination of such ligands (scenarios 2 and 3).



Scheme 2. Reduction of compounds **8**: (a) $BH_3 \cdot THF$ (3 mol equiv); (b) oxidation; (c) $NaCNBH_3$, AcOH; (d) $KMnO_4$, NaOH, CH_2Cl_2 (compounds **9**, **10**, **11** and **12**: $R_1 = CH_3$, $R_2, = R_3 = H$).

investigate the reduction reaction employing $BH_3 \cdot THF$. A solution of $BH_3 \cdot THF$ was added to THF solutions of compounds **8**. The reactions were maintained at room temperature for 3 h then hydrolyzed. Normal workup of the hydrolyzed reactions gave the crude products. In the case of **8a**, compound **9** could be obtained in up to 92% yield. This compound was characterized spectroscopically, the vinylic indole proton signals being observed at 6.43 and 7.07 ppm as doublets ($J = 2.9$ Hz). In contrast to **8a**, the reduction of both **8b** and **8d** with $BH_3 \cdot THF$ gave a mixture of the respective **1a/2a** and **1c/2c**. In the case of the reaction of **8b** the mixture was quantified as being a 7:3 ratio of **1a**:**2a**. These compounds were unambiguously identified in the ^1H NMR spectrum from the presence of the vinylic indole CH doublets in **1a** (6.50 and 7.07 ppm, $J = 2.8$ Hz) and the presence of the two vicinial CH_2 triplets in **2a** (3.00 and 3.30 ppm, $J = 7.8$ Hz). The obtention of substantial quantities of compounds **2** (**a** and **c**) was unexpected based upon our previous experience of the reduction of dioxindole derivatives.[23] The mixtures of **1a/2a** and **1c/2c** could not be chromatographically separated without substantial losses and were found to darken when exposed to the atmosphere at room temperature for any appreciable time. This is most likely due to oxidation of the samples as both anhydrolycorine (**2a**) and assoanine (**2c**) are known to undergo autoxidation in the presence of air and acid.[19c] However, the obtention of a mixture was not seen as a drawback, but rather, the mixture could be used to obtain either compounds **1** (X=O) or **2** (X=O), Figure 1. Compounds **1** (X=O) could, in principle, be obtained by oxidation of either **1** (X=2H) or **2** (X=2H), whilst compounds **2** (X=O) could be obtained by reduction of **1** (X=2H) to **2** (X=2H) followed by oxidation to give **2** (X=O), Figure 1 and Scheme 2.

Compound **9** was reduced with $NaCNBH_3$ in AcOH at room temperature to give **10** in 54% yield.[40] This product readily decomposed on exposure to the atmosphere but was characterized by ^1H NMR which revealed the presence of two triplets at 2.98 and 3.32 ppm ($J = 7.8$ Hz). As a consequence of the instability of **10** it was decided to try reducing **8a** to give **10**, via the sequence (i) $BH_3 \cdot THF$, (ii) $NaCNBH_3$, AcOH, and to directly oxidize crude **10** to give **11** (Scheme 2). When **8a** was reduced to **10**, in this manner, and then directly oxidized with oxone®, in a mixture of water/acetone and $NaHCO_3$, compound **11** was obtained with a global yield of 30%. The structure of **11** was confirmed spectroscopically. The introduction of the amide carbonyl was observed in the IR (1641 cm^{-1}) and in the ^{13}C NMR (160.1 ppm) and by the disappearance of the C-7 methylene hydrogens. The presence of the indoline methylene groups (C4/C5) was confirmed by the two triplets at 3.38 and 4.47 ppm ($J = 8.2$ Hz). An accurate mass measurement of the molecular ion was consistent with that expected for the structure of **11**.

When compound **8b** was subjected to the same sequence of reactions, with the aim of obtaining anhydrolycorin-7-one (**2b**), an amorphous colourless solid of relatively high melting point (227–243 °C) was obtained. It is suspected that this solid was a mixture of 4,5-dihydropyrrolo-9,10-methylenedioxyphenanthridinium salts though the solid could not be properly characterized. Treatment of this amorphous solid with $KMnO_4$ under basic conditions gave **2b** in a global yield (from **8b**) of 31%, Scheme 3. However, when **8b** was reduced to **2a** then oxidized with $KMnO_4$, anhydrolycorin-7-one (**2b**) was obtained in a global yield of 75%. Applying the same three reaction sequence to **8d** gave oxoassoanine (**2d**) in a global yield of 72%. The spectroscopic and melting point data were found to be consistent with published data.[15,19g,41]

Having secured the syntheses of anhydrolycorin-7-one (**2b**) and oxoassoanine (**2d**) via the air unstable anhydrolycorine (**2a**) and assoanine (**2c**), a formal synthesis of hippadine (**1b**) and pratosine (**1d**), via oxidation with DDQ, was also complete.[4,15,19d,42] However, with the mixtures of **1a/2a** and **1c/2c** it was envisaged that a one pot oxidation could lead to the pyrrolophenanthridinones **1b** and **1d**. Initially, **9** was treated with MnO_2–SiO_2 in refluxing benzene. The volatiles were removed and the solid residue was chromatographed resulting in the isolation of **12** in 53% yield (Scheme 2). Treatment of the mixtures **1a/2a** and **1c/2c**, in a similar manner, resulted in the partial oxidation of the mixtures

where **1b** (35% yield) and **1d** (36% yield) were the only eluted products from the respective reactions. These products were recrystallized from MeOH before spectroscopic analysis. Further elution of the column, in the case of the synthesis of **1b**, using MeOH, resulted in the obtention of an amorphous solid. This solid was treated with $KMnO_4$ under basic conditions resulting in the obtention of **2b** in 21% yield after workup. The products **1b** and **1d** gave compatible analyses with those reported in the literature.[15,41,42]

In conclusion, the natural products **1** (**a**, **b**, **d**) and **2** (**a**, **b**, **c**, and **d**) have been prepared in a concise manner from *N*-benzylisatin derivatives via a palladium catalyzed dehydrohalogenation aryl–aryl coupling reaction. The reaction conditions are based upon those developed by Jeffery[43] for the Heck reaction and permit that the palladium catalyzed reactions occur under milder conditions than those originally reported in similar biaryl coupling reactions.[44] The cyclization of a *meta*-substituted *N*-benzyl-7-haloisatin derivative resulted in a mixture of regioisomers and is therefore only a regioselective route to the natural products or analogues. The syntheses were completed through the use of combined reduction ($BH_3 \cdot THF$ and $NaCNBH_3$) and oxidation ($KMnO_4$) reactions or by oxidation of the products obtained from the borane reduction of the respective **8**. In the case of **2b** and **2d**, global yields of the order of 50% were obtained through a sequence of seven reactions starting from the respective isatin **3** and benzyl chloride **4**.

3. Experimental

3.1. General

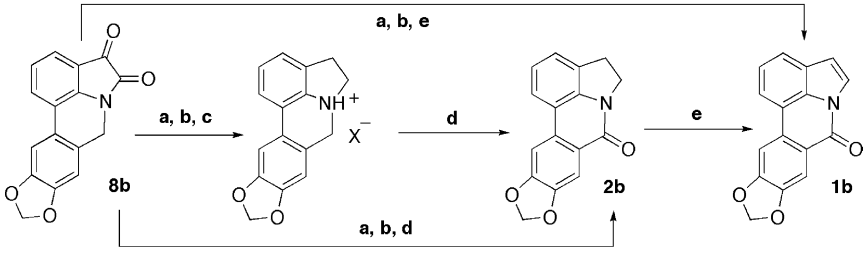
DMF was used as received or distilled under reduced pressure. All other solvents were distilled over standard drying agents under nitrogen before use. 7-Bromo-5-methylisatin was prepared by bromination of 5-methylisatin in 95% ethanol with bromine; 7-iodo-5-methylisatin was prepared by iodination using aqueous $KICl_2$;[45] the benzyl chlorides were prepared by reaction of the respective benzyl alcohol (2-iodo-4,5-methyenedioxybenzyl alcohol,[46] 2-bromo-4,5-methyenedioxybenzyl alcohol,[47] 2-iodo-4,5-dimethoxybenzyl alcohol[48]) with $SOCl_2$ in CH_2Cl_2. MnO_2–SiO_2[49] was prepared according to the indicated literature procedure. All other starting materials were obtained from commercial suppliers and were generally used without further purification. Melting points were determined on a Mel-Temp II-Laboratory Devices Inc, capillary apparatus and are reported as uncorrected values. Column chromatography was performed using silica gel (70–230 mesh, Merck). ^1H and ^{13}C NMR spectra were recorded using Bruker (200 and 300 MHz) spectrometers. The PENDANT pulse sequence was used to distinguish C, CH, CH_2 and CH_3 in the ^{13}C NMR.[50] Mass spectra were obtained by electron impact (70 eV) on a VG Autospec or Hewlett–Packard (GC-MS) spectrometers. Infra-red spectra were recorded using a Perkin–Elmer 1600 FT-IR as KBr discs or films.

3.2. *N*-Benzylisatins

A mixture of the respective isatin (10.0 mmol) and K_2CO_3 (2.00 g, 14.5 mmol) in DMF (10 ml) was stirred with heating (40–60 °C) for 1 h. To the resulting dark coloured suspension were added, the benzyl chloride (11.0 mmol) and KI (0.33 g, 2.0 mmol). Stirring and heating (40–60 °C) were continued until TLC revealed that the reaction had completed. The reaction mixture was hydrolysed with aqueous hydrochloric acid (100 ml, 0.2 mol l^{-1}), extracted with ethyl acetate (4×20 ml) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified by filtration through a short column of silica using CH_2Cl_2. Recrystallization from ethyl acetate/hexane (1:1) gave analytically pure samples.

3.2.1. 1-Benzyl-7-iodo-5-methyl-indole-2,3-dione (5a). Red crystals, 89–94%, mp 145–147 °C. IR (ν_{max}, cm^{-1}): 3052, 2919, 1737, 1612, 1559, 1476, 1436, 1332, 1133, 879, 767, 731. MS (% rel. int.): 377(M^+, 54), 320(6), 286(94), 230(14), 193(9), 165(10), 103(28), 91(100). ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H, CH_3), 5.42 (s, 2H, CH_2-benzyl), 7.18–7.29 (m, 5H, CH-phenyl), 7.42 (d, 1H, J=1.6 Hz, H-4), 7.74 (d, 1H, J=1.6 Hz, H-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.1 (CH_3), 43.69 (CH_2-benzyl), 73.8 (C-7), 120.7 (C), 126.2 (CH), 126.5 (2×CH), 127.6 (CH), 128.9 (2×CH), 136.0 (C), 136.1 (C), 148.8 (C), 151.2 (CH), 159.4 (C-2), 182.9 (C-3). Anal. for $C_{16}H_{12}INO_2$: C 50.95; H 3.21; N 3.71 (calcd); C, 50.91; H, 3.18; N 3.49 (found).

3.2.2. 1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-indole-2,3-dione (5b). Orange crystals, 87–91%, mp 191–192 °C. IR (ν_{max}, cm^{-1}): 3080, 3057, 2924, 2890, 1746, 1732, 1610, 1498, 1471, 1433, 1365, 1346, 1279, 1244, 1175, 1113, 1036, 929, 877, 860, 756. ^1H NMR (200 MHz, $CDCl_3$): δ 4.91 (s, 2H, CH_2-benzyl), 5.96 (s, 2H, OCH_2O), 6.69 (s, 1H, H-6′), 6.81 (d, 1H, J=7.6 Hz, H-7), 7.04 (s, 1H, H-3′), 7.13 (t, 1H, J=7.6 Hz, H-5), 7.53 (t, 1H, J=7.6 Hz, H-6), 7.64 (d, 1H, J=7.6 Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 44.1 (CH_2-benzyl), 102.3 (OCH_2O), 108.2 (CH), 111.4 (CH), 113.1 (CH), 113.6 (C), 117.9 (C), 124.3 (CH), 125.7



Scheme 3. Obtention of anhydrolycorinone (**2b**) and hippadine (**1b**). (a) $BH_3 \cdot THF$ (3 mol equiv); (b) $NaCNBH_3$, AcOH; (c) Oxone™, $NaHCO_3$, H_2O/acetone; (d) $KMnO_4$, NaOH, CH_2Cl_2; (e) MnO_2–SiO_2, benzene, reflux.

(CH), 126.7 (C), 138.8 (CH), 148.4 (C), 148.6 (C), 150.6 (C), 158.6 (C-2), 183.2 (C-3).

3.2.3. 1-(2′-Iodo-4′,5′-methylenedioxybenzyl)-indole-2,3-dione (5c). Orange crystals, 84–92%, mp 191–193 °C. IR (ν_{max}, cm^{-1}): 3076, 2886, 1746, 1732, 1610, 1495, 1471, 1432, 1362, 1347, 1243, 1174, 1035, 927, 756. ^1H NMR (200 MHz, $CDCl_3$): δ 4.91 (s, 2H, CH_2-benzyl), 5.95 (s, 2H, OCH_2O), 6.65 (s, 1H, H-6′), 6.74 (d, 1H, $J=7.5$ Hz, H-7), 7.14 (t, 1H, $J=7.5$ Hz, H-5), 7.29 (s, 1H, H-3′), 7.52 (t, 1H, $J=7.5$ Hz, H-6), 7.64 (d, 1H, $J=7.5$ Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 49.2 (CH_2-benzyl); 85.9 (C-2′), 102.2 (OCH_2O), 107.7 (CH), 111.7 (CH), 117.9 (C), 119.1 (CH), 124.4 (CH), 125.7 (CH), 129.6 (C), 138.8 (CH), 148.6 (C), 149.4 (C), 150.6 (C), 158.6 (C-2), 183.1 (C-3). Anal. for $C_{16}H_{10}INO_4$: C, 47.20; H, 2.48; N, 3.44 (calcd); C, 46.97; H, 2.54; N, 3.27 (found).

3.2.4. 1-(2′-Iodo-4′,5′-dimethoxybenzyl)-indole-2,3-dione (5d). Orange crystals, 90–92%, 173–174 °C. IR (ν_{max}, cm^{-1}): 3079, 2997, 2941, 2837, 1740, 1614, 1504, 1469, 1443, 1345, 1251, 1213, 1162, 1023, 873, 752. MS (% rel. int.): 423(M^+, 7), 296(100), 277(50). ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 4.95 (s, 2H; CH_2-benzyl), 6.70 (s, 1H, H-5′), 6.82 (d, 1H, $J=7.5$ Hz, H-7), 7.15 (t, 1H, $J=7.5$ Hz, H-5), 7.27 (s, 1H, H-2′), 7.51 (t, 1H, $J=7.5$ Hz, H-6), 7.63 (d, 1H, $J=7.5$ Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 49.1 (CH_2-benzyl), 56.2 (CH_3O), 56.4 (CH_3O), 86.4 (C-2′), 110.8 (CH), 112.0 (CH), 117.9 (C), 121.9 (CH), 124.3 (CH), 125.6 (CH), 128.9 (C), 138.8 (CH), 149.7 (C), 150.3 (C), 150.7 (C), 158.7 (C-2), 183.2 (C-3). Anal. for $C_{17}H_{14}INO_4$: C, 48.25; H, 3.33; N, 3.31 (calcd); C, 48.15; H, 3.39; N, 3.42 (found).

3.2.5. 7-Bromo-1-(3′,4′-methylenedioxybenzyl)-5-methyl-indole-2,3-dione (5e). Orange crystals, 85%, mp 157–159 °C. IR (ν_{max}, cm^{-1}): 3061, 2929, 2884, 2790, 1741, 1731, 1619, 1571, 1503, 1480, 1448, 1326, 1248, 1158, 1135, 1037, 928, 816, 801. MS (% rel. int.): 375/373(M^+, 20/21), 240/238(28), 135(100). ^1H NMR (200 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 5.31 (s, 2H, CH_2-benzyl), 5.94 (s, 2H, OCH_2O), 6.75 (m, 3H, H-2′, H-5′ and H-6′), 7.43 (s, 1H, H-4), 7.49 (s, 1H, H-6). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.3 (CH_3), 44.4 (CH_2-benzyl), 101.3 (OCH_2O), 104.2 (C-7), 107.5 (CH), 108.6 (CH), 120.2 (CH), 121.0 (C), 125.6 (CH), 130.0 (C), 135.8 (C), 144.3 (CH), 145.5 (C), 147.3 (C), 148.2 (C), 159.3 (C-2), 182.7 (C-3).

3.2.6. 7-Iodo-1-(3′,4′-methylenedioxybenzyl)-5-methyl-indole-2,3-dione (5f). Orange Crystals, 83%, 165–166 °C. IR (ν_{max}, cm^{-1}): 3059, 2925, 2883, 2789, 1731, 1616, 1502, 1478, 1446, 1326, 1247, 1155, 1137, 1037, 928, 808, 711. ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 5.36 (s, 2H, CH_2-benzyl), 5.94 (s, 2H, OCH_2O), 6.69–6.77 (m, 3H, H-2′, H-5′ and H-6′), 7.46 (s, 1H, H-4), 7.79 (s, 1H, H-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.1 (CH_3), 43.3 (CH_2-benzyl), 73.8 (C-7), 101.3 (OCH_2O), 107.3 (CH), 108.6 (CH), 120.0 (CH), 120.8 (C), 126.3 (CH), 129.7 (C), 136.0 (C), 147.2 (C), 148.2 (C), 148.7 (C), 151.2 (CH), 159.4 (C-2), 182.7 (C-3).

3.2.7. 1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-5-methyl-indole-2,3-dione (5g). Orange crystals, 74%, mp 223–225 °C. IR (ν_{max}, cm^{-1}): 3036, 2980, 2957, 2907, 1736, 1623, 1595, 1503, 1482, 1440, 1359, 1340, 1236, 1113, 1035, 930, 864, 837, 780. ^1H NMR (200 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 4.94 (s, 2H, CH_2-benzyl), 5.95 (s, 2H, OCH_2O), 6.68 (s, 1H, H-6′), 6.69 (d, 1H, $J=7.6$ Hz, H-7), 7.04 (s, 1H, H-3′), 7.33 (d, 1H, $J=7.6$ Hz, H-6), 7.45 (s, 1H, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.9 (CH_3), 44.1 (CH_2-benzyl), 102.2 (OCH_2O), 108.2 (CH), 111.2 (CH), 113.1 (CH), 113.5 (C), 117.9 (C), 126.0 (CH), 126.8 (C), 134.2 (C), 139.2 (CH), 148.3 (C), 148.4 (C), 148.5 (C), 158.7 (C-2), 183.4 (C-3).

3.3. *N*-Benzylisatin ethylenedioxy ketals

The appropriate *N*-benzylisatin (10.0 mmol), ethyleneglycol (10 ml), *p*-toluenesulfonic acid (a few crystals) and toluene (30 ml) were refluxed ($\approx$5 h) with azeotropic removal of water until TLC revealed complete reaction.

On complete reaction the solvent was removed under vacuum, and the residue was treated with aqueous sodium bicarbonate (5%, 30 ml) and extracted with ethyl acetate (4×15 ml). The organic phase was dried with anhydrous sodium sulfate, the solvent removed under reduced pressure and the crude product purified by silica gel column chromatography using CH_2Cl_2 as eluent. The products were recrystallized from ethyl acetate/hexane (1:4).

3.3.1. 1-Benzyl-3,3-ethylenedioxy-7-iodo-5-methyl-indole-2-one (6a). Colourless crystals, 84–94%, 146–147 °C. IR (ν_{max}, cm^{-1}): 3085, 3058, 3030, 2970, 2946, 2905, 1737, 1623, 1567, 1471, 1438, 1414, 1299, 1154, 1038, 999, 945, 866, 725. MS (% rel. int.): 421(M^+, 25), 330(100), 286(37), 91(63). ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H, CH_3), 4.31–4.39 (m, 2H, ketal), 4.54–4.62 (m, 2H, ketal), 5.33 (s, 2H, CH_2-benzyl), 7.15–7.32 (m, 6H, H-4 and 5×CH-phenyl), 7.54 (s, 1H, C-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.3 (CH_3), 43.3 (CH_2-benzyl), 66.2 (2×CH_2-ketal), 72.4 (C-7), 101.1 (C-3), 126.0 (CH), 126.4 (2×CH), 127.2 (CH), 128.8 (2×CH), 135.3 (C), 136.8 (C), 142.1 (C), 144.5 (CH), 174.6 (C-2).

3.3.2. 1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-3,3-ethylenedioxy-indole-2-one (6b). Colourless crystals, 82%, mp 175–177 °C. IR (ν_{max}, cm^{-1}): 3108, 3050, 2979, 2910, 1734, 1621, 1499, 1481, 1468, 1424, 1366, 1321, 1243, 1185, 1131, 1043, 959, 933, 872, 831, 750. ^1H NMR (200 MHz, $CDCl_3$): δ 4.32–4.44 (m, 2H, ketal), 4.55–4.67 (m, 2H, ketal), 4.83 (s, 2H, CH_2-benzyl), 5.92 (s, 2H, OCH_2O), 6.62 (s, 1H, H-6′), 6.67 (d, 1H, $J=7.5$ Hz, H-7), 7.02 (s, 1H, H-3′), 7.08 (dt, 1H, $J=1.2$, 7.5 Hz, H-5), 7.29 (dt, 1H, $J=1.2$, 7.5 Hz, H-6), 7.40 (dd, 1H, $J=1.2$, 7.5 Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 43.4 (CH_2-benzyl), 66.1 (2×CH_2-ketal), 102.0 (OCH_2O), 102.4 (C-3), 108.0 (CH), 109.9 (CH), 112.9 (CH), 113.3 (C), 123.8 (CH), 124.1 (C), 125.1 (CH), 127.4 (C), 131.9 (CH), 143.6 (C), 148.1 (C), 148.2 (C), 173.8 (C-2).

3.3.3. 1-(2′-Iodo-4′,5′-methylenedioxybenzyl)-3,3-ethylenedioxy-indole-2-one (6c). Colourless crystals, 88–95%, mp 191–193 °C. IR (ν_{max}, cm^{-1}): 3095, 3043, 2975, 2906, 1731, 1622, 1497, 1478, 1467, 1422, 1362, 1247, 1185, 1129, 1044, 960, 931, 750. ^1H NMR (300 MHz,

$CDCl_3$): δ 4.33–4.45 (m, 2H, ketal), 4.55–4.67 (m, 2H, ketal), 4.77 (s, 2H, CH_2-benzyl), 5.92 (s, 2H, OCH_2O), 6.59 (s, 1H, H-6′), 6.62 (d, 1H, J=7.6 Hz, H-7), 7.09 (t, 1H, J=7.6 Hz, H-5), 7.27 (s, 1H, H-3′), 7.29 (t, 1H, J=7.6 Hz, H-6), 7.40 (d, 1H, J=7.6 Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 48.6 (CH_2-benzyl), 66.1 (2×CH_2-ketal), 85.6 (C-2′), 102.0 (OCH_2O), 102.5 (C-3), 107.7 (CH), 110.2 (CH), 118.9 (CH), 123.8 (CH), 124.1 (C), 125.1 (CH), 130.4 (C), 132.0 (CH), 143.6 (C), 148.3 (C), 149.3 (C), 173.7 (C-2). Anal. for $C_{18}H_{14}INO_5$: C, 47.91; H, 3.13; N, 3.10 (calcd); C, 48.23; H, 3.31; N, 3.23 (found).

3.3.4. 1-(2′-Iodo-4′,5′-dimethoxybenzyl)-3,3-ethylenedioxy-indole-2-one (6d). Colourless crystals, 93–94%, mp 130–131 °C. IR (ν_{max}, cm^{-1}): 3088, 2966, 2906, 2842, 1721, 1617, 1507, 1464, 1445, 1372, 1250, 1211, 1161, 1126, 1022, 946, 865, 762. MS (% rel. int.): 467(M^+, 2), 340(100), 277(22), 190(73), 146(37). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 4.34–4.38 (m, 2H, ketal), 4.61–4.66 (m, 2H, ketal), 4.81 (s, 2H, CH_2-benzyl), 6.59 (s, 1H, H-6′), 6.65 (d, 1H, J=7.6 Hz, H-7), 7.10 (t, 1H, J=7.6 Hz, H-5), 7.23 (s, 1H, H-3′), 7.25 (t, 1H, J=7.6 Hz, H-6), 7.39 (d, 1H, J=7.6 Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 48.2 (CH_2-benzyl), 56.0 (CH_3O), 56.4 (CH_3O), 66.1 (2×CH_2-ketal), 85.8 (C-2′), 102.6 (C-3), 110.3 (2×CH), 121.8, 123.8, 124.1, 125.0, 129.6, 131.9, 143.6 (C), 149.2 (C), 150.1 (C), 173.9 (C-2).

3.3.5. 7-Bromo-3,3-ethylenedioxy-1-(3′,4′-methylenedioxybenzyl)-5-methyl-indole-2-one (6e). Colourless crystals, 98%, mp 115–116 °C. IR (ν_{max}, cm^{-1}): 2974, 2901, 1732, 1625, 1500, 1479, 1444, 1304, 1244, 1156, 1039, 1000, 942, 916, 858, 798. MS (% rel. int.): 419/417(M^+, 14/15), 284/282(100/98), 238/240(35), 135(91), 103(18), 77(41). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, CH_3), 4.22–4.38 (m, 2H, ketal), 4.53–4.64 (m, 2H, ketal), 5.18 (s, 2H, CH_2-benzyl), 5.90 (s, 2H, OCH_2O), 6.66–6.74 (m, 3H, H-2′, H-5′, H-6′), 7.16 (s, 1H, H-4), 7.24 (s, 1H, H-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.5 (CH_3), 43.9 (CH_2-benzyl), 66.2 (2×CH_2-ketal), 101.4 (C-3), 102.8 (C and OCH_2O), 107.3 (CH), 108.5 (CH), 119.8 (CH), 125.2 (CH), 127.4 (C), 130.8 (C), 135.1 (C), 137.5 (CH), 138.9 (C), 146.9 (C) 148.0 (C), 174.4 (C-2).

3.3.6. 3,3-Ethylenedioxy-7-iodo-1-(3′,4′-methylenedioxybenzyl)-5-methyl-indole-2-one (6f). Colourless crystals, 90–92%, mp 129–131 °C. IR (ν_{max}, cm^{-1}): 2970, 2944, 2891, 1733, 1619, 1492, 1473, 1437, 1328, 1243, 1154, 1037, 1001, 948, 854, 813, 737. MS (% rel. int.): 465(M^+, 13), 330(100), 286(30), 135(39), 77(14). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 4.31–4.36 (m, 2H, ketal), 4.57–4.62 (m, 2H, ketal), 5.23 (s, 2H, CH_2-benzyl), 5.92 (s, 2H, OCH_2O), 6.64 (d, 1H, J=8.0 Hz, H-5′), 6.69 (s, 1H, H-2′), 6.74 (d, 1H, J=8.0 Hz, H-6′), 7.20 (d, 1H, J=1.0 Hz, H-6), 7.56 (d, 1H, J=1.0 Hz, H-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.3 (CH_3), 43.0 (CH_2-benzyl), 66.1(2×CH_2-ketal), 72.4 (C-7), 101.1 (C-3), 101.2 (OCH_2O), 107.2 (CH), 108.5 (CH), 119.6 (CH), 126.0 (CH), 127.2 (C), 130.5 (C), 135.3 (C), 142.0 (C), 144.5 (CH), 146.8 (C), 148.1 (C), 174.6 (C-2).

3.3.7. 1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-3,3-ethylenedioxy-5-methyl-indole-2-one (6g). Colourless crystals, 89%, mp 218–220 °C. IR (ν_{max}, cm^{-1}): 3073, 2964, 2904, 1733, 1635, 1605, 1500, 1484, 1429, 1359, 1300, 1273, 1239, 1181, 1112, 1036, 998, 932, 853, 821, 736. MS (% rel. int.): 419/417(M^+, 1/1), 338(86), 238(23), 215(14), 204(100), 160(47), 104(16), 77(12). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 4.34–4.37 (m, 2H, ketal), 4.60–4.63 (m, 2H, ketal), 4.81 (s, 2H, CH_2-benzyl), 5.92 (s, 2H, OCH_2O), 6.55 (d, 1H, J=8.0 Hz, H-7), 6.60 (s, 1H, H-6′), 7.01 (s, 1H, H-3′), 7.08 (dd, 1H, J=1.0, 8.0 Hz, H-6), 7.22 (d, 1H, J=1.0 Hz, H-4). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.1 (CH_3), 43.5 (CH_2-benzyl), 66.1 (2×CH_2-ketal), 102.1 (OCH_2O), 102.6 (C-3), 108.0 (CH), 109.8 (CH), 112.9 (CH), 113.3 (C), 124.0 (C), 125.8, 127.6, 132.2, 133.6, 141.2 (C-7a), 148.1 (C), 148.2 (C), 173.8 (C-2). Anal. for $C_{19}H_{16}BrNO_5$: C, 54.56; H, 3.86; N, 3.35 (calcd); C, 54.80; H, 4.01; N, 3.46 (found).

3.4. Palladium catalysed coupling reactions

The appropriate *N*-benzylisatin ketal (1.0 mmol), $Pd(OAc)_2$ (23.0 mg, 0.1 mmol), Bu_4NBr (322 mg, 1.1 mmol), KOAc (490.0 mg, 5.0 mmol) and DMF (10 ml) were heated on an oil bath (100 °C, bath temp) in a round bottom flask and the reaction accompanied by TLC. On complete reaction, distilled water (50 ml) was added to the reaction mixture which was then extracted with ethyl acetate (4×15 ml). The organic phase was dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column using hexane/ethyl acetate (4:1) as eluent. Products could be recrystallized from MeOH/H_2O.

3.4.1. 4,4-Ethylenedioxy-6,7-dihydro-2-methyl-pyrrolo[3,2,1-*de*]phenanthridin-5-one (7a). White crystals, 96–98%, 191–193 °C. IR (ν_{max}, cm^{-1}): 3058, 2975, 2954, 2889, 1719, 1636, 1500, 1449, 1349, 1268, 1204, 1054, 1029, 1000, 949, 864, 774, 741. MS (% rel. int.): 293(M^+, 33), 264(100), 220(29), 193(27), 192(22), 165(17), 110(31), 96(29), 82(28). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 4.29–4.34 (m, 2H, ketal), 4.57–4.61 (m, 2H, ketal), 4.91 (s, 2H, H-7), 7.07 (s, 1H, H-3), 7.12 (d, 1H, J=7.3 Hz, H-8), 7.23 (t, 1H, J=7.3 Hz, H-9), 7.29 (t, 1H, J=7.3 Hz, H-10), 7.45 (s, 1H, H-1), 7.70 (d, 1H, J=7.3 Hz, H-11). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.6 (CH_3), 42.4 (CH_2-benzyl), 66.0 (2×CH_2-ketal), 103.4 (C), 117.2 (C), 122.4 (CH), 122.7 (C), 124.6 (CH), 125.1 (CH), 127.8 (CH), 128.1 (CH), 128.3 (C), 128.5 (CH), 128.9 (C), 133.3 (C), 137.1 (C), 172.9 (C-5). Anal. for $C_{18}H_{15}NO_3$: C 73.71, H 5.15, N 4.76 (calcd); C 73.23, H 5.04, N 4.62 (found).

3.4.2. 4,4-Ethylenedioxy-6,7-dihydro-9,10-methylenedioxy-pyrrolo[3,2,1-*de*]phenanthridin-5-one (7b). White crystals, 69–95%, 226–228 °C (decomp.). IR (ν_{max}, cm^{-1}): 3047, 2969, 2900, 1716, 1638, 1508, 1475, 1369, 1238, 1188, 1153, 1042, 1020, 939, 885, 787, 744. MS (% rel. int.): 323(M^+, 42), 294(100), 250(37), 223(27), 222(18), 164(23), 138(14), 124(30), 110(14), 96(43), 82(39), 69(25). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.31–4.39 (m, 2H, ketal), 4.54–4.61 (m, 2H, ketal), 4.88 (s, 2H, H-7), 6.00 (s, 2H, OCH_2O), 6.61 (s, 1H, H-8), 7.03 (t, 1H, J=7.6 Hz, H-2), 7.18 (s, 1H, H-11), 7.19 (d, 1H, J=7.6 Hz, H-3), 7.49 (d, 1H, J=7.6 Hz, H-1). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 42.9 (CH_2-benzyl), 66.0 (2×CH_2-ketal), 101.8 (OCH_2O), 102.9

(CH), 103.5 (C), 107.8 (CH), 117.8 (C), 122.3 (C), 122.6 (C), 122.7 (C), 123.7 (CH), 123.80 (CH), 123.85 (CH), 139.0 (C), 148.1 (C), 148.3 (C), 173.1 (C-5). HRMS for $C_{18}H_{13}NO_5$: 323.0794 (calcd); 323.0796 (found).

3.4.3. 4,4-Ethylenedioxy-6,7-dihydro-9,10-dimethoxy-pyrrolo[3,2,1-*de*]phenanthridin-5-one (7d). White crystals, 81–87%, mp 188–190 °C. IR (ν_{max}, cm^{-1}): 3067, 2966, 2909, 2839, 1719, 1635, 1613, 1531, 1467, 1407, 1358, 1255, 1217, 1185, 1149, 1048, 1002, 940, 854, 780, 737. MS (% rel. int.): 339(M^+, 42), 310(100), 266(21), 239(28). ^1H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3O), 4.31–4.39 (m, 2H, ketal), 4.54–4.65 (m, 2H, ketal), 4.88 (s, 2H, H-7), 6.60 (s, 1H, H-8), 7.03 (t, 1H, J=7.5 Hz, H-2), 7.16 (s, 1H, H-11), 7.18 (d, 1H, J=7.5 Hz, H-3), 7.53 (d, 1H, J=7.5 Hz, H-1). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 42.4 (C-7), 56.20 and 56.21(2×CH_3O), 66.0 (2×CH_2-ketal), 103.4 (C), 105.4 (CH), 110.3 (C-H), 117.8 (C), 120.8 (C), 121.4 (C) 122.6 (C), 123.5 (CH), 123.6 (CH), 123.7 (CH), 139.0 (C), 148.9 (C), 149.6 (C), 173.1 (C-5). HRMS for $C_{19}H_{17}NO_5$: 339.1107 (calcd); 339.1107 (found).

3.4.4. 4,4-Ethylenedioxy-6,7-dihydro-2-methyl-9,10-methylenedioxy-pyrrolo[3,2,1-*de*]phenanthridin-5-one (7e). White crystals, 24–43%, 243–245 °C. IR (ν_{max}, cm^{-1}): 3064, 2972, 2905, 2856, 1713, 1640, 1501, 1470, 1391, 1363, 1239, 1199, 1154, 1052, 1031, 997, 946, 931, 864, 848, 830, 748. MS (% rel. int.): 337(M^+, 34), 308(100), 264(24), 237(26), 131(16), 103(13). ^1H NMR (200 MHz, $CDCl_3$/DMSO-d_6): δ 2.27 (s, 3H, CH_3), 4.20–4.26 (m, 2H, ketal), 4.42–4.49 (m, 2H, ketal), 4.77 (s, 2H, H-7), 5.93 (s, 2H, OCH_2O), 6.56 (s, 1H, H-8), 6.93 (s, 1H, H-3), 7.14 (s, 1H, H-1), 7.52 (s, 1H, H-11). ^{13}C NMR (50.3 MHz, $CDCl_3$/DMSO-d_6): δ 20.8 (CH_3), 42.0 (C-7), 65.2 (2×CH_2-ketal), 101.0 (OCH_2O), 102.0 (CH), 102.9 (C), 107.0 (CH), 116.7 (C), 121.5 (C), 121.8 (C), 122.0 (C), 123.4 (CH), 123.5 (CH), 132.5 (C), 147.4 (C), 147.5 (C), 172.1 (C-5). Anal. for $C_{19}H_{15}NO_5$: C 67.65, H 4.48, N 4.15 (calcd.); C 67.59, H 4.53, N 4.27 (found).

3.4.5. 4,4-Ethylenedioxy-6,7-dihydro-2-methyl-10,11-methylenedioxy-pyrrolo[3,2,1-*de*]phenanthridin-5-one (7e′). White crystals, 74%, 217–219 °C. IR (ν_{max}, cm^{-1}): 3032, 2968, 2904, 1724, 1635, 1506, 1494, 1463, 1442, 1366, 1272, 1247, 1198, 1111, 1064, 1022, 948, 927, 869, 794, 711. MS (% rel. int.): 337(M^+, 28), 308(100), 264(25), 237(21). ^1H NMR (200 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 4.25–4.31 (m, 2H, ketal), 4.36–4.42 (m, 2H, ketal), 4.81 (s, 2H, H-7), 6.18 (s, 2H, OCH_2O), 6.80 (d, 1H; J=8.0 Hz, H-8), 6.89 (d; 1H; J=8.0 Hz, H-9), 7.14 (s, 1H, H-3), 7.74 (s, 1H, H-1). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 21.6 (CH_3), 42.7 (C-7), 66.2 (2×CH_2-ketal), 102.3, 103.2, 108.7, 112.0, 115.1, 121.4, 123.1, 123.6, 125.5, 128.4, 133.2, 137.0, 144.7, 147.6, 172.6 (C-5). Anal. for $C_{19}H_{15}NO_5$: C 67.65, H 4.48, N 4.15 (calcd.); C 67.59, H 4.53, N 4.27 (found).

3.5. 6,7-Dihydro-pyrrolo[3,2,1-*de*]phenanthridin-4,5-diones

4,4-Ethylenedioxy-6,7-dihydro-pyrrolo[3,2,1-*de*]phenanthridin-5-ones (3 mmol), THF (10.0 ml) and aqueous HCl (6 mol l^{-1}, 10.0 ml) were heated at reflux for 5 h. The THF was removed under reduced pressure resulting in the precipitation of red crystals. These were removed by filtration, washed with distilled water and air dried.

3.5.1. 6,7-Dihydro-2-methyl-pyrrolo[3,2,1-*de*]phenanthridin-4,5-dione (8a). Dark red crystals, 94–96%, mp 237–238 °C. IR (ν_{max}, cm^{-1}): 3059, 2920, 2862, 1731, 1626, 1491, 1355, 1305, 1122, 767. MS (% rel. int.): 249(M^+, 47), 220(100), 193(34), 192(35), 165(27), 110(21), 95(41). ^1H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, CH_3), 5.01 (s, 2H, H-7), 7.15 (d, 1H, J=7.2 Hz, H-8), 7.22 (s, 1H, H-3), 7.31 (td, 1H, J=1.3, 7.2 Hz, H-9), 7.36 (t, 1H, J=7.2 Hz, H-10), 7.67 (s, 1H, H-1), 7.74 (dd, 1H, J=1.3, 7.2 Hz, H-11). ^1H NMR (300 MHz, DMSO-d_6): δ 2.30 (s, 3H, CH_3), 4.94 (s, 2H, H-7), 7.22 (s, 1H, H-3), 7.29–7.36 (m, 3H, H-8, H-9 and H-10), 7.93 (d, 1H, J=7.8 Hz, H-11), 7.95 (s, 1H, H-1). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 21.0 (CH_3), 42.3 (C-7), 116.7 (C), 118.2 (C), 123.1 (CH), 124.5 (CH), 127.2 (C), 128.4 (CH), 128.6 (CH), 129.4 (CH), 129.5 (C), 131.3 (CH), 133.3 (C), 144.9 (C), 158.2 (C-5), 183.7 (C-4). Anal. for $C_{16}H_{11}NO_2$: C 77.10, H 4.45, N 5.62 (calcd.); C 77.19, H 4.41, N 5.71 (found).

3.5.2. 6,7-Dihydro-9,10-methylenedioxy-pyrrolo[3,2,1-*de*]phenanthridin-4,5-dione (8b). Dark red crystals, 92%, mp 235–237 °C. IR (ν_{max}, cm^{-1}): 3053, 2919, 2852, 2780, 1732, 1632, 1598, 1507, 1476, 1426, 1388, 1356, 1308, 1239, 1201, 1036, 1020, 927, 867, 775. MS (% rel. int.): 279(M^+, 53), 250(100), 223(25), 164(15). ^1H NMR (200 MHz, Acetone-d_6): δ 5.00 (s, 2H, H-7), 6.09 (s, 2H, OCH_2O), 6.90 (s, 1H, H-8), 7.11 (t, 1H, J=7.7 Hz, H-2), 7.35 (d, 1H, J=7.7 Hz, H-3), 7.48 (s, 1H, H-11), 7.99 (d, 1H, J=7.7 Hz, H-1). ^1H NMR (200 MHz, CD_3CN): δ 5.48 (s, 2H, H-7), 6.58 (s, 2H, OCH_2O), 7.33 (s, 1H, H-8), 7.63 (t, 1H, J=7.6 Hz, H-2), 7.90 (d, 1H, J=7.6 Hz, H-3), 7.91 (s, 1H, H-11), 8.40 (d, 1H, J=7.6 Hz, H-1). ^1H NMR (200 MHz, DMSO-d_6): δ 4.89 (s, 2H, H-7), 6.08 (s, 2H, OCH_2O), 6.94 (s, 1H, H-8), 7.04 (t, 1H, J=7.6 Hz, H-2), 7.33 (d, 1H, J=7.6 Hz, H-3), 7.58 (s, 1H, H-11), 8.01 (d, 1H, J=7.6 Hz, H-1). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 42.6 (C-7), 102.1 (OCH_2O), 103.5 (CH), 108.4 (CH), 116.5 (C), 118.8 (C), 121.2 (C), 123.3 (CH), 123.6 (C), 123.8 (CH), 130.5 (CH), 146.5 (C), 148.1 (C), 148.5 (C), 158.3 (C-5), 183.6 (C-4). HRMS for $C_{16}H_9NO_4$: 279.0532 (calcd); 279.0532 (found).

3.5.3. 6,7-Dihydro-9,10-dimethoxy-pyrrolo[3,2,1-*de*]-phenanthridin-4,5-dione (8d). Dark red crystals, 86–92%, mp 240–242 °C. IR (ν_{max}, cm^{-1}): 3028, 2989, 2924, 2856, 1743, 1726, 1625, 1610, 1525, 1465, 1444, 1359, 1259, 1219, 1147, 1057, 976, 861, 779, 754, 742. MS (% rel. int.): 295(M^+, 89), 266(100), 239(24), 213(16), 196(10), 153(14), 127(14). ^1H NMR (300 MHz, $CDCl_3$/DMSO-d_6): δ 3.88 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.99 (s, 2H, H-7), 6.71 (s, 1H, H-8), 7.07 (t, 1H, J=7.7 Hz, H-2), 7.26 (s, 1H, H-11), 7.32 (d, 1H, J=7.7 Hz, H-3), 7.85 (d, 1H, J=7.7 Hz, H-1). ^1H NMR (200 MHz, DMSO-d_6): δ 3.78 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.90 (s, 2H, H-7), 6.94 (s, 1H, H-8), 7.06 (t, 1H, J=7.5 Hz, H-3), 7.33 (d, 1H, J=7.5 Hz, H-3), 7.46 (s, 1H, H-11), 8.10 (d, 1H, J=7.5 Hz, H-1). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 42.2 (C-7), 56.1 (OCH_3), 56.3 (OCH_3), 106.6 (CH), 111.5 (CH), 116.5 (C), 119.0 (C),

119.5 (C), 121.8 (C), 123.0 (CH), 123.7 (CH), 130.5 (CH), 146.5 (C), 149.1 (C), 150.1 (C), 158.3 (C-5), 183.7 (C-4). Anal. for $C_{17}H_{13}NO_4$: C 69.15, H 4.44, N 4.74 (calcd.); C 69.11, H 4.46, N 4.81 (found).

3.6. Alkaloids

3.6.1. Reduction with BH_3–THF. The appropriate pyrrolophenanthridin-4,5-dione (1.0 mmol) was dissolved in anhydrous THF (5 ml) and cooled on an ice water bath under a slowly flowing nitrogen atmosphere. A solution of $BH_3\cdot$THF (1 mol l^{-1}, 3.0 mmol) was added dropwise by syringe to the stirred reaction. The reaction was monitored by TLC and on complete reaction aqueous HCl (3.0 mol l^{-1}, 3 ml) was added dropwise. The mixture was subsequently neutralized with aqueous NaOH (10%), saturated aqueous NaCl was added and the mixture extracted with CH_2Cl_2(3×15 ml). The organic phase was further washed with water (1×15 ml), dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was chromatographed on a silica gel column using dichloromethane/hexane (2:1) as eluent.

3.6.1.1. 6,7-Dihydro-2-methyl-pyrrolo[3,2,1-*de*]-phenanthridine (9). White crystals, 90–92%, mp 135–137 °C. IR (ν_{max}, cm^{-1}): 3099, 3031, 2919, 2857, 1508, 1451, 1385, 1329, 1271, 1210, 854, 778, 755, 714. MS (% rel. int.): 219(M^+, 54), 218(100), 108(23). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 5.50 (s, 2H, H-7), 6.43 (d, 1H, J=2.9 Hz, H-4), 7.07 (d, 1H, J=2.9 Hz, H-5), 7.14 (d, 1H, J=7.5 Hz, H-8), 7.21–7.32 (m, 4H, H-1, H-3, H-9, H-10), 7.89 (d, 1H, J=7.5 Hz, H-11). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.1 (CH_3), 48.0 (C-7), 102.0 (CH), 115.4 (CH), 118.1 (C), 120.4 (CH), 122.8 (CH), 126.2 (CH), 126.4 (C), 127.4 (CH), 127.8 (CH), 127.9 (CH), 129.7 (C), 130.3 (C), 130.5 (C), 132.2 (C). HRMS for $C_{16}H_{13}N$: 219.1048 (calcd); 219.1050 (found).

3.6.2. Reduction with $NaCNBH_3$–AcOH. To the crude product (~1 mmol) from the $BH_3\cdot$THF reduction reaction was added $NaCNBH_3$ (189.0 mg, 3 mmol) and the mixture was cooled to 10 °C. Acetic acid (3 ml) was added dropwise and the mixture was stirred at room temperature. After 3 h, the mixture was cooled on an ice bath, neutralized with aqueous NaOH (10%) and extracted with dichloromethane (4×15 ml). Evaporation of the solvent under reduced pressure gave the crude product. This was quickly filtered through a short column of silica eluting with CH_2Cl_2. Evaporation of the solvent gave the product.

3.6.2.1. 4,5,6,7-Tetrahydro-2-methyl-pyrrolo[3,2,1-*de*]phenanthridine (10). A semi-solid material that rapidly darkened when exposed to the atmosphere. ^{1}H NMR (200 MHz, $CDCl_3$): 2.31 (s, 3H, CH_3), 2.98 (t, 2H, J=7.8 Hz, H-4,), 3.32 (t, 2H, J=7.8 Hz, H-5), 4.10 (s, 2H, H-7), 6.88 (s, 1H, H-3), 7.11–7.33 (m, 4H, H-1, H-8, H-9, H-10), 7.66 (d, 1H, J=7.4 Hz, H-11).

3.6.3. Reduction with $NaCNBH_3$ and subsequent oxidation with Oxone™. To the crude product from the reduction reaction using $BH_3\cdot$THF (~1 mmol) was added $NaCNBH_3$ (189.0 mg, 3 mmol) and the mixture cooled to 10 °C. Acetic acid (3 ml) was added dropwise and the mixture was stirred at room temperature. After 3 h, the mixture was cooled on an ice bath, neutralized with aqueous NaOH (10%) and extracted with dichloromethane (4×15 ml).

The solvent was removed under reduced pressure, $NaHCO_3$ (252.0 mg, 3 mmol) and acetone (3.0 ml) were added. Oxone® (650.0 mg, 1.0 mmol) was slowly added to the mixture and stirred to room temperature. After 30 min, isopropanol (1 ml) was added, and solvent was removed under vacuum. The residue was chromatographed on silica gel column using heptane/dichloromethane (1:1) as eluent and the product recrystallized from methanol/water (1:1).

3.6.3.1. 4,5-Dihydro-2-methyl-pyrrolo[3,2,1-*de*]-phenanthridin-7-one (11). White crystals, 32%, mp 197–200 °C. IR (ν_{max}, cm^{-1}): 3069, 3030, 2964, 2915, 2856, 1641, 1624, 1600, 1504, 1366, 1344, 1287, 1181, 1032, 888, 854, 766, 722, 689. MS (% rel. int.): 235(M^+, 100), 234(99), 219(20). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 3.38 (t, 2H, J=8.2 Hz, H-4), 4.47 (t, 1H, J=8.2 Hz, H-5), 7.15 (s, 1H, H-3), 7.57 (td, 1H, J=1.0, 7.8 Hz, H-10), 7.70 (s, 1H, H-1), 7.74 (td, 1H, J=1.0, 7.8 Hz, H-9), 8.18 (d, 1H, J=7.8 Hz, H-8), 8.54 (dd, 1H, J=1.0, 7.8 Hz, H-11). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.9 (CH_3), 27.5 (C-4), 46.8 (C-5), 116.6 (C), 120.0 (CH), 122.2 (CH), 126.0 (CH), 127.6 (C), 127.9 (CH), 128.6 (CH), 131.0 (C), 132.1 (CH), 133.3 (C), 134.0 (C), 138.0 (C), 160.1 (C-7). HRMS for $C_{16}H_{13}NO$: 235.0997 (calcd); 235.0994 (found).

3.6.4. Reduction with $NaCNBH_3$ and subsequent oxidation with $KMnO_4$. To the crude product (~1 mmol) from the $BH_3\cdot$THF reduction reaction was added $NaCNBH_3$ (189.0 mg, 3.0 mmol) and the mixture was cooled to 10 °C. Acetic acid (3 ml) was added dropwise and the mixture was stirred at room temperature. After 3 h, the mixture was cooled on an ice bath, neutralized with aqueous NaOH (10%) and extracted with dichloromethane (4×15 ml).

The organic phase was concentrated (~10 ml), aqueous NaOH (3 mol l^{-1}, 10 ml) and $KMnO_4$ (316.0 mg, 2.0 mmol) were added. The suspension was stirred vigorously at room temperature for 2 h, filtered through Celite and extracted with dichloromethane (3×15 ml). The organic phase was washed with aqueous Na_2SO_3 (5% w/v, 15 ml), with distilled water (1×15 ml) and dried over Na_sSO_4. The solvent was removed under vacuum. The residue was chromatographed on a silica gel column using dichloromethane/methanol (9:1) as eluent and the product was recrystallized from methanol/water (1:1).

3.6.4.1. 4,5-Dihydro-9,10-dimethoxy-pyrrolo[3,2,1-*de*]phenanthridin-7-one (Oxoassoanine) (2d). White crystals, 68–75%, mp 267–268 °C (lit.: 266–269[15]; 266–267[19g] °C). IR (ν_{max}, cm^{-1}): 3063, 3016, 3005, 2839, 1644, 1607, 1521, 1478, 1436, 1364, 1303, 1273, 1210, 1125, 1030, 870, 777, 766. MS (% rel. int.): 281(M^+, 100), 280(31), 266(12), 238(20). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.43 (t, 2H, J=8.2 Hz, H-4), 4.04 (s, 3H, OCH_3), 4.08 (s, 3H, CH_3), 4.44 (t, 2H, J=8.2 Hz, H-5), 7.21 (t, 1H, J=7.5 Hz, H-2), 7.30 (d, 1H, J=7.5 Hz, H-3), 7.52 (s, 1H,

H-8), 7.80 (d, 1H, J=7.5 Hz, H-1), 7.93 (s, 1H, H-11). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.6 (C-4), 46.7 (C-5), 56.3 (OCH_3), 56.4 (OCH_3), 103.1 (CH), 108.9 (CH), 116.9 (C), 119.3 (CH), 121.5 (C), 123.3 (CH), 123.7 (CH), 128.6 (C), 131.1 (C), 139.5 (C), 149.8 (C), 153.0 (C), 159.8 (C-7).

3.6.4.2. 4,5-Dihydro-9,10-methylenedioxy-pyrrolo-[3,2,1-*de*]phenanthridin-7-one (Anhydrolycorin-7-one) (2b). White crystals, 75%, mp 228–229 °C (lit.: 231–232[19g]; 230–231[20e,g]; 228–230[41] °C). IR (ν_{max}, cm^{-1}): 3057, 2968, 2908, 1643, 1614, 1587, 1505, 1484, 1468, 1393, 1370, 1352, 1257, 1035, 933, 857, 763. MS (% rel. int.): 265(M$^+$, 100), 264(92), 234(7), 206(18), 178(19). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.42 (t, 2H, J=8.2 Hz, H-4), 4.47 (t, 2H, J=8.2 Hz, H-5), 6.13 (s, 2H, OCH_2O), 7.19 (t, 1H, J=7.7 Hz, H-2), 7.29 (d, 1H, J=7.7 Hz, H-3), 7.53 (s, 1H, H-8), 7.73 (d, 1H, J=7.7 Hz, H-1), 7.90 (s, 1H, H-11). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.6 (C-4), 46.6 (C-5), 101.0 (CH), 102.2 (OCH_2O), 106.9 (CH), 116.9 (C), 119.5 (CH), 123.1 (C), 123.4 (CH), 123.9 (CH), 130.7 (C), 131.0 (C), 139.4 (C), 148.5 (C) 151.9 (C), 159.6 (C-7).

3.6.5. Oxidation with MnO_2–SiO_2. To the crude product ($\sim$1 mmol) from the BH_3·THF reduction reaction was added MnO_2–SiO_2 (3.0 mmol of MnO_2) and solvent (15 ml of anhydrous benzene or THF). The suspension was heated under reflux for 4 h, the solvent was removed and the residue was chromatographed on a short silica gel column using dichloromethane/methanol (20:1) as eluent. The solids were recrystallized from methanol.

3.6.5.1. 9,10-Methylenedioxy-pyrrolo[3,2,1-*de*]-phenanthridin-7-one (Hippadine) (1b). White crystals, 35%, mp 217–218 °C (lit.: 217–218[15,41] °C). IR (ν_{max}, cm^{-1}): 3148, 2958, 2920, 2850, 1672, 1618, 1526, 1479, 1458, 1392, 1365, 1312, 1285, 1243, 1118, 1029, 932, 878, 801, 765, 722. MS (% rel. int.): 263(M$^+$, 100), 205(6), 177(24), 150(12). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.15 (s, 2H, OCH_2O), 6.88 (d, 1H, J=3.4 Hz, H-4), 7.45 (t, 1H, J=7.7 Hz, H-2), 7.61 (s, 1H, H-11), 7.73 (d, 1H, J=7.7 Hz, H-3), 7.88 (d, 1H, J=7.7 Hz, H-1), 7.95 (s, 1H, H-8), 8.02 (d, 1H, J=3.4 Hz, H-5). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 101.8 (CH), 102.5 (OCH_2O), 108.1 (CH), 110.9 (CH), 116.8 (C), 118.5 (CH), 122.6 (C), 122.7 (CH), 123.7 (CH), 124.1 (CH), 128.5 (C), 131.1 (C), 131.7 (C), 148.6 (C), 152.7 (C), 158.3 (C-7).

3.6.5.2. 9,10-Dimethoxy-pyrrolo[3,2,1-*de*]phenanthridin-7-one (Pratosine) (1d). White crystals, 32–36%, mp 233–234 °C (lit.: 234–235[15] °C). IR (ν_{max}, cm^{-1}): 3149, 3111, 3006, 2936, 2836, 1668, 1603, 1529, 1509, 1440, 1363, 1314, 1273, 1213, 1142, 1105, 1001, 870, 765. MS (% rel. int.): 279(M$^+$, 100), 264(16), 236(37), 221(14), 193(15), 165(15). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.05 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 6.88 (d, 1H, J=3.4 Hz, H-4), 7.45 (t, 1H, J=7.6 Hz, H-2), 7.58 (s, 1H, H-11), 7.73 (d, 1H, J=7.6 Hz, H-3), 7.91 (d, 1H, J=7.6 Hz, H-1), 7.94 (s, 1H, H-8), 8.03 (d, 1H, J=3.4 Hz, H-5). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 56.4(2×OCH_3), 103.8 (CH), 110.1 (CH), 110.8 (CH), 116.8 (C), 118.2 (CH), 120.8 (C), 122.5 (CH), 123.6 (CH), 124.0 (CH), 128.6 (C), 129.5 (C), 131.2 (C), 149.7 (C), 153.7 (C), 158.5 (C-7).

3.6.5.3. 2-Methyl-pyrrolo[3,2,1-*de*]phenanthridin-7-one (12). White crystals, 40–53%, mp 157–158 °C. IR (ν_{max}, cm^{-1}): 3132, 3099, 3073, 2922, 2858, 1676, 1634, 1595, 1484, 1449, 1385, 1353, 1304, 1292, 1174, 1151, 847, 787, 759, 728, 691. MS (% rel. int.): 233(M$^+$, 100), 232(80), 204(10), 176(9). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.60 (s, 3H, CH_3), 6.83 (d, 1H, J=3.6 Hz, H-4), 7.55 (s, 1H, H-3), 7.60 (td, 1H, J=1.1, 8.0 Hz, H-9), 7.78 (td, 1H, J=1.1, 8.0 Hz, H-10), 7.82 (s, 1H, H-1), 8.00 (d, 1H, J=3.6 Hz, H-5), 8.24 (d, 1H, J=8.0 Hz, H-11), 8.59 (dd, 1H, J=1.1, 8.0 Hz, H-8). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 22.2 (CH_3), 111.0 (CH), 116.3 (C), 119.6 (CH), 122.7 (CH), 123.5 (CH), 123.6 (CH), 127.3 (C), 128.1 (CH), 128.7 (C), 129.7 (CH), 130.1 (C), 133.1 (CH), 133.9 (C), 134.6 (C), 158.8 (C-7). HRMS for $C_{16}H_{11}NO$: 233.0841 (calcd); 233.0848 (found).

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Synthesis of unexpected six-membered imides by free-radical carbocyclisation on carbohydrate templates

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Abstract—Free-radical reactions of amido-esters anchored to a carbohydrate derived from methyl α-D-glucopyranoside afforded unexpected six-membered cyclic imides. Their structures were elucidated by ESI-MS/MS and NMR spectral analyses, and a mechanism for the formation of these imides is proposed.

1. Introduction

The use of carbohydrate derivatives in the synthesis of carbocycles via free-radical cyclisation reaction has been a theme of interest in our laboratory.[1–5] Encouraged by our previous studies on tri-*n*-butyltin-mediated radical carbocyclisation reaction of *o*-iodobenzamides, we decided to test this methodology for the synthesis of chiral polysubstituted macrocycles exploring the stereocontrolling properties of carbohydrates to create chirality at a 'site' outside the carbohydrate ring.

Thus, we report herein the results of our recent studies on free-radical cyclisation reactions of the amido-esters (**1**–**4**) anchored to a carbohydrate derived from methyl α-D-glucopyranoside. We expected that free-radical cyclisations of these precursors could lead to the macrocycles **A/C** and/or **B/D** by 11-*endo* or 10-*exo* cyclisations, respectively. Although the construction of ten- and eleven-membered ring carbocycles are very difficult,[6,7] we expected that cyclisation could be favored by the conformational restraints imposed by the sugar unit (Scheme 1).

Precursors **1**–**4** were prepared from readily available methyl α-D-glucopyranoside in seven steps using classical carbohydrate chemistry. The C-6 and C-4 hydroxy groups of the starting material were protected as a benzylidene acetal and the C-2 and C-3 hydroxyl groups were *O*-methylated.[8] Hannesian reaction followed by treatment of the 6-bromo derivative[9] with sodium azide gave the 6-azido derivative, which was treated with MeONa in MeOH to give methyl 6-azido-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside **5**.[10] Compound **5** was treated with either crotonic or cinnamic acid, *N*,*N*′-dicyclohexylcarbodiimide (DCC) in CH_2Cl_2 in the presence of catalytic amount of 4-dimethylaminopyridine (DMAP), furnishing the ester derivatives **6** or **7**, respectively. The amido-esters **1**–**4** were finally prepared from the corresponding azido-esters through a two-step one-pot reaction sequence: selective reduction of the azido group with PPh_3 in THF or ethyl ether and subsequent treatment of the resulting 6-amino derivative with 2-iodobenzoic acid, DCC and DMAP or with 3-iodopropanoyl chloride (Scheme 2).

Free-radical reaction of **1** and **3** in boiling benzene (0.01 mol L^{-1}) with Bu_3SnH (1.1 equiv) in the presence of AIBN (catalytic amount) afforded only the hydrogenolysed products **8** (72%) and **11** (62%), respectively. When compounds **2** and **4** were treated under the same conditions, the unexpected six-membered imides **10** and **13** were obtained in 11 and 22% yield, respectively, with none of the anticipates macrocycles **A/C** and/or **B/D**. The

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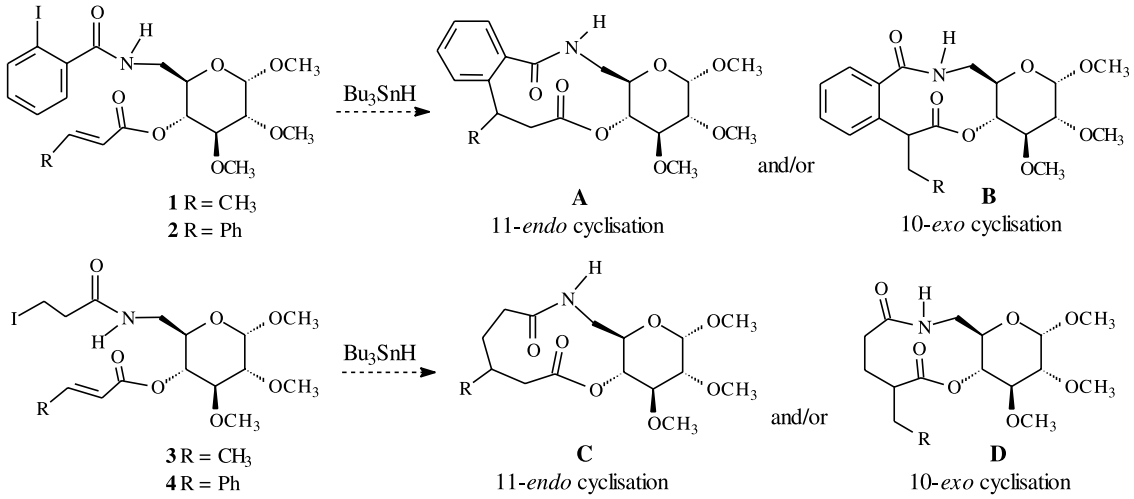
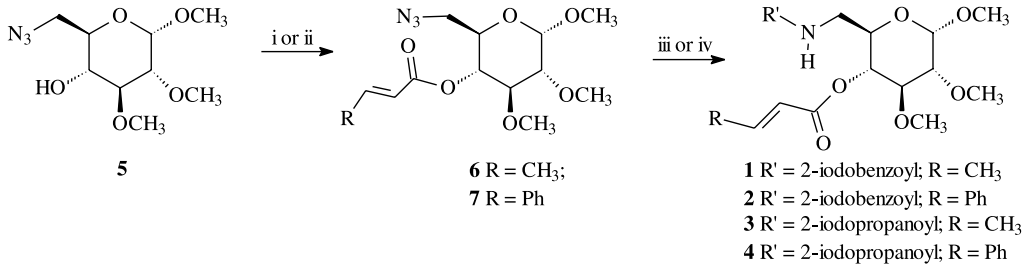


Scheme 1.



Scheme 2. Reagents, conditions and yields i = crotonic acid, DCC, DMAP, CH_2Cl_2 (44%); ii = cinnamic acid, DCC, DMAP, CH_2Cl_2 (85%); iii = (a) PPh_3, THF; (b) 2-iodobenzoic acid, DCC [54% (**1**), 44% (**2**)]; iv = (a) PPh_3, $(C_2H_5)_2O$; (b) HCl, H_2O, (c) Na_2CO_3, 3-iodopropanoyl chloride, acetone [43% (**3**), 71% (**4**)].

corresponding hydrogenolysed products (**9**) and (**12**) were also isolated in 35 and 15% yield, respectively (Scheme 3).

The structures of imides **10** and **13** were determined by ESI-MS/MS analysis, IR, ^1H and ^{13}C NMR spectral data, DEPT experiment, and ^1H–^1H COSY, ^1H–^{13}C HMQC and HMBC experiments.

The ESI-MS spectra of **10** in the positive ion mode show major ions of *m/z* 472.228, (*m/z* 472.197 calculated for $C_{25}H_{29}NO_8+H^+$), *m/z* 494.180 (*m/z* 494.179 calculated for $C_{25}H_{29}NO_8+Na^+$) and *m/z* 510.165 (*m/z* 510.153 calculated for $C_{25}H_{29}NO_8+K^+$). In the negative ion mode, an abundant ion of *m/z* 470.465 corresponding to the deprotonated molecule (*m/z* 470.181 for $C_{25}H_{29}NO_8–H^+$) is detected, as well as its water adduct of *m/z* 488.489. The ESI-MS spectra indicate therefore that a structure with additional 17 u in mass has been formed. This mass shift likely corresponds to the incorporation of a new hydroxyl group. The ESI-MS/MS spectra of the protonated molecule of *m/z* 472 is also in agreement with structure **10** as it shows major dissociation by loss of neutral molecules of methanol (*m/z* 440), water plus methanol (*m/z* 422), two neutral molecules of methanol (*m/z* 408) and two methanol molecules plus a water molecule (*m/z* 390).

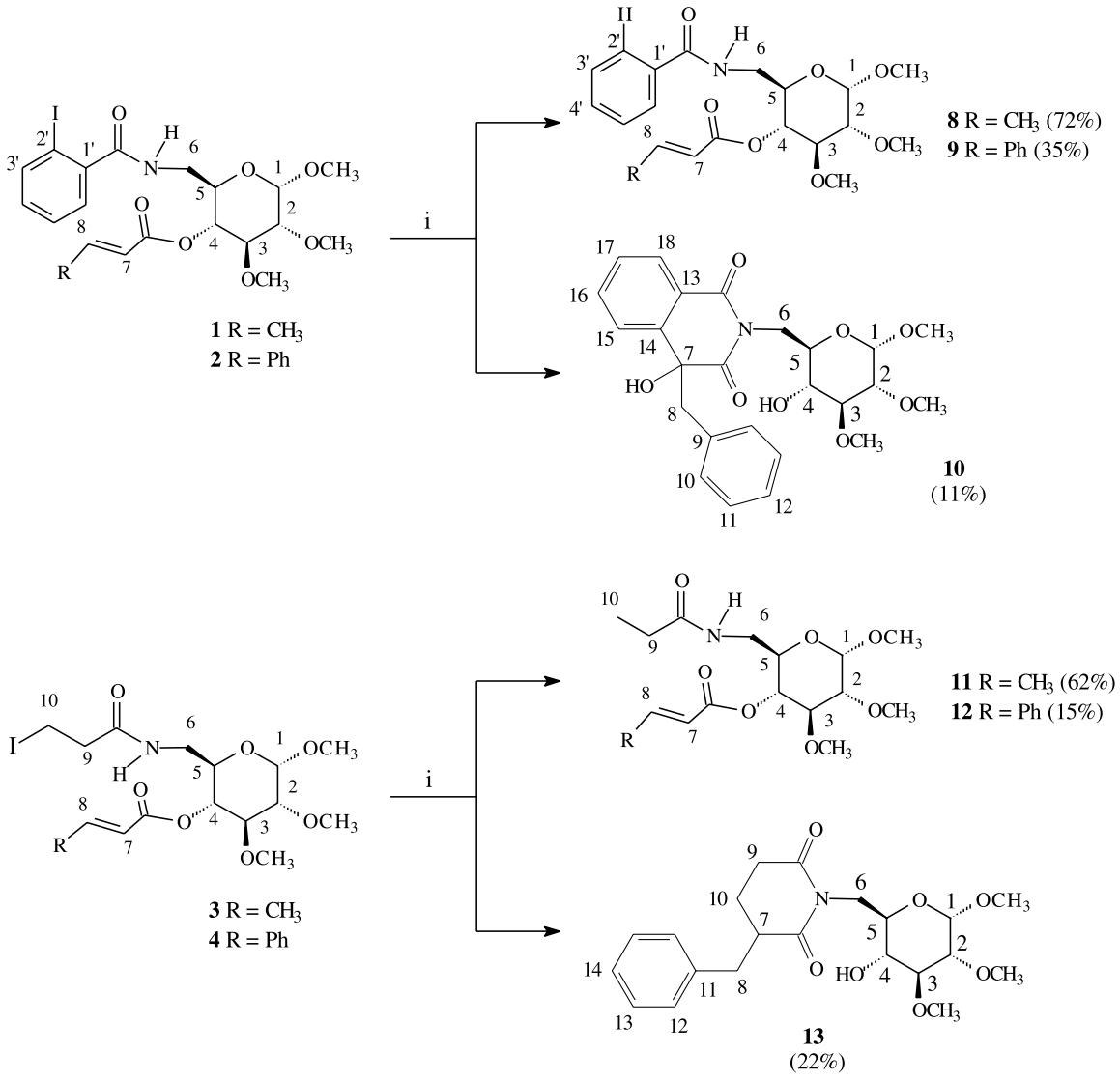
Similarly, the ESI-MS spectra of **13** in the positive ion mode show ions of *m/z* 408.217 (*m/z* 408.202 calculated for $C_{21}H_{29}NO_7+H^+$), *m/z* 430.191 (*m/z* 430.184 calculated for $C_{21}H_{29}NO_7+Na^+$) and *m/z* 446.167 (*m/z* 446.158 calculated for $C_{21}H_{29}NO_7+K^+$) whereas the ESI-MS/MS spectra shows the same dissociation sequence displayed by **10**, that is: losses of methanol (*m/z* 376), methanol plus water (*m/z* 358), two methanol molecules (*m/z* 344) and two methanol molecules plus a water molecule (*m/z* 326). For **13**, the additional 17 u in mass has therefore not been observed.

The comparison of **10** and **13** spectral data with those of their precursors **2** and **4**, respectively, are shown in Table 1.

The IR spectrum of **10** and **13** showed the characteristic absorption bands at 3450 (O–H stretching), 1710 and 1680 cm^{-1} (C=O stretching of cyclic imide-six-membered ring).

The ^1H and ^{13}C NMR data of **10** and **13** reveal the presence of a nearly 1:1 mixture of diastereoisomers. The presence of the hydroxyl group attached to C-4 was deduced on the basis of the chemical shift of H-4 (δ 3.3 ppm) compared to the downfield signal at δ 5.0 and 4.9 ppm for the amido-esters **2** and **4**, respectively.

The conversion of amido-esters into the imides was confirmed by ^1H–^{13}C HMBC correlation. The signals assigned to H-6a and H-6b showed coupling to the carbonyl carbons (Fig. 1). The regioselectivity of the reaction (*exo*-cyclisation mode) was also deduced by ^1H–^{13}C HMBC



Scheme 3. Reagents, conditions and yields i = Bu_3SnH, AIBN (cat.), benzene, reflux.

Table 1. Selected spectroscopic data for compounds **2**, **4**, **10** and **13**

Compound	IR (cm^{-1})			^1H NMR[a] δ (ppm) m, J (Hz)	^{13}C NMR[a] (DEPT) δ (ppm)	
	νN–H	νO–H	νC=O	H-4	C-7	C-8
(**2**)	3300	—	1710 (ester), 1640 (amide)	5.0, t, 9.4	117.00 (CH)	146.27 (CH)
(**4**)	3350	—	1700 (ester), 1650 (amide)	4.9, t, 9.4	116.89 (CH)	146.32 (CH)
(**10**)	—	3450	1710 and 1680 (imide)	3.3, t, 9.4	75.91, 75.82(C)	53.58, 53.49 (CH_2)
(**13**)	—	3450	1710 and 1680 (imide)	3.3, t, 9.2	44.01 (CH)	36.36 (CH_2)

[a] Samples were dissolved in $CDCl_3$.

cross peak, which showed coupling between the multiplet at δ 3.12–3.16 ppm, assigned to benzylic hydrogen, and the *ortho* carbons at δ 130.09 and 130.22 ppm (Fig. 1). The additional hydroxyl group in imide **10** revealed by MS analysis was deduced to be at C-7 on the basis of the chemical shift (δ 75.9 ppm) typical of a hydroxylated tetrasubstituted carbon.

The unexpected formation of six-membered imides **10** and **13** was rationalised as being the result of a 10-*exo* radical cyclisation as initially proposed followed by ring contraction of the unstable ten-membered macrocycles **B** and **D**. The ring strain in macrocycles **B** and **D** associated to proximity between the amide nitrogen atom and the ester carbonyl group might favour the ring contraction. The

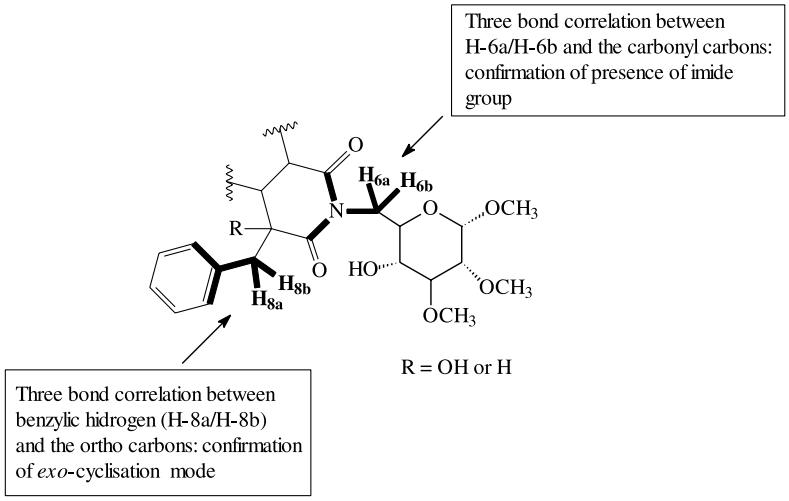


Figure 1.

proposed pathways leading to the formation of imides **10** and **13** are outlined in Figure 2.

In contrast with the guideline that '*endo*-cyclisation modes are favoured in radical macrocyclisation',[11] we have found that cinnamoyl precursors provide exclusively macrocycles resulting from *exo* radical cyclisation. These results can be attributed to the stability of the intermediate benzyl radical from cinnamoyl precursors and to the steric retardation of *endo*-cyclisation.

We have been intrigued by the presence of the additional

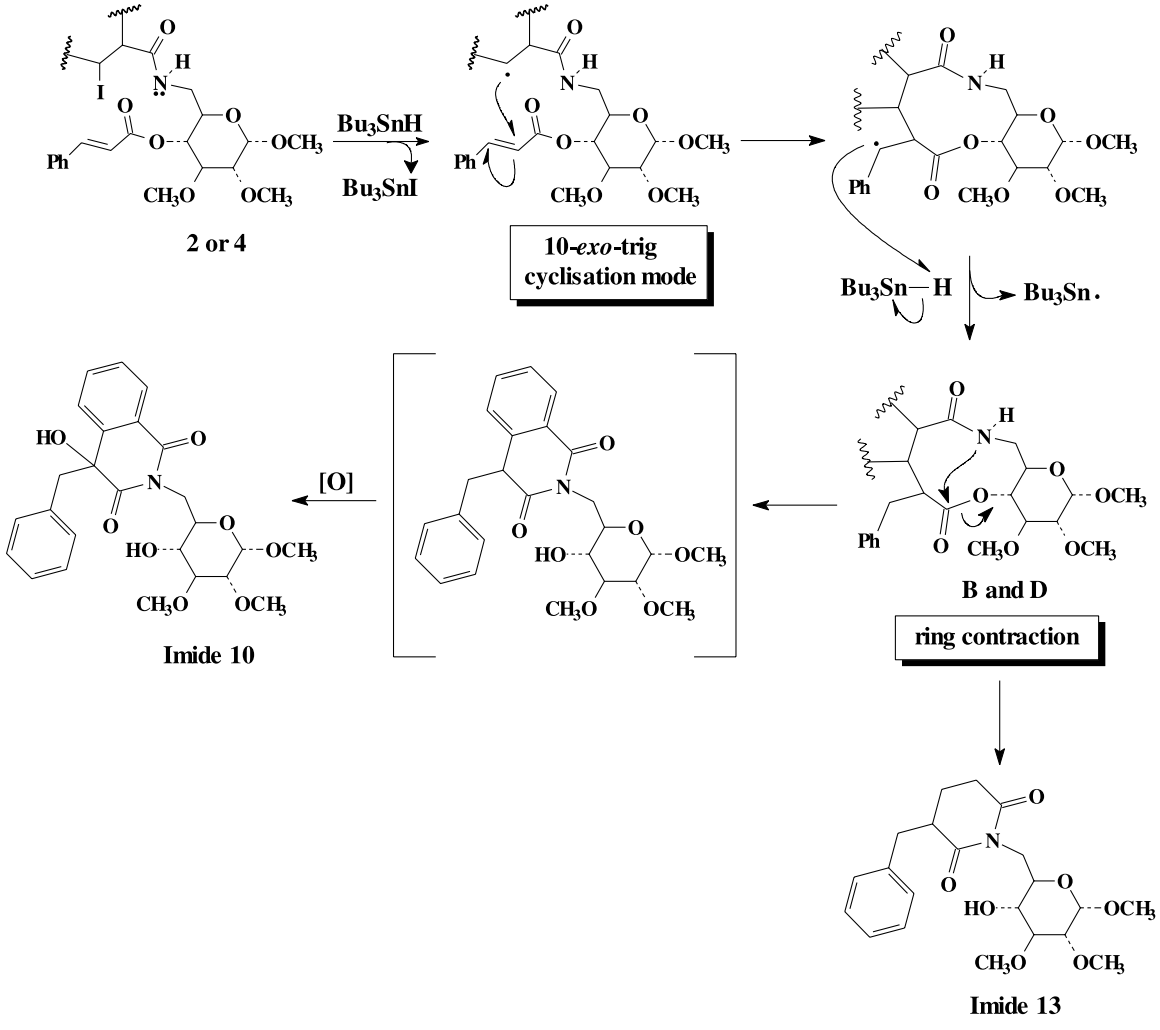


Figure 2.

hydroxyl group in the imide **10**. It is not so straightforward to rationalise how this oxidation occurred. However, the aromatic ring of benzoyl group is likely to play an important role in the oxidation step, since no such reaction was observed for **4**. The ease of oxidation of a given substrate depends markedly on the strength of its weakest C–H bond.[12] In this case, the hydrogen abstraction in C-7 forms a stabilised radical (tertiary, α-carbonyl and benzylic radical), which could account for the observed autoxidation.

In conclusion, we have described the synthesis of six-membered cyclic imides bearing a new stereogenic center via 10-*exo*-trig radical carbocyclisation followed by ring contraction on carbohydrate template. This cyclisation, though regioselective, proved to be nonstereoselective, affording inseparable mixture of diastereoisomers.

2. Experimental

2.1. General information

All melting points were determined on a Kofler Sybron apparatus and are uncorrected. Optical rotations were determined at 25 °C with a Bellingham and Stanley P20 Polarimeter. The IR spectra were recorded on a Shimadsu IR-408 spectrometer. The NMR spectra were recorded on a Bruker *AVANCE* DRX400 or a Bruker *AVANCE* DPX400 instruments. Samples were dissolved in $CDCl_3$ with TMS as the internal standard. Chemical shifts are given in δ (ppm) scale and *J* values are given in Hz. ESI-MS and ESI-MS/MS data were obtained using a Micromass QTOF hybrid quadrupole orthogonal time-of-flight mass spectrometer operating at 7.000 mass resolution and 5 ppm mass accuracy using typical analytical conditions as described elsewhere.[13] ESI-MS spectra for mass measurements were taken using both positive- and negative-ion electronspray ionization from 1:1 H_2O–MeOH solutions with the addition of either a few microliters of formic acid or ammonium hydroxide. Column chromatography was performed with silica gel 60, 70–230 mesh (Merck).

2.2. General procedure for the synthesis of the azido-esters (6) and (7)

To a 0.2 mol L^{-1} solution of **5**[10] in methylene chloride were added carboxylic acid (crotonic or cinnamic acid) (1.6 equiv), *N*,*N*′-dicyclohexylcarbodiimide (1.6 equiv) and 4-dimethylaminopyridine (0.16 equiv). The solution was allowed to stand at room temperature for 12 h. The dicyclohexylurea, which precipitates, was removed by filtration. The filtrate was concentrated to give crude azido-ester, which was submitted to chromatography (hexane–EtOAc). The azido-esters **6** and **7** were unstable if stored for a few hours and, thus, they were reacted soon after their purification.

2.2.1. Methyl 6-azido-4-*O*-crotonyl-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (6). Oil; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.05 (dq, 1H, $J_{8,7}=15.5$ Hz, $J_{8,Me}=6.8$ Hz, H-8), 5.85 (dd, 1H, $J_{7,8}=15.5$ Hz, $J_{7,Me}=1.6$ Hz, H-7), 4.93–4.83 (m, 2H, H-1 and H-4), 3.85 (ddd, 1H, $J_{5,4}=10$ Hz, $J_{5,6a}=7.2$ Hz, $J_{5,6b}=2.8$ Hz, H-5), 3.6 (t, 1H, $J_{3,2}=J_{3,4}=9.4$ Hz, H-3), 3.54 (s, 3H, OMe), 3.49 (s, 6H, 2×OMe), 3.40–3.27 (m, 2H, H-2 and H-6a), 3.20 (dd, 1H, $J_{6b,6a}=13.2$ Hz, $J_{6b,5}=2.8$ Hz, H-6b), 1.91 (dd, 3H, $J_{Me,8}=6.8$ Hz, $J_{Me,9}=1.6$ Hz, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 165.19 (C=O), 146.41 (C-8), 121.72 (C-7), 97.42 (C-1), 81.14 (C-2 or C-3), 80.53 (C-3 or C-2), 70.98 (C-4), 69.10 (C-5), 60.76, 59.19, 55.40 (3×OMe), 51.27 (C-6), 18.03 (Me).

2.2.2. Methyl 6-azido-4-*O*-cinnamoyl-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (7). Oil; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.74 (d, 1H, $J_{8,7}=16$ Hz, H-8), 7.57–7.38 (m, 5H, Ph), 6.44 (d, 1H, $J_{7,8}=16$ Hz, H-7), 4.98 (dd, 1H, $J_{4,5}=10.1$ Hz, $J_{4,3}=9.4$ Hz, H-4), 4.90 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 3.92 (ddd, 1H, $J_{5,4}=10.1$ Hz, $J_{5,6a}=7$ Hz, $J_{5,6b}=3$ Hz, H-5), 3.67 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.55 (s, 3H, OMe), 3.52 (s, 3H, OMe), 3.51 (s, 3H, OMe), 3.42–3.31 (m, 2H, H-6a and H-2), 3.25 (dd, 1H, $J_{6b,6a}=13.2$ Hz, $J_{6b,5}=3$ Hz, H-6b); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 165.63 (C=O), 146.08 (C-8), 133.91–128.08 (Ph), 116.84 (C-7), 97.40 (C-1), 81.14 (C-2 or C-3), 80.51 (C-3 or C-2), 71.24 (C-4), 69.04 (C-5), 60.74, 59.11, 55.37 (3×OMe), 51.23 (C-6).

2.3. General procedure for the synthesis of the amido-esters (1) and (2)

To a 0.08 mol L^{-1} solution of azido-esters **6** or **7** in THF was added triphenylphosphine (1.5 equiv). After 6 h at room temperature, TLC showed complete conversion of the substrate. Then, *N*,*N*′-dicyclohexylcarbodiimide (2.0 equiv) was added, followed by 2-iodobenzoic acid (2.0 equiv), and the stirring was continued for 24 h. The dicyclohexylurea was removed by filtration. The filtrate was concentrated to give crude amido-ester, which was submitted to chromatography (hexane–EtOAc).

2.3.1. Methyl 4-*O*-crotonyl-6-deoxy-6-(2-iodobenzoylamino)-2,3-di-*O*-methyl-α-D-glucopyranoside (1). White solid; mp 149.6–151.2 °C; $[\alpha]_D=+105.7$ (*c* 1.4 in $CHCl_3$); ν_{max}/cm^{-1} 3300 (NH), 1710 (C=O), 1640 (C=O), 1620 (C=C), 1050 (C–O); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.85 (d, 1H, $J_{3',4'}=7.8$ Hz, H-3′), 7.45–7.33 (m, 2H, H-5′ and H-6′), 7.16–7.01 (m, 2H, H-4′ and H-8), 6.31 (t, 1H, $J_{NH,6a}=J_{NH,6b}=6.8$ Hz, NH), 5.90 (dd, 1H, $J_{7,8}=15.5$ Hz, $J_{7,Me}=1.6$ Hz, H-7), 4.90 (t, 1H, $J_{4,3}=J_{4,5}=9.6$ Hz, H-4), 4.84 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.02–3.84 (m, 2H, H-5 and H-6a), 3.64 (t, 1H, $J_{3,4}=J_{3,2}=9.6$ Hz, H-3) 3.53 (s, 3H, OMe), 3.51 (s, 3H, OMe), 3.46 (s, 3H, OMe), 3.27–3.17 (m, 2H, H-2 and H-6b); 1.91 (dd, 3H, $J_{Me,8}=6.8$ Hz, $J_{Me,9}=1.6$ Hz, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 169.13, 165.64 (2×C=O), 146.50 (C-8), 142.08-128.09 (Ar), 121.80 (C-7), 97.51 (C-1), 92.22 (C-2′), 81.33 (C-2), 80.58 (C-3), 71.15 (C-4), 67.94 (C-5), 60.85, 59.21, 55.61 (3×OMe), 39.78 (C-6), 18.07 (Me); Anal. Calc. for $C_{20}H_{26}INO_7$: C, 46.24; H, 5.01; N, 2.70; Found: C, 46.06; H, 4.64; N, 2.68.

2.3.2. Methyl 4-*O*-cinnamoyl-6-deoxy-6-(2-iodobenzoylamino)-2,3-di-*O*-methyl-α-D-glucopyranoside (2). White solid; mp 164.2–165.9 °C; $[\alpha]_D=+211$ (*c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1} 3300 (NH), 1710 (C=O), 1640 (C=O), 1625 (C=C), 1050 (C–O); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm)

7.85 (d, 1H, $J_{3',4'}=7.8$ Hz, H-3′), 7.76 (d, 1H, $J_{8,7}=16$ Hz, H-7) 7.58–7.33 (m, 7H, Ar-H), 7.10 (td, 1H, $J_{4',3'}=J_{4',5'}=7.8$ Hz, $J_{4',6'}=1.2$ Hz, H-4′), 6.49 (d, 1H, $J_{7,8}=16$ Hz, H-7), 6.31 [s (broad), 1H, NH], 4.99 (t, 1H, $J_{4,3}=J_{4,5}=9.4$ Hz, H-4), 4.86 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.06–3.91 (m, 2H, H-5 and H-6a), 3.71 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.54 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.48 (s, 3H, OMe), 3.38–3.26 (m, 2H, H-2 and H-6b); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 169.16, 166.25 (2×C═O), 146.27 (C-8), 142.11–128.13 (Ar), 117.00 (C-7), 97.58 (C-1), 92.26 (C-2′), 81.42 (C-2), 80.67 (C-3), 71.54 (C-4), 67.97 (C-5), 60.96, 59.26, 55.69 (3×OMe), 39.88 (C-6); Anal. Calc. for $C_{25}H_{28}INO_7$: C, 51.64; H, 4.82; N, 2.41; Found: C, 51.44; H, 4.57; N, 2.40.

2.4. General procedure for the synthesis of the amido-esters (3) and (4)

To a 0.13 mol L^{-1} solution of azido-esters **6** or **7** in diethyl ether was added triphenylphosphine (1.5 equiv). After completion of the reduction (~4 h) the reaction mixture was extracted with cold diluted hydrochloric acid (0.2 mol L^{-1}, 15 mL) to separate the triphenylphosphine oxide from the amine. The aqueous layer was transferred to a round-bottom flask immersed in an ice bath and then were added acetone (20 mL), saturated aqueous sodium carbonate (ca. 10 mL), followed by a dropwise solution of the 3-iodopropanoyl chloride (2.5 equiv) in anhydrous acetone (5 mL). After 1 h at room temperature, TLC showed complete conversion of the substrate. For workup, acetone was removed under reduced pressure, water (50 mL) was added and the aqueous layer was washed with $CHCl_3$ (3×50 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography (hexane–EtOAc).

2.4.1. Methyl 4-*O*-crotonyl-6-deoxy-6-(3-iodopropanoylamino)-2,3-di-*O*-methyl-α-D-glucopyranoside (3). White solid; mp 87.9–88.6 °C; $[\alpha]_D=+106.2$ (*c* 2.0 in $CHCl_3$); ν_{max}/cm^{-1} 3350 (NH), 1700 (C═O), 1650 (C═O), 1625 (C═C), 1050 (C–O); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.06 (dq, 1H, $J_{8,7}=15.5$ Hz, $J_{8,Me}=6.9$ Hz, H-8), 6.19 [s (broad), 1H, NH], 5.88 (dd, 1H, $J_{7,8}=15.5$ Hz, $J_{7,Me}=1.6$ Hz, H-7), 4.84 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.80 (t, 1H, $J_{4,3}=J_{4,5}=9.4$ Hz, H-4), 3.90–3.71 (m, 2H, H-5 and H-6a), 3.61 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.53 (s, 3H, OMe), 3.50 (s, 3H, OMe), 3.44–3.33 (m, 4H, OMe and H-6b), 3.27 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.6$ Hz H-2), 3.08–2.59 (m, 4H, H-9a, H-9b, H-10a and H-10b), 1.92 (dd, 3H, $J_{Me,8}=6.9$ Hz, $J_{Me,7}=1.6$ Hz, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 170.19, 165.81 (2×C═O), 146.59 (C-8), 121.77 (C-7), 97.45 (C-1), 81.30 (C-3), 80.50 (C-2), 71.15 (C-4), 67.90 (C-5), 60.83, 59.17, 55.45 (3×OMe), 40.63 (C-9), 39.23 (C-6), 18.07 (Me), -1,92 (C-10); Anal. Calc. for $C_{16}H_{26}INO_7$: C, 40.76; H, 5.52; N, 2.97; Found: C, 41.44; H, 5.13; N, 2.89.

2.4.2. Methyl 4-*O*-cinnamoyl-6-deoxy-6-(3-iodopropanoylamino)-2,3-di-*O*-methyl-α-D-glucopyranoside (4). White solid; mp 101.7–102.8 °C; $[\alpha]_D=+101.2$ (*c* 1.2 in $CHCl_3$); ν_{max}/cm^{-1} 3350 (NH), 1700 (C═O), 1650 (C═O), 1625 (C═C); 1050 (C–O); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.75 (d, 1H, $J_{8,7}=16$ Hz, H-8), 7.58–7.38 (m, 5H, Ph), 6.47 (d, 1H, $J_{7,8}=16$ Hz, H-7), 6.16 [s (broad), 1H, NH], 4.90 (t, 1H, $J_{4,3}=J_{4,5}=9.4$ Hz, H-4),4.86 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 3.95–3.78 (m, 2H, H-5 and H-6a), 3.68 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.54 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.46–3.36 (m, 4H, OMe and H-6b), 3.30 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.6$ Hz H-2), 3.18–2.96 (m, 2H, H-9a, H-9b), 2.94–2.71 (m, 2H, H-10a and H-10b); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 170.20, 166.39 (2×C═O), 146.32 (C-8), 133.95–128.20 (Ph), 116.89 (C-7), 97.48 (C-1), 81.36 (C-3), 80.55 (C-2), 71.48 (C-4), 67.91 (C-5), 60.92, 59.21, 55.50 (3×OMe), 40.66 (C-9), 39.28 (C-6), −1,87 (C-10); Anal. Calc. for $C_{21}H_{28}INO_7$: C, 47.28; H, 5.25; N, 2.67; Found: C, 47.63; H, 5.31; N, 2.55.

2.5. General procedure for free radical cyclisation

To a stirring and boiling solution of amido-esters in nitrogen-saturated benzene (0.01 mol L^{-1}) was added a solution of Bu_3SnH (1.1 equiv) and AIBN (cat.) in nitrogen-saturated benzene (0.2 mol L^{-1}) via an addition funnel during 3 h. The reaction mixture was heated under reflux in nitrogen atmosphere for a further 1 h. After solvent removal the residue was dissolved in acetonitrile (50 mL). The solution was extracted three times with hexane (30 mL) to remove tin compounds. After evaporation of the acetonitrile the residue was chromatographed (hexane–EtOAc).

2.5.1. Free radical cyclisation of amido-ester (1). The uncyclized product (**8**) was obtained as a white solid; mp 129.3–130.2; $[\alpha]_D=+113$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.83 (dd, 2H, $J_{2',3'}=7.8$ Hz, $J_{2',4'}=1.8$ Hz, 2×H-2′), 7.54–7.34 (m, 3H, Ar-H), 7.10 (dq, 1H, $J_{8,7}=15.6$ Hz, $J_{8,Me}=6.8$ Hz, H-8), 7.01–6.94 (m, 1H, NH), 5.91 (dd, 1H, $J_{7,8}=15.6$ Hz, $J_{7,Me}=1.6$ Hz, H-7), 4.87 (t, 1H, $J_{4,3}=J_{4,5}=9.4$ Hz, H-4), 4.84 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.13 (ddd, 1H, $J_{6a,6b}=14.3$ Hz, $J_{6a,NH}=8.5$ Hz, $J_{6a,5}=2.8$ Hz, H-6a), 3.85 (ddd, 1H, $J_{5,4}=9.4$ Hz, $J_{5,6b}=5.6$ Hz, $J_{5,6a}=2.8$ Hz, H-5), 3.65 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.51 (s, 6H, 2×OMe), 3.42 (s, 3H, OMe), 3.26 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.6$ Hz H-2), 3.09 (ddd, 1H, $J_{6b,6a}=14.3$ Hz, $J_{6b,NH}=4.2$ Hz, $J_{6b,5}=5.6$ Hz, H-6b), 1.92 (dd, 3H, $J_{Me,8}=6.8$ Hz, $J_{Me,7}=1.6$ Hz, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 167.11, 166.09 (2×C═O), 146.75 (C-8), 134.20-126.89 (Ph), 121.76 (C-7), 97.40 (C-1), 81.31 (C-3), 80.51 (C-2), 71.51 (C-4), 67.93 (C-5), 60.86, 59.12, 55.28 (3×OMe), 39.47 (C-6), 18.06 (Me); ESI-MS $[M+H]^+$ 394.195 $C_{20}H_{27}NO_7$ requires for $[M+H]^+$ 394.187).

2.5.2. Free radical cyclisation of amido-ester (2). The uncyclized product **9** was obtained as a white solid; mp 80.9–81.5; $[\alpha]_D=+126.9$ (*c* 0.75 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.84 (dd, 2H, $J_{2',3'}=7.8$ Hz, $J_{2',4'}=1.4$ Hz, 2×H-2′), 7.79 (q, 1H, $J_{8,7}=15.8$ Hz, H-8), 7.59–7.39 (m, 8H, Ar-H), 6.96 (dd, 1H, $J_{NH,6a}=8.4$ Hz, $J_{NH,6b}=4.2$ Hz, NH), 6.50 (d, 1H, $J_{7,8}=15.8$ Hz, H-7), 4.96 (dd, 1H, $J_{4,5}=10.0$ Hz, $J_{4,3}=9.4$ Hz, H-4), 4.87 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.18 (ddd, 1H, $J_{6a,6b}=14.3$ Hz, $J_{6a,NH}=8.4$ Hz, $J_{6a,5}=2.8$ Hz, H-6a), 3.92 (ddd, 1H, $J_{5,4}=10.0$ Hz, $J_{5,6b}=5.4$ Hz, $J_{5,6a}=2.8$ Hz, H-5), 3.72 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.55 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.44 (s, 3H, OMe), 3.30 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.6$ Hz H-2), 3.24–3.09 (m, 1H, H-6b); ^{13}C NMR (50 MHz, $CDCl_3$) δ

(ppm) 167.20, 166.75 (2×C=O), 146.54 (C-8), 134.24–126.95 (Ar-C), 116.91 (C-7), 97.50 (C-1), 81.43 (C-2), 80.61 (C-3), 71.96 (C-4), 67.99 (C-5), 61.02, 59.22, 55.40 (3×OMe), 39.59 (C-6); ESI-MS $[M+H]^+$ 456.200 $C_{25}H_{29}NO_7$ requires for $[M+H]^+$ 456.202).

The six-membered cyclic imide **10** was obtained as an oil; ν_{max}/cm^{-1} 3450 (OH), 1710 (C=O), 1680 (C=O), 1050 (C–O); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07–8.02 (m, 2H, H-18 and H-18′), 7.66–7.59 (m, 2H, H-16 and H-16′), 7.56–7.52 (m, 2H, H-15 and H-15′), 7.50–7.45 (m, 2H, H-17 and H-17′), 7.23–7.19 (m, 2H, H-12 and H-12′), 7.16-7.11 (m, 4H, 2×H-11 and 2×H-11′), 6.70–6.65 (m, 4H, 2×H-10 and 2×H-10′), 4.76 (d, 1H, $J_{1',2'}=3.6$ Hz, H-1′), 4.75 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.30 (dd, 1H, $J_{6a,6b}=14.0$ Hz, $J_{6a,5}=4.8$ Hz, H-6a), 4.15–4.13 (m, 2H, H-6b and H-6b′), 4.08 (dd, 1H, $J_{6a',6b'}=14.0$ Hz, $J_{6a',5'}=4.8$ Hz, H-6a′), 3.92 (dt, 1H, $J_{5',4'}=9.4$ Hz, $J_{5',6a'}=J_{5',6b'}=6.0$ Hz, H-5′), 3.84 (dt, 1H, $J_{5,4}=9.4$ Hz, $J_{5,6a}=J_{5,6b}=4.8$ Hz, H-5), 3.62 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.45 (s, 3H, OMe), 3.44–3.39 (m, 5H, OMe, H-3 and H-3′), 3.33 (t, 1H, $J_{4',5'}=J_{4',3'}=9.4$ Hz, H-4′), 3.31 (s, 3H, OMe), 3.27 (t, 1H, $J_{4,5}=J_{4,3}=9.4$ Hz, H-4), 3.24 (s, 3H, OMe), 3.19 (dd, 1H, $J_{2',3'}=9.4$ Hz, $J_{2',1'}=3.6$ Hz, H-2′), 3.16–3.13 (m, 5H, H-2 and H-8a, H-8a′, H-8b and H-8b′); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 177.12, 176.60, 164.12, 163.96 (4×C=O), 139.66, 139.53 (C-14 and C-14′), 133.93 (C-16 and C-16′), 133.24, 133.13 (C-9 and C-9′), 130.22, 130.09 (2×C-10 and 2×C-10′), 128.58, 128.54 (C-17 and C-17′), 128.30, 128.15 (C-18 and C-18′), 128.06, 127.99 (2×C-11 and 2×C-11′), 127.64 (C-12 and C-12′), 125.64, 125.50 (C-15 and C-15′), 124.43 (C-14 and C-14′), 97.40, 97.31 (C-1 and C-1′), 82.52, 82.28 (C-3 and C-3′), 81.66, 81.60 (C-2 and C-2′), 75.91, 75.82 (C-7 and C-7′), 73.33 (C-4), 73.50 (C-4′), 68.92 (C-5), 68.28 (C-5′), 61.24, 58.66, 58.55, 55.18, 55.10 (6×OMe), 53.58, 53.49 (C-8 and C-8′), 42.22 (C-6), 41.33 (C-6′); ESI-MS $[M+H]^+$ 472.228 $C_{25}H_{29}NO_8$ requires for $[M+H]^+$ 472.197).

2.5.3. Free radical cyclisation of amido-ester (3). The uncyclized product **11** was obtained as a white solid; mp 85.5–87.0; $[\alpha]_D=+118$ (*c* 0.8 in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.06 (qd, 1H, $J_{8,7}=15.6$ Hz, $J_{8,Me}=6.8$ Hz, H-8), 6.07 [s (broad), 1H, NH), 5.88 (dd, 1H, $J_{7,8}=15.6$ Hz, $J_{7,Me}=1.6$ Hz, H-7), 4.83 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.79 (t, 1H, $J_{4,5}=J_{4,3}=9.4$ Hz, H-4), 3.89–3.70 (m, 2H, H-6a and H-5), 3.61 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.53 (s, 3H, OMe), 3.50 (s, 3H, OMe), 3.42 (s, 3H, OMe), 3.27 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.6$ Hz, H-2), 3.01–2.88 (m, 1H, H-6b) 2.23 (q, 2H, $J_{9,10}=7.6$ Hz, H-9a and H9b), 1.91 (dd, 3H, $J_{Me,8}=6.8$ Hz, $J_{Me,7}=1.6$ Hz, Me), 1.16 (t, 3H, $J_{10,9a}=J_{10,9b}=7.6$ Hz, H-10); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 173.74, 165.77 (2×C=O), 146.47 (C-8), 121.83 (C-7), 97.43 (C-1), 81.34 (C-3), 80.61 (C-2), 71.25 (C-4), 67.94 (C-5), 60.84, 59.17, 55.23 (3×OMe), 39.14 (C-6), 29.65 (C-9), 18.06 (Me), 9.70 (C-10); ESI-MS $[M+H]^+$ 346.193 $C_{16}H_{27}NO_7$ requires for $[M+H]^+$ 346.187).

2.5.4. Free radical cyclisation of amido-ester (4). The uncyclized product **12** was obtained as a white solid; mp 112.0–113.5; $[\alpha]_D=+79.2$ (*c* 1.0 in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.76 (d, 1H, $J_{8,7}=16$ Hz, H-8), 7.57–7.27 (m, 5H, Ar-H), 6.47 (d, 1H, $J_{7,8}=16$ Hz, H-7), 6.06 [s (broad), 1H, NH), 4.93–4.80 (m, 2H, H-1, H-4), 3.95–3.77 (m, 2H, H-6a and H-5), 3.67 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.54 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.44 (s, 3H, OMe), 3.28 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.4$ Hz, H-2), 3.05–2.97 (m, 1H, H-6b), 2.24 (q, 2H, $J_{9,10}=7.6$ Hz, H-9a and H9b), 1.17 (t, 3H, $J_{10,9a}=J_{10,9b}=7.6$ Hz, H-10); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 173.76, 166.35 (2×C=O), 146.29 (C-8), 134.05–128.24 (Ar-C), 117.03 (C-7), 97.51 (C-1), 81.45 (C-3), 80.71 (C-2), 71.63 (C-4), 67.98 (C-5), 60.99, 59.26, 55.34 (3×OMe), 39.23 (C-6), 29.76 (C-9), 9.78 (C-10); ESI-MS $[M+H]^+$ 408.204 $C_{21}H_{29}NO_7$ requires for $[M+H]^+$ 408.202).

The six-membered cyclic imide **13** was obtained as an oil; ν_{max}/cm^{-1} 3450 (OH), 1710 (C=O), 1680 (C=O), 1050 (C–O); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36–7.18 (m, 10H, Ar-H), 4.79–4.77 (m, 2H, H-1 and H-1′), 4.23 (dd, 2H, $J_{6a,6b}=J_{6a',6b'}=13.6$ Hz, $J_{6a,5}=J_{6a',5'}=4.8$ Hz, H-6a and H-6a′), 4.08 (dd, 2H, $J_{6b,6a}=J_{6b',6a'}=13.6$ Hz, $J_{6b,5}=J_{6b',5'}=5.6$ Hz, H-6b and H-6b′), 3.79–3.73 (m, 2H, H-5 and H-5′), 3.63 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.48 (s, 6H, 2×OMe), 3.47–3.41 (m, 2H, H-8a and H-8a′), 3.41 (t, 2H, $J_{3,4}=J_{3,2}=J_{3',4'}=J_{3',2'}=9.2$ Hz, H-3 and H-3′), 3.35 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.27 (t, 2H, $J_{4,5}=J_{4,3}=J_{4',5'}=J_{4',3'}=9.2$ Hz, H-4 and H-4′), 3.19 (dd, 2H, $J_{2,3}=J_{2',3'}=9.2$ Hz, $J_{2,1}=J_{2',1'}=3.6$ Hz, H-2 and H-2′), 2.80–2.69 (m, 6H, H-7, H-7′, H-8b, H-8b′, H-10a and H-10a′) 2.58–2.47 (m, 2H, H-10b and H-b′), 1.91–1.83 (m, 2H, 2×H-9a and H-9$^{a\prime}$), 1.66–1.55 (m, 2H, H-9b and H-9b′); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.72, 174.52, 172.80, 172.67 (4×C=O), 138.33, 138.28 (C-11 and C-11′), 129.22, 129.17 (2×C-12 and 2×C-12′), 128.57, 128.54 (2×C-13 and 2×C-13′), 126.62 (C-14 and C-14′), 97.21 (C-1 and C-1′), 82.39 (C-3 and C-3′), 81.55 (C-2 and C-2′), 72.96, 72.90 (C-4 and C-4′), 68.49, 68.40 (C-5 and C-5′), 61.14, 58.51, 54.90 (6×OMe), 44.01 (C-7 and C-7′), 40.69, 40.64 (C-6 and C-6′), 36.36 (C-8 and C-8′), 32.08, 32.02 (C-10 and C-10′), 21.70 (C-9 and C-9′); ESI-MS $[M+H]^+$ 408.217 $C_{21}H_{29}NO_7$ requires for $[M+H]^+$ 408.202).

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Effects of geminal disubstitution on C–H and N–H bond dissociation energies

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Abstract—Composite ab initio methods including G3, CBS-Q, and G3B3 were used to calculate the C–H and N–H bond dissociation energies (BDEs) of a variety of disubstituted methane and ammonia molecules. The calculated BDEs were in excellent agreement with the available experimental data. Using these reliable BDEs we studied the effects of geminal disubstitution on C–H and N–H BDEs. It was found that the effects of the two substituents were not additive. Detailed separation of the substituent effects on BDEs to those associated with the parent molecules and those associated with the radicals was then performed using appropriate isodesmic reactions. It was found the geminal substitution effects on the stabilities of methanes, methyl radicals, amines, and amine radicals were all governed by five basic types of energetic effects, namely, hyperconjugation effect (stabilizing), electrostatic attraction (stabilizing) or repulsion (destabilizing), conjugation saturation effect (destabilizing), captodative effect (stabilizing), and steric effect (destabilizing). The conformations of the species played an essential role in determining whether a particular energetic effect could take place. Because the carbon-centered and nitrogen-centered species often had quite different conformational preferences, the geminal substitution effects on these two classes of species were quite dissimilar to each other.

1. Introduction

Homolytic bond dissociation energy (BDE) is usually defined as the enthalpy change at 298 K and 1 atm for the gas-phase reaction $A–B(g) \rightarrow A\cdot(g) + B\cdot(g)$.[1] A sound knowledge of BDEs is fundamental to understanding the thermodynamics and kinetics of radical species. Therefore, considerable efforts have been devoted to the measurement of BDEs during the past several decades.[2] A lot of work has also been done in order to elucidate the structure-activity relationships (SARs) associated with the BDEs.[3]

One difficulty in studying the SARs of BDEs is the lack of reliable experimental data. Some early, sophisticated experimental methods such as radical kinetics, photoionization mass spectrometry, and the acidity/electron affinity cycle could provide accurate BDEs, but their applications are limited to relatively small and simple molecules.[4] Only a small number of BDEs have been obtained using these complicated methods. It is not feasible to study the SARs using the unsystematic data.

In order to overcome the difficulty in BDE measurement, Bordwell et al. recently developed some solution-phase experimental methods to determine BDEs.[5] Using these methods Bordwell et al. have demonstrated that BDEs of many fairly complex molecules could be readily measured. This breakthrough makes easy to study the SARs associated with the BDEs of many types of molecules. Nonetheless, it should be emphasized that the BDEs measured using Bordwell's method are 'solution-phase' BDEs. They may not fully correlate with the intrinsic gas-phase bonding strengths.[6]

Some theoretical methods can also be used to get the BDEs. However, one must be very cautious about the theoretical BDEs because it is hard to deal with open-shell systems theoretically. Due to the spin contamination problem the unrestricted Hartree–Fock (UHF) method and those methods using UHF wave functions as the reference states (e.g., UMP2) cannot provide valid BDEs in general.[7] Thus a lot of early theoretical studies on BDEs, which were conducted at the time when the UHF or UMP2 method was the only available tool, should be re-examined carefully.

Very recently Radom et al. have demonstrated that the composite ab initio methods could provide fairly accurate BDEs for many compounds.[7a,8] They also showed that the density function theory (DFT) method and the restricted Møller–Plesset theory method (specifically RMP2) could be used to calculate the relative BDEs between similar species.

Keywords: Bond dissociation energy; Geminal effect; Anomeric effect; Captodative effect; Composite ab initio.
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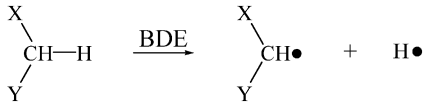
Table 1. Theoretical and experimental C–H BDEs of X-CH_2-Y (kcal/mol)



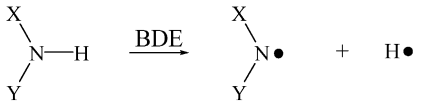
X/Y	NO_2	CN	BH_2	CHO	CF_3	H	F	CH_3	$CH{=}CH_2$	OH	NH_2
NO_2	98.6[a] 102.9[b] 102.8[c] 103.2[d]	—	—	—	—	—	—	—	—	—	—
CN	89.2[a] 93.2[b] 94.0[c] 94.2[d]	82.4[a] 87.1[b] 88.3[c] 88.9[d] (87.6)[e]	—	—	—	—	—	—	—	—	—
BH_2	90.6[a] 94.3[b] 94.1[c] 94.7[d]	83.4[a] 87.7[b] 87.7[c] 87.9[d]	87.1[a] 92.6[b] 92.2[c] 91.8[d]	—	—	—	—	—	—	—	—
CHO	90.1[a] 95.6[b] 94.9[c] 94.0[d]	82.3[a] 87.7[b] 87.9[c] 87.9[d]	88.1[a] 92.9[b] 92.2[c] 91.8[d]	83.8[a] 88.7[b] 88.5[c] 88.0[d]	—	—	—	—	—	—	—
CF_3	99.4[a] 104.5[b] —[c] —[d]	92.0[a] 97.6[b] 97.7[c] 97.7[d]	93.8[a] 98.3[b] 97.6[c] 97.5[d]	91.2[a] 97.1[b] 96.8[c] 96.5[d]	102.2[a] 107.1[b] —[c] —[d]	—	—	—	—	—	—
H	98.1[a] 101.6[b] 101.1[c] 101.3[d] (97.4)[e]	92.4[a] 96.0[b] 96.1[c] 96.2[d] (96)[e]	91.9[a] 95.1[b] 94.3[c] 94.2[d]	91.8[a] 96.0[b] 95.4[c] 95.2[d] (94.3)	103.3[a] 107.0[b] 106.2[c] 106.1[d] (106.7±1.1)[e]	103.0[a] 105.5[b] 104.2[c] 104.3[d] (105.0±0.1)[e]	—	—			
F	94.7[a] 99.9[b] 99.9[c] 99.5[d]	88.4[a] 92.3[b] 92.8[c] 93.1[d]	81.9[a] 84.7[b] 84.3[c] 84.5[d]	84.0[a] 88.0[b] 88.2[c] 88.5[d]	99.0[a] 103.2[b] 102.8[c] 102.7[d]	98.8[a] 101.8[b] 101.3[c] 101.1[d] (101.3±1)[e]	99.0[a] 102.0[b] 101.8[c] 101.8[d] (103.2±1)[e]	—	—	—	—
CH_3	91.3[a] 96.1[b] 96.3[c] 96.5[d]	87.6[a] 92.7[b] 92.8[c] 92.6[d] (94.0±3)[e]	84.3[a] 88.6[b] 88.1[c] 88.0[d]	84.5[a] 89.8[b] 89.5[c] 89.2[d]	97.8[a] 102.9[b] 102.4[c] 102.3[d]	98.4[a] 101.7[b] 101.2[c] 101.0[d] (100.5±0.3)[e]	96.2[a] 99.8[b] 99.6[c] 99.4[d] (98.2±2)[e]	94.7[a] 99.2[b] 98.9[c] 98.6[d] (98.1±0.7)[e]	—	—	—
$CH{=}CH_2$	78.8[a] 82.8[b] 84.2[c] 84.9[d]	75.4[a] 78.6[b] 80.7[c] 81.4[d]	71.0[a] 77.6[b] 78.3[c] 78.9[d]	74.1[a] 78.7[b] 79.6[c] 79.9[d]	83.2[a] 88.2[b] 88.2[c] —[d]	83.9[a] 86.3[b] 86.9[c] 87.4[d] (88.2±0.7)[e]	80.5[a] 83.1[b] 83.9[c] 84.5[d]	80.0[a] 83.1[b] 84.2[c] 84.6[d] (83.8)[e]	69.4[a] 73.6[b] 74.5[c] 75.8[d] (76.6±1.0)[e]	—	—
OH	86.5[a] 92.0[b] 92.2[c] 92.6[d]	81.8[a] 86.0[b] 86.5[c] 87.0[d]	71.6[a] 77.0[b] 76.7[c] 76.2[d]	79.5[a] 84.2[b] 84.1[c] 84.4[d]	92.5[a] 97.5[b] 97.1[c] 97.1[d]	93.3[a] 96.7[b] 96.3[c] 96.3[d] (96.1±0.2)[e]	97.9[a] 101.0[b] 101.0[c] 101.0[d]	91.5[a] 95.5[b] 95.3[c] 95.2[d] (94.8)[e]	75.3[a] 78.1[b] 79.1[c] 79.9[d] (80.1)[e]	96.0[a] 99.3[b] 99.5[c] 99.5[d]	—
NH_2	78.9[a] 82.8[b] 82.6[c] 83.1[d]	76.2[a] 87.1[b] 82.3[c] 84.1[d] (84.9)[e]	62.0[a] 66.1[b] 66.1[c] 66.3[d]	67.5[a] 72.9[b] 73.4[c] 73.6[d]	88.7[a] 94.2[b] 94.0[c] 94.0[d]	89.3[a] 93.3[b] 93.1[c] 93.1[d] (93.9±2)[e]	97.3[a] 99.6[b] 99.3[c] 100.1[d]	87.7[a] 92.2[b] 92.2[c] 92.1[d] (90.1±2)[e]	70.5[a] 74.3[b] 75.4[c] 76.0[d]	91.3[a] 95.6[b] 95.6[c] 95.7[d]	87.7[a] 92.4[b] 92.4[c] 92.1[d]

[a] From UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d) calculation.
[b] From G3 calculation.
[c] From CBS-Q calculation.
[d] From G3B3 calculation.
[e] Experimental BDEs are shown in the brackets.

The results from our own studies are in good agreement with Radom's work.[7b] We demonstrated that the G3 and CBS-Q methods could predict the BDEs with a precision of about 2 kcal/mol by comparing the theoretical predictions with 161 authoritive BDEs.[9] We also preformed some systematic studies on the SARs associated with the BDEs of various substituted phenyl systems using these advanced and reliable theoretical methods.[10]

Herein we report our recent study on the effects of geminal disubstitution on C–H and N–H BDEs. We consider these disubstitution effects to be important in organic chemistry

Table 2. Theoretical and experimental N–H BDEs of X-NH-Y (kcal/mol)



X/Y	NO_2	CN	BH_2	CHO	CF_3	H	F	CH_3	$CH{=}CH_2$	OH	NH_2
NO_2	97.2[a] 97.8[b] 98.6[c] 99.2[d]	—	—	—	—	—	—	—	—	—	—
CN	92.6[a] 94.5[b] 96.1[c] 97.0[d]	82.2[a] —[b] 88.0[c] —[d]	—	—	—	—	—	—	—	—	—
BH_2	110.2[a] —[b] —[c] 116.3[d]	90.2[a] 95.3[b] 97.4[c] 98.9[d]	95.1[a] 101.4[b] 102.1[c] 102.3[d]	—	—	—	—	—	—	—	—
CHO	106.5[a] 107.9[b] 108.7[c] 108.6[d]	97.1[a] 99.2[b] 100.6[c] 102.4[d]	108.6[a] 114.0[b] 114.6[c] 115.0[d]	115.3[a] 118.7[b] 118.7[c] 118.3[d]	—	—	—	—	—	—	—
CF_3	102.9[a] 105.5[b] 106.0[c] —[d]	92.1[a] 95.4[b] 96.4[c] 97.9[d]	107.6[a] 114.1[b] 114.2[c] 114.4[d]	111.5[a] 115.0[b] —[c] 115.5[d]	108.0[a] —[b] —[c] —[d]	—	—	—	—	—	—
H	103.5[a] 104.6[b] 105.3[c] 105.8[d]	91.0[a] 92.6[b] 94.1[c] 95.4[d]	108.7[a] 112.0[b] 112.4[c] 113.2[d]	111.0[a] 113.7[b] 113.7[c] 113.6[d]	106.6[a] 108.7[b] 108.8[c] 109.5[d]	104.8[a] 106.0[b] 106.0[c] 106.7[d] (107.6±0.1)[e]	—	—			
F	85.6[a] 86.2[b] 87.5[c] 88.6[d]	81.8[a] 83.0[b] 85.0[c] 85.8[d]	108.6[a] 112.1[b] 112.1[c] 112.9[d]	90.7[a] 92.1[b] 92.4[c] 92.7[d]	89.3[a] 90.6[b] 91.6[c] 92.6[d]	87.6[a] 88.5[b] 89.3[c] 90.3[d]	71.3[a] 73.0[b] 73.0[c] 74.3[d] (75.7±2.5)[e]	—	—	—	—
CH_3	97.4[a] 99.2[b] 99.5[c] 99.9[d]	86.5[a] 88.9[b] 90.6[c] 91.7[d]	101.1[a] 106.0[b] 106.8[c] 107.1[d]	103.9[a] 107.4[b] 107.5[c] 107.2[d]	98.4[a] 101.6[b] 102.0[c] 102.5[d]	96.1[a] 98.5[b] 98.8[c] 99.4[d] (101.6±2)[e]	81.4[a] 83.0[b] 84.0[c] 84.9[d]	89.9[a] 91.9[b] 92.4[c] 94.7[d] (94.6±2)[e]	—	—	—
$CH{=}CH_2$	83.4[a] 84.2[b] 85.4[c] 86.0[d]	78.2[a] 81.1[b] 82.9[c] 83.9[d]	90.0[a] 93.1[b] 95.2[c] 96.1[d]	93.2[a] 94.4[b] 95.5[c] 96.4[d]	84.3[a] 86.7[b] —[c] 88.7[d]	86.6[a] 86.4[b] 87.9[c] 89.0[d]	71.9[a] 72.9[b] 73.8[c] 75.1[d]	80.9[a] 81.5[b] 83.2[c] 84.3[d]	77.9[a] 77.0[b] 80.3[c] 82.0[d]	—	——
OH	77.7[a] 78.9[b] 80.3[c] 80.7[d]	75.9[a] 77.7[b] 79.4[c] 80.3[d]	97.5[a] 101.7[b] 102.1[c] 102.9[d]	86.3[a] 87.7[b] 88.4[c] 89.0[d]	83.4[a] 85.4[b] —[c] 87.3[d]	81.5[a] 83.1[b] 83.6[c] 84.8[d]	73.7[a] 73.5[b] 75.4[c] 76.6[d]	78.2[a] 79.5[b] 80.3[c] 82.6[d]	69.6[a] 69.6[b] 71.6[c] 73.1[d]	69.0[a] 70.3[b] 71.4[c] 72.7[d]	—
NH_2	76.1[a] 80.7[b] 81.5[c] 80.7[d]	72.3[a] 74.6[b] 76.6[c] 77.4[d]	89.7[a] 94.1[b] 95.1[c] 96.5[d]	82.5[a] 85.0[b] 85.9[c] 85.8[d]	77.8[a] 80.9[b] 81.8[c] 84.0[d]	78.2[a] 80.5[b] 81.4[c] 82.5[d]	78.6[a] 78.0[b] 79.4[c] 80.6[d]	74.9[a] 74.6[b] 75.6[c] 76.5[d]	69.0[a] 69.8[b] 72.2[c] 73.5[d]	71.9[a] 73.2[b] 74.4[c] 75.5[d]	68.3[a] 69.8[b] 71.2[c] 72.3[d]

[a] From UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d) calculation.
[b] From G3 calculation.
[c] From CBS-Q calculation.
[d] From G3B3 calculation.
[e] Experimental BDEs are shown in the brackets.

because difunctionalized radicals are involved in many synthetic and bioorganic processes. However, only several systematic studies have been performed on disubstituted C-centered radicals. All of these studies were done at either UHF or UMP2 levels.[11–19] Moreover, despite that N-centered radicals are gaining increasing attention,[20] very few studies have ever been reported about the disubstitution effects on them.[21]

There are three basic and important questions that interest us. (1) How good are the performances of the DFT and composite ab initio methods on disubstituted XYCH· and XYN· radicals, where complicated spin delocalization may take place? (2) Can we obtain reliable C–H and N–H BDEs associated with disubstituted XYCH· and XYN· radicals, many of which have not been known before? (3) What are the effects of geminal disubstitution on C–H and N–H BDEs? Are these effects caused by the disubstitution effects on the parent molecules or the radical species?

2. Methods

All the calculations were done using the Gaussian 03 programs.[22] Geometry optimization was conducted without any constraint. Each optimized structure was confirmed by the frequency calculation to be the real minimum without any imaginary vibration frequency. In order to find the optimal conformation for each compound, a search of various conformers was conducted using UB3LYP/6-31G(d) method. The optimal conformation from the search was used as the starting geometry for the G3, CBS-Q, or G3B3 calculation. The same optimal structure at UB3LYP/6-31G(d) level was also used for the single-point energy calculation at the UB3LYP/6-311++G(d,p) level. Because only the optimal conformations were considered in the present work, all the BDEs reported below were thermodynamic BDEs (contrasting the kinetic BDEs).

BDEs were calculated using the UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d) and composite ab initio G3, CBS-Q, and G3B3 methods as the enthalpy change of the following reaction in the gas phase at 298 K, 1 atm.

$$\mathrm{A{-}H(g)} \rightarrow \mathrm{A{\cdot}(g)} + \mathrm{H{\cdot}(g)} \quad (1)$$

The enthalpy of each species was calculated using the following equation:

$$H_{298} = \mathrm{E} + \mathrm{ZPE} + \mathrm{H_{trans}} + \mathrm{H_{rot}} + \mathrm{H_{vib}} + \mathrm{RT} \quad (2)$$

ZPE is the zero point energy. H_{trans}, H_{rot}, and H_{vib} are the standard temperature correction term calculated using the equilibrium statistical mechanics with harmonic oscillator and rigid rotor approximations. For the UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d) method, zero point energies and temperature corrections were calculated at B3LYP/6-31G(d) level scaled by 0.9804.[23]

It is worth noting that the composite ab initio methods involve a series of calculations that are designed to recover the errors that result from the truncation of both the one-electron basis set and the number of configurations used for treating correlation energies. G3 (Gaussian-3, G3/MP2)[24] is one of the composite ab initio methods. Its geometry optimization is done at MP2(full)/6-31G(d) level. A scaled HF/6-31G(d) ZPE is used in G3. A base energy calculated at MP4/6-31G(d) level is then corrected to QCISD(T)(full)/G3Large level using several additivity approximations at MP2 and MP4 levels.

CBS-Q is another composite ab initio method.[25] It starts with HF/6-31G* geometry optimization and frequency calculation, which is then followed by the MP2(FC)/6-31G* optimization. The single-point energy is calculated at MP2/6-311+G(3d2f, 2df, 2p), MP4(SDQ)/6-31+G(d(f),p), and QCISD(T)/6-31+G* levels. This energy is then extrapolated to the complete basis set limit.

G3B3 (or G3//B3LYP) method is a variant of G3 theory in which structures and zero point vibrational energies are calculated at the B3LYP/6-31G(d) level of theory.[26] This variation is particularly advantageous for larger systems and for open shell systems showing large spin contamination. For the single-point energy calculation G3B3 is very similar to the original G3 method, for example, a base energy calculated at MP4/6-31G(d) level is corrected to QCISD(T)(full)/G3Large level using several additivity approximations at MP2 and MP4 levels.

3. Results and discussion

3.1. C–H and N–H bond dissociation energies

Four different methods (i.e., UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d), G3, CBS-Q, and G3B3) were used to calculate the C–H and N–H BDEs. The results are listed in Tables 1 and 2.

Comparing the theoretical results with 24 available experimental data,[27] we found that the G3B3 method provided the best predictions for C–H and N–H BDEs (Fig. 1). The standard deviation and mean error between the G3B3 and experimental BDEs are 1.4 and −0.1 kcal/mol, respectively. This calculation accuracy is obviously satisfactory because the experimental error in BDE usually amounts to 1–2 kcal/mol (see Tables 1 and 2).

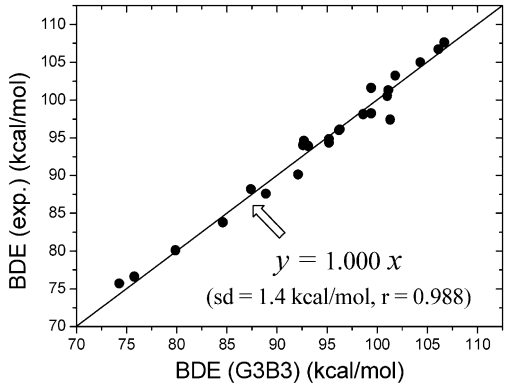
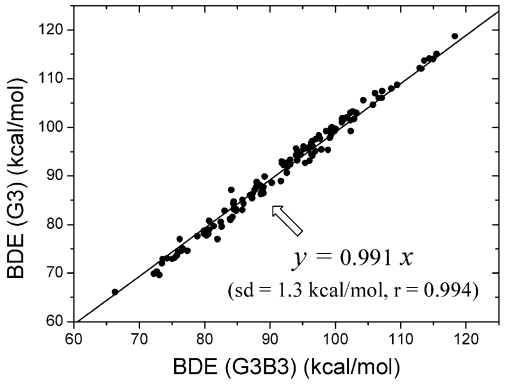


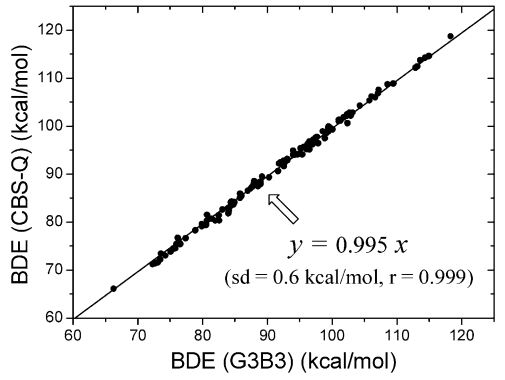
Figure 1. Comparison between G3B3 BDEs and the experimental data.

The G3 and CBS-Q BDEs are in good agreement with the G3B3 data for all the compounds in Tables 1 and 2. The standard deviation and mean error between G3 and G3B3 are 1.3 and 1.0 kcal/mol (Fig. 2). The standard deviation and mean error between CBS-Q and G3B3 are 0.6 and 0.5 kcal/mol. It is worthy to note that G3, CBS-Q, and G3B3 methods utilize fairly different protocols in geometry optimization and extrapolations of correlation and basis set effects. The agreement between these composite ab initio methods on BDEs suggests that the theoretical predictions are reliable.

Despite the great success of the composite ab initio methods in BDE predictions, a significant drawback of these methods is that they demand tremendous CPU time. Therefore, a lot of researchers prefer to use the density functional methods to calculate BDEs.[28] Herein we examined the efficacy of the UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d) method. We found that this method could not reliably provide the absolute BDEs, because it systematically underestimated



(a)



(b)

Figure 2. Comparing G3B3 BDEs with G3 (a) and CBS-Q BDEs (b).

the BDEs by ca. 5 kcal/mol compared to the benchmark G3B3 data (Fig. 3). Nevertheless, the B3LYP method can be used to calculate the relative BDEs as there is a nice correlation between the B3LYP and G3B3 BDEs (correlation coefficient = 0.992).

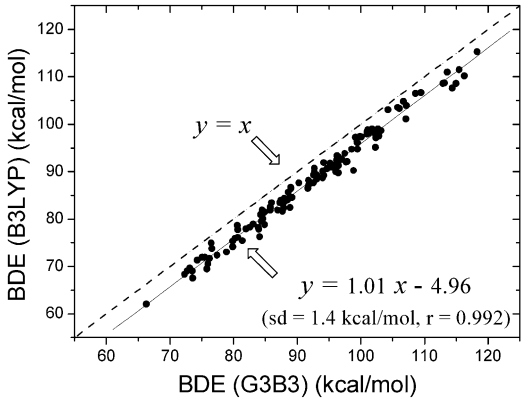


Figure 3. Comparison between G3B3 BDEs and UB3LYP BDEs.

3.2. Substitution effects on C–H and N–H BDEs

The effects of substitution on C–H and N–H BDEs can be quantified by the relative BDEs (ΔBDE) compared to the parent molecules, for example, CH_4 and NH_3 (see Tables 3 and 4).

$$\Delta\text{BDE} = \text{BDE(substituted case)} - \text{BDE(parent)} \quad (3)$$

From Table 3, it can be seen that the ΔBDEs associated with the C–H bonds are negative under most conditions. Very large ΔBDEs (< -20 kcal/mol) are seen in the compounds that have both an electron-withdrawing and an electron-donating group (e.g., NH_2–CH_2–CHO). Sizable ΔBDEs are also seen in the molecules that have the CH=CH_2 group. Only two molecules ($CF_3CH_2CF_3$ and CF_3CH_3) show positive ΔBDEs. They both carry the electron-deficient CF_3 group, which is known to have little ability to delocalize an adjacent odd electron via hyperconjugation.[6]

In comparison with the C–H cases, the ΔBDEs associated with the N–H bonds are also negative under many conditions. However, the largest ΔBDEs (< -30 kcal/mol) are not seen in the compounds that have both an electron-withdrawing and an electron-donating group, but those molecules that have two electron-donating groups (e.g., NH_2–NH–NH_2, HO–NH–OH).

Another difference between the C–H and N–H cases is that some electron-withdrawing groups (e.g., CHO and BH_2), in addition to CF_3, can cause positive ΔBDEs. This behavior may appear surprising because groups like CHO and BH_2 are known to be good radical stabilizing groups. We proposed that the loss of conjugation between the lone pair electrons on nitrogen atom and the electron-withdrawing groups in the course of N–H homolysis should cause the positive ΔBDE (see Scheme 1).[7b] It is worth noting that Radom et al. also reported this interesting behavior very recently.[29]

3.3. Extra substitution effects on BDEs

An important and interesting question in chemical thermodynamics is whether or not an energetic effect is additive.[30] Herein, the issue is whether or not the disubstitution effects on BDEs (i.e., ΔBDE (X–CH_2–Y)) equal to the sum of the effects of mono-substitutions (i.e., ΔBDE (X-CH_3) + ΔBDE (CH_3-Y)). Thus we defined

Extra substitution effect (ESE)

$$= \Delta\text{BDE}(\text{X} - \text{CH}_2 - \text{Y}) - \Delta\text{BDE}(\text{X} - \text{CH}_3) - \Delta\text{BDE}(\text{CH}_3 - \text{Y}) \quad (4)$$

Clearly, if the disubstitution effect is additive, the corresponding ESE should be zero.

It is found that both the C–H and N–H BDEs exhibit nonzero ESEs under disubstitution conditions (see Tables 5 and 6). As both positive and negative ESEs have been obtained, the disubtitution effects on BDEs can either be larger or smaller than the sum of the effects of mono-substitutions. Therefore, geminal disubstitution effects on C–H and N–H BDEs are generally not additive.

Some trends may be recognized for the extra substitution

Table 3. Relative C–H BDEs (ΔBDE) calculated using the G3B3 method[a] (kcal/mol)

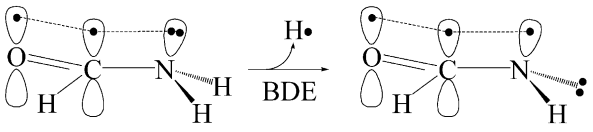
X/Y	NO_2	CN	BH_2	CHO	CF_3	H	F	CH_3	$CH=CH_2$	OH	NH_2
NO_2	-1.1	-	-	-	-	-	-	-	-	-	-
CN	-10.1	-15.4	-	-	-	-	-	-	-	-	-
BH_2	-9.6	-16.4	-12.5	-	-	-	-	-	-	-	-
CHO	-10.3	-16.4	-12.5	-16.3	-	-	-	-	-	-	-
CF_3	-1.0[b]	-6.6	-6.8	-7.8	+2.8[b]	-		-	-	-	-
H	-3.0	-8.1	-10.1	-9.1	+1.8	0.0	-		-	-	-
F	-4.8	-11.2	-19.8	-15.8	-1.6	-3.2	-2.5	-	-	-	-
CH_3	-7.8	-11.7	-16.3	-15.1	-2.0	-3.3	-4.9	-5.7	-	-	-
$CH=CH_2$	-19.4	-22.9	-25.4	-24.4	-16.0[c]	-16.9	-19.8	-19.7	-28.5	-	-
OH	-11.7	-17.3	-28.1	-19.9	-7.2	-8.0	-3.3	-9.1	-24.4	-4.8	-
NH_2	-21.2	-20.2	-38.0	-30.7	-10.3	-11.2	-4.2	-12.2	-28.3	-8.6	-12.2

[a] $\Delta BDE = BDE(X\text{-}CH_2\text{-}Y) - BDE(CH_4)$.
[b] From G3 calculation.
[c] From CBS-Q calculation.

Table 4. Relative N–H BDEs (ΔBDE) calculated using the G3B3 method[a] (kcal/mol)

X/Y	NO_2	CN	BH_2	CHO	CF_3	H	F	CH_3	$CH=CH_2$	OH	NH_2
NO_2	-7.5	-	-	-	-	-	-	-	-	-	-
CN	-9.7	-18.0[b]	-	-	-	-	-	-	-	-	-
BH_2	+9.6	-7.8	-4.4	-	-	-	-	-	-	-	-
CHO	+1.9	-4.3	+8.3	+11.6	-	-	-	-	-	-	-
CF_3	+0.0[b]	-8.8	+7.7	+8.8	+3.2[c]	-	-	-	-	-	-
H	-0.9	-11.3	+6.5	+6.9	+2.8	0.0	-	-	-	-	-
F	-18.1	-20.9	+6.2	-14.0	-14.1	-16.4	-32.4	-	-	-	-
CH_3	-6.8	-15.0	+0.4	+0.5	-4.2	-7.3	-21.8	-12.0	-	-	-
$CH=CH_2$	-20.7	-22.8	-10.6	-10.3	-18.0	-17.7	-31.6	-22.4	-24.7	-	-
OH	-26.0	-26.4	-3.8	-17.7	-19.4	-21.9	-30.1	-24.1	-33.6	-34.0	-
NH_2	-26.0	-29.3	-10.2	-20.9	-22.7	-24.2	-26.1	-30.2	-33.2	-31.2	-34.4

[a] $\Delta BDE = BDE(X\text{-}NH\text{-}Y) - BDE(NH_3)$.
[b] From CBS-Q calculation.
[c] From UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d) calculations.



Scheme 1.

effects on C–H and N–H BDEs. First, geminal substitution of two donor groups (e.g., F, CH_3, $CH=CH_2$, OH, NH_2) usually leads to a positive ESE value for both C–H and N–H BDEs (see the lower-right regions of Tables 5 and 6). Secondly, geminal substitution of two acceptor groups (e.g., NO_2, CN, BH_2, CHO, CF_3) usually leads to a positive ESE value for C–H BDEs, but not N–H BDEs. Finally, geminal substitution of one acceptor and one donor group usually leads to a negative ESE value for C–H BDEs, but not N–H BDEs. Explanations for these interesting behaviors are provided in the following sections.

We need to mention that Pasto has also studied the ESEs on the C–H BDEs associated with disubstituted methyl radicals.[12] His results, obtained using the ROHF/4-31G method, were shown in Table 5. One can see that for most cases the present results are in agreement with Pasto's data. Nevertheless, we noted some significant differences between our and Pasto's data for those molecules having vinyl substitution.

It appears that the ROHF/4-31G method is not adequate for the vinyl cases. This is indicated by the C–H BDE of 1,4-pentadiene, which was measured experimentally to be 76.6 ± 1.0 kcal/mol.[31] Compared to the experimental C–H BDE of CH_4 (105.0 ± 0.1 kcal/mol), one can calculate that ΔBDE (1,4-pentadiene) $= -28.4$ kcal/mol. This number is much lower than the value reported by Pasto (i.e., -20.32 kcal/mol). This is the reason that Pasto obtained a value of -4.0 kcal/mol for the ESE of 1,4-pentadiene. In comparison to Pasto's results, we obtained a value of -28.5 kcal/mol for ΔBDE (1,4-pentadiene) and therefore, $+5.3$ kcal/mol for the ESE. The experimental ESE value of

Table 5. Extra substitution effects on C–H BDEs calculated using the G3B3 method[a] (kcal/mol)

	NO_2	CN	BH_2	CHO	CF_3	H	F	CH_3	$CH=CH_2$	OH	NH_2
NO_2	+4.9	-	-	-	-	-		-	-	-	-
CN	+1.0	+0.8 (-0.5[b])	-	-	-	-		-	-	-	-
BH_2	+3.5	+1.8 (+2.2[b])	+7.7 (+8.3[b])	-	-	-		-	-	-	-
CHO	+1.8	+0.8 (+1.0[b])	+6.7	+1.9 (+0.6[b])	-	-		-	-	-	-
CF_3	+0.2	-0.3	+1.5	-0.5	-0.8	-		-	-	-	-
H	0.0	0.0	0.0	0.0	0.0	0.0		-	-	-	-
F	+1.4	+0.1 (+1.2[b])	-6.5 (-2.9[b])	-3.5 (+0.7[b])	-0.2	0.0	+3.9 (+2.4[b])				
CH_3	-1.5	-0.3	-2.9	-2.7	-0.5	0.0	+1.6	+0.9	-	-	-
$CH=CH_2$	+0.5	+2.1(-2.7[b])	+1.5 (-2.5[b])	+1.6 (-3.6[b])	+1.0	0.0	+0.3 (+0.6[b])	+0.5	+5.3 (-4.0[b])	-	-
OH	-0.7	-1.2 (+0.2[b])	-12.0 (-8.4[b])	-2.8 (-4.7[b])	-1.0	0.0	+7.9 (+11.6[b])	+2.2	+0.5 (+0.3[b])	+11.2	-
NH_2	-2.8	-0.9 (-1.1[b])	-16.7 (-12.0[b])	-10.4 (-8.3[b])	-0.9	0.0	+10.2 (+ 6.8[b]	+2.3	-0.2 (-1.1[b])	+10.6	+10.2

[a] Extra substitution effects on C–H BDEs are calculated as ESE = ΔBDE(X-CH_2-Y) − ΔBDE(X-CH_3) − ΔBDE(Y-CH_3).
[b] Theoretical values at ROHF/4-31G level are taken from Ref. 12. Only the thermodynamic BDEs are considered in the present study.

Table 6. Extra substitution effects on N–H BDEs calculated using the G3B3 method[a] (kcal/mol)

	NO_2	CN	BH_2	CHO	CF_3	H	F	CH_3	$CH=CH_2$	OH	NH_2
NO_2	-5.7	-	-	-	-	-	-	-	-	-	-
CN	+2.5	+5.8[b]	-	-	-	-	-	-	-	-	-
BH_2	+4.0	-3.0	-17.4	-	-	-	-	-	-	-	-
CHO	-4.1	+0.1	-5.1	-2.2	-	-	-	-	-	-	-
CF_3	-1.9	-0.3	-1.6	-0.9	-0.4[c]	-	-		-	-	-
H	0.0	0.0	0.0	0.0	0.0	0.0		-	-	-	--
F	-0.8	+6.8	+16.1	-4.5	-0.5	0.0	+0.4				
CH_3	+1.4	+3.6	+1.2	+0.9	-4.3	0.0	+0.9	+2.6	-	-	-
$CH=CH_2$	-2.1	+6.2	+0.6	+0.5	-3.1	0.0	+2.5	+2.6	+10.7	-	-
OH	-2.8	+6.8	+11.6	-2.7	-0.3	0.0	+8.2	+5.1	+6.0	+9.8	-
NH_2	-0.9	+6.2	+7.5	-3.6	-1.3	0.0	+14.5	+1.3	+8.7	+14.9	+14.0

[a] Extra substitution effects on N–H BDEs are calculated as ESE = ΔBDE(X-NH-Y) − ΔBDE(X-NH_2) − ΔBDE(Y-NH_2).
[b] From G3 calculations.
[c] From UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d) calculations.

1,4-pentadiene is +5.2 kcal/mol, which is in agreement with our result.

3.4. Extra substitution effects on the stabilities of disubstituted methanes

In the above sections we obtained reliable BDEs and we discussed the substitution effects on BDEs. The results from the above sections are useful for experimentalists because these data can be utilized directly to predict or interpret the observed chemical reactivities. However, in order to rationalize the observations reported in the previous sections we cannot merely rely on the BDE data. The reason is that the bond homolysis process is affected by both the stability of the parent molecules and the stability of the resulting radicals. Thus we have to study the disubstitution effects on the stabilities of the parent compounds and the radicals, respectively.

At first we consider the geminal disubstitution effects on the stability of methane. This subject has been studied before by Leroy,[32] Schleyer,[33] Houk,[34] Wiberg,[35] Gajewski[18] etc. The central question is whether the two functional groups attached to the same carbon can cause extra stabilization or destabilization of the system. Mathematically, this equal to asking whether the ESE[36] defined in Eq. 5 is positive or negative.

$$\mathrm{ESE} = H_{298}(\mathrm{X-CH_2-Y}) + H_{298}(\mathrm{CH_4}) - H_{298}(\mathrm{X-CH_3}) - H_{298}(\mathrm{CH_3-Y}) \quad (5)$$

If ESE < 0, there is an extra stabilization effect. If ESE > 0, there is an extra destabilization.

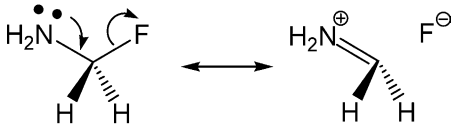
Our results are shown in Table 7. Since a lot of cases have been studied before using either lower level theoretical methods or experimental results, we also show the previous data for comparison. It is clear that the present results are in good agreement with the previous findings.

Table 7. Extra substitution effects on the stability of CH_4 calculated using the G3B3 method[a] (kcal/mol)

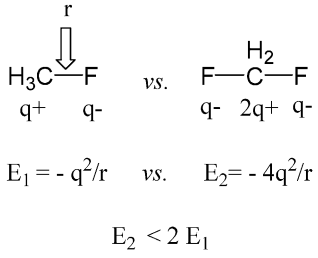
	NO_2	CN	BH_2	CHO	CF_3	H	F	CH_3	$CH=CH_2$	OH	NH_2
NO_2	+6.6 (+6.6[b])	-	-	-	-	-	-	-	-	-	-
CN	+7.0	+7.6 (+7.1[c])	-	-	-	-	-	-	-	-	-
BH_2	-3.9	-1.1	-4.5	-	-	-	-	-	-	-	-
CHO	+1.2	+2.8 (+1.8[c])	-2.4	+1.6 (-0.3[c])	-	-	-	-	-	-	-
CF_3	+5.9[e]	+4.9	-1.6	+2.8	+4.9[e]	-	-	-	-	-	-
H	0.0	0.0	0.0	0.0	0.0	0.0					
F	-2.1	+3.0	-1.2	-0.3	+1.0	0.0	-12.8 (-13.6[b])	-	-	-	-
CH_3	-5.1 (-3.0[d])	-2.3 (-2.6[c])	-0.4	-2.0 (-2.1[b])	-3.1	0.0	-6.5 (-6.6[c])	-2.7 (-2.8[b])	-	-	-
$CH=CH_2$	-3.3	-0.4 (-2.8[b])	-2.0	-1.2	-1.6	0.0	-4.3	-2.5 (-2.9[b])	-2.0 (-2.2[b])	-	-
OH	-8.6	-0.1 (-1.0[c])	-1.5	-2.9 (-3.5[c])	-2.4 (-6.2[d])	0.0	-14.9 (-16.2[d])	-5.8 (-6.1[b])	-4.0 (-4.3[b])	-15.7 (-15.4[d])	-
NH_2	-10.5 (-8.2[d])	-2.1 (-1.0[c])	+0.4	-3.1 (-4.1[c])	-4.2	0.0	-15.3 (-14.9[d])	-4.6 (-4.8[c])	-2.6	-12.7 (-14.1[c])	-9.7 (-9.3[c])

[a] Extra substitution effects on the stability of CH_4 are defined as $ESE = H_{298}(X\text{-}CH_2\text{-}Y) + H_{298}(CH_4) - H_{298}(X\text{-}CH_3) - H_{298}(CH_3\text{-}Y)$.
[b] Calculated using experimental gas-phase heat of formation at 298 K.
[c] MP2/6-31G* data from Ref. 18.
[d] Theoretical data from Ref. 13.
[e] From CBS-Q calculations.

It is generally believed that there is an extra stabilization when the two substituents are both σ-acceptors and π-donors (e.g., F, OH).[34] This explains why all the ESE values in the lower-right region of Table 7 are negative. Negative hyperconjugation (or anomeric effect. 'Negative' means the $\sigma^* \leftrightarrow \pi$ hyperconjugation, in contrast to the positive $\sigma \leftrightarrow \pi^*$ hyperconjugation. See Scheme 2) has been proposed for the extra stabilization,[33] although electrostatic interaction may also be important (see Scheme 3).[35]



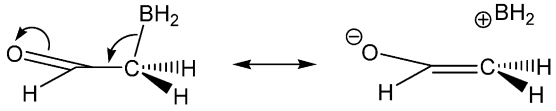
Scheme 2.



Scheme 3.

Most of the ESE values in the upper-left region of Table 7 are positive corresponding to extra destabilization. This can be explained by the electrostatic effects.[35] For instance, in $O_2NCH_2NO_2$ all the N and C atoms are carrying positive charges. Because of the electron-withdrawing effect of NO_2, carbon in $O_2NCH_2NO_2$ carries more positive charge than carbon in CH_3NO_2. Therefore, a stronger electrostatic repulsion between C and N should be seen in $O_2NCH_2NO_2$ than in two CH_3NO_2 molecules.

Interestingly, extra stabilization effects are seen for the compounds possessing a BH_2 group and an electron-withdrawing group. This phenomenon has not been noted before. It indicates that the previous theory,[36] which claimed that two acceptor groups should always cause extra destabilization effect in the closed-shell neutral systems, was incorrect. The reason for the extra stabilization effects associated with the BH_2 group is possibly that BH_2 is a π-acceptor but a σ-donor. This means that the high-lying C-B σ bonding orbital may interact with the π^* antibonding orbitals in the other acceptor substituent via positive hyperconjugation, which results in extra stabilization (see Scheme 4). The optimal conformations of the borane compounds (Fig. 4) are consistent



Scheme 4.

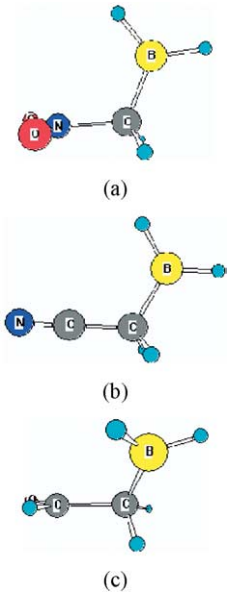


Figure 4. The optimal conformation of (a) $BH_2CH_2NO_2$, (b) BH_2CH_2CN, and (c) BH_2CH_2CHO.

Table 8. Extra substitution effects on the stability of $CH_3\cdot$ radicals calculated using the G3B3 method[a] (kcal/mol)

	NO_2	CN	BH_2	CHO	CF_3	H	F	CH_3	$CH{=}CH_2$	OH	NH_2
NO_2	+11.5 (+18.6[b])	-	-	-	-	-	-	-	-	-	-
CN	+8.0	+8.3 (+10.4[b])	-	-	-	-	-	-	-	-	-
BH_2	-0.4	+0.6	+3.1 (+5.4[b])	-	-	-	-	-	-	-	-
CHO	+2.9	+3.6	+4.3	+3.5	-	-	-	-	-	-	-
CF_3	+6.9[c]	+4.6	-0.1	+2.4	+3.0[c]	-	-	-	-	-	-
H	0.0	0.0	0.0	0.0	0.0	0.0					
F	-0.8	+3.1	-7.7	-3.7	+0.8	0.0	-8.8 (-10.5[b])	-	-	-	-
CH_3	-6.6 (-6.0[d])	-2.6 (-1.6[b])	-3.3	-4.7 (-2.4[b])	-3.6	0.0	-4.9 (-2.5[d])	-1.8 (-2.0[b])	-	-	-
$CH{=}CH_2$	-2.8	+1.5	-0.6	+0.3	-2.3[c]	0.0	-4.1	-2.0 (-2.3[d])	+3.2 (+3.3[d])	-	-
OH	-9.3 (-4.2[b])	-1.4 (+1.4[b])	-13.5	-5.6 (-8.4[b])	-3.3 (-0.8[b])	0.0	-7.0	-3.5 (-3.2[b])	-3.5 (-1.6[d])	-4.5 (-8.7[b])	-
NH_2	-13.3 (-8.1[b])	-3.1 (-1.7[b])	-16.3 (-12.4[b])	-13.5 (-8.2[b])	-5.1 (-4.9[b])	0.0	-5.0	-2.3 (-3.2[b])	-2.8	-2.1	+0.6 (-1.1[b])

[a] Extra substitution effects on the stability of $CH_3\cdot$ radicals are defined as $H_{298}(\text{X-CH}(\cdot)\text{-Y}) + H_{298}(CH_3\cdot) - H_{298}(\text{X-CH}_2\cdot) - H_{298}(CH_2(\cdot)\text{-Y})$.
[b] Theoretical data from Ref. 13.
[c] From CBS-Q calculations.
[d] Calculated using the experimental data reported in Ref. 27.

with the proposed $\sigma(\text{C-B}) \leftrightarrow \pi^*$ hyperconjugation interaction. More detailed study on this issue, which involves a lot of orbital analyses, will be reported somewhere else.

The lower-left region of Table 7 contains those molecules which have both a donor and an acceptor substituent. Most of the molecules here show extra stabilization effects. This can be explained again using the negative hyperconjugation effect (anomeric effect)[33] or the electrostatic interactions.[35] Nonetheless, two molecules (FCH_2CN and FCH_2CF_3) in the lower-left region of Table 7 show extra destabilization effect. This may be caused by the same mechanism (i.e., electrostatic repulsion) that makes the ESE of $CH_2(CN)_2$ and CH_2CNCF_3 positive.

3.5. Extra substitution effects on the stabilities of disubstituted methyl radical

We define the ESE associated with disubstituted methyl radicals using Eq. 6.

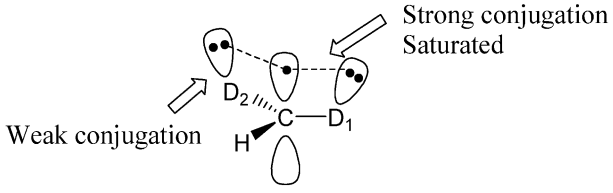
$$\text{ESE} = H_{298}(\text{X}-\text{CH}(\cdot)-\text{Y}) + H_{298}(CH_3\cdot) - H_{298}(\text{X}-\text{CH}_2\cdot) - H_{298}(CH_2 \quad (6)$$

If ESE <0, there is an extra stabilization effect. If ESE >0, there is an extra destabilization.

The results are listed in Table 8. Again, because the disubstitution effects on the stabilities of methyl radicals have been studied by several groups before,[13,17] we listed the previous results in Table 8. It is clear that the present results compare favourably with the earlier experimental measurements and theoretical calculations.

Examination of Table 8 reveals that geminal substitution of two donor groups usually exhibits extra stabilization effect on a carbon-centered radical (see the lower-right region of Table 8). This was explained before by Chandrasekhar et al.[17] using the negative hyperconjugation effect (anomeric effect)[33] or electrostatic effect.[35]

Comparing the ESE values in Table 8 and those in Table 7, one may recognize that the geminal substitution of two donor groups has a larger extra stabilization effect on the saturated carbon precursor than on the radical center. This observation can be explained using the conjugation saturation effect.[13] That is, when a donor group has conjugation interaction with a carbon radical center, the conjugation interaction between the same radical center and the second donor group must be much weaker than that with the first donor (see Scheme 5). It is worth noting that the conjugation saturation effect attenuates conjugative stabilization of the radicals, but does not affect hyperconjugation.



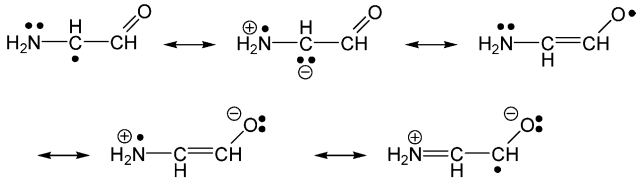
Scheme 5.

The strength of the conjugation saturation effect is determined by the strength of the conjugation interaction. Clearly, a stronger conjugation between the first donor group and the radical center should produce a more sig-nificant conjugation saturation effect. For $\cdot CH(CH{=}CH_2)_2$ and $\cdot CH(NH_2)_2$, the conjugation saturation effect is so strong that it cannot be fully offset by the anomeric effect. Thus $\cdot CH(CH{=}CH_2)_2$ and $\cdot CH(NH_2)_2$ actually show extra destabilization.

In addition to the donor groups, acceptor groups can also have conjugation interactions with the carbon radical center. Thus conjugation saturation effect should also occur in case of the geminal substitution of two acceptor groups. As demonstrated in Section 3.4, two acceptor groups can produce extra destabilization effect due to electrostatic repulsion. Adding the conjugation saturation effect and repulsion effect together, we can predict that geminal substitution of two acceptors on a carbon radical should

show an extra destabilization effect, and this extra destabilization effect is more significant than that on the saturated carbon precursor. This prediction is validated by the calculation results in Table 8.

Certainly the conjugation saturation effect should also occur in case of geminal substitution of both a donor and an acceptor group. However, charge transfer may take place easily from the donor side to the acceptor side via the sp^2-hybridized carbon center in the same system (see the last two resonance forms in Scheme 6). This charge transfer interaction brings about some extra stabilization effect which is not present in the mono-substituted radicals. This extra stabilization effect is usually named as 'captodative effect'[16] (or 'push–pull effects', 'merostabilization'[37,38]).



Scheme 6.

A long-standing controversy about the captodative effect is whether this effect is real. Many evidences suggested that the captodative effect should be valid.[16] However, examples have also been provided showing that the captodative effect was not present.[12] Our own examinations of the literatures reveal a common misunderstanding about the captodative effect. That is, whether we shall regard the captodative effect as one type of energetic effect which may occur simultaneously with other energetic effects, or as a dominant phenomenon.

If we regard the captodative effect as a dominant phenomenon, then the captodative effect cannot be a universally valid concept. As seen in Table 8, the ESE values of four 'captodative' carbon radicals (i.e., ·CHFCN, ·$CHFCF_3$, ·CH($CH{=}CH_2$)CN, and ·CH($CH{=}CH_2$)CHO) are positive which means extra destabilization. Therefore, one cannot claim that a captodative carbon radical is always more stabilized than the mono-substituted ones.

On the other hand, if we regard the captodative effect as one type of energetic effect, then the captodative effect is a useful concept. Using this concept we can easily understand why most of the radicals in the lower-left region of Table 8 show more significant extra stabilization effects than the corresponding saturated precursors. The reason for the net destabilization effects observed for ·CHFCN and ·$CHFCF_3$ is presumably the strong electrostatic repulsion that cannot be fully offset by the captodative effect. The reason for the net destabilization effects observed for ·CH($CH{=}CH_2$)CN and ·CH($CH{=}CH_2$)CHO is presumably the strong conjugation saturation effect caused by $CH{=}CH_2$ that cannot be fully offset by the captodative effect.

At this point, we have discussed all the observations associated with the carbon radials and their precursors. The main findings are summarized as follows.

1. Geminal substitution of two donor groups usually leads to extra stabilization of both the carbon radicals and their saturated precursors. The main driving force for the extra stabilization is the negative hyperconjugation effect and the electrostatic effect. However, because of the conjugation saturation effect, weaker extra stabilization is seen in the carbon radicals than in the saturated precursors. This causes the positive ESE values observed for the C–H BDEs associated with two donor substitutions.
2. Geminal substitution of two acceptor groups usually leads to extra destabilization of both the carbon radicals and their precursors. This main driving force for the extra destabilization is the electrostatic repulsion effect. BH_2 is an exception in this category because it may cause sizable positive hyperconjugation effect. Because of the conjugation saturation effect, larger destabilization effect is seen in the carbon radicals than in the saturated precursors. Thus the observed ESE values for the C–H BDEs associated with two acceptor groups are usually positive.
3. Geminal substitution of one donor and one acceptor group usually leads to extra stabilization of both the carbon radicals and their precursors. The main driving force for the extra stabilization associated with the saturated precursors is the negative hyperconjugation effect and electrostatic effect. Larger extra stabilization is usually seen for the carbon radicals because of the captodative effect. Thus the observed ESE values for the C–H BDEs associated with one acceptor and one donor group are usually negative.
4. It is better to regard the captodative effect as one type of energetic effect than to regard it as a dominant phenomenon. It is not valid to claim that a captodative system must be more stabilized compared to the mono-substituted systems. In order to predict or interpret the net, observable effects associated with carbon radicals, we have to consider other interactions (e.g., conjugation saturation effect, positive or negative hyperconjugation, electrostatic interaction) in addition to the captodative effect. It is the combination of all the energetic effects, but not the captodative effect alone, that should be utilized to study the captodative systems. Nonetheless, the captodative effect, whenever being present, must always bring about extra stabilization (in the same way as the so-called 'electrostatic attraction').

3.6. Extra substitution effects on the stabilities of disubstituted amines

In Section 3.3 we mentioned that some trends that are nicely followed by the carbon radicals cannot be applied to the nitrogen systems. Therefore, we cannot use our knowledge about the carbon radicals straightforwardly to solve the problems associated with the nitrogen radicals.

Herein we studied the extra substitution effects on the stability of disubstituted amines. We define the ESE associated with disubstituted methyl radicals using Eq. 7.

$$\mathrm{ESE} = H_{298}(\mathrm{X-NH-Y}) + H_{298}(\mathrm{NH_3}) - H_{298}(\mathrm{X-NH_2}) - H_{298}(\mathrm{NH_2-Y}) \quad (7)$$

The results are shown in Table 9. Very few literature results

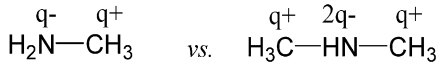
Table 9. Extra substitution effects on the stability of NH_3 calculated using the G3B3 method[a] (kcal/mol)

	NO_2	CN	BH_2	CHO	CF_3	H	F	CH_3	$CH=CH_2$	OH	NH_2
NO_2	+13.9	-	-	-	-	-	-	-	-	-	-
CN	+9.2	+9.2[d]	-	-	-	-	-	-	-	-	-
BH_2	+3.6	+2.9	+10.2 (+9.3[c])	-	-	-	-	-	-	-	-
CHO	+6.0	+5.5	+3.1	+3.6	-	-	-	-	-	-	-
CF_3	+8.2[d]	+6.7	+2.8	+5.7	+9.8[g]	-	-	-	-	-	-
H	0.0	0.0	0.0	0.0	0.0	0.0					
F	+1.3	+6.6	+1.0	+4.6	+3.1	0.0	-12.7 (-8.7[f])	-	-	-	-
CH_3	-7.2	-3.9	-3.6	-4.3	-4.4	0.0	-8.7 (-5.7[f])	-4.7 (-4.7[b])	-	-	-
$CH=CH_2$	-0.2	-0.7	-2.2	-2.6	-0.8	0.0	-2.8	-3.9	-4.1	-	-
OH	-4.5	+2.5	+0.9	+0.9	-0.8	0.0	-15.9	-3.9 (-6.4[f])	-3.0	-12.0 (-11.9[f])	-
NH_2	-10.0	-2.6	-3.4	-3.6	-4.7	0.0	-19.4	-3.7 (-5.7[f])	-4.5	-14.5 (-12.0[c])	-10.3 (-8.8[c])

[a] Extra substitution effects on the stability of NH_3 are defined as H_{298}(X-NH-Y)+H_{298}(NH_3)−H_{298}(X-NH_2)−H_{298}(NH_2-Y).
[b] Experimental values calculated using the gas-phase heat of formation at 298 K.
[c] Theoretical data from Ref. 13.
[d] From G3 calculations.
[f] From Ref. 39.
[g] From B3LYP/6-311++g(d,p)//B3LYP/6-31+g(d) calculations.

can be found for comparison. Nonetheless, our results compared favourably with the several previous data.

First, it is not surprising to see that all the compounds carrying two donor groups show extra stabilization effects. (See the lower-right region of Table 9) The main driving forces for the extra stabilization should also be the negative hyperconjugation effect and the electrostatic interactions. Since nitrogen is more electronegative than carbon, it is worthy mentioning that the electrostatic interaction in the $NH(CH_3)_2$ and $NH(CH{=}CH_2)_2$ cases may involve some positive, but not negative, charges on the substituents (see Scheme 7).



$$E_1 = -q^2/r \quad vs. \quad E_2 = -4q^2/r$$

$$E_2 < 2E_1$$

Scheme 7.

All the compounds carrying two acceptor groups show extra destabilization effects. Presumably the electrostatic repulsion interaction is one of the reasons for the extra destabilization. However, we suspect that the major reason for the extra destabilization comes from the conjugation saturation effect. That is, when one acceptor forms conjugation with the lone pair electrons of nitrogen, the same lone pair will not be easily available for any other acceptor to form conjugation. Thus, two acceptors put on one nitrogen atom cannot get the same amount of conjugation effect as two separate N-acceptor molecules.

More intriguing extra substitution effects are seen for the compounds carrying both a donor and an acceptor group (see the lower-left region of Table 9). Most of the amine compounds in this category show extra stabilization effect, and the largest extra stabilization effect is shown by NH_2–NH–NO_2 (−10.0 kcal/mol). It is possible that captodative effect can occur in these amine compounds using the lone pair electrons on nitrogen as a bridge. Certainly the negative hyperconjugation (i.e., $\pi_{donor} \leftrightarrow \sigma^*_{N\text{-acceptor}}$ interaction) may also contribute to the extra stabilization.

Nonetheless, it is clear that all the F–NH-acceptor and most of the HO–NH-acceptor molecules actually show extra destabilization effect. The reason for these odd behaviours should be attributed to the high electronegativity values of the F and O atoms. As good σ-acceptors, F and O atoms reduce the electron-donating ability of the central nitrogen atom. In consequence the conjugation between the central nitrogen and the acceptor group is less effective, which causes the extra destabilization effect. As seen in Figure 5, in NH_2–CN the cyano nitrogen carries a negative charge of −0.942 e. However, in FNH–CN the cyano nitrogen only carries a negative charge of −0.264 e.

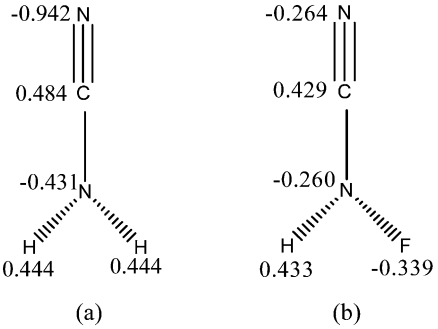


Figure 5. NBO (natural bonding orbital theory[40]) charge distributions in (a) NH_2–CN and (b) FNH–CN calculated using the HF/6-31+G(d) method.

3.7. Extra substitution effects on the stabilities of disubstituted amine radicals

The extra substitution effects (ESEs) on the stabilities of disubstituted amine radicals are defined in Eq. 8.

Table 10. Extra substitution effects on the stability of $NH_2\cdot$ radicals calculated using the G3B3 method[a] (kcal/mol)

	NO_2	CN	BH_2	CHO	CF_3	H	F	CH_3	$CH{=}CH_2$	OH	NH_2
NO_2	+8.2	-	-	-	-	-	-	-	-	-	-
CN	+11.7	+15.8	-	-	-	-	-	-	-	-	-
BH_2	+7.6	-0.2	-7.2	-	-	-	-	-	-	-	-
CHO	+1.9	+5.5	-2.1	+1.4	-	-	-	-	-	-	-
CF_3	+6.0[b]	+6.3	+1.2	+4.8	+9.5[c]	-	-	-	-	-	-
H	0.0	0.0	0.0	0.0	0.0	0.0					
F	+0.5	+13.2	+17.1	+0.1	+2.6	0.0	-12.3	-	-	-	-
CH_3	-5.8	-0.4	-2.5	-3.5	-4.2	0.0	-6.8	-2.1	-	-	-
$CH{=}CH_2$	-2.4	+5.3	-1.6	-2.3	-3.9	0.0	-0.3	-1.4	+6.5	-	-
OH	-7.7	+9.3	+12.5	-1.9	-1.0	0.0	-7.8	+1.2	+2.9	-2.2	-
NH_2	-10.9	+3.5	+4.0	-7.2	-6.0	0.0	-4.9	-2.5	+4.1	+0.4	+3.7

[a] Extra substitution effects on the stability of $NH_2\cdot$ radicals are defined as H_{298} (X-N(·)-Y)+H_{298}(NH_2·)−H_{298}(X-NH·)−H_{298}(NH(·)-Y).
[b] From G3 calculations.
[c] From UB3LYP/6-311++g(d,p)//UB3LYP/6-31+g(d) calculations.

$$\mathrm{ESE} = H_{298}(\mathrm{X-N(=)-Y}) + H_{298}(\mathrm{NH_2}=) - H_{298}(\mathrm{X-NH}=) - H_{298}(\mathrm{NH(=)-Y}) \quad (8)$$

These effects have not been studied before. However, as demonstrated below, there are many intriguing, 'irregular' behaviors associated with nitrogen radicals (see Table 10).

First, geminal substitution of two donor groups on the nitrogen radical can result in both extra stabilization and destabilization. The extra stabilization should be caused by the negative hyperconjugation effects (anomeric effect) and electrostatic effects. Since these two effects are the most significant with the F substitution, it is not surprising to see that all the F–N(·)-donor radicals show extra stabilization.

On the other hand, conjugation saturation effect is expected for the donor-N(·)-donor radicals when the donor group is a strong radical stabilizing group (e.g., $CH{=}CH_2$, NH_2). This conjugation saturation effect can be demonstrated by the less-efficient spin delocalization ability of the substituents in the bis-donor radicals compared to the mono-donor radicals. As shown in Figure 6, a single NH_2 substitution delocalizes 25% of the total spin in NH_2–NH·. However, in NH_2–N(·)–NH_2 each NH_2 group can only delocalize 14% of the total spin.

It is worth noting that the conjugation saturation effect does not occur in the donor-NH-donor systems. Therefore, geminal substitution of two donor groups causes the positive ESE values on the N–H BDEs.

The effects of geminal substitutions of two acceptor groups on the nitrogen radicals are quite complicated. Four categories of acceptor groups must be recognized. The first category includes NO_2 and CHO. They can only form one π-type conjugation with either the odd electron or lone pair electrons on nitrogen. It is clear from Table 10 that two acceptors in this category cause extra destabilization on the nitrogen radicals (e.g., ESE value for NO_2–N(·)–NO_2 is +8.2 kcal/mol). This destabilization can be readily explained using the electrostatic repulsion effects. Nonetheless, this destabilization is less substantial than that produced by the same two acceptors on the saturated amine (e.g., ESE value for NO_2–NH–NO_2 is +13.9 kcal/mol).

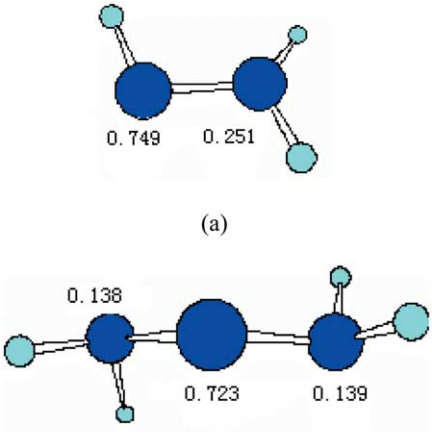


Figure 6. Spin density distributions in (a) NH_2–NH· and (b) NH_2–N(·)–NH_2 calculated using the UB3LYP/6-31+G(d) method.

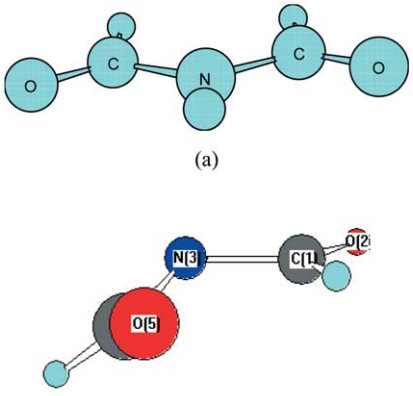


Figure 7. Optimal conformations for (a) HCO–NH–CHO and (b) HCO–N(·)–CHO.

A careful examination of the involved systems reveals some interesting conformation issues. For example, in HCO–NH–CHO (a realistic system) the two CHO groups are in the same plane as the NH moiety (Fig. 7). Thus both the CHO groups are conjugated with the central nitrogen lone pair electrons. However, in HCO–N(·)–CHO (also a realistic system) the two CHO groups are not in the same plane. One of the CHO is conjugated with the odd electron of the central nitrogen. The other CHO is apparently conjugated with the lone pair electrons of the central nitrogen. Because of the conformations, HCO–N(·)–CHO should cause less conjugation saturation effect than HCO–NH–CHO. This is the reason for the lower ESE value in HCO–N(·)–CHO (e.g., +1.4 kcal/mol) compared to that in HCO–NH–CHO (e.g., +3.6 kcal/mol).

The second category of acceptor groups includes CN. This acceptor can form π-type conjugation in two directions because it has two π^* orbitals perpendicular to each other. Thus from RNH–CN to RN(·)–CN the conjugation between the lone pair electrons on the central nitrogen and the CN group is not lost. Meanwhile an additional conjugation between the odd electron on N· and CN is established. The ability to form two π-type conjugations explains why cyano-substituted amines have lower N–H BDEs than NH_3, despite that NO_2, BH_2, and CHO-substituted amines have higher N–H BDEs than NH_3 (see Table 4). The same ability of the CN group also explains why the ESE value of NC–N(·)–CN (+15.8 kcal/mol) is higher than that for NC–NH–CN (+9.2 kcal/mol), because more conjugation saturation effect should occur in NC–N(·)–CN (having four π-type conjugations) than in NC–NH–CN (have two π-type conjugations).

The third category of acceptors includes BH_2. This is a π acceptor but a σ donor. Electron attraction, instead of repulsion, should occur between B and N atoms. The ESE value for BH_2–NH–BH_2 is positive (+10.2 kcal/mol) because the electron attraction interactions cannot offset the strong conjugation saturation effect. However, in BH_2–N(·)–BH_2 there is no conjugation saturation effect because one BH_2 conjugates with the odd electron and one BH_2 conjugates with the lone pair. Therefore, in BH_2–N(·)–BH_2 the electron attraction effect dominates. This results in the negative ESE value (−7.2 kcal/mol) for BH_2–N(·)–BH_2.

The last category of acceptors includes CF_3. This is a strong σ-acceptor. Since little conjugation effect is expected for CF_3, it is not surprising to see a small change of ESE value from CF_3–NH–CF_3 (+9.8 kcal/mol) to CF_3–N(·)–CF_3 (+9.5 kcal/mol).

The effects of geminal substitutions of one donor and one acceptor groups on the nitrogen radicals are also very complicated. Here, one can see extra stabilization effects in radicals including NO_2–N(·)-donor and HCO–(·)-donor. These extra stabilization effects are also more substantial than those in the corresponding precursors (e.g., NO_2–NH-donor and HCO–NH-donor). The only possible reason for these enhanced extra stabilization effects should be the captodative effect (Anomeric effect or electrostatic interactions cannot explain the enhancement). Analysis of the structures of the radicals also supports the occurrence of the captodative effect (Fig. 8).

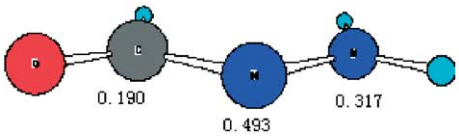


Figure 8. The planar structure of the HCO–N(·)–NH_2 radical is consistent with the captodative effect (the digital numbers are the spins calculated using the UB3LYP/6-31+G(d) method).

For the NC–N(·)-donor cases, however, one can see enhanced extra destabilization effects from saturated precursors to the radicals. The exact reason for this observation is not fully clear, but we suspect that conjugation saturation should be one of the reasons. As seen in Figure 9, the CN group in NC–NH· delocalizes 36% of the total spin. This percentage decreases to 16% in NC–N(·)–NH_2, which indicates a less effective spin delocalization effect. Another possible reason is the weakening of the anomeric effect due to the geometry changes. More detailed analysis on this subject requires careful orbital analyses. We decide not to include this analysis here because the present report focuses on the observable effects and qualitative rationalizations.

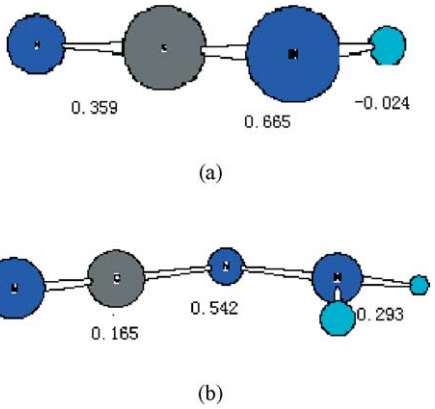


Figure 9. Spin distributions in (a) NC–NH· and (b) NC–N(·)–NH_2 calculated using the UB3LYP/6-31+G(d) method.

Enhanced extra destabilization effects are also seen for the BH_2–N(·)-donor systems. This is quite unexpected. Analysis of the structures reveals that the BH_2 group in these radicals does not conjugate with the odd electron (Fig. 10). Since the NH_2 group is almost perpendicular to the BH_2 group, the captodative effect (in the conventional sense) does not occur in the NH_2–N(·)–BH_2 system. Thus, the

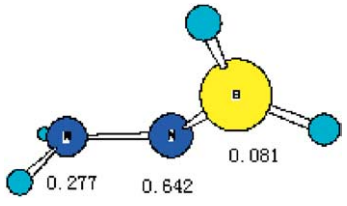


Figure 10. The optimized structure of the BH_2–N(·)–NH_2 radical (The digital numbers are the spins calculated using the UB3LYP/6-31+G(d) method). Notice that NH_2 delocalizes 28% of the total spin while BH_2 only delocalize 8% of the total spin.

captodative effect does not always occur in a captodative radical system.

3.8. Concluding remarks

In the present study we studied the geminal disubstitution effects on the C–H and N–H BDEs. A large number of reliable data were obtained using advanced theoretical methods. We also studied in detail about the geminal disubstitution effects on the stabilities of methanes, methyl radicals, amines, and amine radicals. The study concerning with disubstituted methanes and methyl radicals has been conducted several times before, but we provided many new and 'irregular' findings. The study concerning with disubstituted amines and amine radicals, on the other hand, is new.

We can conclude that geminal disubstitution effects on BDEs or species stabilities do follow some empirical rules (for instance, captodative carbon radicals are more stabilized), but no rule is universally correct because 'irregular' reactivities have been observed almost against every rule. Thus, none of these empirical rules should be important any more, especially when one is able to predict these reactivities relatively easily using computers. What remain important are the detailed energetic effects such as conjugation saturation effects and electrostatic repulsions. These effects are real, universally correct, and mechanistically useful.

In the present study we established the importance of the following energetic effects for geminal disubstituted systems.

(1) Positive ($\sigma \leftrightarrow \pi^*$) and negative hyperconjugation ($\sigma^* \leftrightarrow \pi$). Its validity is warranted by the molecular orbital theories.[41] It always causes extra stabilization.
(2) Electrostatic attraction (e.g., in FCH_2F) and repulsion (e.g., in CF_3–CH_2–CF_3). Its validity is warranted by the Coulomb law. It causes extra stabilization (in cases of attraction) or destabilization (in case of repulsion).
(3) Conjugation saturation effect. Its validity is warranted by the molecular orbital theories. It always causes extra destabilization.
(4) Captodative effect. (Note: we regard this as one type of energetic effect, not any dominant phenomenon) Its validity is also warranted by the molecular orbital theories.[16] It always causes extra stabilization.
(5) Steric repulsion. (Note: we did not utilize this interaction in the analysis presented above, because all the systems in the present study did not appear to involve significant steric problems) Its validity is warranted by the Pauli Exclusion Principle. It always causes extra destabilization.

Using the above five energetic effects we can successfully explain all the observed geminal substitution effects. For those systems where all the possible energetic effects change the energy in the same direction, we can even predict the net substitution effect. For instance, in F–CH_2–F we know that hyperconjugation causes extra stabilization and electrostatic attraction also causes extra stabilization. Since conjugation saturation effect, captodative effect, and steric repulsion are not involved in F–CH_2–F, we can predict that F–CH_2–F should have extra stabilization effect. Nonetheless, prediction is not possible at present for those systems involving opposite energetic effects.

Finally, the presence of certain types of substituents does not necessarily mean that one of the above five energetic effects must occur. For example, captodative effect does not always occur in a captodative radical system (e.g., NH_2–N(•)–BH_2). In order to determine whether an energetic effect can take place, we have to analyze the conformation of the system. In fact, it is the difference in conformations that causes a lot of dramatic dissimilarity for the geminal substitution effects on carbon and nitrogen centered systems.

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A simple synthesis of bis-annulated bicyclo[2.2.2]octenones containing a β,γ-enone chromophore and photochemical reactions: a new entry into angular tetraquinane and other polycyclic systems

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Abstract—Synthesis of *endo*tetracyclo[5.5.2.0.^{2,6}0^{8,12}]tetradeca-3(4),8(12)-dien-13-one from 5-indanol and photoreactions in singlet and triplet excited state leading to complex polycyclic systems is reported. Crystal structure of 14-spiroepoxy*endo*tetracyclo[5.5.2.0.^{2,6}0^{8,12}] tetradeca-3(4),8(12)-dien-13-one is also reported.

1. Introduction

Bridged carbocyclic systems containing a β,γ-enone chromophore have proved to be versatile precursors for the synthesis of a variety of carbocyclic arrays because of their unique reactions in both the ground and excited states.[1–3] The reactions in excited states permit a smooth and stereoselective transformation of bridged structure into ring fused system present in a large number of naturally occurring compounds.[2] However, while there are some methods for the synthesis of simple bicyclo[2.2.2]octenones[4] and monoannulated homologue,[5] there are no methods for bis-annulated bicyclo[2.2.2]octenes of type **1** having a β,γ-enone chromophore. Recently, the reactive species generated from aromatics such as cyclohexadienone ketals, *o*-imido quinones have received greater attention for creation of complex molecular structures.[6,7] In view of our interest[5] in the chemistry of cyclohexa-2,4-dienones and the continuing interest in the synthesis of angular tetraquinanes[8,9] we thought to devise a method for the synthesis of bis-annulated bicyclo[2.2.2]octenones of type **1** containing a β,γ-enone group and explore its photoreactions. We wish to describe an efficient synthesis of tetracyclic compounds of type **1** from a simple aromatic precursor **5** via cycloaddition of the annulated cyclohexa-2,4-dienone **4**, and also report photochemical reactions of **1** in triplet and singlet excited state that provides a new stereoselective entry to **2**, **3** and other carbocyclic systems (Fig. 1).

2. Results and discussion

The tetracyclic dienone **1** was efficiently synthesized from indanol **6** as follows. The hydroxymethyl indanol **5**[10] was prepared by controlled hydroxymethylation of commercially available indanol **6** (Scheme 1). Thus, the treatment of **6** with aq. HCHO and NaOH at ambient temperature gave a mixture of mono- and bis-hydroxymethylated products from which hydroxymethyl indanol **5** was obtained in moderate yield after chromatography. Oxidation of **5** in the presence of a freshly cracked cyclopentadiene with aq. sodium *meta*periodate[11] following a procedure developed in our laboratory,[5] gave the keto-epoxy adduct **8** in excellent yield (83%) as a result of in situ generation of **4** and subsequent interception with cyclopentadiene (Scheme 1). The gross structure of the adduct was deduced from the following spectroscopic data. Thus, the ^{1}H NMR (400 MHz) spectrum of the adduct exhibited characteristic signals at δ 5.67 (m, 1H), 5.39 (m, 1H) for the olefinic protons of the five-membered ring. Further, characteristic AB pattern for protons of the oxirane methylene group was observed at δ 3.10 (part of an AB system, $J_{AB}=6.1$ Hz, 1H), 2.83 (part of an AB system, $J_{AB}=6.1$ Hz, 1H). In addition, signals were observed at δ 3.42–3.39 (superimposed m, 2H), 3.08–3.00 (m, 1H), 2.62–2.49 (m, 3H), 2.44–2.32 (m, 2H), 2.23–2.21

Keywords: Cycloaddition; Cyclohexa-2,4-dienone; Oxa-di-π-methane rearrangement; 1,3-Acyl shift; Photoreaction.
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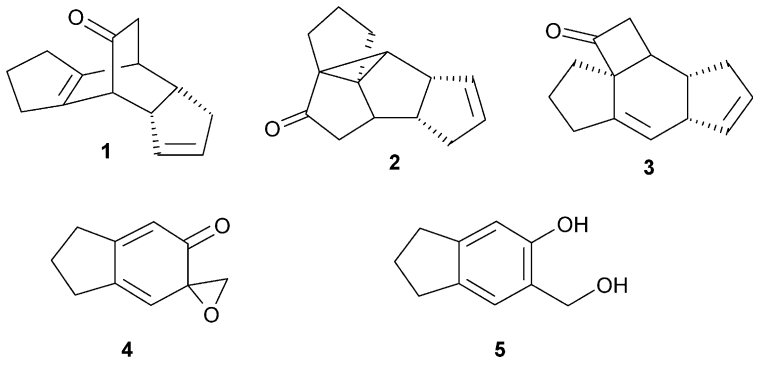
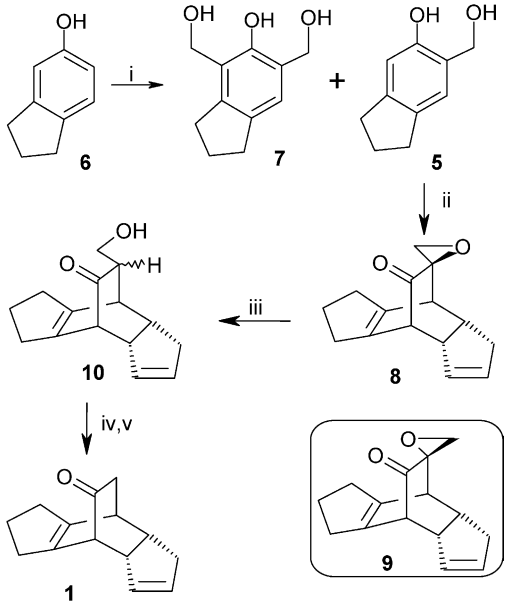


Figure 1.

(m, 1H), 2.02–1.87 (m, 3H) for other methine and methylene protons. ^{13}C NMR spectrum displayed characteristic signals at δ 205.02, and 140.75, 136.64, 133.00, 129.21 for carbonyl carbon and olefinic carbons respectively. Signals due to other carbons were shown at δ 58.95, 53.58, 52.57, 50.44, 44.60, 38.34, 36.89, 35.42, 34.17, 23.69. However, the stereochemical orientation of the oxirane ring was not easily discernible from the spectroscopic data alone and it was difficult to distinguish between **8** and the possible diastereoisomer **9**. Hence, X-ray crystal structure determination was undertaken which confirmed the structure **8** for the adduct (Fig. 2).

The adduct **8** was then converted into the chromophoric system **1**. Thus, the treatment of **8** with zinc in aqueous methanol containing NH_4Cl at ambient temperature gave the β-hydroxy ketone **10** (as a mixture of *syn–anti* isomers) also in excellent yield (92%). Oxidation of **10** with Jones reagent followed by decarboxylation of the resulting β-ketoacid readily furnished the desired chromophoric system **1** (Scheme 1). It may be worth noting that the tetracyclic compounds of type **1** are not readily accessible otherwise.



Scheme 1. Reagents/conditions: (i) NaOH, HCHO, **5** (30%), **7** (30%); (ii) aq. $NaIO_4$, CH_3CN, cyclopentadiene, 0–5 °C, 83%; (iii) Zn, NH_4Cl, aq. MeOH, rt, 92%; (iv) Jones reagent, acetone; (v) aq. THF, △, 55% (for iv and v).

After having an efficient access to the tetracyclic chromophoric system **1**, we first explored its photochemical reaction in excited singlet (^{1}S) state. In general, the rigid β,γ-enones undergo two unique reactions i.e. a 1,2-acyl shift or oxa-di-π-methane rearrangement on triplet sensitized (T_1, π–π*) irradiation and a 1,3-acyl shift upon direct irradiation either via singlet excited state (S_1) and/or higher triplet (T_2, n–π*) state.[1–3] The unusual reactivity is a consequence of the electronic interaction between the chromophores that modulates the structure and properties of the excited states. However, the selectivity in the photoreaction also depends on the structure of the chromophoric systems and functional groups in a subtle fashion. Keeping the above in mind, a solution of **1** in dry benzene was irradiated with a mercury vapor lamp (125 W, APP) in a Pyrex immersion well under nitrogen. Chromatography of the photolysate gave the tetracyclic compound **3** (Scheme 2) containing a cyclobutanone ring in a good yield (40%) as a result of 1,3-acyl shift. The structure of the photoproduct was clearly revealed from the spectroscopic data. In order to examine the photoreaction of **1** in triplet excited state, a solution of **1** in dry acetone (both as a solvent and sensitizer) was irradiated with a mercury vapor lamp

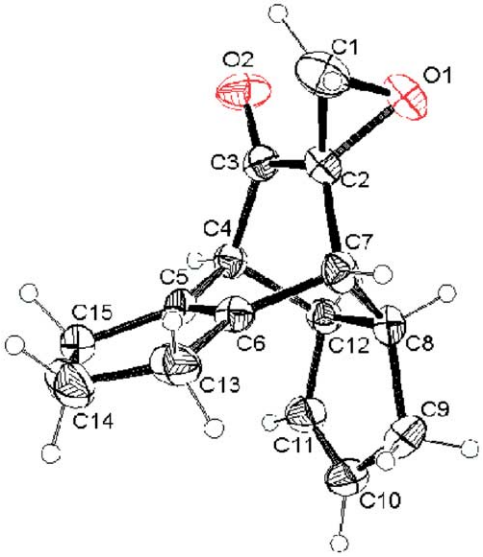
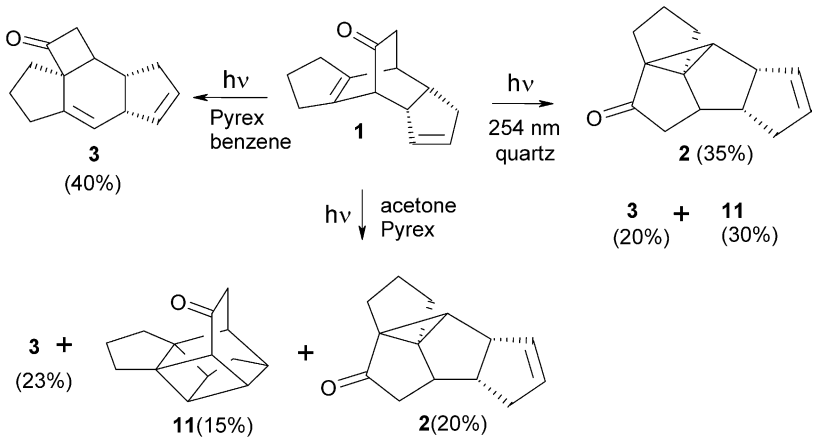


Figure 2. X-ray crystal structure of compound **8**.

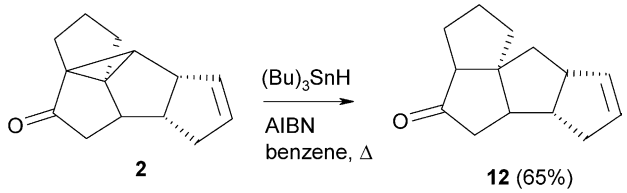


Scheme 2.

(125 W, APP) in a Pyrex immersion well ($\lambda > 290$ nm) under nitrogen for 1 h. Chromatography of the photolysate gave the tetracyclic dienone **3**, the caged ketone **11** and the polyquinane **2** in 23, 15 and 20% yields respectively, as a result of 1,3-acyl shift, intramolecular $\pi^{2s}+\pi^{2s}$ cycloaddition and oxa-di-π-methane rearrangement. In order to improve the efficiency of the oxa-di-π-methane reaction, we also irradiated a solution of **1** in acetone at 254 nm (16 W mercury vapor lamp APP) in a quartz immersion well for 3 h. Under this condition, the oxa-di-π-methane product **2** was obtained in better yield (35%), the formation of 1,3-acyl shift product **3** remained unchanged and the caged product **11** was formed to a greater extent (Scheme 2).

The formation of the 1,3-acyl shift product **3** and, especially the caged product **11** during the sensitized irradiation of **1** was rather surprising since other bicyclo[2.2.2]octenones without the substituents at β,γ-olefinic carbons undergo highly selective photoreaction.[2,3,5] It appears that the unusual behavior of the tetracyclic compound **1** upon sensitized irradiation is due to the presence of the strained five-membered ring across the β,γ-olefinic bond which controls the structure and properties (electronic and steric effects) of both the ground and the excited state so as to populate T_2 and T_1 indiscriminately and also sensitize the π-bonds for intramolecular photocycloaddition.

The oxa-di-π-methane rearrangement in **1**, although it occurred with moderate efficiency, provided a stereoselective route to angular polyquinanes which are present in many natural products.[8,9] In order to convert the pentacyclic compound **2** into tetraquinane, selective cleavage of the peripheral cyclopropane bond was required. Though several methods are available,[12] radical induced reductive cleavage[13] was attempted. Thus, treatment of the pentacyclic compound **2** with tributyltin hydride-AIBN in refluxing benzene furnished the tetraquinane **12** in good yield (65%) (Scheme 3). The presence of an absorption band at 1737 cm^{-1} in IR spectrum and a signal at δ 223.15 in the ^{13}C spectrum of **12**, characteristic of a CO group in five-membered ring, in addition to other spectral data clearly suggested its structure.



Scheme 3.

In summary, transformation of a readily available aromatic precursor to a new complex tetracylic system **1** endowed with a β,γ-enone chromophore and its photoreaction upon singlet and triplet excited state leading to novel carbocyclic systems is described. An unusual effect of structure on the photoreactivity in the triplet excited state is also presented.

3. Experimental

3.1. General

IR spectra were recorded on Nicolet Impact 400 FT-IR Instrument. UV spectra were recorded on Shimadzu UV 160 or Shimadzu U 260 instrument. ^1H NMR and ^{13}C NMR were recorded on Bruker Avance-400 NMR spectrometer, Varian NMR and Varian VXR 300 instruments. Microanalyses were done on a CEST 1106 instrument and HRMS was done on Q-Tof micro (YA-105) and Brucker Daltonics APEX3 Tesla Mass Spectrometer. Melting points were determined on a Veego apparatus of Buchi type and are uncorrected. All the organic extracts were dried over anhydrous sodium sulphate. Reactions were monitored with thin layer chromatography silica gel and spots were visualized with iodine vapor. Column chromatography was performed using Acme/SRL silica gel (60–120 or 100–200 mesh). The elution was done with petroleum ether (60–80 °C) and ethyl acetate mixtures. The fractions eluted from column were concentrated at reduced pressure on a Buchi-RE 111 rotary evaporator.

3.1.1. 6-Hydroxymethyl-5-indanol (5) and 2,6-dihydroxymethylindanol (7). To a solution of indanol **6** (3.0 g, 22.4 mmol) in water (120 mL), NaOH (0.76 g, 19 mmol) and formaldehyde (2 mL, excess) were added at ambient temperature and the reaction mixture was stirred for 3 h. Then the reaction mixture was neutralized with NH_4Cl, at 0 °C and extracted with ethyl acetate (4×50 mL). The

combined organic extract was washed with brine (1× 20 mL) and dried over anhydrous sodium sulphate. The solvent was removed under vaccum and the residue was flash chromatographed. Elution with petroleum ether–ethyl acetate (95:5) first gave the unreacted starting material. Further elution with petroleum ether–ethyl acetate (90:10) furnished the desired compound **5** (1.2 g, 30%) as a colorless solid. Elution with petroleum ether–ethyl acetate (70:30) gave the bis-hydroxymethylated product **7** (1.4 g, 30%) as a colorless crystalline solid.

Data for **5**. Mp 104–106 °C. IR ν_{max}: 3434, 1591 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.04 (s, 1H, phenolic-OH), 6.88 (s, 1H, aromatic proton), 6.76 (s, 1H, aromatic proton), 4.78 (d, $J=3$ Hz, 2H, Ar-CH_2-OH), 2.88–2.77 (m, 4H), 2.26 (br m, 1H, CH_2OH), 2.09–2.00 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.59, 145.93, 135.55, 123.44, 122.54, 112.44, 64.66, 32.91, 31.90, 25.76. Analysis: Found C, 72.99; H, 7.71; requires C, 73.17; H, 7.31 for $C_{10}H_{12}O_2$.

Data for **7**. Mp 108–110 °C. IR ν_{max}: 3405, 3318, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H, phenolic OH), 6.92 (s, 1H), 4.84 (d, $J=3$ Hz, 2H, CH_2OH); 4.75 (d, $J=3$ Hz, 2H, CH_2OH), 2.84–2.79 (m, 4H), 2.64 (br m, 1H, OH), 2.52 (br m, 1H, OH), 2.08–2.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 142.8, 135.3, 124.4, 123.2, 121.5, 63.6, 60.9, 32.1, 31.0, 25.3. HRMS: 217.0848 (M^+ + Na) $C_{11}H_{14}O_3Na$ requires, 217.0841.

3.1.2. 14-Spiroepoxy*endo*tetracyclo[5.5.2.0.^{2,6}0^{8,12}]tetradeca-3(4),8(12)-dien-13-one (8). To a solution of compound **5** (3.0 g, 18.3 mmol) in acetonitrile (90 mL) was added freshly cracked cyclopentadiene (8 mL, excess) at 0–5 °C. To this was added a solution of sodium *meta*periodate (7.7 g, 36 mmol) dropwise. After stirring for 3 h at 0–5 °C, the reaction mixture was brought to ambient temperature and stirred overnight. The organic layer was separated and the aqueous layer was saturated with sodium chloride and extracted with ethyl acetate (3×40 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel. Elution with petroleum ether gave the unreacted cyclopentadiene dimer. Further elution with petroleum ether–ethyl acetate (98:2) gave the desired adduct **8** (3.43 g, 83%) as a solid which was recrystallized with petroleum ether–ethylacetate. Mp 103–104 °C. IR (film) ν_{max}: 1734 cm^{-1}. UV (MeOH) λ_{max}: 215 ($\varepsilon=3.67\times10^3$ L mol^{-1} cm^{-1}), 312 ($\varepsilon=3.31\times10^2$ L mol^{-1} cm^{-1}) nm. ^1H NMR (400 MHz, $CDCl_3$): δ 5.67 (m, 1H), 5.39 (m, 1H), 3.42–3.39 (m, 2H), 3.10 (part of an AB system, $J_{AB}=6.1$ Hz, 1H), 3.08–3.00 (m, 1H), 2.83 (part of an AB system, $J_{AB}=6.1$ Hz, 1H), 2.62–2.49 (m, 3H), 2.44–2.32 (m, 2H), 2.23–2.21 (m, 1H), 2.02–1.87 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.02, 140.75, 136.64, 133.00, 129.21, 58.95, 53.58, 52.57, 50.44, 44.60, 38.34, 36.89, 35.42, 34.17, 23.69. HRMS: 229.1231 [M^++H], $C_{15}H_{16}O_2$ requires 229.1223.

Crystal data. $C_{15}H_{16}O_2$, $M=228.28$, orthorhombic, P 21 21 21 $Z=4$, $\lambda=0.70930$ Å, $a=8.000(2)$ Å, $b=11.2730(12)$ Å, $c=13.0490(19)$ Å, $V=1176.8(4)$ Å^3, $T=293(2)$ K, $D_c=1.288$ mg/m^3, $\mu=0.084$ mm^{-1}, $F(000)=488$, size=0.40×0.35×0.22 mm^3, reflections collected/unique=1873/1873 [R(int)=0.0000], final R indices [$I>2sigma(I)$]: $R_1=0.0383$, $wR_2=0.0866$, R indices (all data): $R_1=0.0579$, $wR_2=0.0979$. CCDC No. 245375. See: http//www.ccdc.cam.ac.uk/conts/retrieving.html (e-mail: deposit@ccdc.cam.ac.uk).

3.1.3. 14-Hydroxymethyl*endo*tetracyclo[5.5.2.0^{2,6}.0^{8,12}]-tetradeca-3,8(12)-dien-13-one (10). To a solution of the adduct **8** (3.0 g, 13.2 mmol) in methanol–water (6:1, 105 mL) was added zinc (activated 18 g, excess) and NH_4Cl (3.3 g, 59 mmol). The reaction mixture was stirred at ambient temperature (~30 °C) for 8 h (TLC). It was filtered on a celite bed and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and diluted with water and extracted with ethyl acetate (4×40 mL). The combined organic layer was washed with brine and dried. The solvent was removed under reduced pressure and the residue was chromatographed. Elution with petroleum ether–ethyl acetate (88:12) gave the alcohol **10** (*syn–anti* mixture) as a colorless liquid (2.8 g, 92%). IR ν_{max}: 3446, 1714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.63–5.59 (m, 1H), 5.38–5.32 (m, 1H), 3.90–3.80 (m, 1H), 3.70–3.64 (m, 1H), 3.55 (d, $J=7.8$ Hz, 1H), 3.30–3.14 (merged m, 3H), 2.97, 2.87 (m, total 1H), 2.80–2.70 (m, 1H), 2.60–2.20 (cluster of m, 6H), 2.0–1.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.77, 143.85, 135.74, 134.62, 129.53, 62.82, 54.46, 50.85, 50.36, 40.46, 40.43, 38.35, 35.48, 35.09, 33.78, 23.50 (signals due to one isomer). HRMS: 253.1205 (M^++Na), $C_{15}H_{18}O_2$ requires 253.1199. This was subjected to oxidation and decarboxylation as described below.

3.1.4. *endo*-Tetracyclo[5.5.2.0^{2,6}.0^{8,12}]tetradeca-3,8(12)-dien-13-one (1). A solution of the β-keto-alcohol **10** (2.0 g, 8.7 mmol) in acetone (60 mL) was oxidized with freshly prepared Jones' reagent at 0 °C. After completion of reaction (TLC), isopropanol was added to destroy excess oxidant. Acetone was removed in vacuum at ambient temperature and the residue was diluted with water (10 mL) and extracted with dichloromethane (3×25 mL). Combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed and the resulting β-keto-acid was dissolved in THF–water mixture (1:1, 30 mL) and refluxed for 10 h. It was brought to ambient temperature, and the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with ether (3×30 mL). The combined organic layer was washed with saturated sodium bicarbonate, brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. Elution with petroleum ether–ethylacetate (98:2) gave the titled compound **1** (0.85 g, 55%) as a colorless solid. Mp 70–71 °C. IR (film) ν_{max}: 1723 cm^{-1}. UV (MeOH) λ_{max}: 218 ($\varepsilon=9.02\times10^2$ L mol^{-1} cm^{-1}), 297 ($\varepsilon=1.6\times10^2$ L mol^{-1} cm^{-1}) nm. ^1H NMR (400 MHz, $CDCl_3$): δ 5.62–5.57 (m, 1H), 5.38–5.34 (m, 1H), 3.28–3.21 (m, 1H), 3.20 (d, $J=2.6$ Hz, 1H), 2.94 (dd, $J=5.61$, 2.81 Hz, 1H), 2.76–2.66 (complex m, 1H), 2.56–2.45 (overlapped m, 2H), 2.42–2.25 (m, 2H), 2.24–2.14 (m, 1H), 2.08 (d of part of an AB system, $J_{AB}=18.2$, 2.4 Hz, 1H), 2.02 (d of part of an AB system, $J_{AB}=18.2$, 3.2 Hz, 1H), 1.97–1.84 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.66, 143.19, 135.67, 132.21, 129.84, 54.19,

49.44, 41.08, 40.44, 38.47, 37.98, 35.04, 33.77, 23.66. HRMS: 223.1096 [M^++Na], $C_{14}H_{16}ONa$ requires 223.1099.

3.1.5. Tetracyclo[9.3.0.0^{1,4}.0^{5,9}]tetradeca-7,10-dien-2-one (3). A solution of the tetracyclic compound **1** (70 mg, 0.35 mmol) in dry benzene (100 mL) was irradiated with a mercury vapor lamp (125 W, APP) in a Pyrex immersion well for about 45 min. Removal of solvent followed by the chromatography of the residue gave the 1,3-acyl shift product **3** (31 mg, 40%) as colorless liquid. IR (film) ν_{max}: 1770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 5.87 (br m, 1H), 5.64 (br m, 1H), 5.18 (s, 1H), 3.14 (br s, 1H), 3.10–2.95 (dd, $J=9.1$, 9.1 Hz, 1H), 2.76–2.70 (m, 1H), 2.69–2.59 (t, $J=8.3$ Hz, 1H), 2.58–2.45 (dd, $J=18$, 8.5 Hz, 1H), 2.44–2.13 (complex m, 4H), 2.02–1.82 (m, 2H), 1.79–1.58 (m, 1H), 1.58–1.49 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 208.10, 136.09, 133.88, 130.30, 117.63, 68.96, 48.46, 40.98, 39.03, 36.25, 33.33, 30.05, 29.46, 21.75. HRMS: 223.1088 [M^++Na], $C_{14}H_{16}ONa$ requires 223.1093.

3.1.6. Pentacyclo[6.6.0.0^{1,11}.0^{2,11}.0^{3,7}]tetradec-4-en-10-one (2) and caged ketone (11). A solution of the compound **1** (0.3 g, 1.5 mmol) in acetone (400 mL) was irradiated with a medium pressure mercury vapor lamp (16 W, λ_{max}: 254 nm) in a quartz immersion well for 3 h under nitrogen. The solvent was removed and the residue was chromatographed. Elution with petroleum ether–ethyl acetate (98:2) first gave the 1,3-acyl shift product **3** (60 mg, 20%) followed by some unreacted starting material. Continued elution gave the photocycloaddition product **11** as a low melting solid (90 mg, 30%). Further elution gave the compound **2** (105 mg, 35%) as a thick colorless liquid.

Data for compound **2**. IR (film) ν_{max}: 1712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.79–5.71 (m, 2H), 3.16 (br s 1H), 2.85 (dd, $J=18.1$, 9.3 Hz, 1H), 2.67 (d, $J=9.3$ Hz, 1H), 2.62–2.49 (m, 2H), 2.38–2.22 (m, 1H), 2.15 (d, $J=18$ Hz, 1H), 2.02–1.84 (m, 3H), 1.84–1.72 (m, 1H), 1.71–1.63 (m, 2H), 1.49–1.34 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 214.27, 133.64, 131.86, 58.48, 57.29, 52.69, 51.50, 50.24, 43.80, 42.50, 38.10, 27.60, 27.16, 26.48. HRMS: 223.1095 [M+Na], $C_{14}H_{16}ONa$ requires 223.1093.

Data for caged product **11**. IR (film) ν_{max}: 1709 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.86–2.72 (merged m, 3H), 2.51 (br s, 1H), 2.44 (br s, 1H), 2.30 (d of part of an AB system, $J_{AB}=17.7$ Hz, $J_2=3.3$ Hz, 1H), 2.20 (br m, 1H), 2.10 (d of part of an AB system, $J_{AB}=17.7$ Hz, $J_2=2.3$ Hz, 1H), 1.90–1.52 (merged m, 5H), 1.42–1.30 (m, 2H), 1.17–1.04 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 211.5, 54.0, 51.8, 48.4, 45.4, 44.4, 43.5, 40.3, 39.9, 38.9, 35.0, 31.9, 30.0, 27.2. HRMS: 201.1274 (M^++H) $C_{14}H_{16}O+H$ requires, 201.1279.

3.1.7. Tetracyclo[6.6.0.0^{1,11}.0^{3,7}]tetradec-4-en-10-one (12). To a stirred solution of pentacyclic compound **2** (80 mg, 0.4 mmol) in dry benzene (10 mL) containing AIBN (64 mg, 0.4 mmol), tributyltin hydride (0.44 mL, 1.5 mmol) was added and the reaction mixture was refluxed for 6 h (TLC) under an atmosphere of nitrogen. Benzene was removed and the residue was chromatographed on a column of silica gel. The column was eluted with petroleum ether to remove the tin impurity. Further elution with petroleum ether–ethyl acetate (98:2) furnished the angular tetraquinane **12** (59 mg, 73%) as a colorless liquid. IR (film) ν_{max}: 1737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.72–5.54 (m, 2H), 3.34–3.21 (br m, 1H), 2.71–2.59 (complex m, 1H), 2.52–2.44 (dd, $J=18.6$, 7.6 Hz, 1H), 2.42–2.34 (m, 1H), 2.33–1.98 (m, 4H), 1.92–1.79 (m, 2H), 1.76–1.55 (m, 5H), 1.52–1.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 223.15, 135.29, 128.21, 60.39, 58.36, 53.33, 51.26, 49.72, 45.87, 44.69, 40.10, 39.78, 29.96, 26.86. HRMS: 203.1438 (M^++H) $C_{14}H_{18}O+H$ requires, 203.1436.

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A short and efficient general synthesis of luotonin A, B and E

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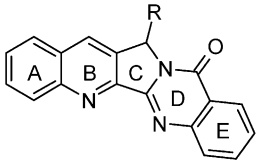
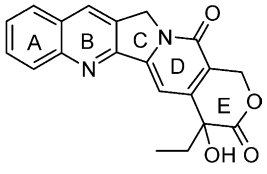
Abstract—Highly convergent synthesis of three luotonins (A, B, and E) has been achieved from readily available starting materials. The key step in the synthesis is formation of quinazolinone skeleton by the condensation of 3-(1,3-dioxolan-2-yl-quinoline-2-carbaldehyde and anthranilamide.

1. Introduction

Luotonins A, B, and E, new heteroaromatic pyrroloquinazolinoquinoline alkaloids,[1] were isolated from the aerial parts of *Peganum nigellastrum* Bunge, a Chinese medicinal plant used for the treatment of rheumatism, inflammation, abscesses and other maladies. Luotonins A (**1**), B (**2**), and E (**3**) possess a unique skeleton comprising of pharmacologically important quinoline[2] and quinazoline[3] framework.



R = H, Luotonin A (**1**)
R = OH, Luotonin B (**2**)
R = OMe, Luotonin E (**3**)



Camptothecin (**4**)

Amongst these, luotonin A showed remarkable cytotoxic activity against mouse leukemia-P388 cells even at low concentrations (IC_{50} 1.8 μg/mL). Luotonin A is reminiscent of camptothecin (CPT) **4**,[4] an inhibitor of topoisomerase I, derivatives of which are clinically useful anti-cancer agents, in its pentacyclic structure as well as cytotoxic activity. Hydroxy lactone E-ring, of CPT considered to be an absolute requirement for high topoisomerase I mediated cytotoxycity[5] as many E-ring modifications like CPT-lactol, CPT-lactam, a ring opened hydroxy amide, an α-halo lactone, an α-azidolactone, an α-aminolactone and an α-exo-methylenelactone were either inactive or showed significantly decreased activity in cell assays relative to parent CPT. The pyridone D-ring also has been considered to be an absolute requirement for the activity.[6] Surprisingly luotonin, which can be regarded as a DE-ring modified analog of camptothecin, is cytotoxic[1a] and very recently, Hecht et al.[7] have demonstrated that luotonin A stabilizes the human DNA topoisomerase I-DNA covalent binary complex and mediates topoisomerase I-dependent cytotoxicity in intact cells (IC_{50} 5.7–12.6 m/mL) in a similar way to camptothecin. These findings has resulted in increased quest for obtaining luotonin based CPT-like analogues for structure-activity relations and hence considerable attention has been focused on their synthesis.[8] Luotonin B has been obtained from luotonin A by CAN mediated oxidation,[9] whereas luotonin E has been synthesized by etherification of luotonin B with methanol in the presence of BF_3–OEt_2. So far, there is no general synthetic approach available to access all three pyrroloquinazolinone luotonins. These considerations, coupled with our interest in quinoline[10] and quinazoline[11] alkaloids, led us to develop a general synthetic route which will enable access to all the three luotonins.

2. Results and discussion

We were intrigued by the possibility of obtaining pyrroloquinazolinone luotonins A, B and E by delaying the C-ring construction, where they differ, as shown in our retro synthetic analysis (Scheme 1).

We envisioned condensation of suitable quinoline aldehyde with anthranilamide to construct the key intermediate. Meth-Cohn's quinoline synthesis[12] is ideally suited for the construction of the AB ring unit with an aldehyde functionality at 2-position for quinazoline formation while keeping the other formyl group masked at the 3-position which could later be unmasked and utilized for the C-ring

Keywords: Luotonin; Synthesis; Quinazolinone; Mitsunobu; Camptothecin.
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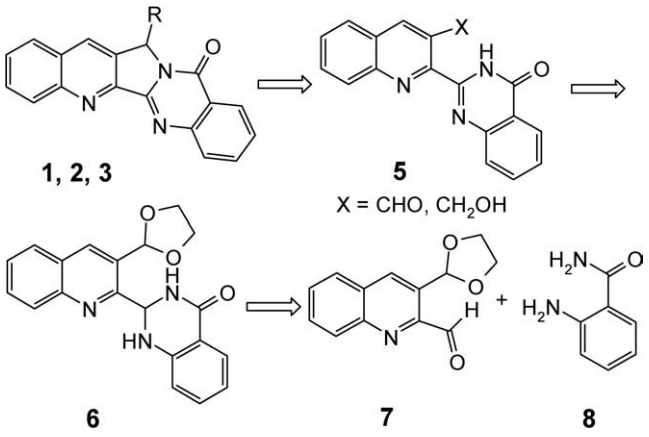
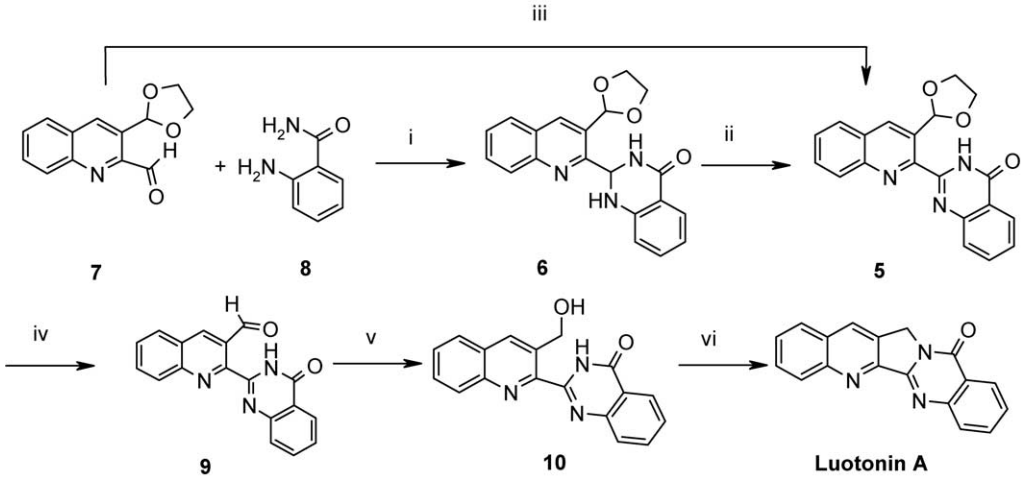


Scheme 1.

annulation on to quinazolinone ring to obtain the title compounds (Scheme 2).

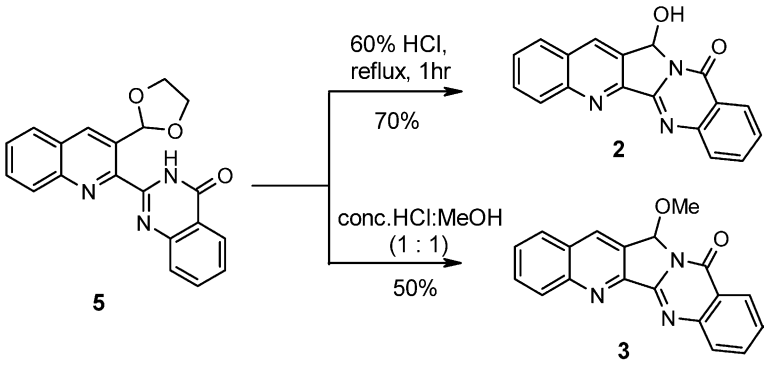
Thus aldehyde **7** was prepared from acetanilide according to Meth-Cohn's procedure.[13] The condensation of **7** with anthranilamide to dihydro quinazolinone **6** was effected under basic medium. Accordingly equimolar mixture of aldehyde **7** and anthranilamide **8** in ethanol was refluxed for 2 h in presence of 15% NaOH solution to afford the dihydroquinazolinone **6** in 92% yield.[14] Dihydroquinazolinone **6** was oxidized to quinazolinone **5** with $KMnO_4$ in refluxing acetone. Alternatively, dihydroquinazolinone **6** was obtained by heating the reactants in *N*,*N*-dimethyl acetamide (DMA) to 80 °C while quinazolinone **5** was obtained by heating the reactants to 150 °C in presence of $NaHSO_3$. Interestingly, the quinazoline **5** could be readily obtained in a single step when 20% KOH was employed in the above transformation. Such facile oxidation of dihydroquinazolinone to the quinazolinone is precedented.[15]

Having been successful in the construction of the key intermediate **5** with AB and DE rings and suitably placed handle for the further C-ring annulation, all that left was to identify and realize the synthetic transformations for the different luotonins which vary in the substitution at the 7-position, that is, on C-ring. In this direction, the deprotection of acetal **5** with 10% HCl: THF unveiled the aldehyde **9**, which was subsequently reduced to alcohol **10** with $NaBH_4$ in quantitative yield. Alcohol **10** was



i) 15% NaOH-Ethanol soln, reflux, 5 h, 80% or DMA, 80°C, 3h, 80%. ii) $KMnO_4$, acetone, reflux, 3 h, 95%. iii) 20% KOH-Ethanol, reflux, 79% or $NaHSO_3$, DMA, 150°C, 2h, 98%. iv) 10% HCl-THF, 0.5 h, 98%. v) $NaBH_4$, MeOH, 95%. vi) 60% Ethanolic H_2SO_4, reflux, 73% (or) PPh_3, DEAD, THF, 68%.

Scheme 2.



Scheme 3.

subjected to Mitsunobu conditions to obtain luotonin A. However this operation required the laborious column chromatography to obtain pure luotonin A. Alternatively, cyclodehydration of **10** with 60% ethanolic H_2SO_4 at 80 °C afforded luotonin A **1**. Luotonin B **2**, E **3** can be regarded structurally as α- hydroxy amide and α- alkoxy amide respectively, which are normally obtained by the treatment of aldehyde with amide under strong acidic conditions. We reasoned that the treatment of acetal **5** with strong acid[16] would provide luotonin B via intramolecular addition of amide on to aldehyde, formed by the deprotection of acetal. Addition of methanol to the above conditions would lead to the formation of luotonin E (Scheme 3).

As anticipated, the treatment of the acetal **5** with 60% HCl at 100 °C in THF resulted in the formation of luotonin B. Treatment of **5** with conc. HCl in methanol at room temperature furnished luotonin E.

In conclusion we have developed a short, highly practical, and efficient synthesis of luotonin A, B, and E which is amenable to the synthesis of substituted analogues as the substituted starting materials are readily accessible[2,17] and obviates the need for the costly and unstable aminobenzaldehyde. We have elaborated the repertoire of Meth-Cohn aldehyde annulation for synthesis of quinazoline heterocycles.

3. Experimental

3.1. General

Melting points are uncorrected. IR spectra were recorded with a Perkin–Elmer FT-IR 16015 spectrometer and ^1H and ^{13}C NMR spectra with a Bruker AC-200 or Bruker MSL-300. Chemical shifts are given on a δ (ppm) scale with tetramethylsilane (TMS) as the internal standard. Mass Spectra were recorded on Finnigan-Mat 1020C Mass spectrometer and were obtained at an ionization potential of 70 eV and mass values are expressed as *m*/*z* values. Column chromatography was carried out on silica gel (60–120 mesh).

3.1.1. 2-(3-[1,3]Dioxalon-2-yl-quinolin-2-yl)-2,3-dihydro-1*H*-quinazoli-4-one [6]. *Method A*. To a solution of anthranilamide (3.40 g, 25 mmol) and quinoline aldehyde[12,13] **7** (5.75 g, 25 mmol) in 100 mL of 95% ethanol was added 1.6 mL of 15% aq. NaOH solution. The mixture was heated under reflux for 1 h and the precipitated solid was filtered and air-dried to give dihydroquinazolinone **6** (7 g, 80%) as a white solid.

Method B. Anthranilamide (3.40 g, 25 mmol) and quinoline aldehyde **7** (5.75 g, 25 mmol) were heated in 25 mL of *N*,*N*-dimethylacetamide (DMA) at 80 °C for 3 h and then poured into ice water (300 mL). The precipitated solid was filtered and air-dried to give dihydroquinazolinone **6** (7.0 g, 80%) as a white solid; mp 140 °C. IR (KBr): 3366, 3185, 2911, 1676, 1664, 1508, 1487, 1377, 935 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$): 8.38 (s, 1H), 8.08 (d, J=8.3 Hz, 1H), 7.95 (dd, J=1.48, 7.52 Hz, 1H), 7.79 (d, J=8.18 Hz, 1H),7.68 (dt, J=1.5, 6.95 Hz, 1H), 7.53 (dt, J=1.22, 8.3 Hz, 1H3HH), 7.28 (dt, J=1.78, 7.39 Hz, 1H), 7.20 (bs, 1H), 6.89 (dt, J=1.22, 7.52 Hz, 1H), 6.76 (d, J=8.3 Hz, 1H), 6.27 (d, J=1.78 Hz, 1H), 6.07 (s, 1H), 5.83 (bs,1H), 4.03–4.42 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ: 165.07 (C), 153.04 (C), 147.62 (C), 147.00 (C), 137.04 (CH), 133.69 (CH), 130.94 (CH), 129.55 (CH), 128.66 (CH), 127.93 (2 CH), 127.55 (C), 127.39 (C), 119.81 (CH), 117.52 (C), 115.75 (CH), 101.80 (CH), 65.70 (CH_2), 65.59 (CH_2), 65.33 (CH). Mass (*m*/*z*): 347 (M^+), 304 (40), 288 (70), 273 (51), 251 (39), 231 (60), 204 (20), 158 (36), 132 (55), 119 (40), 77 (70) Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69. 08; H, 4.91; N, 12.15.

3.1.2. 2-(3-[1,3]Dioxolan-2-yl-quinolin-2-yl)-1*H*-quinazolin-4-one [5]. *Method A*. To a solution of **6** (3.47 g, 10 mmol) in acetone (100 mL) was added $KMnO_4$ (1.00 g) and the mixture was refluxed on a steam bath. Slowly the pink color of $KMnO_4$ disappeared. $KMnO_4$ was added in portions of 50 mg each time and refluxing was continued until the pink color persisted. The hot acetone solution was filtered, excess of acetone was distilled off and excess of $KMnO_4$ in the filtrate was destroyed with sodium sulphite. The resulting solution was extracted with $CHCl_3$ (5× 50 mL) and solvent was dried (anhydrous Na_2SO_4), filtered and removed under reduced pressure to furnish the pure quinazolinone **5** (3.20 g, 95% yield) as white solid.

Method B. Sodium hydrogen sulfite (1.07 g, 10 mmol) was added to a solution of anthranilamide (1.37 g, 10 mmol) and quinoline aldehyde **7** (2.29 g, 10 mmol) in *N*,*N*-dimethylacetamide (DMA) (30 mL). The mixture was heated with stirring at 150 °C for 2 h and poured into ice water (300 mL). The precipitate was collected, washed with water, and dried in vacuo to give pure quinazolinone **5** (3.40 g, 98% yield) as white solid; mp 214 °C. IR (KBr) 3310, 3125, 2956, 2883, 1675, 1598, 1509, 1482, 1437, 1215, 950 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$): δ: 11.12 (bs, 1H), 8.60 (s, 1H), 8.27 (d, J=8.15 Hz, 1H), 8.07 (d, J=8.15 Hz, 1H), 7.82 (d, J=8 Hz, 1H), 7.6–7.74 (m, 3H), 7.53 (s, 1H), 7.54 (t, J=8.46 Hz, 1H), 7.42 (t, J=8.46 Hz, 1H), 4.06 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ: 161.51 (C), 149.20 (C), 148.69 (C), 146.07 (C), 145.85 (C), 136.36 (CH), 134.35 (CH), 131.57 (C), 130.90 (CH), 129.66 (CH), 128.55 (CH), 128.47 (CH),128.27 (C), 127.97 (CH), 127.63 (CH),126.5 (CH), 122.35 (C), 99.86 (CH), 65.28 ($2CH_2$). Mass (*m*/*z*): 345 (M^+, 5), 301 (20), 285 (10), 273 (100), 245 (30), 119 (50). Anal. Calcd for $C_{20}H_{15}N_3O_3$: C, 69.56; H, 4.38; N, 12.17. Found: C, 69.48; H, 4.21; N, 12.23.

3.1.3. 2-(3-Hydroxymethyl-quinolin-2-yl)-3*H*-quinazolin-4-one [10]. A solution of **5** (0.450 g, 1.5 mmol) in a 1:1 mixture of 10% HCl: THF (15 mL) was stirred for 2 h. After the reaction was completed (TLC), the reaction mixture was extracted with CH_2Cl_2 (3×20 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated. The aldehyde **9** obtained thereby was suspended in methanol (20 mL) to which $NaBH_4$ (114 mg, 3.2 mmol) was added at 0 °C and the resulting solution was stirred for 1 h at room temperature. Methanol was removed under the reduced pressure and the residue quenched with dil HCl (2 mL), and the solution was stirred for 5 min. Water (15 mL) and DCM (25 mL) were then added. The layers were separated, and the aqueous layer was extracted with DCM (3×15 mL).

The combined organic layers were washed with brine and then dried (anhydrous Na_2SO_4). Evaporation and column chromatography yielded the alcohol **10** (0.370 g, overall 93%) as a white solid; mp 211–212 °C. IR (KBr): 3373, 1681, 1518, 1461, 1377, 945 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$): δ: 11.49 (br s, 1H), 8.43 (d, $J=7.81$ Hz, 1H), 8.31 (s, 1H), 8.20 (d, $J=8.31$ Hz, 1H), 7.93–7.78 (m, 4H), 7.72–7.57 (m, 2H), 6.4 (t, 6.5 Hz, 1H), 5.09 (d, 6.5 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ: 161.02 (C), 150.52(C), 148.13 (C), 147.10 (C), 146.23 (C), 141.21 (CH), 135.06 (CH), 134.53 (C), 131.17 (CH), 130.61 (CH), 129.62 (CH), 129.21 (CH), 128.69 (C), 128.34 (CH), 127.50 (CH), 127.11 (CH), 122.72 (C), 64.5 (CH_2). Mass (*m*/*z*): 303 (M^+, 70), 285 (95), 274 (20), 257 (18), 246 (40), 229 (15), 155 (28), 143 (35), 128 (100), 119 (38), 101 (30), 92 (35). Anal. Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85. Found: C, 71.19; H, 4. 44; N, 13.89.

3.1.4. Luotonin A. *Method A*. A solution of alcohol **10** (0.303 g, 1 mmol) in 60% ethanolic H_2SO_4 (20 mL) was heated to 115 °C for 3 h. The cooled reaction mixture was added to sat. aq. $NaHCO_3$ solution carefully and extracted with dichloromethane (4×25 mL). The extracts were dried (Na_2SO_4), concentrated. The column chromatographic purification of the residue (SiO_2, 9:1 ethyl acetate–hexane) furnished luotonin A (**1a**) as a white soild (0.208 g) in 73% yield; mp 284–285 °C (lit.[1a] mp 283–285 °C); Spectral data was in agreement with that reported.[1a]

Method B. Solution of DEAD (0.227 mL, 1.25 mmol) in THF (5 mL) was added dropwise to the solution of alcohol **10** (0.303 g, 1 mmol) and TPP (0.327 g, 1.25 mmol) in THF(10 mL) and reaction mixture was further stirred for 2 h. The reaction mixture was concentrated in vacuo. The column chromatographic purification of the residue (SiO_2, ethyl acetate) furnished luotonin A (**1a**) as a white soild (0.186 g) in 65% yield.

3.1.5. Luotonin B. To a solution of crude acetal **5** (0.301 g, 1 mmol) in THF (20 mL) was added slowly [with out allowing the temperature to raise beyond the rt] HCl (50%) at 0 °C. The resulting solution was stirred for 1 h at room temperature and refluxed for 1 h. Water (15 mL) and DCM (25 mL) were then added. The layers were separated, and the aqueous layer was extracted with DCM (3×25 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). Evaporation and column chromatography over silica gel employing ethylacetate as eluent yielded luotonin B 2 as a white solid; mp 272–274 °C (lit.[8i] mp 271–274 °C); Spectral data was in agreement with the reported.[1a]

3.1.6. Luotonin E. To a solution of crude acetal **5** (0.301 g, 1 mmol) in MeOH (20 mL) was added slowly [with out allowing the temperature to raise beyond the rt] conc. HCl at 0 °C. The resulting solution was stirred for 1 h at room temperature and refluxed for 2 h. Water (15 mL) was added and carefully neutralized with $NaHCO_3$ and extracted with DCM (3×25 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). Evaporation and column chromatography over silica gel employing ethylacetate as eluent yielded luotonin E 3 as a solid; mp 220–223 °C (lit.[1b] mp 222–225 °C); Spectral data was in agreement with the reported.[1b]

Acknowledgements

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Synthesis of indazole-*N*-oxides via the 1,7-electrocyclization of azomethine ylides

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Abstract—The first examples of the 1,7-electrocyclization of azomethine ylides onto a nitro group, to give benz-1,2,6-oxadiazepine intermediates are reported. Subsequent ring contraction results in the formation of indazole-*N*-oxides.

1. Introduction

As part of our continuing work on the synthesis of the pyrrolo[3,2-*c*]quinoline ring system of the martinelline alkaloids (bradykinin receptor antagonist)[1] we have investigated the formation and reactions of the non-stabilised azomethine ylide **2a**. This azomethine ylide **2a** was formed by the reaction of *o*-nitrobenzaldehyde **1a** with sarcosine in refluxing benzene[2] and, despite the presence of a large excess of active dipolarophiles, for example, ethyl acrylate or methyl vinyl ketone, we did not observe any trace of the expected cycloadduct **3** in the ^{1}H NMR spectrum of the crude reaction mixture.

Two products, an indazole-*N*-oxide **5a** and an oxazolidine **7a** were, however, isolated after chromatographic separation (in 40 and 43% yields respectively) and their structures confirmed by spectroscopic analysis, Scheme 1. The isoxazoline product **7a** was independently synthesized by a method recently described by us,[3] and was found to be identical with the product **7a** obtained from the reaction of nitrobenzaldehyde **1a** and sarcosine. The indazole-*N*-oxide **5a** was deoxygenated in the presence of Pd-on-C, resulting in the formation of the known 2-methyl-2*H*-indazole **8**, Scheme 2.[4]

Keywords: Cycloadditions; Electrocyclic reactions; Indazoles; Isoquinolines; Nitro compounds.
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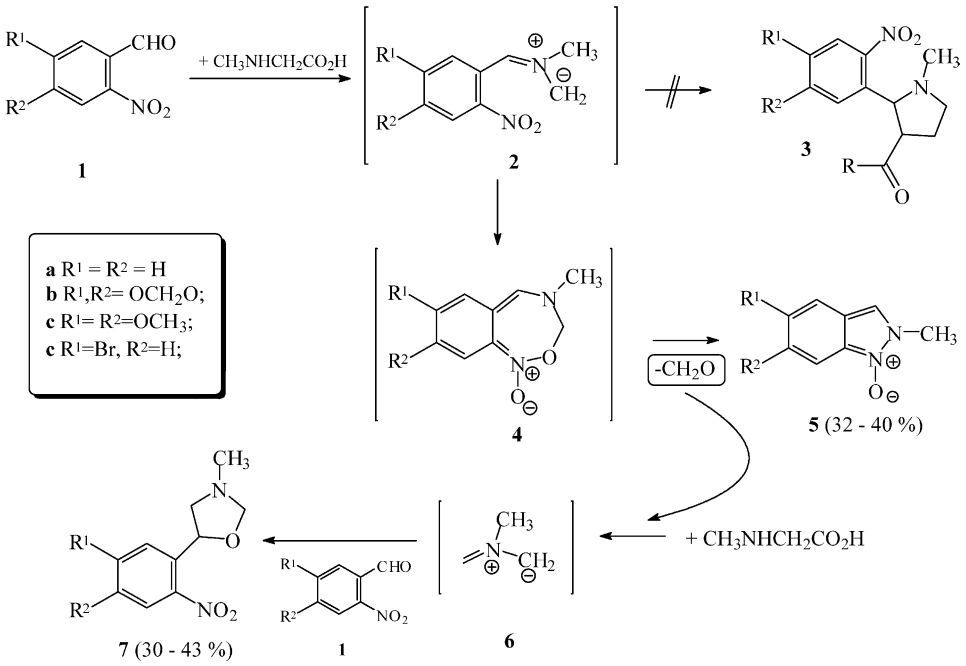
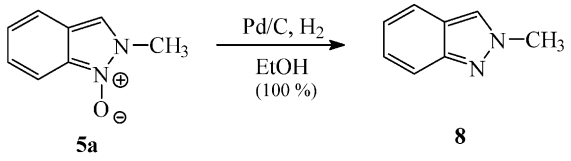
2. Results and discussion

The indazole-*N*-oxide **5a** and the isoxazolidine **7a** probably arise from the fragmentation of the unstable benz-1,2,6-oxadiazepine intermediate **4**, Scheme 1, formed by the decarboxylative condensation[5] of *o*-nitro-benzaldehyde **1** and sarcosine, followed by a 1,7-electrocyclization[6] of the non-stabilised azomethine ylide **2**. As such, this represents the first 1,7-electrocyclization of an azomethine ylide onto a pendant nitro group. The seven-membered ring of **4** subsequently then undergoes a ring contraction, resulting in the elimination of formaldehyde and the production of 2-methyl-2*H*-indazol-*N*-oxide **5a**. The formaldehyde by-product is then able to react with the excess sarcosine present in the reaction mixture, resulting in the formation of azomethine ylide **6**, which can then react with the other starting material, *o*-nitrobenzaldehyde **1**, to yield the 3-methyl-5-aryl-oxazolidine **7a** as the second product.[3] Similar processes have been reported for the 1,7-electrocyclization of an azomethine imine and a nitrile ylide onto a nitro group, leading to the formation of the corresponding benzotriazole-*N*-oxide[7] and 1-acyloxyindazoles,[8] respectively.

We have investigated the scope of this reaction via the generation of further azomethine ylides and found that substitution on the aromatic ring does not have a significant effect, although the yields were somewhat lower than in the unsubsubstituted case, Table 1. The reaction of *o*-nitro-benzaldehyde **1a** and *N*-benzylglycine **9** proceeded in a



Scheme 1.



Scheme 2.

Table 1

Entry	R^1	R^2	Reaction time (h)	Products	
1	H	H	2	5a 40%	7a 43%
2	CH_3O	CH_3O	6	5b 32%	7b 30%
3	OCH_2O		8	5c 34%	7c 38%
4	Br	H	3	5d 37%	7d 33%

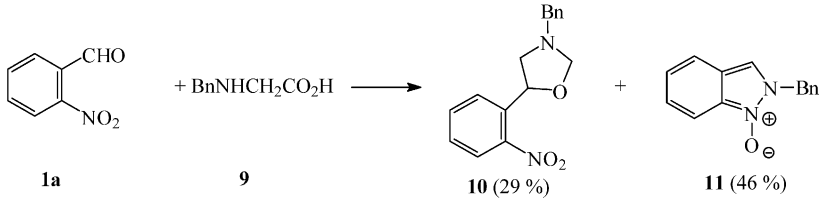
similar manner to give the analogue isoxazoline **10** and 2-benzyl-indazole-*N*-oxide **11**, Scheme 3.

We next chose to form the azomethine ylide **14** from 6,7-dimethoxy-3,4-dihydro-*N*-(2-nitrobenzyl)isoquinolinium chloride **13** (prepared from 3,4-dimethoxy-6,7-dihydro-isoquinoline **12** and 2-nitro-benzylchloride)[9] by dehydrohalogenation with triethylamine, Scheme 4.[10] In the presence of *N*-phenylmaleimide a 2:1 mixture of the cycloadduct **17** (as a single isomer, shown by NOE experiments to have *syn-endo* stereochemistry) and an indazole-*N*-oxide, **16** were obtained, while in the absence of the dipolarophile the *N*-oxide **16** was formed in quantitative yield. In contrast to the examples described above, the aldehyde in this case (which remains attached to the indazole component), arising from the fragmentation of **15**, is not sufficiently reactive to act as a C=O dipolarophile in a 1,3-dipolar cycloaddition process in competition with the 1,7-electrocyclization.

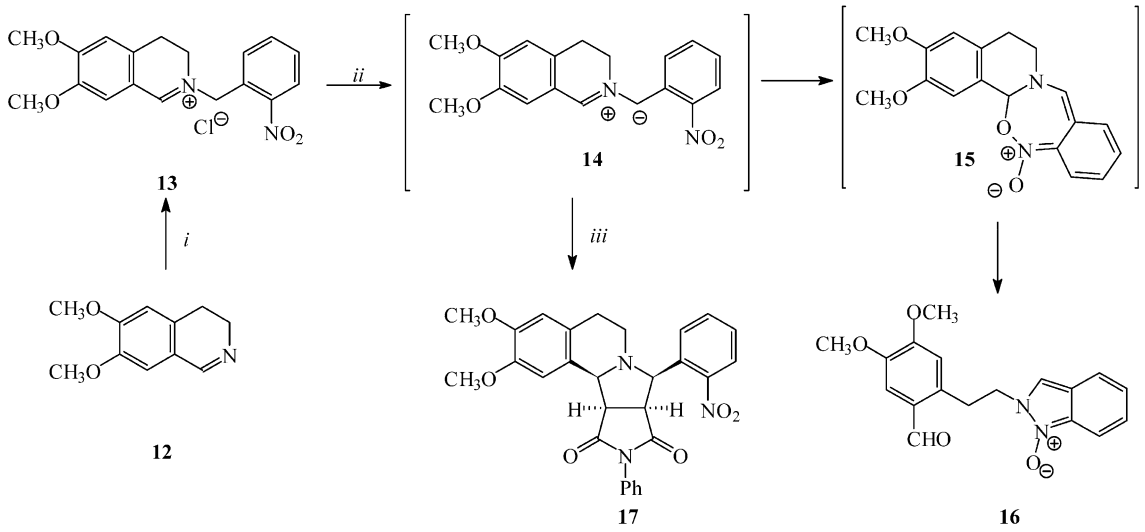
With regard to the proposed mechanism we performed the next series of experiments with 3,4-dihydro-1-(2-nitrophenyl)-*N*-substituted-isoquinolinium bromides **20** (prepared from the corresponding halide and 3,4-dihydroisoquinoline **18**). In all cases the isoquinoline fused indazole-*N*-oxide **22** was formed, Scheme 5, Table 2. In one case (**20a** R=CO_2CH_3) the competitive formation of the 1,3-dipolar cycloadduct **23** as a single isomer (the relative stereochemistry of the which was again proven by NOE experiments) was observed (ratio of **22a**:**23** approx. 3:1) due to the high reactivity of the electron-deficient C=O double bond of the aldehyde by-product.

3. Experimental

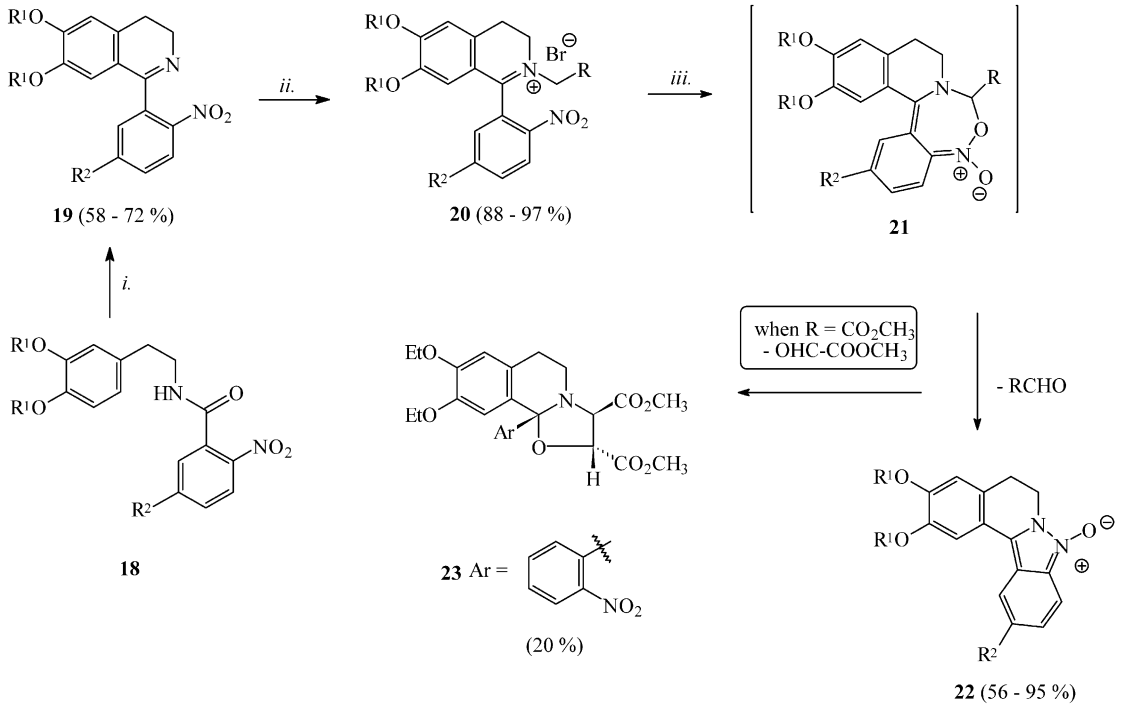
Melting points were determined on a Gallenkamp apparatus



Scheme 3.



Scheme 4. Reagents and conditions: (i) 2-$O_2NC_6H_4CH_2Cl$, dry Et_2O, 95%; (ii) Et_3N, MeOH, rt, 85%; (iii) *N*-phenylmaleimide, Et_3N, MeOH, rt, 58%.



Scheme 5. Reagents and conditions: (i) $POCl_3$, P_2O_5, xylene, reflux; (ii) RCH_2Br; (iii) Et_3N, MeOH.

and are uncorrected. Column chromatography was performed using Merck Kieselgel 60 70–230 mesh, TLC on aluminium sheets coated with Kieselgel 60 F_{254}. Plates were stained with anisaldehyde solution (100 mL glacial acetic acid, 2 mL cc. sulphuric acid and 1 mL anisaldehyde) and heated at ca. 150 °C. IR spectra were measured on a NICOLET FT-IR instrument. NMR spectra were obtained on a Bruker 250 instrument. Chemical shifts are given

Table 2

Entry	R^1	R^2	R	Yield of 20	Yield of 22
1	Et	H	$–CO_2Me$	20a 97%	22a: 56%
2	Et	H	$–CH_2Ph$	20b 95%	22a: 66%
3	Et	H	$–CH{=}CH_2$	20c 92%	22a: 88%
4	Me	H	$–CH{=}CH_2$	20d 88%	22b: 95%
5	Me	Cl	$–CH{=}CH_2$	20e 94%	22c: 95%
6	Et	Cl	$–CH{=}CH_2$	20f 96%	22d: 92%

relative to δ_{TMS}. All solvents were purified according to standard procedures and the amides **18** were prepared by the method of Cortes et al.[11]

3.1. Reaction of 2-nitrobenzaldehydes with sarcosine. General procedure

The appropriate 2-nitrobenzaldehyde (1 mmol) was dissolved in benzene or toluene (50 mL) and sarcosine (0.18 g, 2 mmol) was added. The reaction mixture was refluxed for 2–8 h and the water formed was removed with the aid of a Dean–Stark trap. After cooling, the precipitated solid was filtered off and all the solvent was removed in vacuo. The resulting products were separated by column chromatography on silica, eluting with hexane–ethyl acetate (50:50 to 0:100). The corresponding yields are given in Table 1.

3.1.1. 3-Methyl-5-(2′-nitrophenyl)oxazolidine (7a). As a pale yellow oil; δ_H (250 MHz, $CDCl_3$) 8.03 (1H, d, J=8.2 Hz, Ar–3′H), 7.87 (1H, d, J=8.2 Hz, Ar–6′H), 7.65 (1H, t, J=8.2 Hz, Ar–5′H), 7.41 (1H, t, J=8.2 Hz, Ar–4′H), 5.53 (1H, t, J=6.7 Hz, H-5), 4.64 (1H, d, J=5.1 Hz, H-2), 4.47 (1H, d, J=5.1 Hz, H-2), 3.62 (1H, dd, J=11.6, 6.7 Hz, H-4), 2.80 (1H, dd, J=11.6, 6.7 Hz, H-4), 2.49 (3H, s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 147.8 (quat., C-1′), 139.3 (quat.), 133.8 (CH), 127.6 (CH), 127.0 (CH), 124.5 (CH), 89.3 (CH_2, C-2), 73.3 (CH, C-5), 61.1 (CH_2, C-4), 41.5 (N–CH_3); ν_{max}/cm^{-1} (liquid film) 2851, 2867, 2799, 1524, 1452, 1346, 1058; (HRMS Found: m/z 208.0822. $C_{10}H_{12}N_2O_3$ requires 208.0835).

3.1.2. 2-Methyl-2*H*-indazole-*N*-oxide (5a). As a pale yellow powder, mp 90 °C [Found: C, 64.9; H, 5.6; N, 19.0. $C_8H_8N_2O$ requires C 64.8; H 5.45; N 18.9%]; δ_H (250 MHz, DMSO-d_6) 7.95 (1H, s, H-3), 7.60 (1H, d, J=8.1 Hz, H-7), 7.50 (1H, d, J=8.1 Hz, H-4), 7.20 (1H, t, J=8.1 Hz, H-5), 7.06 (1H, t, J=8.1 Hz, H-6), 3.95 (3H, s, CH_3); δ_C (62.5 MHz, DMSO-d_6) 127.6 (quat.), 125.6 (CH), 123.0 (CH), 120.9 (CH), 115.1 (quat.), 112.2 (CH), 110.5 (CH), 33.0 (CH_3); ν_{max}/cm^{-1} (liquid film) 3224, 3098, 1670, 1622, 1510, 1458, 1374, 1240, 1178, 1112, 757.

3.1.3. 3-Methyl-5-(3′,4′-dimethoxy-6′-nitrophenyl)oxazolidine (7b). As a pale yellow oil; δ_H (250 MHz, $CDCl_3$) 7.57 (1H, s, Ar–5′H), 7.24 (1H, s, Ar–2′H), 5.49 (1H, t, J=5.0 Hz, H-5), 4.54 (1H, d, J=5.0 Hz, H-2), 4.35 (1H, d, J=5.0 Hz, H-2), 3.90 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.52 (1H, dd, J=11.4, 5.0 Hz, H-4), 2.73 (1H, dd, J=11.4, 5.0 Hz, H-4), 2.39 (3H, s, NCH_3); δ_C (62.5 MHz, $CDCl_3$) 153.6 (quat.), 147.3 (quat.), 138.6 (quat.), 134.8 (quat.), 107.8 (CH), 107.7 (CH), 89.1 (CH_2), 73.7 (CH), 61.8 (CH_2), 56.1 (OCH_3), 56.0 (OCH_3), 41.5 (CH_3); ν_{max}/cm^{-1} (liquid film) 2949, 2896, 2857, 1580, 1518, 1471, 1440, 1336, 1275, 1220, 1067, 1030, 1015, 986; (HRMS Found: m/z 268.1021. $C_{12}H_{16}N_2O_5$ requires 268.1029).

3.1.4. 2-Methyl-5,6-dimethoxy-2*H*-indazole-*N*-oxide (5b). As a pale yellow powder, mp 122–3 °C [Found: C, 57.9; H, 5.8; N, 13.6. $C_{10}H_{12}N_2O_3$ requires C 57.7; H 5.8; N 13.5%]; δ_H (250 MHz, DMSO-d_6) 8.24 (1H, s, H-3), 7.41 (1H, s, H-7), 7.08 (1H, s, H-4), 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.47 (3H, s, NCH_3); δ_C (62.5 MHz, DMSO-d_6) 154.3 (quat.), 148.7 (quat.), 146.9 (CH), 144.2 (quat.), 114.5 (quat.), 107.7 (CH), 104.8 (CH), 55.9 (CH_3), 55.7 (CH_3), 33.5 (CH_3); ν_{max}/cm^{-1} (KBr) 3428, 2940, 2832, 1665, 1612, 1500, 1457, 1436, 1398, 1362, 1341, 1270, 1217, 1167, 1131, 1051, 1013.

3.1.5. 3-Methyl-5-(3′,4′-methylenedioxy-6′-nitrophenyl)-oxazolidine (7c). As a pale yellow oil; δ_H (250 MHz, $CDCl_3$) 7.42 (1H, s, H-5′), 7.16 (1H, s, H-2′), 6.00 (2H, s, OCH_2O) 5.39 (1H, t, J=6.3 Hz, H-5), 4.50 (1H, d, J=4.9 Hz, H-2), 4.30 (1H, d, J=4.9 Hz, H-2), 3.46 (1H, dd, J=11.5, 6.3 Hz, H-4), 2.73 (1H, dd, J=11.5, 6.3 Hz, H-4), 2.36 (3H, s, NCH_3); δ_C (62.5 MHz, $CDCl_3$) 152.5 (quat.), 146.6 (quat.), 140.3 (quat.), 137.4 (quat.), 105.8 (CH), 105.0 (CH), 102.8 (CH_2), 89.1 (CH_2), 73.9 (CH), 62.1 (CH_2), 41.5 (CH_3); ν_{max}/cm^{-1} (liquid film) 2951, 2894, 1581, 1515, 1472, 1441, 1332, 1221, 1067, 1031, 1015; (Found: 252.0740. $C_{11}H_{12}N_2O_5$ requires 252.0746).

3.1.6. 2-Methyl-5,6-methylenedioxy)-2*H*-indazole-*N*-oxide (5c). As a pale yellow powder; mp 118–9 °C; [Found: C, 56.2; H, 4.3; N, 14.4. $C_9H_8N_2O_3$ requires C 56.25; H 4.2; N 14.6%]; δ_H (250 MHz, DMSO-d_6) 8.23 (1H, s, H-3), 7.40 (1H, s, H-7), 7.07 (1H, s, H-4), 6.18 (2H, s, OCH_2O), 3.46 (3H, s, NCH_3); δ_C (62.5 MHz, DMSO-d_6) 154.6 (quat.), 148.4 (quat.), 147.1 (CH), 144.1 (quat.), 114.5 (quat.), 107.6 (CH), 105.0 (CH), 102.7 (CH_2), 33.4 (CH_3); ν_{max}/cm^{-1} (KBr) 3422, 2942, 2838, 1664, 1611, 1504, 1453, 1402, 1364, 1343, 1212, 1167, 1132, 1011.

3.1.7. 3-Methyl-5-(3′-bromo-6′-nitrophenyl)oxazolidine (7d). As a pale yellow oil; δ_H (250 MHz, $CDCl_3$) 8.00 (1H, d, J=2.0 Hz, H-2′), 7.92 (1H, d, J=8.7 Hz, H-5′), 7.52 (1H, dd, J=8.7, 2.0 Hz, H-4′), 5.50 (1H, t, J=6.7 Hz, H-5), 4.62 (1H, d, J=5.2 Hz, H-2), 4.43 (1H, d, J=5.2 Hz, H-2), 3.58 (1H, dd, J=11.6, 6.7 Hz, H-4), 2.78 (1H, dd, J=11.6, 6.7 Hz, H-4), 2.46 (3H, s, NCH_3); δ_C (62.5 MHz, $CDCl_3$) 141.5 (quat.), 138.1 (quat.), 131.1 (CH), 130.5 (CH), 129.5 (quat.), 126.4 (CH), 89.5 (CH_2), 73.3 (CH), 62.0 (CH_2), 41.6 (CH_3); ν_{max}/cm^{-1} (liquid film) 3432, 2951, 1662, 1611, 1501, 1458, 1431, 1367, 1279, 1168, 1132, 1051, 1009; (Found: 252.9991. $C_{10}H_{11}N_2O_3Br$ requires 285.9953).

3.1.8. 2-Methyl-5-bromo-2*H*-indazole-*N*-oxide (5d). As a pale yellow powder, mp 130–1 °C; [Found: C, 42.6; H, 3.2; N, 12.3. $C_8H_7N_2OBr$ requires C 42.3; H 3.1; N 12.3%]; δ_H (250 MHz, DMSO-d_6) 8.15 (1H, s, H-3), 7.85 (1H, s, H-4), 7.62 (1H, d, J=8.5 Hz, H-7), 7.44 (1H, d, J=8.5 Hz, H-6), 3.48 (3H, s, NCH_3); δ_C (62.5 MHz, DMSO-d_6) 137.6 (quat.), 132.0 (quat.) 124.6 (CH), 122.9 (CH), 120.1 (quat.), 119.2 (CH), 114.5 (CH), 33.5 (CH_3); ν_{max}/cm^{-1} (KBr) 3228, 3100, 1673, 1629, 1511, 1375, 1311, 1242, 1177, 1100.

3.1.9. 2-Methyl-2*H*-indazole (8).[4] The indazole-*N*-oxide **5a** (0.15 g, 1 mmol) was dissolved in ethanol (25 mL) and palladium on charcoal (10%, 10 mg) was added. The reaction mixture was stirred under an hydrogen atmosphere (1 atm), at room temperature, for 12 h. The catalyst was then filtered of with the aid of Celite© and the solvent was removed in vacuo to give the product as a colourless oil, (0.13 g, 100%); δ_H (250 MHz, $CDCl_3$) 7.81 (1H, s, H-3), 7.69 (1H, d, J=8.7 Hz, H-7), 7.61 (1H, d, J=8.7 Hz, H-4), 7.26 (1H, t, J=8.7 Hz, H-6), 7.05 (1H, t, J=8.7 Hz, H-5),

4.14 (3H, s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 127.3 (quat.), 125.8 (CH), 123.5 (CH), 121.6 (quat.), 121.5 (CH), 119.9 (CH), 116.9 (CH), 40.2 (CH_3); ν_{max}/cm^{-1} (nujol) 3416, 2932, 1730, 1628, 1517, 1386, 1300, 1159, 1009; *m/z* 42 (100%), 51 (52), 63 (57), 77 (18), 104 (6), 133 (M, 43).

3.1.10. 3-Benzyl-5-(2-nitrophenyl)oxazolidine (10) and 2-benzyl-2*H*-indazole-*N*-oxide (11). To a solution of 2-nitrobenzaldehyde (0.50 g, 3.3 mmol) in dry THF (50 mL) was added *N*-benzylglycine (0.80 g, 4.97 mmol) and molecular sieves (4 Å, 2 g). The reaction mixture was heated at reflux for 5 h, under nitrogen. After cooling, the solid was filtered off and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica, eluting with hexane–ethyl acetate (from 80:20 to 0:100) to give two products; **10**: as a yellow solid (0.27 g, 29%), mp 133 °C; δ_H ($CDCl_3$, 270 MHz): 8.03 (1H, dd, J=7.9, 1.3 Hz, H-3′), 7.90 (1H, d, J=7.9 Hz, H-6′), 7.63 (1H, t, J=7.9 Hz, H-5′), 7.21–7.41 (6H, m, H-4′ and Ar–H), 5.55 (1H, t, J=6.6 Hz, H-5), 4.66 (1H, d, J=5.9 Hz, H-2′), 4.59 (1H, d, J=5.9 Hz, H-2), 3.72–3.80 (3H, m, Bn–CH_2 and H-5), 2.82 (1H, dd, J=11.9, 6.6 Hz, H-5); δ_C ($CDCl_3$, 67.5 MHz): 146.8 (quat.), 139.5 (quat.), 138.4 (quat.), 134.0 (CH), 128.7 (2×CH), 128.4 (2×CH), 127.8 (CH), 127.3 (CH), 127.1 (CH), 124.7 (CH), 87.4 (CH_2), 73.3 (CH), 60.2 (CH_2), 58.3 (CH_2); ν_{max}/cm^{-1} (KBr) 2921, 2855, 2801, 1527, 1455, 1368, 1347, 1166, 1052; (Found: 284.1132. $C_{16}H_{16}N_2O_3$ requires 284.1160); **11**: as a white solid (0.33 g, 46%), mp 155–6 °C; δ_H ($CDCl_3$, 270 MHz) 5.60 (2H, s, CH_2), 7.06 (1H, t, J=7.5 Hz, Ar–H), 7.21–7.45 (8H, m, Ar–H), 7.71 (1H, d, J=8.0 Hz, Ar–H); δ_C ($CDCl_3$, 67.5 MHz) 49.5 (CH_2), 108.6 (CH), 112.9 (CH), 116.0 (quat.), 120.2 (CH), 123.7 (CH), 126.3 (CH), 128.7 (3×CH) 129.0 (2×CH and 1 quat.), 133.7 (quat.); ν_{max}/cm^{-1} (KBr) 3229, 3111, 1666, 1611, 1517, 1459, 1373, 1246, 1167, 1115; (Found: 224.0922. $C_{14}H_{12}N_2O$ requires 224.0950).

3.1.11. 4,5-Dimethoxy-2-[2′-(2″*H*-2″-indazolyl-1″-*N*-oxide)ethyl]benzaldehyde (16). 6,7-Dimethoxy-3,4-dihydro-2-(2′-nitrobenzyl)isoquinolinium chloride (0.36 g, 1.0 mmol) was dissolved in methanol (5 mL) and triethylamine (0.14 mL, 0.10 g, 1.0 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, then the solvent was removed in vacuo. The residue was dissolved in dichloromethane (30 mL) and washed with water (3× 20 mL). The organic layer was dried over magnesium sulphate and evaporated to give the product as a pale brown solid (0.28 g, 85%), mp 114–6 °C; [Found: C, 66.2; H, 5.6; N, 8.5. $C_{18}H_{18}N_2O_4$ requires C 66.3; H 5.6; N 8.6%]; δ_H (250 MHz, $CDCl_3$) 10.06 (1H, s, CHO), 7.70 (1H, d, J=8.8 Hz, H-7″), 7.44 (1H, d, J=8.8 Hz, H-4″), 7.28 (1H, s, H-3″), 7.25 (1H, t, J=8.8 Hz, H-5″), 7.21 (1H, s, H-3), 7.07 (1H, t, J=8.8 Hz, H-6″), 6.51 (1H, s, H-6), 4.69 (2H, t, J=6.9 Hz, CH_2), 3.92 (3H, s, *O*CH_3), 3.65 (3H, s, *O*CH_3), 3.64 (2H, t, J=6.9 Hz, CH_2); δ_C (62.5 MHz, $CDCl_3$) 191.3 (CHO), 153.3 (quat.), 150.2 (quat.), 148.0 (quat.), 133.7 (quat.), 129.4 (quat.), 126.8 (quat.), 126.5 (CH), 123.7 (CH), 120.3 (CH), 115.7 (CH), 114.3 (CH), 112.6 (CH), 109.7 (CH), 56.1 (CH_3), 56.0 (CH_3), 47.6 (CH_2), 31.7 (CH_2); ν_{max}/cm^{-1} (KBr) 2902, 1710, 1562, 1490, 1444, 1251, 1105, 1037.

3.1.12. 2,3-Dimethoxy-8-(2-nitrophenyl)-10-phenyl-8,8a,11a,11b-tetrahydro-6*H*-pyrrolo[3′,4′:3,4]pyrrolo-[2,1-*a*]isoquinoline-9,11(5*H*,10*H*)-dione (17). Isoquinolinium, 3,4-dihydro-6,7-dimethoxy-2-[(2-nitrophenyl)-methyl]-, chloride (**13**) (0.50 g, 1.4 mmol) and *N*-phenylmaleimide (0.23 g, 1.4 mmol) were dissolved in methanol (15 mL) and triethylamine (0.20 mL, 0.14 g, 1.4 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo, and the residue was dissolved in dichloromethane (30 mL) and it washed with water (3×20 mL). The organic layer was dried over magnesium sulphate and evaporated to give a pale brown solid which was further purified by column chromatography on silica, eluting with ethyl acetate–hexane (1:1). The product was obtained as a white powder (0.41 g, 58%), mp 236–8 °C; [Found: C, 67.5; H, 5.0; N, 8.5. $C_{28}H_{25}N_3O_6$ requires C 67.3; H 5.0; N 8.4%]; δ_H (250 MHz, $CDCl_3$) 8.07 (1H, d, J=7.7 Hz, H-3′), 7.94 (1H, d, J=7.7 Hz, Ar–H), 7.66 (1H, t, J=7.7 Hz, Ar–H), 7.46 (1H, t, J=7.7 Hz, Ar–H), 7.43–7.30 (3H, m, Ar–H), 7.15 (2H, m, Ar–H), 6.81 (1H, s, H-1), 6.55 (1H, s, H-4), 5.13 (1H, s, H-11b), 4.95 (1H, d, J=8.6 Hz, H-8), 4.01 (1H, t, J=8.6 Hz, H-8a), 3.93 (3H, s, CH_3), 3.88 (3H, s, CH_3), 3.73 (1H, d, J=8.6 Hz, H-11a), 3.17 (1H, dt, J=13.3, 4.5 Hz, CH_2), 3.00–2.70 (2H, m, CH_2), 2.30 (1H, dd, J=16.7, 3.9 Hz, CH_2); δ_C (62.5 MHz, $CDCl_3$) 177.6 (quat.), 174.7 (quat.), 149.7 (quat.), 148.3 (quat.), 148.2 (quat.), 133.6 (CH), 133.3 (quat.), 131.8 (quat.), 129.1 (2×CH), 129.0 (CH), 128.9 (CH), 128.5 (CH), 126.2 (2×CH), 126.1 (quat.), 125.8 (quat.), 125.2 (CH), 111.9 (C-4), 108.7 (C-1), 64.0 (C-11b), 59.1 (CH), 56.1 (CH_3), 55.9 (CH_3), 51.0 (CH), 49.0 (CH), 41.9 (CH_2), 20.5 (CH_2); ν_{max}/cm^{-1} (KBr) 3099, 2992, 2931, 2834, 1714, 1515, 1450, 1376, 1357, 1253, 1182, 1099, 1020.

3.2. Synthesis of isoquinolines (19). General procedure

Phosphorus pentoxide (14.2 g, 0.1 mol) was suspended at 0 °C in dry xylene (300 mL) and freshly distilled phosphorus oxychloride (18.5 mL, 30.7 g, 0.2 M) was added dropwise to the well-stirred mixture. To this mixture was added the corresponding amide **18** and the reaction mixture was stirred at reflux for 3 h followed by cooling to room temperature. The xylene was decanted and the semi-solid residue was stirred overnight with an excess of 10% aqueous sodium hydroxide solution. The solid precipitate which formed was filtered off and recrystallized from ethanol.

3.2.1. 6,7-Dimethoxy-1-(2′-nitrophenyl)-3,4-dihydro-isoquinoline (19a). As a pale yellow solid (58%), mp 112–3 °C (lit.[11] 110–2 °C); δ_H (250 MHz, $CDCl_3$) 8.00 (1H, d, J=7.5 Hz, H-3′), 7.67 (1H, t, J=8.3 Hz, H-5′), 7.54 (1H, t, J=8.3 Hz, H-4′), 7.52 (1H, d, J=8.3 Hz, H-6′), 6.73 (1H, s, H-8), 6.29 (1H, s, H-5), 3.86 (3H, s, OCH_3), 3.79 (2H, t, J=7.6 Hz, CH_2), 3.58 (3H, s, OCH_3), 2.77 (2H, t, J=7.6 Hz, CH_2); δ_C (62.5 MHz, $CDCl_3$) 164.2 (quat.), 151.2 (quat.), 148.4 (quat.), 147.3 (quat.), 134.7 (quat.), 133.3 (CH), 131.3 (quat.), 130.9 (CH), 129.5 (CH), 124.2 (CH), 121.3 (quat.), 110.3 (CH), 109.1 (CH), 55.9 (CH_3), 55.8 (CH_3), 47.6 (CH_2), 25.3 (CH_2); ν_{max}/cm^{-1} (KBr) 2966, 2836, 1606, 1568, 1526, 1353, 1324, 1284, 1270, 1215, 1123, 1024.

3.2.2. 6,7-Diethoxy-1-(2′-nitrophenyl)-3,4-dihydroisoquinoline (19b). As a pale yellow solid (65%), [Found: C, 67.2; H, 5.9; N, 8.4. $C_{19}H_{20}N_2O_4$ requires C 67.05; H 5.9; N 8.2%]; mp 118–20 °C; δ_H (250 MHz, $CDCl_3$) 8.07 (1H, d, 1H, $J=7.8$ Hz, H-3′), 7.68 (1H, t, $J=7.8$ Hz, H-5′), 7.68 (1H, t, $J=7.8$ Hz, H-4′), 7.58 (1H, d, $J=7.8$ Hz, H-6′), 6.76 (1H, s, H-8), 6.34 (1H, s, H-5), 4.14 (2H, q, $J=6.9$ Hz, OCH_2), 3.83 (2H, m, $2\times CH_2$), 2.80 (2H, t, $J=7.6$ Hz, CH_2), 1.47 (3H, t, $J=6.9$ Hz, CH_3), 1.30 (3H, t, $J=6.9$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 164.5 (quat.), 151.5 (quat.), 147.5 (quat.), 145.9 (quat.), 136.0 (quat.), 133.1 (CH), 131.2 (quat.), 129.9 (CH), 129.6 (CH), 124.0 (CH), 121.5 (quat.), 110.6 (CH), 109.8 (CH), 65.5 (CH_2), 65.2 (CH_2), 47.6 (CH_2), 25.3 (CH_2), 14.5 ($2\times CH_3$); ν_{max}/cm^{-1} (KBr) 2968, 2830, 1611, 1564, 1525, 1320, 1283, 1271, 1215, 1175, 1122, 1054, 1021.

3.2.3. 6,7-Dimethoxy-1-(5′-chloro-2′-nitrophenyl)-3,4-dihydroisoquinoline (19c). As a yellow solid (72%), mp 128–9 °C; [Found: C, 60.0; H, 4.5; N, 8.0. $C_{17}H_{15}N_2O_4Cl$ requires C 59.9; H 4.4; N 8.1%]; δ_H (250 MHz, $CDCl_3$) 8.04 (1H, d, $J=8.3$ Hz, H-3′), 7.58 (1H, s, H-6′), 7.56 (1H, d, $J=8.3$ Hz, H-4′), 6.78 (1H, s, H-8), 6.31 (1H, s, H-5), 3.93 (3H, s, OCH_3), 3.85 (2H, t, $J=7.5$ Hz, CH_2), 3.66 (3H, s, OCH_3), 2.83 (2H, t, $J=7.5$ Hz, CH_2); δ_C (62.5 MHz, $CDCl_3$) 163.3 (quat.), 151.4 (quat.), 147.5 (quat.), 146.7 (quat.), 140.0 (quat.), 136.5 (quat.), 131.4 (quat.), 131.1 (CH), 129.6 (CH), 125.7 (CH), 120.9 (quat.), 110.5 (CH), 108.8 (CH), 56.1 (CH_3), 55.9 (CH_3), 47.7 (CH_2), 25.3 (CH_2); ν_{max}/cm^{-1} (KBr) 2986, 2947, 2904, 1606, 1564, 1523, 1397, 1357, 1312, 1213, 1132, 1111, 1087, 1039.

3.2.4. 6,7-Diethoxy-1-(5′-chloro-2′-nitrophenyl)-3,4-hydroisoquinoline (19d). As a yellow solid (70%), mp 126–8 °C; [Found: C, 60.8; H, 5.1; N, 7.5. $C_{19}H_{19}N_2O_4Cl$ requires C 60.9; H 5.1; N 7.5%]; δ_H (250 MHz, $CDCl_3$ + DMSO-d_6) 8.06 (1H, d, $J=8.1$ Hz, H-3′), 7.59 (1H, d, $J=8.1$ Hz, H-4′), 7.57 (1H, s, H-6′), 6.78 (1H, s, H-8), 6.32 (1H, s, H-5), 4.14 (2H, q, $J=7.0$ Hz, OCH_2), 3.86 (4H, m, $2\times CH_2$), 2.82 (2H, t, $J=7.5$ Hz, CH_2), 1.47 (3H, t, $J=7.0$ Hz, CH_3), 1.32 (3H, t, $J=7.0$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$ + d_6-DMSO) 163.4 (quat.), 151.6 (quat.), 146.7 (quat.), 146.4 (quat.), 139.8 (quat.), 136.0 (quat.), 131.6 (quat.), 130.9 (CH), 129.6 (CH), 125.6 (CH), 120.6 (quat.), 111.7 (CH), 111.6 (CH), 65.0 (CH_2), 64.2 (CH_2), 47.4 (CH_2), 25.1 (CH_2), 14.4 ($2\times CH_3$); ν_{max}/cm^{-1} (KBr) 2966, 2949, 2898, 2832, 1603, 1561, 1526, 1395, 1358, 1318, 1271, 1211, 1182, 1129, 1108, 1039.

3.3. Synthesis of quaternery salts. General procedures

Method A. The 3,4-dihydroisoquinoline (2.5 mmol) was dissolved in dry diethyl ether (25 mL) and 2-nitrobenzylchloride (0.44 g, 2.5 mmol) or methly bromoacetate (0.28 mL, 0.46 g, 3.0 mmol) were added. The mixture was left without stirring for 3 days at room temperature, under an argon atmosphere. The yellow precipitate was filtered off, washed with dry diethyl ether and dried in vacuo.

Method B. The 3,4-dihydroisoquinoline (2.5 mmol) was dissolved in allyl bromide (4 mL). The resulting solution was heated for 24 h under reflux, under an argon atmosphere. The excess allyl bromide was removed in vacuo and the residue was triturated with dry diethyl ether. The yellow precipitate was filtered off, washed with diethyl ether and dried in vacuo.

3.3.1. Isoquinolinium, 3,4-dihydro-6,7-dimethoxy-2-[(2-nitrophenyl)methyl]-, chloride (13). The title compound was prepared via method A to give a yellow powder (95%), mp 190–2 °C; [Found: C, 59.4; H, 5.1; N, 7.5. $C_{18}H_{19}N_2O_4Cl$ requires C 59.6; H 5.3; N 7.7%]; δ_H (250 MHz, DMSO-d_6) 9.25 (1H, s, H-1′), 8.25 (1H, d, $J=8.1$ Hz, H-3′), 7.87 (2H, m, H-4′ and H-5′), 7.76 (1H, d, $J=8.1$ Hz, H-6′), 7.56 (1H, s, H-8), 7.21 (1H, s, H-5), 5.55 (2H, s, NCH_2Ar), 3.99 (2H, t, $J=6.6$ Hz, CH_2), 3.97 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.20 (2H, t, $J=6.6$ Hz, CH_2); δ_C (62.5 MHz, DMSO-d_6) 165.8 (quat.), 157.7 (quat.), 148.5 (quat.), 148.1 (quat.), 134.9 (CH), 133.1 (CH), 132.4 (CH), 130.9 (CH), 127.0 (CH), 125.8 (quat.), 117.2 (quat.), 115.9 (CH), 111.5 (CH), 59.2 ($ArCH_2N$), 56.7 (CH_3), 56.0 (CH_3), 48.3 (CH_2), 25.0 (CH_2); ν_{max}/cm^{-1} (KBr) 3376, 3002, 2975, 1641, 1602, 1562, 1527, 1344, 1303, 1274, 1139, 1006.

3.3.2. 6,7-Diethoxy-3,4-dihydro-2-(methoxycarbonylmethyl)-1-(2′-nitrophenyl)isoquinolinium bromide (20a). The title compound was prepared via method A to give a yellow powder, mp 100–2 °C; [Found: C, 53.4; H, 5.2; N, 5.7. $C_{22}H_{25}N_2O_6Br$ requires C 53.6; H 5.1; N 5.7%]; δ_H (250 MHz, DMSO-d_6) 8.55 (1H, d, $J=8.0$ Hz, H-3′), 8.14 (1H, t, $J=8.0$ Hz, H-5′), 8.06 (1H, t, $J=8.0$ Hz, H-4′), 7.76 (1H, d, $J=8.0$ Hz, H-6′), 7.33 (1H, s, H-8), 6.18 (1H, s, H-5), 4.18 (2H, s, CH_2COO), 4.28 (4H, m, $2\times CH_2CH_3$), 3.76 (3H, s, $COOCH_3$), 3.37 (4H, m, H-6 and H-7), 1.36 (3H, t, $J=6.7$ Hz, CH_2CH_3), 1.11 (3H, t, $J=6.7$ Hz, CH_2CH_3); δ_C (62.5 MHz, DMSO-d_6) 173.0 (quat.), 166.1 (quat.), 157.0 (quat.), 147.1 (quat.), 145.7 (quat.), 135.9 (CH), 135.2 (quat.), 133.9 (CH), 129.3 (CH), 126.6 (CH), 124.2 (quat.), 118.1 (CH), 115.0 (CH), 112.3 (quat.), 65.3 (CH_2), 64.3 (CH_2), 58.1 (CH_2), 53.2 (CH_3), 51.5 (CH_2), 25.0 (CH_2), 14.4 (CH_3), 14.2 (CH_3); ν_{max}/cm^{-1} (KBr) 2988, 2955, 2913, 1720, 1625, 1523, 1375, 1234, 1222, 1137, 1039.

3.3.3. Isoquinolinium, 6,7-diethoxy-3,4-dihydro-1-(2-nitrophenyl)-2-(phenylmethyl)-, bromide (20b). 6,7-Diethoxy-1-(2′-nitrophenyl)-3,4-dihydroisoquinoline (1.0 g, 2.9 mmol) was dissolved in dry toluene (10 mL) and benzyl bromide (0.36 mL, 0.50 g, 3 mmol) was added. The resulted solution was heated for 48 h at reflux under an argon atmosphere. The solvent was removed in vacuo and the residue was triturated with dry diethyl ether. The yellow precipitate was filtered off, washed with diethyl ether and dried in vacuo to give a yellow powder (1.45 g, 95%), mp 190–2 °C; [Found: C, 59.9; H, 5.1; N, 5.5. $C_{26}H_{27}N_2O_4Br$ requires C 60.0; H 5.3; N 5.5%]; δ_H (250 MHz, $CDCl_3$) 8.92 (1H, d, $J=7.5$ Hz, H-3′), 8.47 (1H, d, $J=7.5$ Hz, H-6′), 8.18 (1H, t, $J=7.5$ Hz, H-4′), 8.08 (1H, t, $J=7.5$ Hz, H-5′), 7.35 (5H, s, ArH), 7.02 (1H, s, H-8), 6.09 (1H, s, H-5), 5.50 (1H, d, $J=14.9$ Hz, NCH_2Ph), 5.07 (1H, d, $J=14.9$ Hz, NCH_2Ph), 4.90–4.60 (1H, m, CH_2CH_2), 4.40–4.00 (4H, m, $2\times CH_2CH_3$), 3.88–3.52 (2H, m, CH_2CH_2), 3.50–3.15 (1H, m, CH_2CH_2), 1.48 (3H, t, $J=6.5$ Hz, CH_3), 1.27 (3H, t, $J=6.6$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 171.2 (quat.), 157.4 (quat.), 147.9 (quat.), 146.1 (quat.), 136.2 (CH), 134.3

(quat.), 133.8 (CH), 132.2 (CH), 131.7 (quat.), 129.5 (2× CH), 129.4 (CH), 128.9 (2×CH), 125.6 (CH), 125.4 (quat.), 118.6 (quat.), 114.9 (CH), 112.1 (CH), 65.5 (CH_2CH_3), 65.1 (CH_2CH_3), 61.8 (CH_2), 49.8 (CH_2), 26.0 (CH_2), 14.4 (CH_3), 14.3 (CH_3); ν_{max}/cm^{-1} (KBr) 2979, 1602, 1552, 1525, 1386, 1342, 1272, 1213, 1186, 1029, 754.

3.3.4. 2-Allyl-6,7-diethoxy-3,4-dihydro-1-(2′-nitrophenyl)isoquinolinium bromide (20c). The title compound was prepared via method B to give a yellow powder, mp 245–7 °C; [Found: C, 57.0; H, 5.5; N, 6.0. $C_{22}H_{25}N_2O_4Br$ requires C 57.3; H 5.5; N 6.1%]; δ_H (250 MHz, $CDCl_3$) 8.43 (1H, d, J=7.5 Hz, H-3′), 8.38 (1H, d, J=7.5 Hz, H-6′), 8.24 (1H, t, J=7.5 Hz, H-4′), 7.93 (1H, t, J=7.5 Hz, H-5′), 6.98 (1H, s, H-8), 6.09 (1H, s, H-5), 5.83–5.63 (1H, m, allyl-H), 5.48–5.23 (2H, m, allyl-H), 4.85–4.60 (2H, m, allyl-H), 4.39–4.18 (4H, m, 2×CH_2CH$_3$), 3.82–3.53 (2H, m, CH_2), 3.29 (2H, m, CH_2), 1.47 (3H, t, J=6.9 Hz, CH_3), 1.26 (3H, t, J=6.9 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 170.9 (quat.), 157.3 (quat.), 147.7 (quat.), 145.6 (quat.), 137.0 (quat.), 134.5 (quat.), 133.1 (CH), 131.8 (CH), 131.7 (quat.), 128.3 (CH), 125.2 (CH), 123.5 (CH_2), 118.9 (CH), 115.3 (CH), 112.1 (CH), 65.5 (CH_2), 65.2 (CH_2), 61.1 (CH_2), 50.1 (CH_2), 25.9 (CH_2), 14.4 (CH_3), 14.3 (CH_3); ν_{max}/cm^{-1} (KBr) 2984, 2888, 1712, 1635, 1553, 1381, 1277, 1202, 1124, 1103, 1039.

3.3.5. 2-Allyl-6,7-dimethoxy-3,4-dihydro-1-(2′-nitrophenyl)isoquinolinium bromide (20d). The title compound was prepared via method B to give a yellow powder, mp 237–8 °C; [Found: C, 55.2; H, 4.7; N, 6.5 $C_{20}H_{21}N_2O_4Br$ requires C 55.4; H 4.9; N 6.5%]; δ_H (250 MHz, $CDCl_3$) 8.89 (1H, d, J=7.5 Hz, H-3′), 8.46 (1H, d, J=7.5 Hz, H-6′), 8.14 (1H, t, J=7.5 Hz, H-4′), 8.00 (1H, t, J=7.5 Hz, H-5′), 7.03 (1H, s, H-8), 6.07 (1H, s, H-5), 5.91–5.80 (1H, m, allyl-H), 5.39–5.36 (2H, m, allyl-H), 4.89–4.69 (2H, m, allyl-H), 4.38 (1H, m, CH_2), 4.17 (1H, m, CH_2), 4.05 (3H, s, OCH_3), 3.66 (1H, m, CH_2), 3.58 (3H, s, OCH_3), 3.41 (1H, m, CH_2); δ_C (62.5 MHz, $CDCl_3$) 170.7 (quat.), 157.0 (quat.), 148.3 (quat.), 145.5 (quat.), 135.9 (quat.), 134.0 (quat.), 133.1 (CH), 131.5 (CH), 131.4 (quat.), 128.0 (CH), 125.2 (CH), 123.3 (CH_2), 118.8 (quat.), 112.5 (CH), 111.0 (CH), 60.9 (CH_2), 56.7 (CH_3), 55.8 (CH_3), 49.4 (CH_2), 25.6 (CH_2); ν_{max}/cm^{-1} (KBr) 3013, 2943, 1604, 1557, 1526, 1467, 1387, 1344, 1294, 1274, 1222, 1186, 1124, 1082.

3.3.6. 2-Allyl-6,7-dimethoxy-3,4-dihydro-1-(2′-nitro-5′-chlorophenyl)isoquinolinium bromide (20e). The title compound was prepared via method B to give a yellow powder, mp 252–3 °C; [Found: C, 51.2; H, 4.5; N, 6.1 $C_{20}H_{20}N_2O_4BrCl$ requires C 51.4; H 4.3; N 6.0%]; δ_H (250 MHz, $CDCl_3$) 9.01 (1H, s, H-6′), 8.48 (1H, d, J=8.8 Hz, H-3′), 7.98 (1H, d, J=8.8 Hz, H-4′), 7.07 (1H, s, H-8), 6.11 (1H, s, H-5), 5.90–5.77 (1H, m, allyl-H), 5.44–5.32 (2H, m, allyl-H), 4.88–4.32 (2H, m, allyl-H), 4.40 (1H, m, CH_2), 4.18 (1H, m, CH_2), 4.10 (3H, s, OCH_3), 3.71 (3H, s, OCH_3) 3.45 (2H, m, CH_2); δ_C (62.5 MHz, $CDCl_3$) 169.1 (quat.), 157.2 (quat.), 148.3 (quat.), 143.8 (quat.), 142.7 (quat.), 134.3 (quat.), 133.4 (CH), 131.0 (CH), 127.8 (CH), 126.8 (CH), 126.5 (CH), 123.4 (CH_2), 118.4 (quat.), 112.4 (CH), 111.2 (CH), 61.0 (CH_2), 56.7 (CH_3), 56.0 (CH_3), 49.6 (CH_2), 25.5 (CH_2); ν_{max}/cm^{-1} (KBr) 3088, 2974, 2933, 2866, 1598, 1565, 1551, 1525, 1393, 1373, 1339, 1299, 1272, 1217, 1187, 1108, 1029.

3.3.7. 2-Allyl-6,7-diethoxy-3,4-dihydro-1-(2′-nitro-5′-chlorophenyl)isoquinolinium bromide (20f). The title compound was prepared via method B to give a yellow powder (95%), mp 255 °C; [Found: C, 53.2; H, 4.9; N, 5.7 $C_{22}H_{24}N_2O_4BrCl$ requires C 53.3; H 4.9; N 5.65%]; δ_H (500 MHz, DMSO-d_6) 8.54 (1H, d, J=9.0 Hz, H-3′), 8.31 (1H, d, J=1.0 Hz, H-6′), 8.14 (1H, dd, J=9.0, 1.0 Hz, H-4′), 7.31 (1H, s, H-8), 6.32 (1H, s, H-5), 5.89–5.84 (1H, m, allyl-H), 5.36–5.32 (2H, m, allyl-H), 4.39 (2H, m, allyl-H), 4.29–4.22 (4H, m, 2×CH_2CH$_3$), 3.73 (2H, m, CH_2), 3.41 (1H, m, CH_2), 3.26 (1H, m, CH_2), 1.35 (3H, t, J=7.0 Hz, CH_3), 1.14 (3H, t, J=7.0 Hz, CH_3); δ_C (75.5 MHz, DMSO-d_6) 169.5 (quat.), 156.5 (quat.), 147.0 (quat.), 144.3 (quat.), 140.8.0 (quat.), 134.4 (quat.), 133.5 (CH), 129.6 (quat.), 129.2 (quat.), 128.3 (CH), 126.2 (CH), 121.7 (CH_2), 118.1 (quat.), 115.1 (CH), 112.3 (CH), 65.0 (CH_2), 64.4 (CH_2), 59.8 (CH_2), 49.7 (CH_2), 24.8 (CH_2), 14.3 (CH_3), 14.1 (CH_3); ν_{max}/cm^{-1} (KBr) 2982, 2877, 1713, 1633, 1566, 1377, 1284, 1226, 1200, 1124, 1101, 1037.

3.3.8. 1,7-Electrocyclizations. General procedures. The 3,4-dihydro-1-(2′-nitrophenyl)isoquinolinium halide (2.9 mmol) was dissolved in dry methanol (10 mL) and triethylamine (0.42 mL, 0.30 g, 3.0 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (50 mL) and washed with water (3×20 mL) and brine (20 mL). The organic layer was dried over magnesium sulphate and evaporated in vacuo. The residue was further purified by column chromatography on silica gel, eluting with acetone to give the product.

3.3.9. 2,3-Diethoxy-5,6-dihydroindazolo[3,2-*a*]isoquinoline-8-oxide (22a). The title compound was obtained as an orange solid, mp 90 °C; [Found: C, 70.6; H, 6.1; N, 8.5. $C_{19}H_{20}N_2O_3$ requires C 70.35; H 6.2; N 8.6%]; δ_H (250 MHz, $CDCl_3$) 7.87 (1H, d, J=8.6 Hz, H-9), 7.71 (1H, d, J=8.6 Hz, H-12), 7.38 (1H, s, H-1), 7.31 (1H, t, J=8.6 Hz, H-11), 7.16 (1H, t, J=8.6 Hz, H-10), 6.81 (1H, s, H-4), 4.57 (2H, t, J=7.0 Hz, H-6), 4.15 (2H, q, J=7.3 Hz, OCH_2), 4.12 (2H, q, J=7.3 Hz, OCH_2), 3.15 (2H, t, J=7.0 Hz, H-5), 1.50 (3H, t, J=7.3 Hz, CH_3), 1.47 (3H, t, J=7.3 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 149.5 (quat.), 148.1 (quat.), 131.3 (quat.), 127.0 (CH), 124.2 (quat.), 124.0 (CH), 120.1 (CH), 119.5 (quat.), 118.9 (quat.), 113.4 (CH), 112.9 (CH), 112.0 (quat.), 109.7 (CH), 65.1 (CH_2), 64.7 (CH_2), 39.9 (CH_2), 27.6 (CH_2), 14.8 (CH_3), 14.7 (CH_3); ν_{max}/cm^{-1} (KBr) 2983, 2938, 1604, 1558, 1525, 1388, 1344, 1274, 1031.

3.3.10. 2,3-Dimethoxy-5,6-dihydroindazolo[3,2-*a*]isoquinoline-8-oxide (22b). The title compound was obtained as an orange solid, mp 122–3 °C; [Found: C, 69.0; H, 5.6; N, 9.5 $C_{17}H_{16}N_2O_3$ requires C 68.9; H 5.4; N 9.45%]; δ_H (250 MHz, $CDCl_3$) 7.91 (1H, d, J=8.6 Hz, H-9), 7.70 (1H, d, J=8.6 Hz, H-12), 7.39 (1H, s, H-1), 7.31 (1H, t, J=8.6 Hz, H-11), 7.20 (1H, t, J=8.6 Hz, H-10), 6.87 (1H, s, H-4), 4.58 (2H, t, J=7.0 Hz, H-6), 4.01 (3H, s, CH_3), 3.94 (3H, s, CH_3), 3.21 (2H, t, J=7.0 Hz, H-5); δ_C (62.5 MHz, $CDCl_3$) 149.3 (quat.), 147.8 (quat.), 131.7 (quat.), 129.4

(CH), 125.9 (quat.), 123.5 (CH), 120.4 (CH), 120.1 (quat.), 118.1 (quat.), 112.4 (CH), 112.1 (quat.), 111.3 (CH), 106.6 (CH), 55.7 (CH_3), 55.5 (CH_3), 39.1 (CH_2), 27.0 (CH_2); ν_{max}/cm^{-1} (KBr) 3023, 2993, 2931, 2830, 1606, 1531, 1505, 1464, 1431, 1368, 1350, 1286, 1250, 1222, 1211, 1168, 1146, 1124, 1080, 1024.

3.3.11. 2,3-Dimethoxy-11-chloro-5,6-dihydroindazolo[3,2-*a*]isoquinoline-8-oxide (22c). The title compound was obtained as an orange solid, mp 133 °C; [Found: C, 61.7; H, 4.6; N, 8.5 $C_{17}H_{15}N_2O_3Cl$ requires C 61.7; H 4.6; N 8.5%]; δ_H (250 MHz, $CDCl_3$+DMSO-d_6) 7.86 (1H, s, H-12), 7.67 (1H, d, J=9.2 Hz, H-9), 7.28 (1H, s, H-1), 7.22 (1H, d, J=9.2 Hz, H-10), 6.87 (1H, s, H-4), 4.56 (2H, t, J=6.8 Hz, H-6), 4.02 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.21 (2H, t, J=6.8 Hz, H-5); δ_C (62.5 MHz, $CDCl_3$+DMSO-d_6) 148.9 (quat.), 148.3 (quat.), 129.2 (quat.), 127.8 (quat.), 127.2 (CH), 123.8 (quat.), 118.5 (CH), 118.2 (quat.), 117.4 (quat.), 114.2 (CH), 111.6 (quat.), 111.4 (CH), 106.7 (CH), 55.0 (CH_3), 55.7 (CH_3), 39.3 (CH_2), 27.2 (CH_2); ν_{max}/cm^{-1} (KBr) 3380, 3005, 1610, 1538, 1506, 1489, 1470, 1359, 1281, 1221, 1205, 1161, 1076, 1054, 1012, 989.

3.3.12. 2,3-Diethoxy-11-chloro-5,6-dihydroindazolo[3,2-*a*]isoquinoline-8-oxide (22d). The title compound was obtained as an orange solid, mp 129–30 °C; [Found: C, 63.6; H, 5.4; N, 7.6. $C_{19}H_{19}N_2O_3Cl$ requires C 63.6; H 5.3; N 7.8%]; δ_H (250 MHz, $CDCl_3$) 7.82 (1H, s, H-12), 7.68 (1H, d, J=9.2 Hz, H-9), 7.28 (1H, s, H-1), 7.21 (1H, d, J=9.2 Hz, H-10), 6.82 (1H, s, 1H, H-4), 4.56 (2H, t, J=7.0 Hz, H-6), 4.19 (2H, q, J=7.0 Hz, OCH_2), 4.16 (2H, q, J=7.0 Hz, OCH_2), 3.17 (2H, t, J=7.0 Hz, H-5), 1.53 (3H, t, J=7.0 Hz, CH_3), 1.49 (3H, t, J=7.0 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 148.8 (quat.), 147.8 (quat.), 129.0 (quat.), 127.7 (quat.), 127.1 (CH), 123.9 (quat.), 118.5 (CH), 118.1 (quat.), 117.8 (quat.), 114.0 (CH), 113.1 (CH), 111.5 (quat.), 109.3 (CH),64.9 (CH_2), 64.2 (CH_2), 39.3 (CH_2), 27.1 (CH_2), 14.4 (CH_3), 14.3 (CH_3); ν_{max}/cm^{-1} (KBr) 2975, 2914, 2867, 1613, 1603, 1534, 1505, 1472, 1445, 1396, 1360, 1344, 1284, 1250, 1217, 1198, 1170, 1080, 1056.

3.3.13. Dimethyl 8,9-diethoxy-10b-(2-nitrophenyl)-2,3,6,10b-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline-2,3-dicarboxylate (23). 6,7,-Diethoxy-3,4-dihydro-2-(methoxycarbonylmethyl)-1-(2′-nitrophenyl)isoquinolinium bromide (**20a**) (0.49 g, 1.0 mmol) was dissolved in methanol (5 mL) and triethylamine (0.14 mL, 0.10 g, 1.0 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (30 mL) and washed with water (3×20 mL). The organic layer was dried over magnesium sulphate and evaporated to give a mixture of 10,11-diethoxy-7,8-dihydroindazolo[3,2-a]isoquinoline-5-oxide **22a** and the title compound, which was separated by column chromatography, eluting with hexane–ethyl acetate (2:1) to give a white powder (0.10 g, 20%), mp 168–170 °C; [Found: C, 60.1; H, 5.7; N, 5.6. $C_{25}H_{28}N_2O_9$ requires C 59.99; H 5.64; N 5.60%]; δ_H (250 MHz, $CDCl_3$) 8.01 (1H, d, J=7.8 Hz, H-3′), 7.57 (1H, dt, J=7.8, 1.8 Hz, ArH), 7.49–7.38 (2H, m, ArH), 6.71 (1H, s, H-10), 6.67 (1H, s, H-7), 4.87 (1H, d, J=4.6 Hz, H-2), 4.08 (2H, q, J=7.0 Hz, OCH_2), 4.00–3.77 (3H, m, H-3 and OCH_2), 3.75 (OCH_3), 3.53 (OCH_3), 3.27–3.05 (3H, m, CH_2), 2.75–2.62 (1H, m, CH_2), 1.43 (3H, t, J=7.0 Hz, CH_3), 1.31 (3H, t, J=7.0 Hz CH_3); δ_C (62.5 MHz, $CDCl_3$) 170.8 (quat.), 169.9 (quat.), 149.5 (quat.), 148.7 (quat.), 146.8 (quat.), 135.5 (quat.), 131.2 (CH), 129.7 (CH), 129.4 (CH), 127.7 (quat.), 126.0 (quat.), 124.4 (CH), 113.4 (CH), 112.0 (CH), 99.6 (quat.), 74.0 (CH), 71.5 (CH), 64.6 (CH_2), 64.2 (CH_2), 52.6 (CH_3), 52.4 (CH_3), 50.1 (CH_2), 28.3 (CH_2), 14.7 (CH_3×2); ν_{max}/cm^{-1} (KBr) 1735 (C═O), 1535 (NO_2), 1367 (NO_2), 1263 (C–O).

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The reaction of 2-fluoroalkyl-1-iodoethylenes with arylamines: a facile method for the synthesis of fluoroalkylated quinolines and enaminoketones

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Abstract—The reaction of 2-fluoroalkyl-1-iodoethylenes with arylamines (**1**) and the subsequent acid promoted transformation of the products were described. In the presence of $ZnCl_2$ and triethylamine, **1** reacted readily with various *p*-substituted anilines in HMPA under a vacuum of 60–70 mmHg to give the corresponding enaminoaldehydes (**2**) as a mixture of *E*- and *Z*-isomers. Cyclization of **2**, without further purification in refluxing toluene, catalyzed by strong acids such as *p*-toluene sulfonic acid and trifluoromethanesulfonic acid gave 2-fluoroalkylquinolines (**3**) in good yields, while fluoroalkylated enaminoketones (**4**) were obtained predominantly when **2** was treated with acids in aqueous THF solution. A possible mechanism was proposed for the formation of **3** and **4**.

1. Introduction

Recently fluorinated compounds have been of great interest to both synthetic and medicinal chemists due to their unique physical and biological properties imparted by fluorine.[1] Among these compounds, fluorinated quinolines are the focus of considerable research and some of them have found applications in medicinal and pharmaceutical fields. For example, mefloquine ((2,8-bis(trifluoromethyl)-4-quinolinyl)(2-piperidinyl) methanol) has been used as highly effective antimalarial drug.[2] Therefore many methods have been developed for the preparation of fluoroalkylated quinolines. The traditional methods comprise two main approaches, namely, fluorination of suitable functional groups, such as $-CX_3$ (X = Cl, Br)[3] and $-CO_2H$,[4] and direct introduction of fluoroalkyl group by the reaction of fluoroalkyl iodides and haloquinolines in the presence of copper powder.[5] Recently much attention was paid to the synthesis of these fluorinated compounds by means of fluorine-containing building blocks. Many fluorinated precursors such as fluorine-containing enaminoketones,[6] *N*-arylimines,[7] propynoic acid esters,[8] α-fluoroalkyl aldehydes[9] and α-fluoroalkyl esters[10] have been used to synthesize 2-fluoroalkylquinolines. However, these fluorinated precursors are not easily available and the yields of some reactions are low. Herein we report a facile synthesis of 2-fluoroalkylquinolines and fluorinated enaminoketones from 2-fluoroalkyl-1-iodoethylenes.

2-Fluoroalkyl-1-iodoethylene (**1**), easily prepared from the reaction of fluoroalkyl iodides and acetylene,[11] are versatile fluorine-containing precursors. They have been reported to react with various nucleophilic reagents, and many fluoroalkylated heterocyclic compounds such as pyrazoles,[12] isoxazoles,[13] pyrimidines,[14] indolizines[15] and 1,4-diazepines[16] were prepared from these reactions. In the continuation of our study on their applications in the synthesis of fluorine-containing compounds, it was found that 2-fluoroalkylquinolines or fluoroalkylated enaminoketones could be conveniently synthesized in good yields from the reaction of **1** and substituted anilines under different conditions.

2. Results and discussion

In the presence of excess Et_3N, the reaction of 1-iodo-3,3,4,4,5,5,6,6,6-nonafluorohexene (**1a**) and *p*-methoxy aniline occurred at 80 °C in DMF (monitored by TLC or ^{19}F NMR). After workup a new compound was obtained. The spectral data showed that it was a mixture of *E*- and *Z*-isomer of 3-heptafluoropropyl-3-enaminoaldehyde (**2aa**). Treatment of **2aa** with polyphosphoric acid (PPA) at 170 °C

Keywords: 2-Fluoroalkyl-1-iodoethylene; Aniline; Fluoroalkylated quinoline; Fluoroalkylated enaminoketone; Acid.
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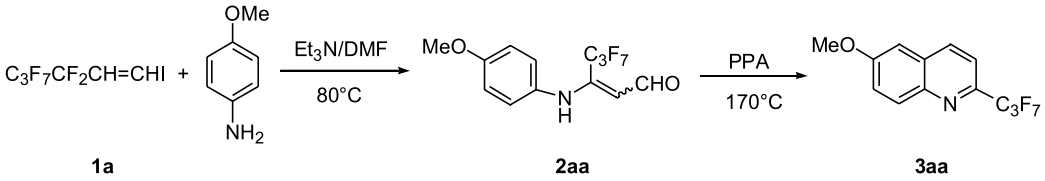


Scheme 1.

gave the corresponding cyclization product, 2-heptafluoropropyl-6-methoxyquinoline (**3aa**) (Scheme 1). The structure of **3aa** was characterized by its spectral data and further confirmed by the X-ray crystallography of its analogue, 2-(1,1,2,2,3,3-hexafluoro-3-chloropropyl)-6-methylquinoline (**3bb**) (Fig. 1).

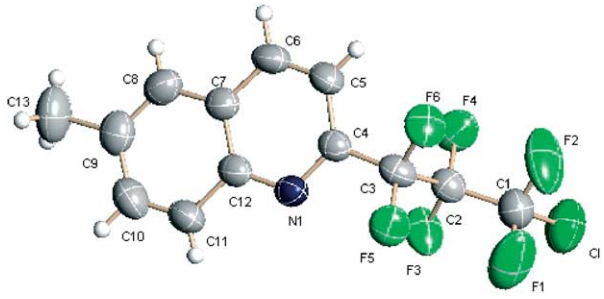


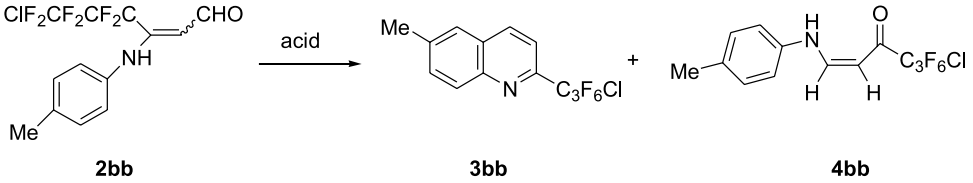
Figure 1. X-ray crystallographic structure of **3bb**.

Obviously, an acid promoted cyclization reaction was involved in the second step. In order to simplify the reaction and improve the yields of **3**, other acids such as *p*-toluene sulfonic acid, trifluoromethanesulfonic acid and concentrated hydrochloric acid were tested. It was found that the cyclization reaction of **2bb** took place readily in toluene at 120 °C in the presence of catalytic amount of TsOH or CF_3SO_3H (about 10 mol% based on **1**) to give compound **3bb** in nearly quantitative yields. However, a by-product, fluoroalkylated enaminoketone (**4bb**), was obtained in addition to the expected product **3bb** when concentrated hydrochloride acid was used in the reaction. It was hypothesized that the formation of **4bb** was attributed to the water in concentrated hydrochloric acid. Thus, 5% hydrochloric acid was tested and the expected results were obtained: **4bb** was formed as the major product. As shown in Table 1, solvent had distinct effect on the reaction and the best result was obtained in THF, as **4bb** being formed in almost quantitative yield when THF was used as the solvent (entry 4). The same result was obtained with TsOH or CF_3SO_3H when the reaction was carried out in aqueous THF solution (entries 8 and 9), confirming that water was essential for the formation of compound **4**.

A possible mechanism for the formation of **3** and **4** was proposed as shown in Scheme 2. Nucleophilic addition of the amino group in anilines to **1** followed by the elimination of a HI gave intermediate **A**, which eliminated a HF in the presence of base to afford intermediate **B**. Nucleophilic substitution of **B** by another aniline resulted in the formation of intermediate **C**. Hydrolysis of **C** gave the corresponding aldehyde **2**, which underwent cyclization promoted by strong acids to give **3**.[17] While intermediate **D** was formed from **2** in the presence of acid and water, an aniline was released at the same time. Similar transformation has been reported in the literature.[18] Subsequent reaction of **D** with aniline gave compound **4**. As a proof, intermediate **C** (Ar= 4-$MeOC_6H_4$, R_f=C_3F_7) was isolated from the reaction mixture and characterized by its spectral data.

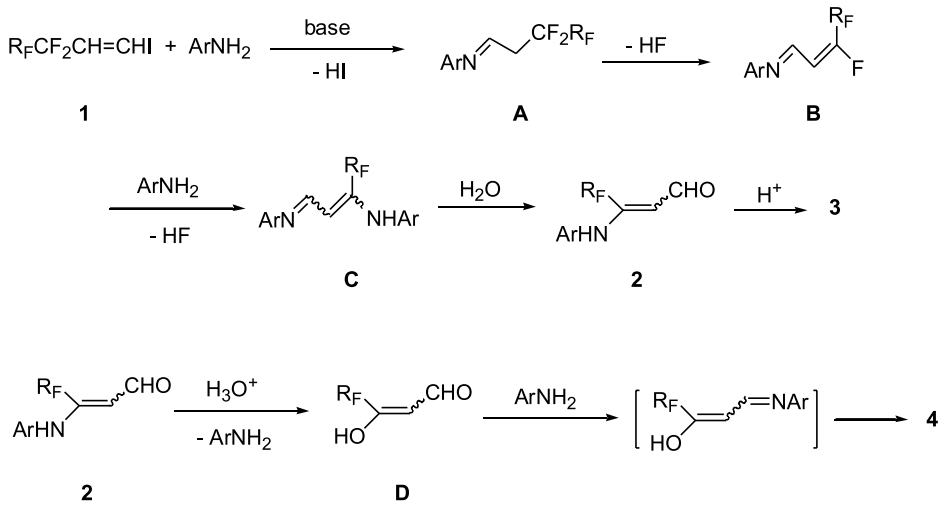
From the above results, it is very convenient to make fluoroalkylated quinolines and enaminoketones selectively from **1** by the two-step reaction using different conditions, but yields of the first step were unsatisfactory. Therefore, the conditions of the first step were optimized using the reaction of *p*-methoxyaniline with **1a** as a model reaction. It was found that in the presence of equal mole of $ZnCl_2$ and excess Et_3N, the reaction proceeded smoothly in HMPA under a vacuum of 60–70 mmHg to give **2aa** in high yield. Without purification, **2aa** was treated with TsOH directly in

Table 1. The acid promoted reaction of **2bb**



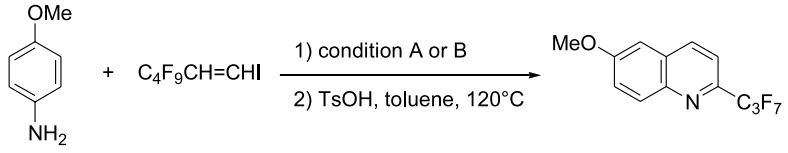
Entry	Acid	Solvent	Temperature (°C)	Time (h)	**3bb** (%)[a]	**4bb** (%)[a]
1	PPA	—	170	3	>98	—
2	TsOH	Toluene	120	3	>99	—
3	HCl(conc)	Toluene	120	4	85	15
4	5% HCl	THF	70	1	—	>99
5	5% HCl	CH_2Cl_2	60	6	—	Trace
6	5% HCl	EtOH (95%)	70	1	33	67
7	TsOH	THF/H_2O	70	2	—	>99
8	CF_3SO_3H	THF/H_2O	70	2	—	>99

[a] Determined by ^{19}F NMR.



Scheme 2.

Table 2. The reaction of **1a** with *p*-methoxyaniline under different conditions



1a **3aa**

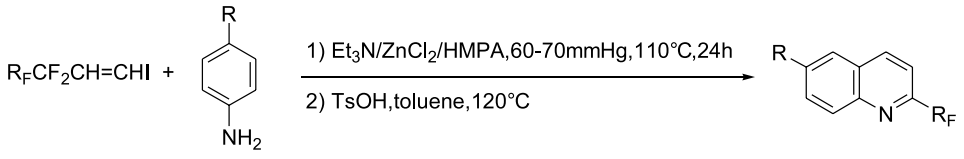
Entry	Condition[a]	Temperature (°C)[b]	Time (h)[b]	Yield (%)[c]
1	A	80	24	58
2	A	110	24	61
3	A	80	48	61
4	B	110	24	92

[a] Condition A: Et_3N/DMF, △; condition B: $Et_3N/ZnCl_2$/HMPA, 60–70 mmHg, △.
[b] Conditions for the first step.
[c] Isolated yields based on **1a**.

toluene and **3aa** was obtained in 92% overall yield. Some of the results are summarized in Table 2.

Using the optimized reaction conditions, the reaction of **1** with various substituted anilines was studied and the results were listed in Table 3. As shown in the table, the length of fluoroalkyl chains had little influence on the reaction, but the reaction results were obviously affected by the

Table 3. Synthesis of 2-fluoroalkylquinolines from **1**

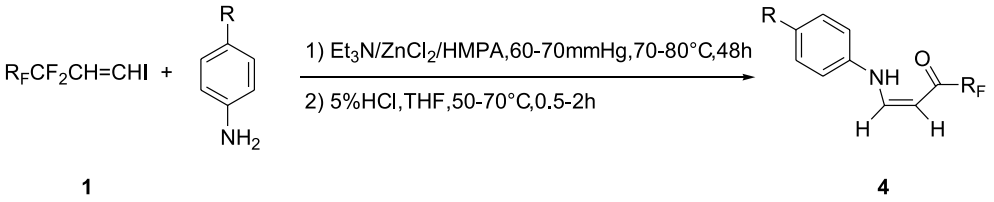


1 **3**

Entry	**1**	R	R_f	**3**	Yield (%)[a]
1	**1a**	MeO	C_3F_7	**3aa**	92
2	**1a**	Me	C_3F_7	**3ab**	87
3	**1b**	Me	C_3F_6Cl	**3bb**	83
4	**1c**	Me	CF_2Cl	**3cb**	85
5	**1d**	Me	C_5F_{11}	**3db**	75
6	**1a**	H	C_3F_7	**3ac**	79
7	**1a**	Cl	C_3F_7	**3ad**	75
8	**1a**	Br	C_3F_7	**3ae**	71
9	**1b**	Br	C_3F_6Cl	**3be**	75
10	**1a**	NO_2	C_3F_7	**3af**[b]	31

[a] Isolated yields based on **1**.
[b] Obtained directly from the first step without further treatment with acid.

Table 4. Synthesis of fluoroalkylated enaminoketones from **1**



1 **4**

Entry	**1**	R	R_f	**4**	Yields (%)[a]
1	**1a**	MeO	C_3F_7	**4aa**[b]	68
2	**1a**	Me	C_3F_7	**4ab**	74
3	**1b**	Me	C_3F_6Cl	**4bb**	73
4	**1c**	Me	CF_2Cl	**4cb**	64
5	**1d**	Me	C_5F_{11}	**4db**	73
6	**1b**	MeO	C_3F_6Cl	**4ba**[b]	68
7	**1b**	H	C_3F_6Cl	**4bc**	75
8	**1a**	H	C_3F_7	**4ac**	74
9	**1c**	H	CF_2Cl	**4cc**	71
10	**1b**	Cl	C_3F_6Cl	**4bd**	68
11	**1b**	Br	C_3F_6Cl	**4be**	68

[a] Isolated yields based on **1**.
[b] Hydrolysis was performed at 50 °C for 1 h.

substituent in anilines and better results were obtained with electron-donating substituents such as methoxy and methyl. In the case of *p*-nitroaniline, the reaction was kind of slow, and the yield of **3af** was very low due to its weak nucleophilicity caused by strong electron-withdrawing nitro group (entry 10).

Similarly, reaction of **1** with various anilines in HMPA in the presence of Et_3N and $ZnCl_2$ at 70–80 °C under a vacuum of 60–70 mmHg followed by the treatment of the product with 5% hydrochloric acid at 50–70 °C gave compound **4** in good overall yields. The results were summarized in Table 4. In the case of *p*-methoxyaniline, acidic hydrolysis was performed at 50 °C because cyclization products were formed at higher temperature. The reaction of **1a** with *p*-nitroaniline gave only cyclization product **3af**, and the corresponding fluoroalkylated enaminoaldehyde **2af** was not obtained. All fluoroalkylated enaminoketones obtained were in *Z*-configuration as indicated by the coupling constants ($J=7.3$–7.8 Hz) of the two olefinic protons in their ^{1}H NMR spectra. This is probably due to the formation of an intramolecular hydrogen bond between N–H and carbonyl oxygen. Similar result was reported in the literature.[19]

In conclusion, the reaction of 2-fluoroalkyl-1-iodoethylenes with various anilines and the subsequent acid promoted transformation of products are achieved under mild conditions, providing a convenient method for the preparation of 2-fluoroalkylquinolines and fluoroalkylated (*Z*-) enaminoketones. Compared to the reported procedures, this method has the advantage of easily available starting material, mild reaction conditions and good selectivity.

3. Experimental

3.1. General

Melting points were uncorrected. IR spectra were taken on a Perkin–Elmer jeol 983 spectrophotometer. ^{1}H NMR spectra were measured on a Bruker AM300 (300 MHz) spectrometer using TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM300 (282 MHz) spectrometer. Chemical shifts were reported using $CFCl_3$ as external standard [$\delta(CFCl_3)=0$], upfield shift being designated as negative. Mass spectra were obtained on a Hewlett-Packard HP-5989A spectrometer. Column chromatography was performed using silica H, particle size 10–40 μ.

3.2. General procedure for the preparation of intermediate 2

A mixture of **1** (1 mmol), arylamine (3 mmol), Et_3N (5 mmol) and anhydrous $ZnCl_2$ (1 mmol) were stirred in HMPA (10 mL) at 70–80 °C under a vacuum of 60–70 mmHg. After 24–48 h, the mixture was cooled to room temperature, diluted with 1% HCl (15 mL) and then extracted with ether (3×20 mL). The organic layer was combined, washed with saturated NaCl solution and dried over sodium sulfate. After the solvent was removed by rotary evaporation, the residue was chromatographed on silica gel eluting with petroleum–ethyl ether to give **2**.

3.2.1. Data for compound 2aa. Yellow solid. Mp 108–110 °C. IR (KBr): 3231, 3120, 3036, 2903, 2841, 1623, 1587, 1519, 1412, 1350, 1289, 1220, 1181, 1146, 1079, 959, 830, 730 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 10.92 (br, 1H, NH), 9.69 (d, 1H, $J=8.4$ Hz), 9.39 (d, 1H, $J=2.7$ Hz), 7.13–7.08 (m, 4H), 6.95–6.85 (m, 4H), 6.22 (br, 1H, NH), 5.62 (d, 1H, $J=8.4$ Hz), 5.56 (d, 1H, $J=2.7$ Hz), 3.82 (s, 6H). ^{19}F NMR ($CDCl_3$): δ −80.28 (3F), −80.54 (3F), −110.71 (2F), −111.64 (2F), −125.19 (2F), −126.72 (2F). EIMS *m/z* (%): 345 (M^+, 57.08), 176 ($M^+-C_3F_7$, 100.00). EI-HRMS: calcd for $C_{13}H_{10}F_7NO_2$ [M^+] 345.0600, found 345.0612.

3.2.2. Data for intermediate C. IR (film): 3208, 3095, 3003, 2960, 2839, 1641, 1596, 1575, 1516, 1467, 1443, 1296, 1243, 1181, 1151, 1037, 824 cm^{-1}. ^{1}H NMR

(acetone-*d6*): δ 8.71 (br, 1H), 7.58 (br, d, *J*=13.5 Hz, 1H), 7.02–6.76 (m, 8H), 5.55 (d, *J*=13.5 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H). ^{19}F NMR (acetone-*d6*): δ −80.54 (3F), −111.59 (2F), −125.78 (2F). EIMS *m/z* (%): 451 (M^++1, 52.01), 450 (M^+, 59.99), 328 (M^+−NHC_6H_4-OMe, 3.19), 281 (M^+−C_3F_7, 100.00). EI-HRMS: calcd for $C_{20}H_{17}F_7N_2O_2$ [M^+] 450.1170, found: 450.1158.

3.3. General procedure for the preparation of 2-fluoroalkylquinolines (3)

A mixture of **1** (1 mmol), arylamine (3 mmol), Et_3N (5 mmol) and anhydrous $ZnCl_2$ (1 mmol) were stirred in HMPA (10 mL) at 110 °C under a vacuum of 60–70 mmHg. After 24 h, the mixture was cooled to room temperature, diluted with 1% HCl (15 mL) and then extracted with ether (3×20 mL). The organic layer was combined, washed with saturated NaCl solution and dried over sodium sulfate. After the solvent was removed by rotary evaporation, the residue was dissolved in toluene (5 mL), and TsOH (0.1 mmol) was added. The mixture was stirred under reflux for 3–4 h (monitored by TLC). After the reaction was complete, the solvent was removed under vacuum, the residue was chromatographed on silica gel eluting with petroleum–ethyl ether to give **3** as a solid.

3.3.1. 2-Heptafluoropropyl-6-methoxyquinoline (3aa). Mp 70–72 °C. IR (KBr): 3018, 2965, 2938, 1627, 1593, 1506, 1485, 1386, 1230, 1109, 1032, 885, 854, 748 cm^{-1}. ^{1}H NMR (acetone-d6): δ 8.42 (d, 1H, *J*=9.0 Hz), 7.95 (d, 1H, *J*=9.0 Hz), 7.72 (d, 1H, *J*=9.0 Hz), 7.44–7.36 (m, 2H), 3.87 (s, 3H). ^{19}F NMR (acetone-d6): δ −81.37 (3F), −114.42 (2F), −127.18 (2F). EIMS *m/z* (%): 327 (M^+, 76.59), 308 (M^+−F, 10.92), 208 (M^+−C_2F_5, 100.00). EI-HRMS: calcd for $C_{13}H_8F_7NO$ [M^+] 327.0494, found 327.0479.

3.3.2. 6-Methyl-2-heptafluoropropylquinoline (3ab).[20] Mp 75–77 °C. IR (KBr): 3077, 2928, 1594, 1574, 1503, 1357, 1225, 1111, 931, 879, 836 cm^{-1}. ^{1}H NMR (acetone-d6): δ 8.72 (d, 1H, *J*=8.7 Hz), 8.23 (d, 1H, *J*=8.7 Hz), 8.03 (d, 2H, *J*=9.0 Hz), 7.94 (d, 1H, *J*=8.7 Hz), 2.74 (s, 3H). ^{19}F NMR (acetone-d6): δ −81.02 (3F), −114.33 (2F), −126.80 (2F).

3.3.3. 6-Methyl-2-(1,1,2,2,3,3-hexafluoro-3-chloropropyl)quinoline (3bb). Mp 50–52 °C. IR (KBr): 3030, 2971, 1595, 1499, 1320, 1193, 1112, 823, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.25 (d, 1H, *J*=9.0 Hz), 8.15 (d, 1H, *J*=9.0 Hz), 7.71–7.65 (m, 3H), 2.60 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −66.80 (2F), −112.81 (2F), −120.22 (2F). EIMS *m/z* (%): 329 (M^++2, 9.73), 327 (M^+, 28.85), 292 (M^+−Cl, 10.35), 192 (M^+−C_2F_4Cl, 100.00). EI-HRMS: calcd for $C_{13}H_8ClF_6N$ [M^+] 327.0250, found 327.0228.

3.3.4. 6-Methyl-2-chlorodifluoromethylquinoline (3cb). Mp 68–70 °C. IR (KBr): 3053, 2959, 1594, 1501, 1314, 1294, 1145, 1127, 1081, 965, 937, 833, 775, 734 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.26 (d, 1H, *J*=9.0 Hz), 8.13 (d, 1H, *J*=9.0 Hz), 7.74–7.66 (m, 3H), 2.60 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −55.12 (s). EIMS *m/z* (%): 229 (M^++2, 9.43), 227 (M^+, 28.38), 192 (M^+−Cl, 100.00). EI-HRMS: calcd for $C_{11}H_8ClF_2N$ [M^+] 227.0313, found 227.0295.

3.3.5. 6-Methyl-2-undecafluoropentylquinoline (3db). Mp 64–66 °C. IR (KBr): 3064, 2978, 2918, 1599, 1502, 1364, 1243, 1205, 1137, 727, 663, 630 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.26 (d, 1H, *J*=9.0 Hz), 8.15 (d, 1H, *J*=9.0 Hz), 7.71–7.66 (m, 3H), 2.60 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −81.20 (3F), −113.82 (2F), −122.11 (2F), −122.62 (2F), −126.51 (2F). EIMS *m/z* (%): 411 (M^+, 46.68), 392 (M^+−F, 10.69), 192 (M^+−C_4F_9, 100.00). EI-HRMS: calcd for $C_{15}H_8F_{11}N$ [M^+] 411.0481, found 411.0495.

3.3.6. 2-Heptafluoropropylquinoline (3ac).[21] Light yellow oil. IR (film): 3070, 1622, 1598, 1508, 1352, 1230, 1183, 1118, 1056, 911, 820, 757, 741 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.38 (d, 1H, *J*=8.7 Hz), 8.27 (d, 1H, *J*=8.7 Hz), 7.94–7.67 (m, 4H). ^{19}F NMR ($CDCl_3$): δ −80.40 (3F), −114.81 (2F), −126.42 (2F).

3.3.7. 2-Heptafluoropropyl-6-chloro-quinoline (3ad). Mp 112–115 °C. IR (KBr): 3045, 3071, 1597, 1498, 1466, 1355, 1286, 1230, 1116, 865, 831, 747 cm^{-1}. ^{1}H NMR (acetone-d6): δ 8.57 (d, 1H, *J*=9.0 Hz), 8.09 (d, 2H, *J*=9.0 Hz), 7.88–7.78 (m, 2H). ^{19}F NMR (acetone-d6): δ −81.01 (3F), −114.53 (2F), −126.82 (2F). EIMS *m/z* (%): 333 (M^++2, 15.66), 331 (M^+, 47.38), 312 (M^+−F, 7.42), 212 (M^+−C_2F_5, 100.00). EI-HRMS: calcd for $C_{12}H_5ClF_6N$ [$(M-F)^+$] 312.0015, found 312.0015.

3.3.8. 2-Heptafluoropropyl-6-bromoquinoline (3ae). Mp 126–128 °C. IR (KBr): 3042, 1595, 1496, 1465, 1355, 1286, 1230, 1116, 857, 829, 746 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.27 (d, 1H, *J*=8.7 Hz), 8.14–8.09 (m, 2H), 7.92–7.88 (m, 1H), 7.76 (d, 1H, *J*=8.7 Hz). ^{19}F NMR ($CDCl_3$): δ −80.39 (3F), −114.83 (2F), −126.36 (2F). EIMS *m/z* (%): 377 (M^++2, 46.18), 375 (M^+, 47.31), 356 (M^+−F, 5.89), 258 (97.11), 256 (M^+−C_2F_5, 100.00). EI-HRMS: calcd for $C_{12}H_5BrF_7N$ [M^+] 374.9494, found 374.9523.

3.3.9. 2-(1,1,2,2,3,3-Hexafluoro-3-chloropropyl)-6-bromoquinoline (3be). Mp 118–120 °C. IR (KBr): 3042, 1595, 1492, 1464, 1315, 1296, 1187, 1113, 797, 757 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.24 (d, 1H, *J*=9.0 Hz), 8.11–8.06 (m, 2H), 7.89–7.85 (m, 1H), 7.73 (d, 1H, *J*=9.0 Hz). ^{19}F NMR ($CDCl_3$): δ −67.20 (2F), −113.20 (2F), −120.43 (2F). EIMS *m/z* (%): 393 (M^++2, 46.15), 391 (M^+, 35.71), 372 (M^+−F, 2.18), 356 (M^+−Cl, 9.55), 258 (96.56), 256 (M^+−C_2F_4Cl, 100.00). EI-HRMS: calcd for $C_{12}H_5BrClF_6N$ [M^+] 390.9198, found 390.9174.

3.3.10. 2-Heptafluoropropyl-6-nitroquinoline (3af). Mp 140–143 °C. IR (KBr): 3099, 1628, 1608, 1549, 1502, 1355, 1284, 1230, 1117, 937, 817, 749 cm^{-1}. ^{1}H NMR (acetone-d6): δ 9.19 (d, 1H, *J*=2.4 Hz), 9.10 (d, 1H, *J*=9.0 Hz), 8.68 (dd, 1H, *J*=9.0, 2.4 Hz), 8.45 (d, 1H, *J*=9.0 Hz), 8.18 (d, 1H, *J*=9.0 Hz). ^{19}F NMR (acetone-d6): δ −81.30 (3F), −115.22 (2F), −127.01 (2F). EIMS *m/z* (%): 342 (M^+, 98.70), 296 (M^+−NO_2, 40.17), 223 (M^+−C_2F_5, 100.00), 177 (M^+−C_2F_5-NO_2, 48.78). EI-HRMS: calcd for $C_{12}H_5F_7N_2O_2$ [M^+] 342.0239, found 342.0207.

3.4. General procedure for the preparation of fluoroalkylated enaminoketones (4)

A mixture of **1** (1 mmol), arylamine (3 mmol), Et_3N

(5 mmol) and anhydrous $ZnCl_2$ (1 mmol) were stirred in HMPA (10 mL) at 80 °C under a vacuum of 60–70 mmHg. After 48 h, the mixture was cooled to room temperature, diluted with 1%HCl (15 mL) and then extracted with ether (3×20 mL). The organic layer was combined, washed with water and saturated NaCl solution and dried over sodium sulfate. After the solvent was removed by rotary evaporation, the residue was dissolved in THF (5 mL) and 5% HCl (1 mL) was added. The mixture was stirred at 50–70 °C for 0.5–2 h (monitored by ^{19}F NMR). After the reaction was complete, the mixture was cooled to room temperature, diluted with water (10 mL) and then extracted with ether (3×20 mL). The organic layer was combined, washed with water and saturated NaCl solution, and dried over sodium sulfate. After the solvent was removed, the residue was chromatographed on silica gel eluting with petroleum–ethyl ether to give **4** as a light yellow solid.

3.4.1. *cis*-4,4,5,5,6,6,6-Heptafluoro-1-(4-methoxyphenylamino)hex-1-en-3-one (4aa). Mp 58–60 °C. IR (KBr): 3015, 2966, 1643, 1598, 1565, 1494, 1301, 1243, 1212, 1120, 889, 835, 780, 752, 715 cm^{-1}. ^1H NMR ($CDCl_3$): δ 12.05 (br, 1H, NH), 7.58 (dd, 1H, J=13.2, 7.5 Hz), 7.10 (d, 2H, J=9.0 Hz), 6.93 (d, 2H, J=9.0 Hz), 5.68 (d, 1H, J=7.5 Hz), 3.83 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −80.84 (3F), −121.43 (2F), −127.21 (2F). EIMS m/z (%): 345 (M^+, 46.42), 326 (M^+-F, 2.36), 176 ($M^+-C_3F_7$, 100.00). EI-HRMS: calcd for $C_{13}H_{10}F_7NO_2$ [M^+] 345.0600, found 345.0579.

3.4.2. *cis*-6-Chloro-4,4,5,5,6,6-hexafluoro-1-(4-methoxyphenylamino)hex-1-en-3-one (4ba).[19] Mp 70–72 °C. IR (KBr): 2966, 2843, 1645, 1598, 1565, 1493, 1289, 1182, 1122, 1035, 836, 770, 705 cm^{-1}. ^1H NMR ($CDCl_3$): δ 12.03 (br, 1H, NH), 7.57 (dd, 1H, J=13.2, 7.2 Hz), 7.10 (d, 2H, J=9.0 Hz), 6.93 (d, 2H, J=9.0 Hz), 5.68 (d, 1H, J=7.2 Hz), 3.83 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −67.62 (2F), −119.84 (2F), −121.20 (2F).

3.4.3. *cis*-4,4,5,5,6,6,6-Heptafluoro-1-(tolylamino)hex-1-en-3-one (4ab).[20] Mp 63–64 °C. IR (KBr): 1644, 1598, 1565, 1496, 1305, 1233, 1212, 1120, 888, 815, 752 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.96 (br, 1H, NH), 7.63 (dd, 1H, J=13.2, 7.5 Hz), 7.19 (d, 2H, J=8.4 Hz), 7.04 (d, 2H, J=8.4 Hz), 5.69 (d, 1H, J=7.5 Hz), 2.35 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −81.02 (3F), −121.63 (2F), −127.41 (2F).

3.4.4. *cis*-6-Chloro-4,4,5,5,6,6-hexafluoro-1-(tolylamino)-hex-1-en-3-one (4bb). Mp 77–79 °C. IR (KBr): 2926, 1641, 1600, 1561, 1496, 1365, 1313, 1286, 1197, 1175, 1123, 812, 706 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.98 (br, 1H, NH), 7.64 (dd, 1H, J=13.2, 7.2 Hz), 7.21 (d, 2H, J=8.4 Hz), 7.05 (d, 2H, J=8.4 Hz), 5.69 (d, 1H, J=7.2 Hz), 2.36 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −67.67 (2F), −119.93 (2F), −121.26 (2F). EIMS m/z (%): 347 (M^++2, 13.92), 345 (M^+, 42.31), 310 (M^+-Cl, 7.27), 160 ($M^+-C_3F_6Cl$, 100.00). EI-HRMS: calcd for $C_{13}H_{10}ClF_6NO$ [M^+] 345.0355, found 345.0357.

3.4.5. *cis*-1-Chloro-1,1-difluoro-4-(tolylamino)but-3-en-2-one (4cb).[22] Mp 72–74 °C. IR (KBr): 2805, 1641, 1602, 1568, 1494, 1310, 1211, 1157, 1141, 1074, 945, 900, 757, 713 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.76 (br, 1H, NH), 7.65 (dd, 1H, J=13.2, 7.5 Hz), 7.21 (d, 2H, J=8.4 Hz), 7.04 (d, 2H, J=8.4 Hz), 5.64 (d, 1H, J=7.5 Hz), 2.36 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −65.20 (s).

3.4.6. *cis*-4,4,5,5,6,6,7,7,8,8,8-Undecafluoro-1-(tolylamino)oct-1-en-3-one (4db). Mp 94–95 °C. IR (KBr): 1647, 1598, 1563, 1496, 1310, 1197, 1143, 811, 778, 746 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.98 (br, 1H, NH), 7.65 (dd, 1H, J=13.2, 7.5 Hz), 7.21 (d, 2H, J=8.4 Hz), 7.05 (d, 2H, J=8.4 Hz), 5.70 (d, 1H, J=7.5 Hz), 2.36 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −81.01 (3F), −120.52 (2F), −122.84 (4 F), −126.50 (2F). EIMS m/z (%): 429 (M^+, 38.30), 410 (M^+-F, 3.47), 160 ($M^+-C_5F_{11}$, 100.00). Anal. calcd for $C_{15}H_{10}F_{11}NO$: C, 41.97; H, 2.35; N, 3.26. Found C, 42.30; H, 2.60; N, 3.24.

3.4.7. *cis*-6-Chloro-4,4,5,5,6,6-hexafluoro-1-(phenylamino)hex-1-en-3-one (4bc). Mp 73–75 °C. IR (KBr): 3076, 1647, 1610, 1581, 1486, 1290, 1194, 1113, 754, 710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.94 (br, 1H, NH), 7.68 (dd, 1H, J=13.2, 7.5 Hz), 7.44–7.39 (m, 2H), 7.25–7.14 (m, 3H), 5.73 (d, 1H, J=7.5 Hz). ^{19}F NMR ($CDCl_3$): δ −67.63 (2F), −119.94 (2F), −121.21 (2F). EIMS m/z (%): 333 (M^++2, 9.44), 331 (M^+, 27.77), 146 ($M^+-C_3F_6Cl$, 100.00). MALDI-HRMS: calcd for $C_{12}H_9ClF_6NO$ [(M+H)$^+$] 332.0271, found 332.0282.

3.4.8. *cis*-4,4,5,5,6,6,6-Heptafluoro-1-(phenylamino)hex-1-en-3-one (4ac).[10] Mp 48–50 °C. IR (KBr): 3120, 3050, 1648, 1605, 1581, 1489, 1459, 1309, 1216, 1122, 888, 777, 753, 720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.96 (br, 1H, NH), 7.68 (dd, 1H, J=13.2, 7.5 Hz), 7.44–7.38 (m, 2H), 7.27–7.15 (m, 3H), 5.73 (d, 1H, J=7.5 Hz). ^{19}F NMR ($CDCl_3$): δ −80.82 (3F), −121.54 (2F), −127.21 (2F).

3.4.9. *cis*-1-Chloro-1,1-difluoro-4-(phenylamino)but-3-en-2-one (4cc). Mp 88–90 °C. IR (KBr): 3249, 1675, 1604, 1565, 1483, 1370, 1303, 1209, 1139, 1071, 954, 754 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.73 (br, 1H, NH), 7.69 (dd, 1H, J=13.2, 7.5 Hz), 7.43–7.37 (m, 2H), 7.23–7.12 (m, 3H), 5.67 (d, 1H, J=7.5 Hz). ^{19}F NMR ($CDCl_3$): δ −65.30 (s). EIMS m/z (%): 233 (M^++2, 6.40), 231 (M^+, 19.53), 146 (M^+-CF_2Cl, 100.00). Anal. calcd for $C_{10}H_8ClF_2NO$: C, 51.85; H, 3.48; N, 6.05. Found C, 52.06; H, 3.77; N, 5.89.

3.4.10. *cis*-6-Chloro-4,4,5,5,6,6-hexafluoro-1-(4-chlorophenylamino)hex-1-en-3-one (4bd). Mp 62–64 °C. IR (KBr): 1639, 1593, 1558, 1488, 1306, 1287, 1177, 829, 771 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.90 (br, 1H, NH), 7.60 (dd, 1H, J=13.2, 7.5 Hz), 7.39 (d, 2H, J=9.0 Hz), 7.10 (d, 2H, J=9.0 Hz), 5.75 (d, 1H, J=7.5 Hz). ^{19}F NMR ($CDCl_3$): δ −67.44 (2F), −119.72 (2F), −120.92 (2F). EIMS m/z (%): 367 (M^++2, 29.25), 365 (M^+, 45.10), 180 ($M^+-C_3F_6Cl$, 100.00). EI-HRMS: calcd for $C_{12}H_7Cl_2F_6NO$ [M^+] 364.9809, found 364.9797.

3.4.11. *cis*-6-Chloro-4,4,5,5,6,6-hexafluoro-1-(4-bromophenylamino)hex-1-en-3-one (4be). Mp 80–82 °C. IR (KBr): 1639, 1593, 1558, 1585, 1305, 1286, 1178, 827, 771 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.86 (br, 1H, NH), 7.61 (dd, 1H, J=13.2, 7.8 Hz), 7.52 (d, 2H, J=9.0 Hz), 7.03 (d, 2H, J=9.0 Hz), 5.75 (d, 1H, J=7.8 Hz). ^{19}F NMR ($CDCl_3$) δ −67.73 (2F), −120.02 (2F), −121.23 (2F). EIMS m/z

(%): 411 ($M^+ + 2$, 57.78), 409 (M^+, 44.42), 224 ($M^+ - C_3F_6Cl$, 86.08), 145 ($M^+ - C_3F_6Cl$–Br, 100.00). EI-HRMS: calcd for $C_{12}H_7BrClF_6NO$ [M^+] 408.9304, found 408.9330.

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Reaction of 3-aminoquinoline-2,4-diones with nitrourea. Synthetic route to novel 3-ureidoquinoline-2,4-diones and imidazo[4,5-*c*]quinoline-2,4-diones

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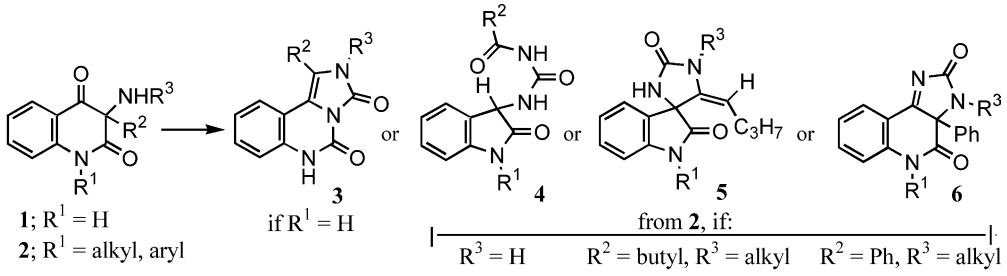
Abstract—1-Unsubstituted 3-alkyl/aryl-3-amino-1*H*,3*H*-quinoline-2,4-diones react with 1-substituted and 1,1-disubstituted ureas in boiling acetic acid to give 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones. In contrast, the reaction of these amines with nitrourea in dioxane affords novel 3-alkyl/aryl-3-ureido-1*H*,3*H*-quinoline-2,4-diones or 9b-hydroxy-3a-alkyl/aryl-3,3a,5,9b-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-2,4-diones, which can smoothly be dehydrated to 3a-alkyl/aryl-3,3a-dihydro-5*H*-imidazo[4,5-*c*]quinoline-2,4-diones. All three types of products can be converted to 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones by refluxing in acetic acid.

1. Introduction

Recently, an unprecedented reaction of 3-amino-1*H*,3*H*-quinoline-2,4-diones **1** with urea in boiling acetic acid has been described by us.[1] The expected 3,3a-dihydro-5*H*-imidazo[4,5-*c*]-quinoline-2,4-diones **6** ($R^1 = H$) do not arise but a molecular rearrangement takes place, producing novel 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones **3** (Scheme 1). In contrast, the study of the reaction of urea with compounds **1** containing a tertiary lactam group in the quinoline ring showed that these compounds react to give three different types of compounds.[2] Depending on the character of substitution in the starting compounds **2**, either a molecular rearrangement of the quinolone system to indolinone system occurs with formation of previously undescribed 3-(3-acylureido)-2,3-dihydro-1*H*-indol-2-ones **4** or 4-alkylidene-1′*H*-spiro[imidazolidine-5,3′-indole]-2,2′-diones **5**, or the expected 3,3a-dihydro-5*H*-imidazo[4,5-*c*]quinoline-2,4-diones **6** arise (Scheme 1). A reaction mechanism for these transformations was proposed.[2]

Owing to the unexpected course of substances **1** and **2** reacting with urea to produce new heterocyclic systems, we



Scheme 1.

Keywords: Molecular rearrangement; Nitrourea; Urea derivatives; α-Aminoketones; α-Ureidoketones.
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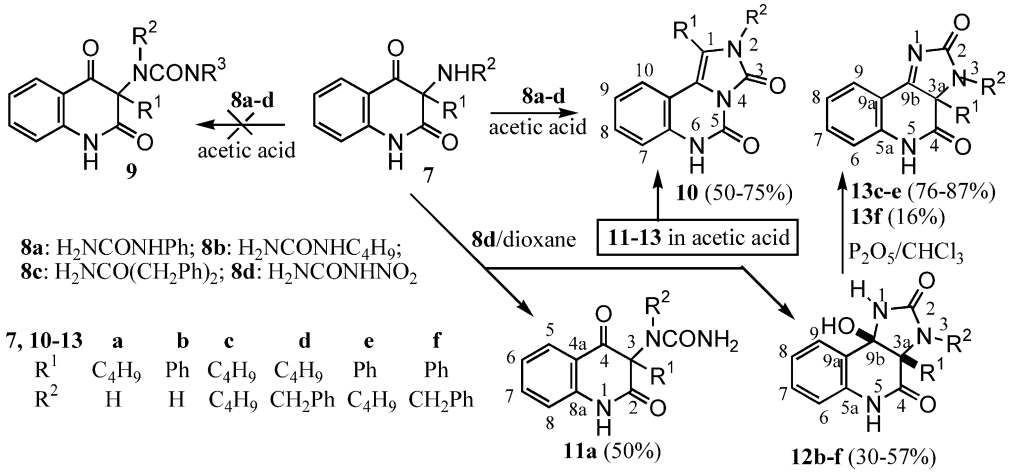


Scheme 2.

also decided to study reactions of these α-aminoketones with some substituted ureas. We demonstrate in this work that differently substituted 3-amino-1*H*,3*H*-quinoline-2,4-diones **7** react with 1-substituted and 1,1-disubstituted ureas in acetic acid in the same manner as with urea[1] forming 2,6-dihydro-imidazo(1,5-*c*(quinazoline-3,5-diones **10**. With nitrourea, however, substances **7** react in various manners depending on the character of reaction medium.

2. Results and discussion

The starting amines **7** were obtained from the corresponding 3-chloro derivatives in accordance with procedures described in the literature.[3] We first dealt with reactions of compounds **7** with substituted ureas **8a–c**. Reactions were performed in the same manner as in our previous papers,[1,2] that is, by boiling amines **7** with **8** in a solution of acetic acid. The reaction of **7a** with phenylurea (**8a**) yielded the

Table 1. ^{1}H, ^{13}C, and ^{15}N NMR shifts (δ, ppm) of compounds **10f** and **11a** in DMSO-d_6

Position	**10f**		**11a**	
	δ_H	δ_C or δ_N	δ_H	δ_C or δ_N
1	—	117.8	10.81	−246.2[a]
2	—	−241.3	—	172.4
3	—	148.4	—	66.9
4	—	−230.6	—	194.7
4a	—	—	—	119.1
5	—	145.0	7.79	126.9
6	10.51	−263.8[b]	7.13	122.2
6a	—	134.5	—	—
7	7.04	115.3	7.62	135.8
8	7.18	128.3	7.12	116.3
8a			—	141.8
9	6.79	122.6	—	—
10	6.73	121.3	—	—
10a	—	112.9	—	—
10b	—	113.8	—	—
1′(3)			2.79	36.4
2′(3)			1.21	24.6
3′(3)			1.21	22.2
4′(3)			0.80	13.8
*NH*CONH$_2$			7.00	−284.7[c]
NH*C*ONH$_2$			—	157.9
NHCO*NH*$_2$			5.70	−306.1[d]
NH$_2$(CO)			5.70	—
i-Ph (1)	—	128.1	—	—
o-Ph (1)	7.40	131.0	—	—
m-Ph (1)	7.54	128.5	—	—
p-Ph (1)	7.60	130.1	—	—
CH$_2$Ph	4.72	43.9	—	—
i-PhCH$_2$	—	137.0		
o-PhCH$_2$	6.99	126.8		
m-PhCH$_2$	7.26	129.5		
p-PhCH$_2$	7.38	127.3		

[a] $^{1}J(^{15}N, ^{1}H)$ (Hz): 90.7.
[b] $^{1}J(^{15}N, ^{1}H)$ (Hz): 92.7.
[c] $^{1}J(^{15}N, ^{1}H)$ (Hz): 90.5.
[d] $^{1}J(^{15}N, ^{1}H)$ (Hz): 87.2.

Table 2. ^{1}H, ^{13}C, and ^{15}N NMR shifts (δ, ppm) of compounds **12b–f** in DMSO-d_6

Position	**12b**		**12c**		**12d**		**12e**		**12f**	
	δ_H	δ_C or δ_N	δ_H	δ_C or δ_N	δ_H	δ_C or δ_N	δ_H	δ_C or δ_N	δ_H	δ_C or δ_N
1	7.54	−264.3[a]	7.27	−267.6[b]	7.51	−267.4[c]	7.54	−268.4[d]	7.87	−268.3[e]
2	—	160.5	—	158.9	—	159.2	—	160.6	—	160.7
3	7.66	−290.8[f]	—	−283.8	—	−284.2	—	−285.4	—	−287.2
3a	—	70.4	—	68.8	—	69.1	—	75.2	—	75.3
4	—	171.1	—	171.2	—	171.4	—	170.4	—	170.6
5	10.83	−247.6[g]	10.50	−245.7[h]	10.59	−244.9[i]	10.94	−243.6[j]	11.06	−242.9[k]
5a	—	135.3	—	134.7	—	134.7	—	134.9	—	135.8
6	7.07	115.4	6.90	114.9	6.94	115.0	7.05	115.3	7.09	115.4
7	7.37	129.8	7.27	129.4	7.29	129.6	7.32	129.8	7.37	129.9
8	7.11	122.9	7.06	122.5	7.09	122.6	7.02	122.9	7.08	122.8
9	7.61	127.3	7.64	126.2	7.70	126.3	7.51	127.5	7.58	127.6
9a	—	123.4	—	124.6	—	124.5	—	123.0	—	123.1
9b	—	85.5	—	83.6	—	83.8	—	84.1	—	85.0
1′(3)	—	—	3.52, 3.34	40.5	—	—	3.27, 3.03	44.1	—	—
2′(3)	—	—	1.60, 1.48	32.7	—	—	2.01, 1.56	31.0	—	—
3′(3)	—	—	1.35, 1.32	20.0	—	—	1.26, 1.20	20.2	—	—
4′(3)	—	—	0.94	14.0	—	—	0.88	14.0	—	—
OH	6.29	—	6.54	—	6.59	—	6.44	—	6.55	—
1′(3a)	—	135.8	1.92, 1.89	31.2	1.77, 1.73	31.0	—	133.7	—	133.3
2′(3a)	7.26	126.4	1.12, 0.94	24.5	1.14, 0.93	24.5	7.35	128.3	7.48	127.1
3′(3a)	7.29	128.0	0.94	22.7	1.12	22.5	7.37	128.1	7.35	127.9
4′(3a)	7.29	127.7	0.75	13.8	0.62	13.5	7.37	128.3	7.29	126.2
CH_2	—	—	—	—	4.89, 4.75[l]	43.7	—	—	4.69, 4.43[m]	46.8
i-Ph(CH_2)	—	—	—	—	—	140.8			—	139.8
o-Ph(CH_2)	—	—	—	—	7.45	126.8			7.24	128.0
m-Ph(CH_2)	—	—	—	—	7.35	128.1			7.24	128.1
p-Ph(CH_2)	—	—	—	—	7.25	126.4			7.25	128.3

[a] $^{1}J(^{15}N, ^{1}H)$ (Hz): 92.2.
[b] $^{1}J(^{15}N, ^{1}H)$ (Hz): 92.6.
[c] $^{1}J(^{15}N, ^{1}H)$ (Hz): 92.3.
[d] $^{1}J(^{15}N, ^{1}H)$ (Hz): 92.0.
[e] $^{1}J(^{15}N, ^{1}H)$ (Hz): 92.7.
[f] $^{1}J(^{15}N, ^{1}H)$ (Hz): 92.2.
[g] $^{1}J(^{15}N, ^{1}H)$ (Hz): 90.2.
[h] $^{1}J(^{15}N, ^{1}H)$ (Hz): 90.3.
[i] $^{1}J(^{15}N, ^{1}H)$ (Hz): 89.8.
[j] $^{1}J(^{15}N, ^{1}H)$ (Hz): 90.4.
[k] $^{1}J(^{15}N, ^{1}H)$ (Hz): 90.0.
[l] AB system, $^{2}J(H,H)=17.0$ Hz.
[m] AB system, $^{2}J(H,H)=17.0$ Hz.

same product **10a** as reaction with urea.[1] The analogous product **10b** was obtained through reaction of **7b** with butylurea (**8b**), but also through reaction of **7b** with 1,1-dibenzylurea (**8c**) (Scheme 2).

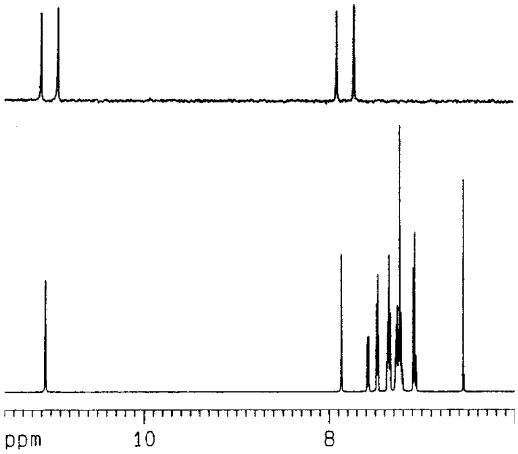


Figure 1. Part of ^{1}H NMR spectrum of compound **12f** (bottom trace) and 1D gs ^{1}H–^{15}N HMBC spectrum optimised for $^{1}J(^{15}N, ^{1}H)=95$ Hz (upper trace).

The 3′-substituted ureido derivative **9** was obtained in no case. In accord with expectations, it thus seems that substituted ureas **8a–c** fragment under given reaction conditions only to the respective amine and isocyanic acid and not to isocyanate and ammonia. Isocyanic acid subsequently reacts with amines **7a**,**b** to give products **10a**,**b** through the anticipated[1] intermediate **13a**,**b**. Compounds **10** may hence be obtained by boiling amines **7** with an arbitrary 1-substituted or 1,1-disubstituted urea in a solution of acetic acid. As expected, we also obtained compounds **10** by reacting amines **7a** and **7b** with nitrourea (**8d**) in a solution of acetic acid.

Owing to the well-known fact that nitrourea decomposes into isocyanic acid with simultaneous formation of water and N_2O far more easily than urea, we set about studying its reaction with amines **7** in a non-acidic environment. Performing the reaction in dioxane or aqueous dioxane, completely different products were surprisingly obtained (Scheme 2).

When comparing the ^{13}C NMR spectra of products from the reaction of **7a–f** with nitrourea in dioxane, it followed that two different types of products were originating.

Compounds of the first group are represented in the set under study by only one compound (from starting compound **7a**), which exhibits in the ^{13}C NMR spectrum, beside signals of sp^2 hybridised carbon atoms, a signal pertaining to a carbon atom in sp^2 hybridisation (apart from carbons of the butyl group) and three signals of carbonyl groups (Table 1), which is in accord with the anticipated structure **11a**. In the ^1H NMR spectrum of **11a** (Table 1), there appear discernible signals of an aromatic ABCD system in the 7.12–7.79 ppm range, and signals corresponding to hydrogen atoms of a butyl group. In addition, signals of four NH protons are to be found at 5.70 (2H), 7.00, and 10.81 ppm. The presence of an $-NHCONH_2$ group was also confirmed by results of ^{15}N NMR spectra. Based on a 2D experiment, all signals were assigned to their respective atoms (Table 1).

The product of reaction of **7b** with nitrourea displays in the ^{13}C NMR spectra signals fundamentally different from that of compound **11a**. Structure **12b** resulted for this compound mainly from the appearance of two signals of sp^3 hybridised carbon atoms in the ^{13}C NMR spectrum (apart from sp^3 hybridised carbon atoms of butyl or benzyl group) at 85.5 and 70.4 ppm (Table 2). The last signal corresponds to the carbon atom C-3 of starting amine **7b**, and the signal at 85.5 ppm must correspond to a carbon that arose through transformation of the initial CO group in position 4 of starting amine **7b** because no signal of the keto group in the ^{13}C NMR spectrum of product **7b** with urea is present, and signals of amide groups at 160.5 and 171.1 ppm are to be found (Table 2). As the signal of an OH group at 7.61 ppm was also found in the ^1H NMR spectrum of this compound, besides signals of three NH protons at 7.54, 7.66 and 10.83 ppm, the product of reaction of **7b** with nitrourea must possess structure **12b**. This structure was confirmed by results of a NOE experiment proving interactions of the hydroxyl group at C-9b with the proton at the nitrogen atom in position 1, with proton at C-9, and with *o*-protons of the phenyl group. The latter proved interaction is to certify that the hydroxyl group at C-9b and the phenyl group at C-3a are *cis*-oriented. Also proved was the interaction of proton N(5)–H with the proton at C-6 as well as interaction of hydrogen at N(3) with *o*-protons of the phenyl group. The ^{15}N NMR spectrum (Table 2) of the product is in accordance with structure **12b**.

It is noteworthy that both products of the reaction of **7a**,**b** with nitrourea displayed two well discernible spots by TLC. Their ratio in different crystallisation fractions varied, but dependence of this ratio on crystallisation conditions could not be found. All our attempts at separating the individual compounds through repeated crystallisation or column chromatography met with failure. We suppose an equilibrium exists between tautomeric forms **11a**,**b** and **12a**,**b**, however, with only one form of greater stability being preferred in the solution of strongly polar DMSO-d_6. The formation of an equilibrium mixture of cyclic and acyclic tautomers during hydration of 4-oxoazetidines substituted with carbamoylthioacetyl group in position 2 was described by Sápi et al.[4] Unfortunately, due to insolubility of compounds **11a** and **12b** in non-polar solvents, the tautomeric equilibrium could not be more closely investigated.

All secondary amines **7c–f** yield merely cyclic carbinolamide forms **12c–f** as products of the reaction with nitrourea in dioxane or aqueous dioxane. Based on results of 2D experiments, all signals in ^1H, ^{13}C and ^{15}N NMR spectra of compounds **12c–f** were assigned to particular atoms (Table 2).

Figure 1 shows a part of the ^1H NMR spectrum of compound **12f** in which three broadened singlets ($\delta(^1H)=$ 11.06, 7.87, 6.55) are visible, two of them giving doublets in 1D gs ^1H–^{15}N HMBC spectrum due to the existence of $^1J(^{15}N, ^1H)=95$ Hz and, thus, these protons must belong to NH fragments. The third signal resonating at 6.55 ppm gave neither any doublet in 1D gs ^1H–^{15}N HMBC nor any correlation in 2D gs ^1H–^{13}C HSQC spectrum optimised for $^1J(^{13}C, ^1H)$. Taking the above-mentioned results as well as results following from mass spectra into account, the signal resonating at 6.55 ppm must belong to an OH group proton.

Analysis of 2D gs ^1H–^{15}N HMBC spectrum of compound **12f** optimised for $^nJ(^{15}N, ^1H)=7$ Hz allowed us to assign all three ^{15}N resonances undoubtedly and confirm the structure proposal. The ^{15}N signal at -242.9 ppm represents a resonance of nitrogen of N(5)HCO group because residual doublet due to $^1J(^{15}N(5), ^1H)$ coupling constant and the cross-peak due to $^3J(^{15}N, C(6)^1H)$ were observed. Residual doublet due to $^1J(^{15}N(1), ^1H)$ coupling constant and the cross-peak due to $^3J(^{15}N, O^1H)$ belong to nitrogen in position 1 ($\delta(^{15}N)=-268.3$). Nitrogen atom of $N(3)CH_2C_6H_5$ group ($\delta(^{15}N)=-287.2$) showed correlations with both prochiral methylene protons of benzyl group and N(1)H proton via $J(^{15}N, C(=O)N^1H)$.

Similarly as in compound **12b**, the two signals of sp^3 hybridised carbon atoms C-3a and C-9b can be found in the ^{13}C NMR spectrum of **12f**. Protonated carbons were assigned by gs-HMQC and quaternary carbons were assigned by gs-HMBC.

The ^1H, ^{13}C and ^{15}N NMR spectra of compounds **12c–e** were analysed in the same manner.

Compounds **11a** and **12c–f** are quite stable in a solution of acetic acid up to a temperature of approx. 50 °C, when boiling, however, their rapid rearrangement to imidazoquinazolines **10a–f** takes place.

The APCI mass spectra of all compounds **11** and **12** under study yielded the peaks of $[M+H]^+$ ions in the positive-ion mode and $[M-H]^-$ ions in the negative-ion mode. Mostly, these ions are base peaks or at least very intensive peaks in the spectra. The typical neutral loss for all compounds containing the tertiary hydroxyl group (**12b–12f**) is the loss of water. The other characteristic neutral loss, NHCO ($\Delta m/z$ 43), is observed for all compounds containing third 5-membered cycle (**12b–12f**) and also for **11a**, where the NHCO moiety can be lost from the side $-NHCONH_2$ chain as well.

Yields of compounds **11** or **12** (Table 3) depend mainly on the character of substitution in starting compounds **7**, but also on reaction conditions. In the cases where primary amines **7a**,**b** are used as starting compounds, they reach

Table 3. Results of the reaction of amines **7** with nitrourea in dioxane (method A) or aqueous dioxane (method B)

Entry	Starting compound	Method	Reaction time (h)	Isolated compounds (%)
1	**7a**	A	1.5	**11a** (43)
2	**7a**	A	1.5	**11a** (50)
3	**7b**	A	2	**12b** (55)
4	**7b**	A	2	**12b** (51)
5	**7b**	A	2.5	**12b** (57)
6	**7b**	B	2.5	**12b** (58)
7	**7c**	A	4	**12c** (49), **10c** (16)
8	**7d**	A	5	**12d** (31), **7d** (17)
9	**7d**	A	9	**12d** (11), **7d** (37)
10	**7d**	A	15	**12d** (35), **7d** (19)
11	**7e**	A	5.5	**12e** (52), **7e** (4), **10e** (5)
12	**7e**	B	2.5	**7e** (21), **10e** (52), **13e** (6)
13	**7f**	A	6	**12f** (30), **7f** (49), **10f** (2)
14	**7f**	B	5.5	**12f** (16), **7f** (33)[a]

[a] 4-Hydroxy-3-phenyl-1*H*-quinolin-2-one (2%) was also isolated.

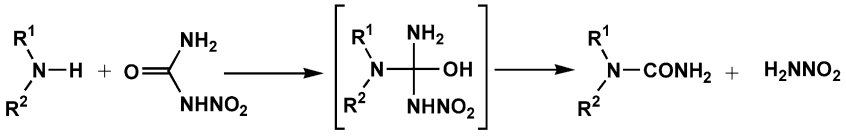
levels around 50%, are not overly affected by character of reaction medium and display good reproducibility (entries 1–6). When secondary amines **7c–f** are employed, yields of compounds **12**, as expected, are lower. In these cases, as is obvious in Table 3, non-reacted starting compounds **7** and products of rearrangement **10** were also isolated from the reaction mixture. Employing here non-aqueous dioxane as reaction medium (Method A) is more appropriate. Isocyanic acid arising during the reaction in aqueous dioxane slowly reacts with a secondary amine and breaks down at the same time, to disappear from the reaction mixture in a short time. During the reaction, bubbles of escaping N_2O may be observed, and their production soon comes to a stop. During the reaction in non-aqueous dioxane, however, bubbles of N_2O do not arise. A possible explanation may be found in the anhydrous conditions, under which nitrourea does not directly decompose to isocyanic acid and N_2O but under which the reaction proceeds as a nucleophilic addition of amine to activated carbonyl group of nitrourea (Scheme 3). The intermediate thus created then breaks down to the corresponding substituted urea and nitramide, which is destroyed only during subsequent processing of the reaction mixture.

The reaction of amines **7** with nitrourea in dioxane or aqueous dioxane runs quite unambiguously. Apart from products **11a** and **12b–f**, only non-reacted starting amines **7** and rearranged compounds **10** were isolated, and other minor products were successfully obtained in just two cases (Table 3). The first side product is 4-hydroxy-3-phenyl-1*H*-quinolin-2-one, arising through hydrolysis of starting amine **7f** in a reaction in aqueous dioxane.

The second minor compound isolated is 3-butyl-3a-phenyl-3,3a-dihydro-5*H*-imidazo(4,5-*c*(quinoline-2,4-dione (**13e**), isolated from the reaction of **7e** with urea in aqueous dioxane. This compound showed a completely different melting point and different IR spectrum than compound **10e** but its ^1H and ^{13}C NMR spectra measured in DMSO-d_6 were identical with NMR spectra of compound **10e**. Only after measuring NMR spectra of this minor compound in $CDCl_3$ was it determined that the substance in question really was a new compound **13e**, which is so unstable that it already rearranges to compound **10e** through merely standing in a solution of DMSO-d_6. The NMR spectra of compound **13e** (Table 4) were very similar to those for analogous substances having methyl or phenyl groups in position 5 instead of a proton.[2]

We also attempted to prepare the other 3a-alkyl/aryl-3,3a-dihydro-5*H*-imidazo-(4,5-*c*(quinoline-2,4-diones **13** through dehydration of carbinolamides **12c–f**. Our first attempts (using acetic anhydride, acetic anhydride in pyridine, or thionyl chloride in pyridine) proved unsuccessful, and on processing the reaction mixture, rearranged compounds **10c–f** were always obtained. Only action of phosphorus pentoxide on the suspension of compounds **12c–f** in chloroform produced the corresponding products **13c–f** (NMR data in Table 4). These are very unstable compounds, which already rearrange to compounds **10c–f** through mild heating up in methanol or standing for several hours in a DMSO solution. The reverse addition of water to compounds **13** was not observed, though this reaction was described in 1-methoxy-1,5-dihydroimidazol-2-one series.[5]

Our attempts at preparing compounds **13a**,**b** were not successful. According to TLC monitoring, compounds **11a** and **12a** do not undergo dehydration through action of P_2O_5 in chloroform at room temperature. Compounds whose characteristic yellow fluorescence at UV irradiation (366 nm) of TLC chromatograms is analogous to that displayed by compounds **13c–f**, arise only when boiling. Nevertheless, all attempts at isolating them failed, and rearranged products **10a** and **10b** were obtained after processing the reaction mixture. The high instability of compounds **13** is surprising, because their N(5)-substituted derivatives are stable[2] as well as their 3-sulfa analogues.[6] Measurements of APCI-MS spectra of compounds **13c–f**



Scheme 3.

Table 4. ^{1}H and ^{13}C NMR shifts (δ, ppm) of compounds **13c–f** in $CDCl_3$

Position	**13c**		**13d**		**13e**		**13f**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	—	166.7	—	166.8	—	166.8	—	167.2
3a	—	75.6	—	75.3	—	78.4	—	78.3
4	—	170.0	—	170.3	—	168.1	—	168.5
5	9.27	—	9.08	—	9.04	—	9.47	—
5a	—	139.0	—	138.7	—	138.4	—	138.3
6	7.11	11666.4	6.90	116.5	6.98	116.4	6.73	116.6
7	7.56	135.2	7.52	135.4	7.44	135.0	7.40	135.2
8	7.24	124.6	7.21	124.7	7.15	124.6	7.13	124.6
9	7.96	127.0	7.95	127.0	7.94	127.3	7.94	128.0
9a	—	115.7	—	115.7	—	116.7	—	116.6
9b	—	184.6	—	184.8	—	183.9	—	184.4
1′(3)	3.67, 3.40	42.2	—	—	3.48, 3.21	42.9	—	—
2′(3)	1.88	31.0	—	—	1.67, 1.41	30.4	—	—
3′(3)	1.44	20.4	—	—	1.23	20.3	—	—
4′(3)	0.99	13.9	—	—	0.83	13.7	—	—
1′(3a)	2.24, 1.94	30.5	2.06, 1.82	36.9	—	132.4	—	131.9
2′(3a)	0.96, 0.89	24.5	0.89, 0.66	21.7	7.22	126.5	7.14	126.6
3′(3a)	1.19	21.9	0.68	24.5	7.33	129.7	7.26	129.6
4′(3a)	0.79	13.6	0.58	13.5	7.33	130.1	7.26	130.0
CH_2	—	—	5.02, 4.96[a]	45.6	—	—	4.73, 4.47[b]	46.3
i-Ph(NCH_2)	—	—	—	137.5	—	—	—	137.3
o-Ph(NCH_2)	—	—	7.54	129.0	—	—	7.14	128.0
m-Ph(NCH_2)	—	—	7.31	128.4	—	—	7.26	128.4
p-Ph(NCH_2)	—	—	7.27	127.6	—	—	7.14	126.9

[a] AB system, $^{2}J(H,H)=15.0$ Hz.
[b] AB system, $^{2}J(H,H)=15.3$ Hz.

indicated their spectra are completely identical with spectra of compounds **10c–f** and it cannot be judged whether conversion of **13c–f** to **10c–f** takes place during dissolution in acetonitrile or only later during ionisation.

Compounds **11**, **12** and also **13** exhibit a relatively wide range of melting points despite being chromatographically pure. Some of them first melt at a lower temperature, and after re-crystallisation of the melt they exhibit another melting point corresponding to pertaining compound **10**, some of them even melt at the same temperature as **10**. In all cases, the TLC analysis of the rests after melting point determination of compounds **11**, **12**, and **13** proved that their thermal transformation to compounds **10** proceeds.

In our earlier work[1] we expressed the assumption that the reaction of amines **7** with urea in boiling acetic acid produces, as primary reaction intermediates, compounds **11**, which are cyclodehydrated to intermediates **13**. The following base-catalysed breaking of bond C(3a)–C(4) in **13** creates an isocyanate group to which nitrogen atom N(1) of the imidazole nucleus adds, thus giving rise to product **10**. This concept is impaired by our discovery that compounds **11** and **12** rearrange in acetic acid to **10** in the absence of any basic compound, and undergo thermal rearrangement as well. Compound **12f** also rearranges to **10f** by boiling in pyridine, but much more slowly than in acetic acid hence ruling out basic catalysis. We found, however, that rearrangement of compound **12d** to **10d** also occurs through boiling in cyclohexanol. This rules out formation of the corresponding intermediate isocyanate because such an intermediate would have to react with cyclohexanol to the respective carbamic acid ester at least in part. Based on hitherto obtained knowledge of the stability of prepared compounds as reaction intermediates,[1] we may assume that transformation of amines **7** through their reaction with urea in acetic acid to final product **10** really proceeds via intermediates **11**, **12** and **13**. In strongly unstable intermediates **13**, the nucleophilic migration of the whole ArNHCO group has to take place. Whether the action in question is direct 1,3-migration to nitrogen atom N(1) or two successive 1,2-migrations is an issue that will be decided only through results of experiments on N(1)-substituted analogues of compounds **7**, which we are presently starting.

The described reaction of 3-amino-1*H*,3*H*-quinoline-2,4-diones **7** with nitrourea is not merely interesting from a theoretical point of view but, owing to the simple reaction protocol, presents an easy pathway to preparing novel heterocyclic systems. Compounds **11** and **12** can serve as suitable starting materials for studying the equilibrium between α-ureido ketones (or hitherto undescribed α-ureido-β-dicarbonyl compounds) and their cyclic carbinolamide forms. Analogues of **13**, containing the C═N–C(O)–N grouping, are not described in the literature with only the exception of our recent paper.[2] Only several simple imidazolin-2-ones were prepared,[5,7–10] but just one reaction of them has previously been described.[5]

3. Experimental

Melting points were determined on a Kofler block or Gallencamp apparatus. IR (KBr) spectra were recorded on a Mattson 3000 spectrophotometer. NMR spectra were recorded on a Bruker Avance spectrometer (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C, 50.68 MHz for ^{15}N) in DMSO-d_6 or $CDCl_3$. ^{1}H and ^{13}C chemical shifts are given on the δ scale (ppm) and are referenced to internal TMS. ^{15}N

chemical shifts were referred to external neat nitromethane in co-axial capillary ($\delta=0.0$). All 2D experiments (gradient-selected (gs)-COSY, NOESY, gs-HMQC, gs-HMBC) were performed using manufacturer's software. Proton signals were assigned using gs-COSY. Protonated carbons were assigned by gs-HMQC. Quaternary carbons were assigned by gs-HMBC. The positive-ion and negative-ion APCI mass spectra were measured on an ion trap analyser Esquire 3000 (Bruker Daltonics, Bremen, Germany) within the mass range $m/z=50$–600. Samples were dissolved in acetonitrile and analysed by direct infusion at the flow rate of 50 μL/min. The ion source temperature was 350 °C, the APCI probe temperature was 350 °C, the flow rate and the pressure of nitrogen were 4 L/min and 45 psi, respectively. For MS/MS measurements, the isolation width of precursor ions was 4 *m/z* and the collision amplitude was in the range 0.7–0.9 V. Column chromatography was carried out on Silica gel (Merck, grade 60, 70–230 mesh) using chloroform and then successive mixtures of chloroform–ethanol (in rations from 99:1 to 8:2, solvent system S1) or benzene and then successive mixtures of benzene–ethyl acetate (in rations from 99:1 to 8:2, solvent system S2). Reactions as well as the course of separation and also the purity of substances were monitored by TLC (elution systems benzene–ethyl acetate, 4:1 (S3), chloroform–ethanol, 9:1 (S4) and/or 19:1 (S5)), and chloroform–isopropylalcohol, 9:1 (S6) on Alugram® SIL G/UV_{254} foils (Macherey–Nagel). Elemental analyses (C, H, N) were performed with a EA 1108 Elemental Analyzer (Fisons Instrument).

3-Amino-1*H*,3*H*-quinoline-2,4-diones (**7a**–**f**) were prepared according to the general procedure described in the literature.[3]

3.1. General procedures for the preparation of 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones (10a–f)

Method A. A mixture of appropriate 3-amino-1*H*,3*H*-quinoline-2,4-dione (**7a**,**b**) (3 mmol) and substituted urea **8a**–**d** (6 mmol) in acetic acid (10 mL) was refluxed for 1–2.5 h and the course of the reaction was monitored by TLC. After cooling, the reaction mixture was diluted with water. The precipitated products **10a**,**b** were filtered off with suction and crystallized from appropriate solvent or column chromatographed.

Method B. A solution of appropriate compound **11** or **12** (0.5 mmol) in acetic acid (5 mL) was refluxed for 1 h. The reaction mixture was evaporated to dryness in vacuo and the residue was crystallized from appropriate solvent or column chromatographed.

Method C. A solution of appropriate compound **12** (0.5 mmol) in appropriate solvent (see below) was refluxed for 6–10 h. The reaction mixture was evaporated to dryness and the residue was crystallized from ethanol.

3.1.1. 1-Butyl-2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (10a). Compound was prepared from **7a** and **8a** (Method A, 2.5 h, yield 58%), from **7a** and **8d** (Method A, 30 min, yield 65%), and from **11a** (Method B, 1 h, yield 68%). Colourless crystals, identical in all respects with authentic sample.[1]

3.1.2. 1-Phenyl-2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (10b). Compound was prepared from **7b** and **8b** (1.5 h, yield 37%), from **7b** and **8c** (1.5 h, yield 64%), and from **7b** and **8d** (2.5 h, yield 58%) by Method A, and from **12b** by Method B (yield 84%). Colourless crystals, identical in all respects with authentic sample.[1]

3.1.3. 1,2-Dibutyl-2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (10c). Compound was prepared from **12c** by Method B (yield 50%). Colourless crystals, identical in all respects with authentic sample.[1]

3.1.4. 2-Benzyl-1-butyl-2,6-dihydro-imidazo[1,5-*c*]-quinazoline-3,5-dione (10d). Compound was prepared from **12d** by Method B (yield 52%) and by Method C (cyclohexanol, 10 mL, 10 h, yield 53%). Colourless crystals, identical in all respects with authentic sample.[1]

3.1.5. 2-Butyl-1-phenyl-2,6-dihydro-imidazo[1,5-*c*]-quinazoline-3,5-dione (10e). Compound was prepared from **12e** by Method B (53%) and by Method C (acetic anhydride, 10 mL, 10 h, yield 52%). Colourless crystals, identical in all respects with authentic sample.[1]

3.1.6. 2-Benzyl-1-phenyl-2,6-dihydro-imidazo[1,5-*c*]-quinazoline-3,5-dione (10f). Compound was prepared by refluxing of the solution of **7f** (0.5135 g, 1.5 mmol) and urea (0.5405 g, 9 mmol) in acetic acid (2 mL) for 60 min. After evaporation in vacuo, the residue was washed with water and crystallized from ethanol. Yield 417 mg (75%). By the same procedure, but using pyridine instead of acetic acid, 340 mg (62%) of **10f** was obtained after 5 h. Colourless crystals, mp 291–294 °C (ethanol). IR: 3295, 3250, 3065, 3003, 2932, 1764, 1753, 1679, 1613, 1589, 1482, 1444, 1376, 1366, 1347, 1326, 1315, 1266, 1173, 923, 755, 741, 697, 669, 654, 598, 582 cm^{-1}. Positive-ion APCI-MS: *m/z* 368 $[M+H]^+$ (100%). Positive-ion APCI-MS/MS of *m/z* 368: 290 $[M+H-C_6H_6]^+$, 276 $[M+H-C_6H_5CH_3]^+$, 250 $[(C_6H_5CH_2)NCH(C_6H_5)CHNCO]^+$ (100%), 234 $[M+H-C_6H_5CH_3-NCO]^+$. Negative-ion APCI-MS: 366 $[M-H]^-$ (100%), 275 $[M-H-C_6H_5CH_2]^-$. Negative-ion APCI-MS/MS of *m/z* 366: 275 $[M-H-C_6H_5CH_2]^-$ (100%). Anal. Calcd (found) for $C_{23}H_{17}N_3O_2$: C 75.19 (75.34); H 4.66 (4.73); N 11.44 (11.15).

3.2. General procedure for the preparation of 3-ureido-1*H*,3*H*-quinoline-2,4-dione (11a) and 9b-hydroxy-3a-alkyl/aryl-3,3a,5,9b-tetrahydro-1*H*-imidazo[4,5-*c*]-quinoline-2,4-diones (12b–f)

Method A. A mixture of appropriate 3-amino-1*H*,3*H*-quinoline-2,4-dione (**7a**–**f**) (3 mmol) and nitrourea (0.631 g, 6 mmol) in dioxane (11 mL) was stirred at 80 °C for the time given in Table 3 and the course of the reaction was monitored by TLC. After cooling, the reaction mixture was evaporated to dryness in vacuo. The residue was extracted with water, the insoluble portion was filtered off with suction and crystallized from appropriate solvent. In some cases, mother liquors after crystallization of the product were column chromatographed.

Method B. A mixture of appropriate 3-amino-1*H*,3*H*-quinoline-2,4-dione (**7a**–**f**) (3 mmol) and nitrourea

(0.631 g, 6 mmol) in aqueous dioxane (70%, 10 mL) was stirred at 100 °C for the time given in Table 3. The work up of the reaction mixture was carried out in the same way as in Method A.

3.2.1. 3-Butyl-3-ureido-1*H*,3*H*-quinoline-2,4-dione (11a). Yield 50% (Method A, 90 min). Colourless crystals, mp 220–224 °C, IR: 3408, 3335, 3236, 3092, 2960, 2930, 2871, 1712, 1666, 1613, 1548, 1523, 1486, 1433, 1365, 1256, 1192, 1116, 951, 940, 775, 753, 668, 623, 548, 529 cm^{-1}. Positive-ion APCI-MS: *m/z* 276 $[M+H]^+$, 233 $[M+H–NHCO]^+$ (100%), 215 $[M+H–NHCO–H_2O]^+$, 188 $[M+H–NHCO–NH_2CHO]^+$, 177 $[M+H–NHCO\text{-butene}]^+$. Positive-ion APCI-MS/MS of *m/z* 276: 259 $[M+H–NH_3]^+$, 233 $[M+H–NHCO]^+$ (100%), 215 $[M+H–NHCO–H_2O]^+$. Negative-ion APCI-MS: 274 $[M-H]^-$ (100%), 231 $[M-H–NHCO]^-$, 161 $[C_6H_4NHCOCH_2CO]^-$, 146 $[C_6H_4(CO)NCO]^-$. Negative-ion APCI-MS/MS of *m/z* 274: 256 $[M-H–H_2O]^-$, 231 $[M-H–NHCO]^-$ (100%), 213 $[M-H–NHCO–H_2O]^-$. Anal. Calcd (found) for $C_{14}H_{17}N_3O_3$: C 61.08 (60.88); H 6.22 (6.35); N 15.26 (15.03).

3.2.2. 9b-Hydroxy-3a-phenyl-3,3a,5,9b-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-2,4-dione (12b). Yield 57% (Method A, 150 min) or 58% (Method B, 135 min). Colourless crystals, mp 269–274 °C (methanol), IR: 3365, 3262, 3195, 3078, 2991, 2919, 1712, 1690, 1617, 1598, 1494, 1441, 1402, 1231, 1058, 998, 894, 880, 848, 763, 700, 649, 602, 570 cm^{-1}. Positive-ion APCI-MS: *m/z* 296 $[M+H]^+$, 278 $[M+H–H_2O]^+$, 253 $[M+H–NHCO]^+$ (100%), 236 $[M+H–NH_2CONH_2]^+$, 223 $[M+H–NHCO–HCHO]^+$, 208 $[M+H–NH_2CONH_2–CO]^+$. Positive-ion APCI MS/MS of *m/z* 296: 278 $[M+H–H_2O]^+$, 253 $[M+H–NHCO]^+$ (100%), 236 $[M+H–NH_2CONH_2]^+$. Negative-ion APCI-MS and MS/MS of *m/z* 294 are the same: 294 $[M-H]^-$ (100% for MS), 276 $[M-H–H_2O]^-$, 251 $[M-H–NHCO]^-$, 233 $[M-H–NHCO–H_2O]^-$ (100% for MS/MS), 207, 161. Anal. Calcd (found) for $C_{16}H_{13}N_3O_3$: C 65.08 (64.83); H 4.44 (4.65); N 14.23 (14.09).

3.2.3. 3,3a-Dibutyl-9b-hydroxy-3,3a,5,9b-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-2,4-dione (12c). Yield 49% (Method A, 4 h). Colourless crystals, mp 170–176 °C and 281–285 °C (ethyl acetate), IR: 3384, 3263, 3202, 3067, 2958, 2932, 2870, 1696, 1677, 1601, 1496, 1466, 1432, 1384, 1245, 1122, 1063, 849, 755, 658, 625, 543, 524 cm^{-1}. Positive-ion APCI-MS: *m/z* 332 $[M+H]^+$ (100%), 314 $[M+H–H_2O]^+$, 289 $[M+H–NHCO]^+$. Positive-ion APCI-MS/MS of *m/z* 332: 289 $[M+H–NHCO]^+$ (100%). Negative-ion APCI-MS: 330 $[M-H]^-$ (100%), 312 $[M-H–H_2O]^-$, 269 $[M-H–H_2O–NHCO]^-$, 255 $[M-H–H_2O\text{-butyl}]^-$. Negative-ion APCI-MS/MS of *m/z* 330: 312 $[M-H–H_2O]^-$, 287 $[M-H–NHCO]^-$, 230 $[M-H–NHCO\text{-butyl}]^-$. Anal. Calcd (found) for $C_{18}H_{25}N_3O_3$: C 65.23 (65.12); H 7.60 (7.42); N 12.68 (12.73).

3.2.4. 3-Benzyl-3a-butyl-9b-hydroxy-3,3a,5,9b-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-2,4-dione (12d). Yield 35% (Method A, 15 h). Colourless crystals, mp 178–187 °C and 280–283 °C (ethyl acetate), IR: 3368, 3349, 3199, 3098, 2962, 2930, 2868, 1710, 1664, 1598, 1486, 1441, 1416, 1384, 1229, 1123, 1061, 947, 886, 800, 773, 763, 712, 658, 613, 540 cm^{-1}. Positive-ion APCI-MS: *m/z* 366 $[M+H]^+$ (100%), 348 $[M+H–H_2O]^+$, 323 $[M+H–NHCO]^+$. Positive-ion APCI-MS/MS of *m/z* 366: 323 $[M+H–NHCO]^+$, 233 $[M+H–C_6H_5CH_2NCO]^+$ (100%), 216 $[M+H–C_6H_5CH_2NCO–NH_3]^+$, 177 $[M+H–C_6H_5CH_2NCO\text{-butene}]^+$, 146. Negative-ion APCI-MS: 364 $[M-H]^-$ (100%), 346 $[M-H–H_2O]^-$, 316 $[M-H–H_2O–HCHO]^-$, 255, 161. Negative-ion APCI-MS/MS of *m/z* 364: 346 $[M-H–H_2O]^-$, 321 $[M-H–NHCO]^-$ (100%), 229 $[M-H–NHCO–C_6H_5CH_3]^-$, 216 $[M-H–NHCO–C_6H_5–CO]^-$. Anal. Calcd (found) for $C_{21}H_{23}N_3O_3$: C 69.02 (69.15); H 6.34 (6.09); N 11.50 (11.33).

3.2.5. 3-Butyl-9b-hydroxy-3a-phenyl-3,3a,5,9b-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-2,4-dione (12e). Yield 52% (Method A, 5.5 h). Colourless crystals, mp 174–183 °C and 294–297 °C (2-propanol), IR: 3411, 3334, 3195, 3066, 2957, 2928, 1705, 1678, 1599, 1496, 1446, 1413, 1371, 1217, 1135, 1071, 952, 865, 762, 751, 701, 680, 656, 633, 597 cm^{-1}. Positive-ion APCI-MS: *m/z* 352 $[M+H]^+$, 334 $[M+H–H_2O]^+$ (100%), 309 $[M+H–NHCO]^+$. Positive-ion APCI-MS/MS of *m/z* 352: 309 $[M+H–NHCO]^+$ (100%). Negative-ion APCI-MS: 350 $[M-H]^-$, 332 $[M-H–H_2O]^-$ (100%), 306 $[M-H–NH_2CO]^-$, 249 $[M-H–NH_2CHO\text{-butene}]^-$. Negative-ion APCI-MS/MS of *m/z* 350: 332 $[M-H–H_2O]^-$, 306 $[M-H–NHCO]^-$ (100%), 293 $[M-H\text{-butyl}]^-$, 275 $[M-H–H_2O\text{-butyl}]^-$, 249 $[M-H–NH_2CHO\text{-butene}]^-$. Anal. Calcd (found) for $C_{20}H_{21}N_3O_3$: C 68.36 (68.51); H 6.02 (6.23); N 11.96 (11.71).

3.2.6. 3-Benzyl-9b-hydroxy-3a-phenyl-3,3a,5,9b-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-2,4-dione (12f). Yield 30% (Method A, 6 h) or 16% (Method B, 5.5 h). Colourless crystals, mp 186–196 °C (ethanol), IR: 3384, 3351, 3198, 3095, 2907, 1712, 1675, 1597, 1485, 1434, 1399, 1368, 1349, 1231, 1125, 1078, 934, 896, 802, 773, 747, 717, 697, 671, 655, 607, 593, 576 cm^{-1}. Positive-ion APCI-MS: *m/z* 386 $[M+H]^+$ (100%), 368 $[M+H–H_2O]^+$, 343 $[M+H–NHCO]^+$, 253 $[M+H–C_6H_5CH_2NCO]^+$. Positive-ion APCI-MS/MS of *m/z* 386: 343 $[M+H–NHCO]^+$ (100%), 278, 253 $[M+H–C_6H_5CH_2NCO]^+$, 236 $[M+H–C_6H_5CH_2NCO–NH_3]^+$, 208 $[M+H–C_6H_5CH_2NCO–NH_3–CO]^+$. Negative-ion APCI-MS and MS/MS of *m/z* 384 are the same: 384 $[M-H]^-$ (100% for MS), 366 $[M-H–H_2O]^-$, 340 $[M-H–NH_2CO]^-$, 275 $[M-H–H_2O–C_6H_5CH_2]^-$ (100% for MS/MS), 249, 236. Anal. Calcd (found) for $C_{23}H_{19}N_3O_3$: C 71.67 (71.45); H 4.97 (5.21); N 10.90 (10.69).

3.3. General procedure for the preparation of 3,3a-dihydro-5*H*-imidazo[4,5-*c*]quinoline-2,4-diones (13c–f)

To the stirred suspension of compound 12c–f (0.5 mmol) in chloroform (25 mL), powdered phosphorus pentoxide (107 mg, 0.75 mmol) was added in one portion at rt. After 10 min, the mixture was filtrated through a column filled with silica gel (7.5 g). Column was washed with chloroform (250 mL), collected filtrates were evaporated to dryness in vacuo and the residue was crystallized from benzene or benzene–hexane.

3.3.1. 3,3a-Dibutyl-3,3a-dihydro-5*H*-imidazo[4,5-*c*]-quinoline-2,4-dione (13c). Yield 87%. Colourless crystals,

mp 139–147 °C and 277–283 °C (benzene), IR: 3416, 3241, 2958, 2932, 2871, 1709, 1615, 1596, 1477, 1343, 1260, 1237, 1158, 779, 768, 650, 566 cm^{-1}. Positive-ion APCI-MS: *m/z* 314 $[M+H]^+$ (100%), 258 $[M+H\text{-butene}]^+$. Positive-ion APCI-MS/MS of *m/z* 314: 258 $[M+H\text{-butene}]^+$ (100%), 241 $[M+H\text{-butene-}NH_3]^+$, 215 $[M+H\text{-butene-NHCO}]^+$, 202 $[M+H\text{-2*butene}]^+$. Negative-ion APCI-MS: 312 $[M-H]^-$ (100%), 256 $[M-H\text{-butene}]^-$. Negative-ion APCI-MS/MS of *m/z* 312: 284 $[M-H-CO]^+$, 269 $[M-H-NHCO]^-$, 255 $[M-H\text{-butyl}]^-$ (100%), 212 $[M-H\text{-butyl-NHCO}]^-$. Anal. Calcd (found) for $C_{18}H_{23}N_3O_2$: C 68.98 (68.73); H 7.40 (7.59); N 13.41 (13.23).

3.3.2. 3-Benzyl-3a-butyl-3,3a-dihydro-5*H*-imidazo[4,5-*c*]-quinoline-2,4-dione (13d). Yield 77%. Yellow crystals, mp 278–282 °C (benzene–hexane), IR: 3241, 3211, 2931, 1720, 1614, 1591, 1475, 1427, 1365, 1344, 1290, 1237, 1151, 1126, 1102, 1051, 951, 841, 773, 748, 721, 666, 651, 565. Positive-ion APCI-MS: *m/z* 348 $[M+H]^+$ (100%), 292 $[M+H\text{-butene}]^+$. Positive-ion APCI-MS/MS of *m/z* 348: 331 $[M+H-NH_3]^+$, 305 $[M+H-NHCO]^+$, 292 $[M+H\text{-butene}]^+$, 256 $[M+H-C_6H_5CH_3]^+$ (100%), 230, 214 $[M+H\text{-butene-}C_6H_6]^+$, 202. Negative-ion APCI-MS: 346 $[M-H]^-$ (100%), 290 $[M-H\text{-butene}]^-$, 255 $[M-H-C_6H_5CH_2]^-$. Negative-ion APCI-MS/MS of *m/z* 346: 290 $[M-H\text{-butene}]^-$, 255 $[M-H-C_6H_5CH_2]^-$ (100%). Anal. Calcd (found) for $C_{21}H_{21}N_3O_2$: C 72.60 (72.41); H 6.09 (6.20); N 12.10 (11.96).

3.3.3. 3-Butyl-3a-phenyl-3,3a-dihydro-5*H*-imidazo[4,5-*c*]-quinoline-2,4-dione (13e). Yield 76%. Yellow crystals, mp 89–102 °C (benzene–hexane), IR: 3475, 3416, 2960, 2931, 2872, 1713, 1615, 1600, 1477, 1448, 1360, 1331, 1241, 1073, 779, 761, 695, 680, 653, 573. Positive-ion APCI-MS: *m/z* 334 $[M+H]^+$ (100%). Positive-ion APCI-MS/MS of *m/z* 334: 316 $[M+H-H_2O]^+$, 290 $[M+H-NH_2CO]^+$, 278 $[M+H\text{-butene}]^+$ (100%), 235 $[M+H\text{-butene-NHCO}]^+$, 203, 160. Negative-ion APCI-MS: 332 $[M-H]^-$ (100%). Negative-ion APCI-MS/MS of *m/z* 332: 289 $[M-H-NHCO]^-$, 275 $[M-H\text{-butyl}]^-$ (100%). Anal. Calcd (found) for $C_{20}H_{19}N_3O_2$: C 72.05 (71.90); H 5.74 (5.87); N 12.60 (12.45).

3.3.4. 3-Benzyl-3a-phenyl-3,3a-dihydro-5*H*-imidazo-[4,5-*c*]quinoline-2,4-dione (13f). Yield 16%. Yellow crystals, mp 161–167 °C (benzene–hexane), IR: 3446, 3227, 3175, 2994, 2930, 2865, 1711, 1616, 1596, 1478, 1449, 1370, 1357, 1322, 1238, 1131, 1061, 1032, 774, 710, 695, 655, 568. Positive-ion APCI-MS: *m/z* 368 $[M+H]^+$ (100%). Positive-ion APCI-MS/MS of *m/z* 368: 290 $[M+H-C_6H_6]^+$, 276 $[M+H-C_6H_5CH_3]^+$ (100%), 250 $[(C_6H_5\text{-}CH_2)NCH(C_6H_5)CHNCO]^+$, 234 $[M+H-C_6H_5CH_3-NCO]^-$. Negative-ion APCI-MS: 366 $[M-H]^-$ (100%), 275 $[M-H-C_6H_5CH_2]^-$. Negative-ion APCI-MS/MS of *m/z* 366: 275 $[M-H-C_6H_5CH_2]^-$ (100%). Anal. Calcd (found) for $C_{23}H_{17}N_3O_2$: C 75.19 (75.32); H 4.66 (4.51); N 11.44 (11.26).

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Polymer-supported selenium-induced electrophilic cyclization: solid-phase synthesis of poly-substituted dihydrofurans and tetrahydrofurans

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Abstract—Poly-substituted dihydrofurans and tetrahydrofurans have been synthesized through polymer-supported selenium-induced intramolecular electrophilic cyclization, followed by selenoxide *syn*-elimination or novel nucleophilic substitution cleavage of selenium resin with good yields and purities.

1. Introduction

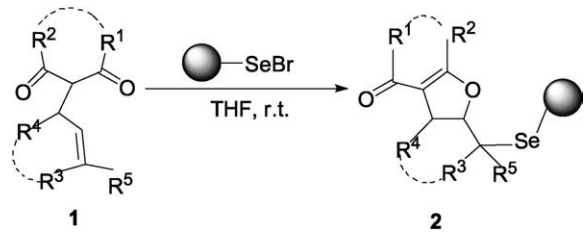
The preparation of diverse libraries of organic compounds is an important fact of modern drug discovery programs. One of the most commonly employed methods in library production is solid phase organic synthesis (SPOS).[1] It has shown that compounds with biological activities are often derived from heterocyclic structures.[2]

Dihydrofurans and tetrahydrofurans are two important classes of heterocycles with widespread occurrence in nature.[3] Possessing a variety of biological activities, they are used as pharmaceutical, flavor, insecticidal, and fish antifeedant agents.[4] Despite having important biological activities there are very few reports dealing with the polymer-supported synthesis of libraries based on functionalized dihydrofurans and tetrahydrofurans.[5] And also, most of the dihydrofurans and tetrahydrofurans prepared by a solid-phase method are mono- or di-substituted.

Since the first organoselenium resin[6] was reported in 1976, several groups have developed organoselenium resins as convenient linkers.[7,8] Recently, our research group has been interested in the application of organic selenium resins in organic synthesis.[9] A simple preparation of polysubstituted dihydrofuran and tetrahydrofuran is reported by polystyrene-supported selenium-induced regioselective intramolecular electrophilic cyclization of allyl substituted 1,3-dicarbonyl compounds. Evident advantages of this reaction are easy operations, odorlessness and good purity of the products. And also the resins can be regenerated and reused.

2. Results and discussion

We began our efforts from polystyrene-supported selenenyl bromide[7] (dark-red resin, Se: 1.02 mmol/g), which was treated with α-allyl substituted 1,3-dicarbonyl compounds **1**, followed by the conditions that Ferraz et al.[10] had devised in solution phase. The rapid decolorization of polystyrene-supported selenenyl bromide occurred when 2.5 equiv of the compound **1** were used (Scheme 1). After stirred at rt for 3 h, the ring-closure reaction on solid-phase completed, which was determined by the elemental analysis of resin **2** (Br was undetectable). The reaction was also monitored by



1 2

Scheme 1.

Keywords: Solid phase synthesis; Selenium mediated intramolecular cyclization; Allyl-substituted 1,3-dicarbonyls; Dihydrofurans; Tetrahydrofurans.
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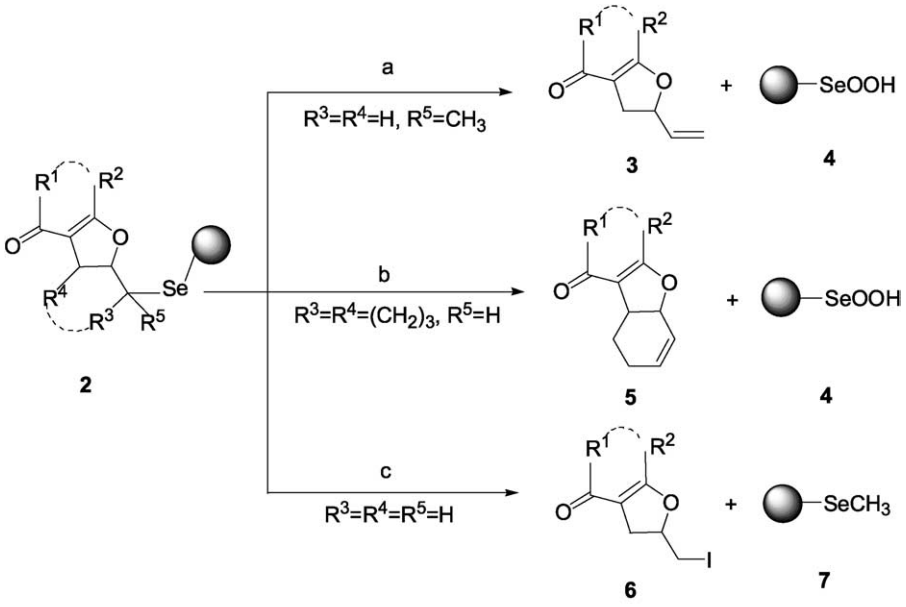


Scheme 2.

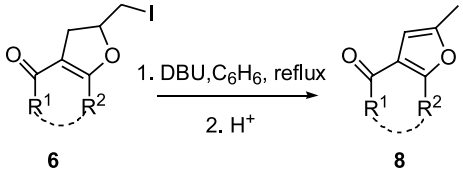
FT-IR, which showed a strong peak of carbonyl absorption between 1680–1730 cm^{-1}.

In our reaction, the cleavage reaction of resins **2** was fully determined by the substituents R^3 and R^5 (Scheme 2). When R^3 or R^5 was not hydrogen, selenoxide *syn*-elimination underwent smoothly to give poly-substituted dihydrofuran **3** and **5** respectively (Scheme 2 step a and b). The generated resin **4** can be recycled and reused.[9a] But when R^3 and R^5 were both hydrogen, selenoxide *syn*-elimination did not occur when we treated resin **2** with H_2O_2 even at 50 °C in THF.

Common cleavage protocols of selenium linkers[11] have been reported using two strategies: selenoxide *syn*-elimination and radical hydride transfer. $^nBu_3SnH$ could be used here as a good radical hydride transfer reagent, but it was too toxic. Herein we report a new cleavage protocol using CH_3I/NaI in DMF under mild conditions that Corey et al.[12] devised in the solution conditions (Scheme 2 step c). Iodomethyl-substituted dihydrofurans **6** were obtained in good yields and purities. The results are listed in Table 1.

A significant feature of this novel nucleophilic substitution cleavage reaction (Scheme 2 step c) was that a new functional group (iodine), with versatile reactivities in organic synthesis, was introduced during the cleavage stage. Iodomethyl dihydrofurans **6** could be dehydrohalogenated to afford the corresponding furans **8** by treated with DBU followed by acid-catalyzed rearrangement (Scheme 3). The results are summarized in Table 2.

In order to expand the diversity of this method, γ-allyl substituted 1,3-dicarbonyl compounds **9** were used to perform the intramolecular electrophilic cyclization with polymer-supported selenenyl bromide (Scheme 4). It was not surprised that resins **10** were obtained almost



Scheme 3.

Table 1. Synthesis of poly-substituted dihydrofurans

Product[a]	R^1	R^2	R^3	R^4	R^5	Yield[b] (%)	Purity[c] (%)
3a[d]	OCH_3	CH_3	H	H	CH_3	85	90
5a[d]	OCH_3	CH_3	$-CH_2CH_2CH_2-$		H	80	87
5b[d]	OC_2H_5	CH_3	$-CH_2CH_2CH_2-$		H	82	82
6a	$-CH_2CH_2CH_2-$		H	H	H	89	89
6b	$-CH_2C(CH_3)_2CH_2-$		H	H	H	88	87
6c	OCH_3	CH_3	H	H	H	80	95
6d	OC_2H_5	CH_3	H	H	H	78	95
6e	C_6H_5	C_6H_5	H	H	H	76	90
6f	CH_3	C_6H_5	H	H	H	79	86
6g	CH_3	CH_3	H	H	H	86	92

[a] NaI, CH_3I, DMF, 75 °C.
[b] Overall yield based on the loading of selenium bromide resin (1.02 mmol/g).
[c] Purity determined by HPLC.
[d] H_2O_2 (30%), 7.0 equiv, THF, 0 °C–rt.

Table 2. Synthesis of poly-substituted furans

Product	R_1	R_2	Yield[a] (%)
8a	$-CH_2CH_2CH_2-$		80
8b	$-CH_2C(CH_3)_2CH_2-$		78
8c	OCH_3	CH_3	74
8d	OC_2H_5	CH_3	71
8e	CH_3	C_6H_5	72
8f	C_6H_5	C_6H_5	79

[a] Isolated yield.

quantitatively. Followed by the deselenenylation reaction with methyl iodide and sodium iodide in DMF at 75 °C, poly-substituted iodomethyl tetrahydrofurans **11**[13] were obtained in good yields and purities. The results are summarized in Table 3.

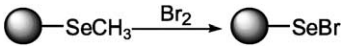
Table 3. Synthesis of poly-substituted tetrahydrofurans

Product	R^1	R^2	R^3	Yield[a] (%)	Purity[b] (%)
11a	CH_3	H	H	85	95
11b	CH_3	H	C_2H_5	80	95
11c	CH_3	H	n-C_4H_9	73	90
11d	CH_3	$CH_2CH{=}CH_2$	H	72	86
11e	CH_3	H	$PhCH_2$	86	88
11f	C_2H_5	H	H	86	95
11g	C_2H_5	CH_3	H	78	93
11h	C_2H_5	C_2H_5	H	82	93
11i	C_2H_5	$PhCH_2$	H	83	87

[a] Overall yield based on the loading of selenium bromide resin (1.02 mmol/g).
[b] Purity determined by HPLC.

It is noteworthy that polystyrene-supported methyl selenide (resin **7**) was generated after the cleavage stage. Resin **7** could be reused as the starting material and recycled in the same reaction for several times without the loss of purities of the products but with a slight decrease in yields. Results are given in Table 4.

Table 4. Circulation of the polymer selenium resin



Substrate	Times	Yield[a] (%)	Purity[b] (%)
6a	1	89	89
6a	2	87	89
6a	3	87	87
6a	4	84	88

[a] Overall yield based on the loading of selenium bromide resin (1.02 mmol/g).
[b] Purity determined by HPLC.

3. Conclusion

In conclusion, a novel preparation of poly-substituted dihydrofurans and tetrahydrofurans has been developed by a polystyrene-supported selenium induced regioselective intramolecular cyclization, followed by the selenoxide *syn*-elimination or a novel nucleophilic substitution cleavage of selenium resin.

4. Experimental

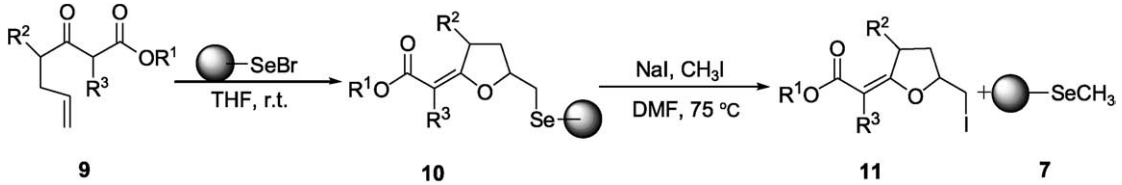
4.1. General

Starting materials were obtained from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone immediately prior to use. Polystyrene (H 1000, 100–200 mesh, cross-linked with 1% divinylbenzene) for the preparation of selenenyl bromide resin (1.02 mmol Br/g) according to the procedure described by Nicolaou and co-workers[7] was purchased from commercial sources. Allyl substituted 1,3-dicarbonyl compounds **1** and **9** were prepared according to the literature procedures.[14,15] ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as an internal standard. Mass spectra (EI, 70 eV) were recorded on a HP5989B mass spectrometer. Infrared spectra were recorded on a Shimadzu IR-408 spectrometer and measured as thin film or in KBr. Elemental analyses were performed on a Flash EA1112 instrument. HPLC was performed on an Agilernt 1100 High performance liquid chromatograph. The samples were further purified by TLC for ^{13}C NMR and microanalyses.

4.2. General procedure for the preparation of dihydrofurans (3a, 5a, 5b)

To a suspension of the swellen polymer-supported selenium bromide resin (1.0 g, 1.02 mmol/g) in dry THF (15 mL), α-allyl-1, 3-dicarbonyl compounds (2.5 equiv) was added. The suspension was stirred at rt for 3 h. The mixture was filtered and the resin was washed with THF (10 mL×3) and CH_2Cl_2 (10 mL×3) and dried in vacuum at 65 °C to afford dry selenocyclic enol ether resin **2**.

To a suspension of the swellen selenocyclic enol ether resin **2** (1.0 g) in THF (15 mL), 30% H_2O_2 (1.5 mL) was added at 0 °C. The suspension was stirred at 0 °C for 0.5 h and rt for 1.0 h, the mixture was filtered and the resin was washed with CH_2Cl_2 (10 mL×3), the filtrate was washed with saturated $NaHCO_3$, and H_2O, respectively, dried over



Scheme 4.

$MgSO_4$, and evaporated to dryness in vacuum to afford dihydrofurans **3a**, **5a** and **5b**.

4.2.1. 2-Methyl-5-vinyl-4, 5-dihydro-furan-3-carboxylic acid methyl ester (3a). The title compound was obtained as a light yellow oil (85%). ν (neat) 3078, 2975, 1695, 1645, 1226, 990 and 908 cm^{-1}; δ_H 5.95–5.88 (1H, m), 5.30 (1H, d, J=17.2 Hz), 5.20 (1H, d, J=10.4 Hz), 5.08–5.00 (1H, m), 3.70 (3H, s), 3.05 (1H, dd, J=12.4, 14.0 Hz), 2.67 (1H, dd, J=7.6, 14.0 Hz), 2.21 (3H, s); δ_C 168.8, 166.6, 135.6, 115.1, 101.2, 80.0, 50.8, 34.2, 13.4; *m/z* 169 (100%), 168 (M^+, 27), 137 (16), 116 (8). Anal. calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.20; H, 7.08%.

4.2.2. 2-Methyl-3a, 4, 5, 7a-tetrahydro-benzofuran-3-carboxylic acid methyl ester (5a). The title compound was obtained as a light yellow oil (80%). ν (neat) 2978, 1694, 1649, 1444, 1380, 1224, 1084, 964, 758, 615 cm^{-1}; δ_H 6.21–6.17 (1H, m), 5.92 (1H, d, J=10.4 Hz), 4.71 (1H, d, J=8.8 Hz), 3.70 (3H, s), 3.04–2.96 (1H, m), 2.18 (3H, s), 2.13–2.20 (2H, m), 1.92–1.81 (1H, m), 1.28–1.17 (1H, m); δ_C 168.6, 166.6, 134.5, 123.1, 107.6, 78.1, 50.5, 40.0, 24.9, 23.1, 14.5; *m/z* 195 (100%), 194 (M^+, 52), 163 (39), 162 (22), 161 (12), 119 (15), 116 (34), 91 (53), 79 (15), 65 (13), 43 (85). Anal. calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.12; H, 7.35%.

4.2.3. 2-Methyl-3a, 4, 5, 7a-tetrahydro-benzofuran-3-carboxylic acid ethyl ester (5b). The title compound was obtained as a light yellow oil (82%). ν (neat) 2928, 1697, 1636, 1382, 1218, 1099, 1080, 954, 876, 840, 705 cm^{-1}; δ_H 6.13 (1H, dt, J=8.4, 6.8 Hz), 5.92 (1H, d, J=9.6 Hz), 4.71 (1H, d, J=7.6 Hz), 4.13 (2H, t, J=7.2 Hz), 3.02–2.91 (1H, m), 2.15 (3H, s), 2.02 (2H, t, J=12 Hz), 1.93–1.85 (1H, m), 1.24 (3H, t, J=8.0 Hz), 1.28–1.12 (1H, m); δ_C 168.2, 166.2, 134.4, 123.2, 107.8, 77.9, 59.2, 40.1, 24.9, 23.1, 14.4, 14.4; *m/z* 209 (100%), 208 (M^+, 39), 163 (33), 162 (15), 130 (12), 91 (27), 43 (44). Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.30; H, 7.63%.

4.3. General procedure for the preparation of iodomethyldihydrofurans (6a–6g)

To a suspension of the swellen selenocyclic enol ether resin **2** (1.0 g), in dry DMF (15 mL), NaI (1.5 g) and CH_3I (1.5 mL) were added under nitrogen. The suspension was stirred at 75 °C for 18 h. The mixture was filtered and the resin was washed with CH_2Cl_2 (10 mL×3), the filtrate was washed with saturated $Na_2S_2O_3$ and H_2O respectively and extracted with CH_2Cl_2 (10 mL×3), dried over $MgSO_4$, and evaporated to dryness in vacuum to afford iodomethyldihydrofurans **6a–6g**.

4.3.1. 2-Iodomethyl-3, 5, 6, 7-tetrahydro-2*H*-furan-benzofuran-4-one (6a). The title compound was obtained as a light yellow oil (89%). ν (neat) 2946, 1631, 1402, 1231, 1179, 917, 731 cm^{-1}; δ_H 4.82 (1H, ddt, J=10.4, 6.8, 6.0 Hz); 3.33 (2H, d, J=6.0 Hz); 2.96 (1H, dd, J=14.4, 10.4 Hz); 2.56 (1H, dd, J=14.4, 6.8 Hz); 2.42 (2H, t, J=6.0 Hz); 2.32 (2H, t, J=6.0 Hz); 2.02 (2H, quintet, J=6.0 Hz); δ_C ($CDCl_3$) 195.3, 176.6, 112.9, 83.5, 36.4, 32.5, 23.8, 21.6, 8.1; *m/z* 278 (M^+, 10), 279 (100), 250 (8), 151 (78), 152 (11), 123 (14), 105 (8), 95 (21), 81 (23), 67 (14), 55 (21), 53 (31), 52 (11), 51 (11), 43 (19), 42 (13), 41 (32). Anal. calcd for $C_9H_{11}IO_2$: C, 38.87; H, 3.99; I, 45.63. Found: C, 38.78; H, 4.06; I, 45.58%.

4.3.2. 2-Iodomethyl-6, 6-dimethyl-3, 5, 6, 7-tetrahydro-2*H*-benzofuran-4-one (6b). The title compound was obtained as a light yellow oil (88%). ν (neat) 2957, 1637, 1402, 1218, 1037, 731, 629 cm^{-1}; δ_H 4.86–4.82 (1H, m), 3.31 (2H, d, J=5.2 Hz), 2.92 (1H, dd, J=14.0, 6.8 Hz), 2.53 (1H, dd, J=14.0, 6.8 Hz), 2.24 (2H, s), 2.15 (2H, s), 1.11 (6H, s); δ_C 194.6, 175.6, 111.3, 83.3, 60.8, 37.6, 34.0, 32.4, 28.8, 28.5, 8.9; *m/z* 307 (100%), 306 (M^+, 12), 250 (17), 180 (15), 179 (94) 123 (39), 95 926), 83 (25), 81 (29), 77 (13), 67 (29), 65 (14), 55 (43), 53 (52), 52 (17), 51 (17), 43 (32), 42 (12), 41 (77). Anal. calcd for $C_{11}H_{15}IO_2$: C, 43.16; H, 4.94; I, 41.45. Found: C, 43.22; H, 4.87; I, 41.52%.

4.3.3. 5-Iodomethyl-3-methoxycarbonyl-2-methyl-4, 5-dihydrofuran (6c). The title compound was obtained as a light yellow oil (80%). ν (neat) 2949, 1702, 1650, 1262, 1226, 1086, 981, 761, 613 cm^{-1}; δ_H 4.72–4.67 (1H, m), 3.70 (3H, s), 3.34–3.26 (2H, m); 3.03 (1H, dd, J=13.6, 11.2 Hz), 2.66 (1H, dd, J=14.8, 6.8 Hz), 2.20 (3H, s); δ_C 167.4, 166.1, 101.5, 80.4, 50.9, 36.9, 14.0, 8.8; *m/z* 283 (49%), 282 (M^+, 34), 251 (18), 155 (73), 123 (58), 113 (11), 95 (13), 81 (59), 59 (11), 53 (33), 43 (100), 41 (12). Anal. calcd for $C_8H_{11}IO_3$: C, 34.06; H, 3.93; I, 44.99. Found: C, 33.99; H, 3.85; I, 45.06%.

4.3.4. 3-Ethoxycarbonyl-5-iodomethyl-2-methyl-4, 5-dihydrofuran (6d). The title compound was obtained as a light yellow oil (78%). ν (neat) 2949, 2926, 1702, 1635, 1436, 1382, 1219, 1187, 1099, 994, 875 cm^{-1}; δ_H 4.72–4.64 (1H, m); 4.16 (2H, q, J=7.2 Hz); 3.36–3.24 (2H, m); 3.04 (1H, dd, J=14.4, 11.2 Hz), 2.65 (1H, dd, J=14.4, 6.4 Hz), 2.19 (3H, s); 1.28 (3H, t, J=7.2 Hz); δ_C 167.1, 166.7, 101.7, 80.4, 69.5, 36.9, 14.4, 14.0, 8.8; *m/z* 297 (100%), 296 (M^+, 33), 251 (32), 169 (51), 123 (57), 95 (10), 81 (34), 53 (17), 43 (46). Anal. calcd for $C_9H_{13}IO_3$: C, 36.51; H, 4.43; I, 42.86. Found: C, 36.60; H, 4.37; I, 42.91%.

4.3.5. 3-Benzoyl-5-iodomethyl-2-phenyl-4, 5-dihydrofuran (6e).[16] The title compound was obtained as a light yellow oil (76%). ν (neat) 1620, 1404, 1220, 1033, 734, 628 cm^{-1}; δ_H 7.65–7.51 (2H, m), 7.48–7.41 (2H, m), 7.32–6.98 (6H, m), 5.02 (1H, m), 3.43 (1H, dd, J=9.2, 15.2 Hz), 3.40 (1H, dd, J=5.6, 12.4 Hz), 3.23 (1H, dd, J=7.2, 12.4 Hz), 3.12 (1H, dd, J=7.2, 15.2 Hz); *m/z* 390 (M^+, 11%), 263 (100), 43 (50).

4.3.6. 3-Acetyl-5-iodomethyl-2-phenyl-4, 5-dihydrofuran (6f). The title compound was obtained as a light yellow oil (79%). ν (neat) 2923, 1624, 1592, 1491, 1378, 1243, 1115, 1070, 909, 698 cm^{-1}; δ_H 7.55 (2H, d, J=7.6 Hz), 7.51–7.42 (3H, m), 4.82–4.74 (1H, m), 3.41 (2H, d, J=5.2 Hz), 3.29 (1H, dd, J=10.4, 15.2 Hz), 2.91 (1H, dd, J=6.8, 15.2 Hz), 1.95 (3H, s); δ_C 194.4, 165.4, 130.7, 130.6, 129.1, 129.1, 126.4, 126.4, 114.5, 80.1, 37.7, 26.9, 8.9; *m/z* 328 (M^+, 18%), 327 (25), 201 (15), 115 (12), 105 (100), 77 (60), 51 (23), 43 (95). Anal. calcd for $C_{13}H_{13}IO_2$: C, 47.58; H, 3.99; I, 38.67. Found: C, 47.48; H, 4.07, I, 38.58%.

4.3.7. 3-Acetyl-5-iodomethyl-2-methyl-4, 5-dihydrofuran (6g). The title compound was obtained as a light yellow oil (86%). ν (neat) 2950, 1639, 1404, 1220, 1037, 732, 628 cm^{-1}; δ_H 4.71–4.67 (1H, m); 3.32 (2H, d, $J=6.0$ Hz), 3.10 (1H, dd, $J=14.4$, 10.8 Hz), 2.72 (1H, dd, $J=14.4$, 7.2 Hz), 2.23 (3H, s), 2.22 (3H, s); δ_C 194.2, 166.8, 111.9, 80.4, 36.7, 29.5, 15.0, 8.7; *m/z* 267 (M+1, 100%), 139 (11), 123 (13), 43 (58). Anal. calcd for $C_8H_{11}IO_2$: C, 36.11; H, 4.17; I, 47.69. Found: C, 36.20; H, 4.25; I, 47.62%.

4.4. General procedure for the preparation of alkylidenedihydrofurans (8a–8e)

The mixture of iodomethyldihydrofurans **6a**–**6e** (0.7 mmol) and DBU (2.1 mmol) was stirred under nitrogen for 12 h at 60 °C. The mixture was filtered and the resin was washed with diluted HCl and CH_2Cl_2, the filtrate was extracted with Et_2O (10 mL×3). The organic layer was washed with brine to neutrality, then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was dissolved in dry Et_2O (0.05 M) and a few drops of H_2SO_4 (10 M) were added. The solution was stirred under nitrogen at rt until the completion of the reaction (TLC monitoring). Then the solution was diluted with Et_2O and washed with brine. After the usual work-up the furan **8a**–**8e** were obtained.

4.4.1. 2-Methyl-6, 7-dihydro-5*H*-benzofuran-4-one (8a). The title compound was obtained as a colorless oil (80%). ν (neat) 1674, 1581, 1434, 1237, 1163, 1010, 913, 732 cm^{-1}; δ_H 6.24 (1H, s), 2.83 (2H, t, $J=6.2$ Hz), 2.46 (2H, t, $J=6.2$ Hz), 2.29 (3H, s), 2.15 (2H, quintet, $J=6.3$ Hz); δ_C 194.6, 166.0, 152.6, 122.0, 101.7, 37.5, 23.3, 22.6, 13.3; *m/z* 150 (M^+, 15%), 122 (59), 94 (90), 79 (11), 53 (13), 52 (11), 51 (26), 50 (22), 43 (100), 42 (16), 41 (14). Anal. calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.90; H, 6.63%.

4.4.2. 2, 6, 6-Trimethyl-6, 7-dihydro-5*H*-benzofuran-4-one (8b). The title compound was obtained as a colorless oil (78%). ν (neat) 1670, 1582, 474, 1252, 1034, 905 cm^{-1}; δ_H 6.23 (1H, s), 2.69 (2H, s), 2.34 (2H, s), 2.29 (3H, s), 1.13 (6H, s); δ_C 194.0, 166.1, 162.8, 120.7, 101.7, 51.9, 37.3, 36.2, 28.5, 28.5, 13.4; *m/z* 178 (M^+, 7%) 122 (100), 94 (97), 51 (11), 43 (81). Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.08; H, 8.01%.

4.4.3. 2, 5-Dimethyl-3-methoxycarbonyl-furan (8c).[17] The title compound was obtained as a colorless oil (74%). ν (neat) 2953, 1713, 1439, 1207, 1085, 734 cm^{-1}; δ_H 6.21 (1H, s), 3.78 (3H, s), 2.51 (3H, s), 2.22 (3H, s); *m/z* 154 (M^+, 53%), 139 (51), 123 (63), 94 (20), 81 (18), 53 (21), 43 (100).

4.4.4. 2, 5-Dimethyl-3-ethoxycarbonyl-furan (8d).[17] The title compound was obtained as a colorless oil (71%). ν (neat) 2926, 1713,, 1229, 1204, 1075, 988 cm^{-1}; δ_H 6.25 (1H, s), 4.16 (2H, q, $J=7.2$ Hz), 2.52 (3H, s), 2.24 (3H, s), 1.26 (3H, t, $J=7.2$ Hz); *m/z* 168 (M^+, 7), 153 (22), 137 (36), 123 (14), 95 (17), 51 (33), 43 (100).

4.4.5. 3-Acetyl-5-methyl-2-phenyl-furan (8e). The title compound was obtained as a colorless oil (72%). ν (neat) 2926, 1673, 1557, 1234, 908, 733 cm^{-1}; δ_H 7.70–7.72 (2H, m), 7.47–7.36 (3H, m), 6.09 (s, 1H), 2.41 (s, 3H), 2.21 (s, 3H); δ_C 191.8, 158.0, 154.7, 139.3, 131.9, 128.9, 128.9, 128.2, 128.2, 121.1, 107.4, 14.1, 13.2; *m/z* 200 (M^+, 13), 105 (100). Anal. calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.90; H, 6.12%.

4.4.6. 3-Benzoyl-5-methyl-2-phenyl-furan (8f).[18] The title compound was obtained as a colorless oil (79%). ν (neat) 2923, 1618, 1221, 986 cm^{-1}; δ_H 7.9–7.75 (2H, m), 7.75–7.6 (2H, m), 7.6–7.15 (6H, m), 6.25 (s, 1H), 2.35 (s, 3H); *m/z* 262 (M^+, 8), 105 (100).

4.5. General procedure for the preparation of iodomethyltetrahydrofurans (11a–11j)

To a suspension of the swellen selenocyclic enol ether resin **2** (1.0 g), in dry DMF (15 mL), NaI (1.5 g) and CH_3I (1.5 mL) were added under nitrogen. The suspension was stirred at 75 °C for 18 h. The mixture was filtered and the resin was washed with CH_2Cl_2 (10 mL×3), the filtrate was washed with saturated $Na_2S_2O_3$ and H_2O respectively and extracted with CH_2Cl_2 (10 mL×3), dried over $MgSO_4$, and evaporated to dryness in vacuum to afford iodomethyltetrahydrofurans **11a**–**11j**.

4.5.1. (5-Iodomethyl-dihydrofuran-2-ylidene)-acetic acid methyl ester (11a). The title compound was obtained as a light yellow oil (85%). ν (neat) 2951, 1706, 1643, 1436, 1363, 1118 cm^{-1}; δ_H 5.32 (1H, s), 4.50–4.48 (1H, m), 3.66 (3H, s), 3.37–3.24 (3H, m), 3.06–3.01 (1H, m), 2.36–2.30 (1H, m), 1.91–1.86 (1H, m); δ_C 175.6, 168.7, 90.0, 82.3, 50.7, 30.2, 29.7, 6.7; *m/z* 283 (100%), 282 (M^+, 21), 251 (42), 155 (37), 123 (25), 101 (55), 99 (14), 95 (17), 85 (14), 81 (21), 71 (13), 69 (58), 67 (15), 59 (16), 57 (12), 55 (49), 54 (11), 53 (25), 43 (44), 42 (15), 41 (32). Anal. calcd for $C_8H_{11}IO_3$: C, 34.06; H, 3.93; I, 44.99. Found: C, 34.13; H, 3.84; I, 44.90%.

4.5.2. 2-(5-Iodomethyl-dihydrofuran-2-ylidene)-butyric acid methyl ester (11b). The title compound was obtained as a light yellow oil (74%). ν (neat) 2962, 1698, 1635, 1434, 1318, 1255, 1183, 1101, 1027, 780 cm^{-1}; δ_H 4.47–4.44 (1H, m), 3.69 (3H, s), 3.38–3.22 (3H, m), 3.05–2.96 (1H, m), 2.31 (3H, q, $J=7.2$ Hz), 1.90–1.85 (1H, m), 0.99 (3H, t, $J=7.2$ Hz); δ_C 169.3, 169.2, 104.9, 81.4, 50.8, 30.8, 30.0, 19.4, 13.7, 7.6; *m/z* 311 (100%), 310 (M^+, 21) 279 (42), 151 (23), 123 (10), 109 (12), 99 (17), 97 (18), 97 (17), 81 (35), 71 (19), 69 (39), 67 (16), 59 (50), 57 (55), 55 (92), 53 (38), 43 (90), 41 (80). Anal. calcd for $C_{10}H_{15}IO_3$: C, 38.73; H, 4.87; I, 40.92. Found: C, 38.68; H, 4.80; I, 40.86%.

4.5.3. 2-(5-Iodomethyl-dihydrofuran-2-ylidene)-hexanoic acid methyl ester (11c). The title compound was obtained as a light yellow oil (80%). ν (neat) 2954, 2859, 1699, 1634, 1434, 1182, 1113, 733 cm^{-1}; δ_H 4.49–4.42 (1H, m), 3.68 (3H, s), 3.35 (1H, dd, $J=10.0$, 4.8 Hz), 3.31–3.21 (2H, m), 3.07–2.95 (1H, m), 2.30 (3H, t, $J=6.8$ Hz), 1.93–1.80 (1H, m), 1.43–1.23 (4H, m), 0.90 (3H, t, $J=7.2$ Hz); δ_C 169.5, 169.4, 103.5, 81.4, 50.8, 31.3, 30.9, 30.0, 25.6, 22.5, 14.0, 7.5; *m/z* 339 (100%), 338 (M^+, 44), 307 (72), 295 (36), 211 (10), 179 (16), 151 (13), 133 (12), 113 (10), 81 (12), 55

(32), 53 (18), 43 (27), 41 (45). Anal. calcd for $C_{12}H_{19}IO_3$: C, 42.62; H, 5.66; I, 37.53. Found: C, 42.69; H, 5.74; I, 37.60%.

4.5.4. (3-Allyl-5-iodomethyl-dihydrofuran-2-ylidene)-acetic acid methyl ester (11d). The title compound was obtained as a light yellow oil (80%). ν (neat) 2926, 1715, 1650, 1434, 1373, 1277, 1194, 1040, 999, 806 cm^{-1}; δ_H 6.79–6.71 (1H, m), 6.15–5.10 (2H, m), 4.85 (1H, s), 4.57–4.51 (1H, m), 3.68 (3H, s), 3.55 (1H, dd, $J=10.0$, 4.0 Hz), 3.27 (1H, dd, $J=10.0$, 8.8 Hz), 3.08–2.93 (1H, m), 2.57–2.39 (2H, m), 2.27–2.12 (1H, m), 1.53–1.37 (1H, m); δ_C 173.3, 166.0, 134.2, 117.9, 88.1, 82.9, 50.7, 43.4, 36, 35.9, 6.2; *m/z* 322 (M^+, 8%), 195 (12), 163 (40), 135 (30), 122 (14), 121 (35), 119 (16), 117 (27), 113 (10), 109 (33), 107 (27), 101 (72), 95 (66), 81 (97), 69 (100), 55 (77), 43 (80). Anal. calcd for $C_{11}H_{15}IO_3$: C, 41.01; H, 4.69; I, 39.39. Found: C, 40.13; H, 4.59; I, 39.47%.

4.5.5. 2-(5-Iodomethyl-dihydrofuran-2-ylidene)-3-phenyl-propionic acid methyl ester (11e). The title compound was obtained as a light yellow oil (80%). ν (neat) 1705, 1655, 1192, 1047, 913, 734 cm^{-1}; δ_H 7.28–7.22 (2H, m), 7.20–7.11 (3H, m), 4.70–4.65 (1H, m), 3.69 (3H, s), 3.57–3.52 (2H, m), 3.46 (1H, dd, $J=10.0$, 4.5 Hz), 3.26 (1H, dd, $J=5.2$, 4.8 Hz), 2.83 (1H, dd, $J=10.0$, 4.8 Hz), 2.73–2.67 (1H, m), 2.36–2.25 (1H, m),1.78–1.86 (1H, m); δ_C 168.3, 167.3, 140.4, 128.3, 128.3, 127.8, 127.8, 125.9, 99.7, 84.1, 51.2, 34.4, 30.5, 28.8, 6.9; *m/z* 373 (M+1, 100%), 341 (33), 213 (45), 143 (17), 131 (30), 91 (44), 55 (20), 43 (23). Anal. calcd for $C_{15}H_{17}IO_3$: C, 48.41; H, 4.60; I, 34.10. Found: C, 48.47; H, 4.51; I, 34.02%.

4.5.6. (5-Iodomethyl-dihydrofuran-2-ylidene)-acetic acid ethyl ester (11f). The title compound was obtained as a light yellow oil (80%). ν (neat) 2978, 1710, 1653, 1199, 1138, 1044, 804 cm^{-1}; δ_H 4.85 (1H, s), 4.76–4.68 (1H, m), 4.13 (2H, t, $J=6.8$ Hz), 3.50 (1H, dd, $J=10.0$, 3.6 Hz), 3.28 (1H, dd, $J=10.0$, 8.4 Hz), 2.85–2.72 (2H, m), 2.38–2.30 (1H, m), 1.91–1.82 (1H, m), 1.26 (3H, t, $J=6.8$ Hz); δ_C 170.9, 166.6, 88.9, 84.8, 59.3, 31.8, 28.9, 14.4, 6.4; *m/z* 297 (57%), 296 (M^+, 13), 251 (48), 169 (21), 123 (30), 115 (54), 99 (12), 95 (18), 87 (37), 81 (17), 69 (100), 67 (22), 55 (65), 54 (15), 53 (23), 43 (46), 42 (18), 41 (38). Anal. calcd for $C_9H_{13}IO_3$: C, 36.51; H, 4.43; I, 42.86. Found: C, 36.57; H, 4.50; I, 42.78%.

4.5.7. (5-Iodomethyl-3-methyl-dihydrofuran-2-ylidene)-acetic acid ethyl ester (11g). The title compound was obtained as a light yellow oil (80%). ν (neat) 2966, 2873, 1713, 1652, 1372, 1190, 1045, 1003, 806 cm^{-1}; δ_H (two diastereoisomers, ratio 51:49) 4.71 and 4.68 (1H, 2×s), 4.82–4.72 and 4.58–4.47 (1H, 2×m), 4.15 (2H, t, $J=7.2$ Hz), 3.54 and 3.45 (1H, 2×dd, $J=10.0$, 4.4 Hz), 3.29 and 3.23 (1H, 2×t, $J=9.6$ Hz), 3.08–2.96 (1H, m), 2.59–2.53 and 2.22–2.08 (1H, 2×m), 1.99–1.89 and 1.46–1.33 (1H, 2×m), 1.30–1.16 (6H, m); *m/z* 311 (83%), 310 (M^+, 23), 265 (54), 137 (12), 115 (42), 109 (14), 95 (13), 87 (25), 81 (28), 69 (100), 67 (18), 55 (18), 53 (23), 43 (37), 41 (92). Anal. calcd for $C_{10}H_{15}IO_3$: C, 38.73; H, 4.87; I, 40.92. Found: C, 38.65; H, 4.94; I, 40.99%.

4.5.8. (5-Iodomethyl-3-ethyl-dihydrofuran-2-ylidene)-acetic acid ethyl ester (11h). The title compound was obtained as a light yellow oil (80%). ν (neat) 2968, 2873, 1712, 1651, 1459, 1376, 1193, 1045, 1003, 804 cm^{-1}; δ_H (two diastereoisomers, ratio 51:49) 4.80 and 4.77 (1H, 2×s), 4.80–4.73 and 4.57–4.50 (1H, 2×m), 4.19–4.07 (2H, m), 3.46 and 3.54 (1H, 2×dd, $J=10.0$, 4.8 Hz), 3.21 and 3.15 (1H, 2×t, $J=9.6$ Hz), 2.85–2.74 (1H, m), 2.59–2.50 and 2.11–1.99 (1H, 2×m), 2.11–1.99 and 1.89–1.75 (1H, 2×m), 1.75–1.63 and 1.53–1.34 (1H, 2×m), 1.53–1.34 (1H, m), 1.26 (3H, t, $J=7.2$ Hz), 1.00 (3H, t, $J=7.2$ Hz); *m/z* 325 (100%), 324 (M^+, 23), 279 (54), 169 (12), 123 (15), 115 (29), 97 (15), 95 (23), 87 (19), 81 (31), 69 (59), 67 (19), 55 (47), 53 (24), 43 (38), 41 (68). Anal. calcd for $C_{11}H_{17}IO_3$: C, 40.76; H, 5.29; I, 39.15. Found: C, 40.82; H, 5.20; I, 39.22%.

4.5.9. (5-Iodomethyl-3-benzyl-dihydrofuran-2-ylidene)-acetic acid ethyl ester (11i). The title compound was obtained as a light yellow oil (80%). ν (neat) 1708, 1652, 1192, 1045, 911, 732 cm^{-1}; δ_H (two diastereoisomers, ratio 55:45) 7.31 (2H, t, $J=7.2$ Hz), 7.24 (1H, t, $J=7.2$ Hz), 7.20–7.13 (2H, m), 4.92 and 4.83 (1H, 2×s), 4.67–4.60 and 4.48–4.42 (1H, 2×m), 4.19–4.08 (2H, m), 3.46 and 3.40 (1H, 2×dd, $J=10.4$, 4.0 Hz), 3.20 (2H, q, $J=9.6$ Hz), 3.11 and 2.96 (1H, 2×dd, $J=13.6$, 4.4 Hz), 2.67 and 2.60 (1H, 2×dd, $J=13.6$, 9.6 Hz), 2.31–2.22 and 2.10–2.01 (1H, 2×m), 1.93–1.84 and 1.50–1.39 (1H, 2×m), 1.25 (3H, dd, $J=12.0$, 7.2 Hz); *m/z* 386 (M^+, 10%), 341 (6), 145 (19), 115 (47), 91 (100), 69 (25), 41 (21). Anal. calcd for $C_{16}H_{19}IO_3$: C, 49.76; H, 4.96; I, 32.86. Found: C, 49.82; H, 4.89; I, 32.91%.

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Kunzeanones A, B, and C: novel alkylated phloroglucinol metabolites from *Kunzea ambigua*

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Abstract—Three new metabolites, kunzeanones A (**1**), B (**2**), and C (**3**), along with three known compounds, cryptostrobin (**4**), (+)-spathulenol (**5**), and (−)-globulol (**6**), were isolated from the non-polar fraction of the dried leaves of *Kunzea ambigua* (Myrtaceae), which shows ichthyotoxicity toward a small fish, medaka. The structures of these new compounds were elucidated as condensates of alkylated phloroglucinol with methylflavanone and germacrane-type sesquiterpene, respectively, on the basis of spectral analyses including 1-D and 2-D NMR spectra. The stereochemistries of kunzeanones A and B were determined by X-ray crystallographic analysis. A sesquiterpene, (+)-spathulenol (**5**), among the isolates was characterized as the ichthyotoxic principle of the extract.

1. Introduction

Species of the Myrtaceae are known to be rich sources of bioactive terpenoids, tannins, flavonoids, and phloroglucinol derivatives.[1,2] About 30 species of the genus *Kunzea* belonging to this family are distributed in Australia and New Zealand. Essential oils of some *Kunzea* species, including *K. ambigua* (SM.) Druce, have been used as folk medicines for the treatment of diarrhea, cold, inflammation, and wounds in New Zealand.[3–5] Previous chemical studies of their oils have demonstrated the presence of a variety of monoterpenes, sesquiterpenes, and phloroglucinol derivatives that have antimicrobial,[6–8] insecticidal,[9,10] and/or spasmolytic activities.[3] However, there are few phytochemical reports on the leaves of the *Kunzea* species. We recently reported the isolation and characterization of a new dimeric flavonol glycoside and several new chromone glucosides from the leaves of *K. ambigua*.[11]

In a survey of biologically active natural products, ichthyotoxic assay using a small fish, medaka (killie-fish; *Oryzias latipes*) has been successfully used as a convenient primary screening because ichthyotoxic substances often exhibit a wide array of biological activity such as antifungal, anti-tumor and anti-ulcer effects.[12] In our ongoing search for bioactive compounds from myrtaceous plants, we have found that the hexane soluble portion of the *K. ambigua* leaves showed a significant ichthyotoxic activity toward medaka, which prompted us to further investigate a non-polar fraction of the leaves. This paper describes the structural elucidation of new phloroglucinol metabolites isolated from the *n*-hexane extract of the leaves and evaluates the ichthyotoxic activity of the isolates.

2. Results and discussion

The dried leaves of *K. ambigua* were homogenized in 70% aqueous acetone. The homogenate was concentrated and extracted with *n*-hexane. The *n*-hexane extract, which showed a significant ichthyotoxic activity toward killie-fish, was submitted to successive chromatographic fractionation and purification, yielding three new compounds designated as kunzeanones A (**1**), B (**2**), and C (**3**), along with three known compounds which were identified as cryptostrobin (**4**),[13,14] (+)-spatulenol (**5**),[15,16] and (−)-globulol (**6**),[17–19] by comparison of their spectral data with those reported in the literature.

2.1. Structure of kunzeanone A (1)

Kunzeanone A (**1**) was obtained as colorless prisms, mp 199–202 °C; $[\alpha]_D = +87.8°$ ($CHCl_3$). Its molecular formula of $C_{31}H_{34}O_6$ with 15 unsaturations was determined from a

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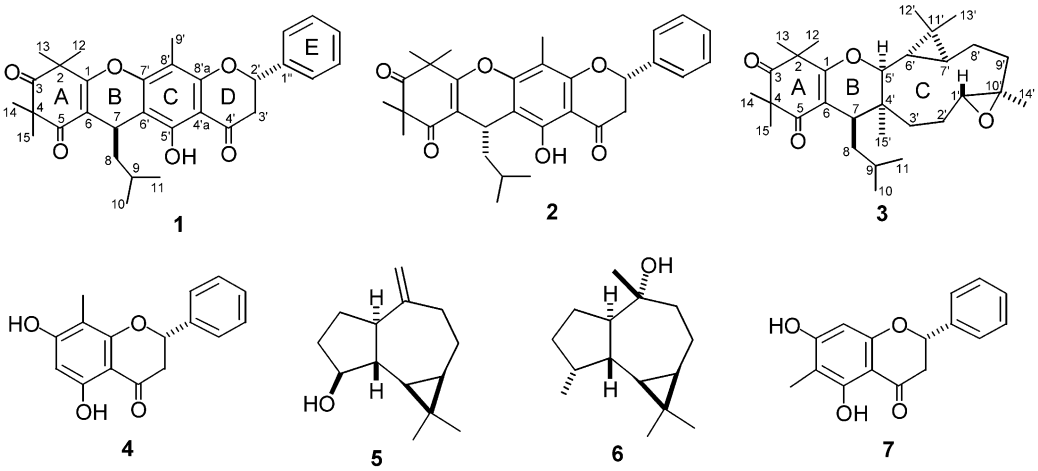

pseudomolecular ion peak, *m/z* 503.2427 $[M+H]^+$ in high resolution electrospray ionization (HRESI) MS. The ^1H NMR spectrum of **1** (Table 1) indicated the presence of a cryptostrobin (**4**) unit as a partial structure, as revealed by signals due to a hydrogen-bonded OH group (δ 12.16, s), a monosubstituted benzene ring (δ 7.40–7.49), a methine proton (δ 5.49, dd, $J=3$, 13 Hz, H-2′) coupled with methylene protons (δ 3.08, dd, $J=13$, 17 Hz; 2.91, dd, $J=3$, 17 Hz, H-3′), and an aryl methyl group (δ 2.17, s, H-9′). This partial structure was further evidenced by the appearance of the ^{13}C NMR resonances corresponding to those of **4**. The presence of a tetramethylcyclohexenedione ring (C-1–C-6), which is frequently encountered in phloroglucinol derivatives from myrtaceous plants, was also revealed by the ^1H and ^{13}C NMR spectra, which showed signals from an isolated ketonic carbonyl carbon (δ_C 212.1), an enolated 1,3-dione system (δ_C 197.3, 114.3, 166.8), two sp^3 quaternary carbons (δ_C 47.3, 56.1) and four tertiary methyl groups [δ_C 24.3, 24.4, 25.0 25.2; δ_H 1.37, 1.41, 1.47, 1.59 (each s)]. Additionally, two secondary methyl protons, two methine protons, and one methylene protons were determined from the signals at δ 0.88, 0.90 (each 3H, d, $J=6$ Hz, H-10, H-11), 4.31 (1H, dd, $J=5.5$, 6.5 Hz, H-7) and 1.38–1.50 (3H, overlapped signal, H-8, H-9) in the ^1H NMR spectrum. The ^1H–^1H COSY spectrum indicated the correlations of the signal at δ 1.38–1.50 (H-8, H-9) with both secondary methyl protons (H-10, H-11) and the methine signal at δ 4.31 (H-7), implying the presence of a disubstituted isopentyl group (C-7–C-11). The 14 degrees of unsaturation can be accounted for by the above partial structures; hence kunzeanone A is pentacyclic.

Table 1. ^1H and ^{13}C NMR spectral data for kunzeanone A (**1**) in $CDCl_3$

Position	δ_H[a]	δ_C[b]	HMBC
1		166.8	
2		47.3	
3		212.1	
4		56.1	
5		197.3	
6		114.3	
7	4.31 (1H, dd, $J=5.5$, 6.5 Hz)	24.9	C-1, 6, 8, 9, 5′, 6′, 7′
8	1.38–1.50	46.5	C-6, 6′
9	1.38–1.50	24.9	
10	0.88 (3H, d, $J=6$ Hz)	22.9	C-8, 9
11	0.90 (3H, d, $J=6$ Hz)	23.5	C-8, 9
12	1.37 (3H, s)	24.3	C-1, 3
13	1.41 (3H, s)	24.4	C-1, 3
14	1.47 (3H, s)	25.0	C-3, 5
15	1.59 (3H, s)	25.2	C-3, 5
2′	5.49 (1H, dd, $J=3$, 13 Hz)	78.9	C-4′, 1″, 2″, 6″
3′	3.08 (1H, dd, $J=13$, 17 Hz) 2.91 (1H, dd, $J=3$, 17 Hz)	43.5	C-2′, 4′, 4′a, 1″
4′		197.0	
4′a		105.1	
5′		158.3	
6′		107.3	
7′		156.4	
8′		104.2	
8′a		157.8	
9′	2.17 (3H, s)	7.7	C-7′, 8′, 8′a
1″		138.5	
2″, 6″	7.40–7.49	128.8	C-2″, 4″, 6″
3″, 5″	7.40–7.49	128.9	C-3″, 5″
4″	7.40–7.49	125.9	C-2″, 6″
5′-OH	12.16 (1H, s)		C-4′a, 5′, 6′

[a] Measured at 500 MHz.
[b] Measured at 126 MHz.

The fifth ring was assigned as a pyran ring (ring B) associated with the isopentyl group on the basis of the analysis of HMBC data (Table 1). Thus, the signal at δ 4.31 (H-7) showed two-and three-bond correlations with C-6 and C-1 of ring A at δ 114.3 and 166.8, respectively, as well as those with C-6′ (δ 107.3) and C-5′ (δ 158.3) (ring C), which were assigned by the correlations with the hydrogen-bonded 5′-OH signal; this clearly indicates that the tetramethylcyclohexenedione unit (ring A) was connected through C-7 methine to the flavanone unit. Although the NOE experiment of **1** was not informative regarding the stereochemistry, the relative configuration was unambiguously determined by a single crystal X-ray diffraction analysis of **1**,[20] as shown in Figure 1, which showed the *trans* relationship of the phenyl group at C-2′ and the isobutyl group at C-7.

2.2. Structure of kunzeanone B (2)

Kunzeanone B was first obtained in a nearly inseparable mixture with **1** as revealed by the ^1H NMR spectrum, which showed paired signals for some protons. The compounds

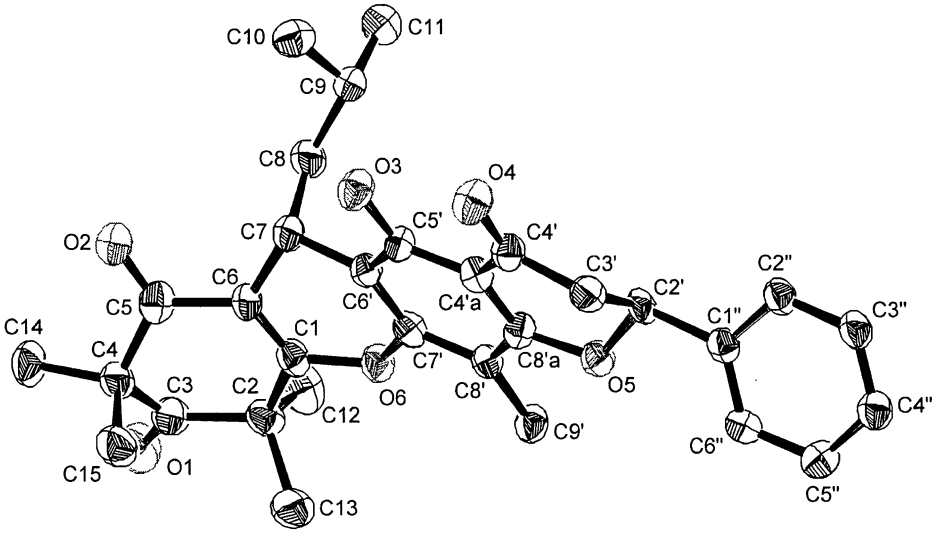

Figure 1. Perspective drawing of **1**. H atoms have been omitted for clarity.

were separated by preparative HPLC, after the determination of an adequate solvent system, to give **2** as pure fine colorless needles with mp 167–168 °C; $[\alpha]_D = -144.8°$ ($CHCl_3$). The molecular formula of **2** was found to be the same as that of **1** ($C_{31}H_{34}O_6$), as deduced from HRESIMS (*m/z* 503.2434 $[M+H]^+$) and NMR data. The ^1H and ^{13}C NMR spectra of **2** were almost superimposable on those of **1**, except for slight chemical shift differences for the H-2′ signal (Δ 0.07 ppm) and one methylene proton at C-3′ (Δ 0.04 ppm) in the ^1H NMR, and the C-3′ signal (Δ 0.3 ppm) in the ^{13}C NMR spectrum. This implies that kunzeanone B (**2**) is most likely a stereoisomer of **1** with respect to the configuration at C-2′ or C-7. In order to elucidate the stereochemistry of **2**, we subsequently attempted an X-ray analysis of **2**, but crystals suitable for an X-ray analysis have not been obtained. However, when we were preparing a MeOH solution of almost 1:1 mixture of **1** and **2** for HPLC separation, fairly large pale yellow crystals precipitated out of the solution. Thus the X-ray analysis of these crystals was carried out.[20] Surprisingly, as shown in Figure 2, the epimeric pair of **1** and **2** were found to be located together in a unit cell in the crystal as if they formed one independent molecule having a formula $C_{62}H_{68}O_{12}$ (see Section 3). To the best of our knowledge, this situation is the first case, and it could be a quite rare case for the crystals that are composed of chiral compounds. Thus **2** was established to be a C-7 epimer of **1**. The results also revealed that the ring B in **1** exists in a boat conformation, which is nearly planar, and the isobutyl group stands up on the bow of the boat almost perpendicularly to the boat deck as seen in Figure 1. Notably, the boat conformation of ring B in **2** was flipped into the reverse orientation from that in **1**, and consequently the part of rings A–C constitutes an enantiomeric circumstance. These structural features can satisfactorily explain the superimposable NMR chemical shifts except for the ring D resonances in **1** and **2**. Although we were unable to determine the absolute stereochemistry of **1** and **2** by X-ray analysis, 2′*S*, 7*R* configurations for **1** and 2′*S*, 7*S* for **2** were tentatively assigned on the basis of the biogenetic consideration that most flavanone derivatives known to date have a 2*S* configuration.[21]

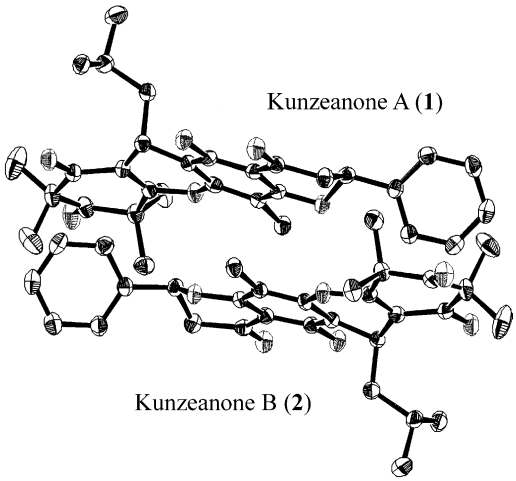

Figure 2. Perspective drawing of **1** and **2**. H atoms and all atom labels have been omitted for clarity.

Previously, two analogous compounds in which an alkylated β-triketone is attached to the C-8 position of the flavanone unit have been isolated from *Baeckea frutescens*,[22] *Kunzea baxterii*, and *K. ambigua*.[10] However, these compounds were obtained as an inseparable mixture of stereoisomers with respect to the configuration of an alkyl side chain but not in pure states. The separation of kunzeanones A (**1**) and B (**2**) is thus the first isolation of each isomer in a pair of this type of diastereoisomer.

2.3. Structure of kunzeanone C (3)

Kunzeanone C (**3**), a colorless oil; $[\alpha]_D = -115°$ ($CHCl_3$), was assigned the molecular formula $C_{30}H_{46}O_4$, as established from HRESIMS (*m/z* 471.3471 $[M+H]^+$), indicating eight degrees of unsaturation. The ^1H and ^{13}C NMR spectra revealed the presence of a tetramethylcyclohexenedione and a pyran ring with an isobutyl side-chain, as found in **1** and **2** (Table 2). In addition to the signals due to ring A and a part of C-7–C-11, 15 sp^3 carbons comprised of two quaternary, four methylene, five methine, and four

Table 2. ^{1}H and ^{13}C NMR spectral data for kunzeanone C (**3**) in pyridine-d_5

Position	δ_H[a]	δ_C[b]
1		168.9
2		48.3
3		212.9
4		55.6
5		198.5
6		115.9
7	3.09 (1H, t, J=5 Hz)	35.5
8	1.25 (2H, m)	39.8
9	2.05 (1H, m)	27.9
10	1.10 (3H, d, J=6.5 Hz)	23.0
11	0.95 (3H, d, J=6.5 Hz)	23.8
12	1.36 (3H, s)	26.4
13	1.51 (3H, s)	23.0
14	1.38 (3H, s)	25.6
15	1.45 (3H, s)	23.1
1′	2.95 (1H, dd, J=2, 10 Hz)	63.9
2′	1.69 (1H, m)	23.2
	1.99 (1H, br dd, J=7.5, 15 Hz)	
3′	1.73 (1H, m)	32.5
	1.87 (1H, dd, J=7.5, 15 Hz)	
4′		41.5
5′	3.60 (1H, d, J=6 Hz)	83.9
6′	0.94 (1H, m)	26.7
7′	0.57 (1H, br t, J=9.5 Hz)	31.5
8′	0.95 (1H, m)	21.6
	1.77 (1H, m)	
9′	1.20 (1H, m)	39.8
	2.10 (1H, m)	
10′		60.1
11′		21.7
12′	1.22 (3H, s)	19.8
13′	1.17 (3H, s)	30.3
14′	0.98 (3H, s)	17.02
15′	1.25 (3H, s)	16.95

[a] Measured at 500 MHz.
[b] Measured at 126 MHz.

tertiary methyl carbons were observed in the HMQC spectrum, indicating that **3** has a sesquiterpene unit instead of the flavanone moiety of **1** and **2**. Moreover, these spectral features revealed that a total of 46 protons were attached to carbons, implying the absence of hydroxyl groups in the molecule of **3**. The ^{1}H–^{1}H COSY and HMBC spectra of **3**, taking into account the unsaturation degrees, allowed the assignment of the tricyclic sesquiterpene unit with the germacrane skeleton as follows. A cyclopropane ring was suggested by two high-field methine signals at δ 0.94 (m, H-6′) and 0.57 (br t, J=9.5 Hz, H-7′). The HMBC spectrum showed correlations from the tertiary methyl proton signals (H-12′ and 13′) to the C-6′ and 7′ as well as C-11′, indicating the presence of *gem*-dimethyl groups at C-11′. A proton signal (H-1′) at δ 2.95 (dd, J=2, 10 Hz) attached to an oxygen-bearing carbon (δ 63.9, C-1′) showed HMBC cross-peaks with an oxygenated quaternary carbon (δ 60.1, C-10′) and a tertiary methyl carbon (δ 17.02, C-14′) as well as a methylene carbon (δ 39.8, C-9′), suggesting the presence of a trisubstituted epoxide ring. Further key HMBC correlations were those of H-5′ (δ 3.60, d, J=6 Hz) with C-7′ (δ 31.5) and C-4′ (δ 41.5), and those of H-15′ (δ 1.25, s) with C-3′ (δ 32.5), C-4′ (δ 41.5), C-5′ (δ 83.9), and C-7 (δ 35.5) (Fig. 3), establishing connectivity between rings A and C. The methylene proton signals (H-3′) assigned by HMQC were indicated to correlate with H-1′ through the H-2′ signals from the COSY and TOCSY spectra. All of these data indicated that **3** is a condensate of

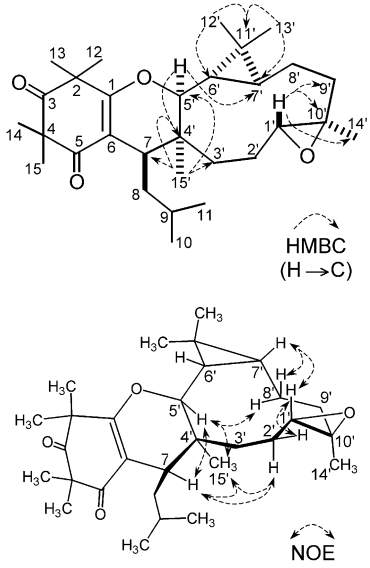

Figure 3. Selected HMBC and NOE correlations for **3**.

alkylated phloroglucinol with a tricyclic sesquiterpene based on a germacrane framework.

The relative stereochemistry of kunzeanone C was elucidated by the NOESY spectrum (Fig. 3). The spectrum of **3** displayed correlations between H-5′/H-15′ (Me), H-5′/H-7, and H-7/H-15′, indicating a *cis* fused ring system between ring B and the sesquiterpene unit (ring C), and furthermore indicating a *trans* relationship between the isobutyl side-chain and the methyl group (C-15′). Important NOE was also observed between H-7′ and H-1′. The non-equivalent methylene proton signals (δ 1.77 and 0.95) at C-8′ showed NOE cross peaks with H-7′ and H-5′, respectively. These NOEs along with those illustrated in Figure 3 satisfy the stereochemistries of cyclopropane and epoxide rings, as shown in the formula **3**. The absolute configuration of **3** shown here is most likely because it was in accord with that reported for the analogous germacrane sesquiterpenoid, madolin A from *Aristolochia cucurbitafolia*.[23]

The ichthyotoxic activities of the isolated compounds toward medaka were investigated by evaluating the median tolerance limit (TLm) value after 24 h, except for **2**, which was not isolated in sufficient amounts. As some alkylated flavonoids are reported to be ichthyotoxic,[24] strobopinin (5,7-dihyroxy-6-methylflavanone) (**7**),[13] which is a regio-isomer of **4** with respect to the methyl group, was also evaluated for comparison. Compounds **1**, **3**, and **4** had no toxicity to fish (TLm>30 μg/ml), whereas **5** and **7** were ichthyotoxic, with TLm values of 8.0 and 1 μg/ml, respectively. The potency of **7** was comparable to that of buddeldin B[25] (TLm, 0.8 μg/ml) and iripallidal[26] (TLm, 1 μg/ml) which were used as positive controls.

3. Experimental

3.1. General

Melting points were measured on a Yanaco micro-melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR

spectra were recorded on a Varian VXR-500 instrument (500 MHz for ^{1}H, and 126 MHz for ^{13}C), and the chemical shifts are given in δ (ppm) values relative to that of the solvent [$CDCl_3$ (δ_H 7.26; δ_C 77.0) and pyridine-d_5 (δ_H 7.20; δ_C 123.5)] and tetramethylsilane. The standard pulse sequences that were programmed into the instrument (VXR-500) were used for each two-dimensional measurement. The J_{CH} value was set at 6 Hz in the HMBC spectra. Optical rotations were measured with a Jasco DIP-1000 polarimeter. UV spectra were measured with a Hitachi U-2000 spectrophotometer. CD spectra were obtained on a JASCO J-720 spectrometer. ESIMS including high-resolution mass spectra were recorded on a Micromass Auto Spec OA-TOF mass spectrometer (solvent: 50% aqueous MeOH containing 0.1% $AcONH_4$; flow rate: 0.03 ml/min). Normal-phase HPLC was conducted on a YMC-Pack SIL A-003 column (4.6 i.d.×250 mm; YMC Co., Ltd.) and was developed at room temperature with a solution of *n*-hexane/MeOH/tetrahydrofuran/formic acid (55:33:11:1) containing 450 mg/l oxalic acid (flow rate: 1.5 ml/min; detection: UV 280 nm). Reverse-phase HPLC analysis and preparative HPLC were performed with a YMC-Pack ODS-A A-302 column (4.6 mm i.d.×150 mm) and developed at 40 °C with MeOH/H_2O (4:1). Column chromatography was carried out on Silica gel 60 (Merck). Preparative TLC was performed on a Silica gel 60 F_{254} (Merck).

3.2. Plant material

The dried leaves of *K. ambigua* (SM.) Druce were collected in April 1998 from the herbal garden of Pola Co. Ltd., Japan. Voucher specimens have been deposited in the herbarium of Pola Co. Ltd and in the Medicinal Herbal Garden of Okayama University (specimen No. OKP-MY98003).

3.3. Extraction and isolation

The dry leaves (700 g) of *K. ambigua* were homogenized in 70% aqueous acetone (10 l). A precipitate was formed after concentration and filtration of the homogenate. The precipitate was extracted with *n*-hexane (3 l). A 1.5 g part of the 7.5 g *n*-hexane extract was chromatographed over a silica gel column (1.5 cm i.d.×50 cm) with *n*-hexane containing increasing amounts of EtOAc in a stepwise gradient. The eluate of *n*-hexane/EtOAc (95:5) was subjected to preparative silica gel TLC with ligroin/acetone/chloroform (4:1:3), to furnish kunzeanone A (**1**) (5.5 mg), a mixture of **1** and kunzeanone B (**2**) (5.9 mg), and (+)-spathulenol (**5**) (9.7 mg). The mixture was purified by preparative reverse-phase HPLC to give **2** (1.2 mg). The EtOAc/*n*-hexane (1:9) eluate was purified by repeated preparative silica gel TLC with ligroin/acetone/chloroform (4:1:3 or 3:1:4) and/or toluene/EtOAc (5:1) to yield kunzeanone C (**3**) (6.9 mg), cryptostrobin (**4**) (0.8 mg), and (−)-globulol (**6**) (6.0 mg).

3.3.1. Kunzeanone A (1). Colorless prisms; mp 199–202 °C; $[\alpha]_D^{23}=+87.8°$ (*c* 1, $CHCl_3$); UV (MeOH) λ_{max} 265 (log ε 4.05), 308 (log ε 4.20), 354 (log ε 3.61) nm; CD ($CHCl_3$) $\Delta\varepsilon$ (nm) +23.3 (227), −28.6 (265), +8.3 (298); ^{1}H and ^{13}C NMR, see Table 1; ESIMS *m/z* 503 $[M+H]^+$; HRESIMS *m/z* 503.2427 $[M+H]^+$ (calcd for $C_{31}H_{34}O_6$+H, 503.2434).

3.3.2. Kunzeanone B (2). Colorless needles; mp 167–168 °C; $[\alpha]_D^{23}=-144.8°$ (*c* 0.1, $CHCl_3$); UV (MeOH) λ_{max} 265 (log ε 3.97), 309 (log ε 4.17), 354 (log ε 3.57); CD ($CHCl_3$) $\Delta\varepsilon$ (nm) +4.8 (230), −10.4 (298), +1.3 (363); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.16 (1H, s, 5′-OH), 7.40–7.49 (5H, m, H-2″-6″), 5.49 (1H, dd, *J*=3, 13 Hz, H-2′), 4.31 (1H, dd, *J*=5.5, 6.5 Hz, H-7), 3.08 (1H, dd, *J*=13, 17 Hz, H-3′), 2.91 (1H, dd, *J*=3, 17 Hz, H-3), 2.17 (3H, s, CH_3-9′), 1.59 (3H, s, CH_3-15), 1.47 (3H, s, CH_3-14), 1.41 (3H, s, CH_3-13), 1.38–1.50 (2H, m, H-8, 9), 1.37 (3H, s, CH_3-12), 0.90 (3H, d, *J*=6 Hz, CH_3-11), 0.88 (3H, d, *J*=6 Hz, CH_3-10); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.1 (C-3), 197.3 (C-5), 197.0 (C-4′), 166.8 (C-1), 158.3 (C-5′), 157.8 (C-8′a), 156.4 (C-7′), 138.5 (C-1″), 128.9 (2C) (C-3″, 5″), 128.8 (2C) (C-2″, 6″), 125.9 (C-4″), 114.3 (C-6), 107.3 (C-6′), 105.1 (C-4′a), 104.2 (C-8′), 78.9 (C-2′), 56.1 (C-4), 47.3 (C-2), 46.5 (C-8), 43.8 (C-3′), 25.2 (C-15), 25.0 (C-14), 24.9 (2C) (C-7, 9), 24.4 (C-13), 24.3 (C-12), 23.5 (C-11), 22.9 (C-10), 7.7 (C-9′); ESIMS *m/z* 503 $[M+H]^+$; HRESIMS *m/z* 503.2434 $[M+H]^+$ (calcd for $C_{31}H_{34}O_6$+H, 503.2434).

3.3.3. Kunzeanone C (3). Colorless oil; $[\alpha]_D^{23}=-115°$ (*c* 0.7, $CHCl_3$); CD ($CDCl_3$) $\Delta\varepsilon$ (nm) −17.7 (224), −6.5 (264), +1.3 (300); ^{1}H and ^{13}C NMR, see Table 2; ESIMS *m/z* 471 $[M+H]^+$; HRESIMS *m/z* 471.3471 $[M+H]^+$ (calcd for $C_{30}H_{46}O_4$+H, 471.3474).

3.4. X-ray crystallographic analyses of 1 and 2

3.4.1. Kunzeanone A (1). Single crystals suitable for X-ray analysis were obtained by recrystallization from MeOH. A colorless prism crystal having approximate dimensions of 0.20×0.05×0.02 mm was mounted on a glass fiber. All X-ray measurements were made on a Rigaku RAXIS-RAPID imaging plate area detector with graphite-monochromated Cu Kα radiation (λ=1.5419 Å) at 113 K. Crystal data: $C_{31}H_{34}O_6$, M_r=502.61, orthorhombic, space group $P2_12_12_1$, a=7.335(2) Å, b=18.293(4) Å, c=19.405(5) Å, V=2603(1) Å^3, Z=4, D_x=1.282 Mg m^{-3}. Of the 4648 reflections that were collected, 2689 were independent. The structure was solved by direct methods (SIR92[27]) and expanded using Fourier techniques (DIRDIF99[28]). The anisotropic and isotropic temperature factors were applied to the non-hydrogen atoms and the hydrogen atoms, respectively. The final cycle of full-matrix least-squares refinement was based on 1622 observed reflections ($I>3.00\sigma(I)$) and converged with unweighted and weighted agreement factors of R=0.038 and R_w=0.041, respectively. All calculations were performed using the CrystalStructure[29] crystallographic software package.

3.4.2. Kunzeanones A and B [an epimeric mixture of 1 and 2 (1:1)]. Pale yellow blocks were deposited from the MeOH solution of the 1:1 mixture. Crystal data: $C_{62}H_{68}O_{12}$, M_r=1005.21, monoclinic, space group $P2_1$, a=12.881(2) Å, b=13.304(4) Å, c=14.988(5) Å, β=94.13(1)°, V=2561(1) Å^3, Z=2, D_x=1.303 Mg m^{-3}. A crystal having approximate dimensions of 0.20×0.20×0.15 mm was mounted on a glass fiber. The data collection, structure

solution and refinement of this crystal were carried out in the same way as the crystal of **1** above described. Of the 4648 reflections collected, 4595 were independent. The final cycle of full-matrix least-squares refinement was based on 4150 observed reflections ($I>3.00\sigma(I)$) and converged with unweighted and weighted agreement factors of $R=0.037$ and $R_w=0.045$, respectively.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 244263 (kunzeanone A) and 244264 (kunzeanone A and B). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

3.5. Ichthyotoxic assay

The assay was conducted essentially as reported previously[30] using medaka (*Oryzias latipes*). A test solution was prepared by adding an acetone solution (0.5 ml) of the compounds of known concentration into aerated water (100 ml). The median tolerance limit (TLm) after 24 h was evaluated for five fish/group by straight-line graphical interpolation. A control experiment was carried out under the same conditions, adding only acetone (0.5 ml).

Acknowledgements

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Sonogashira coupling with aqueous ammonia directed to the synthesis of azotolane derivatives

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Abstract—Sonogashira coupling with aqueous ammonia is tolerable for the reaction of aryl iodides or terminal alkynes bearing an azobenzene group. The reaction of (4-heptyloxyphenyl)ethyne with (4-heptyloxyphenyl)-(4-iodophenyl)diazene in the presence of 1 mol% of $PdCl_2(PPh_3)_2$, 2 mol% of CuI, and 2 equiv of 0.5 M aqueous ammonia gives the corresponding azotolane in 87% isolated yield after stirring at room temperature for 15 h.

1. Introduction

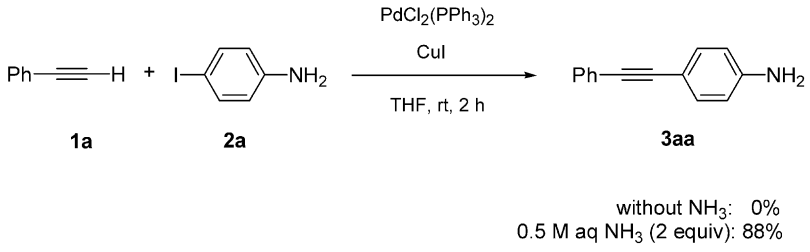
Organic holographic materials recently attract considerable interest for storage and reconstruction of three-dimensional image in the organic compound.[1,2] Azotolanes,[3] which contain a carbon–carbon triple bond as well as an azobenzene group, are potentially important component of holographic materials since these compounds show liquid crystalline and highly birefringent characteristics that enable photo-induced order-disorder change to form holographic gratings of high diffraction efficiency.[1a,4] Hence, the synthetic methodology for azotolanes that is tolerable to various functional groups would be the key for flexible and efficient design of the target molecule.

We have recently shown that the Sonogashira coupling takes place with aqueous ammonia to afford a variety of substituted alkynes highly efficiently.[5,6] Our concern has thus turned to apply the reaction for substrates bearing an azobenzene moiety leading to azotolane derivatives.[3] Herein, we report that the Sonogashira coupling with aqueous ammonia takes place efficiently with several substrates bearing an azobenzene group.

2. Results and discussion

Prior to the coupling reaction to synthesize azotolanes, we studied the Sonogashira coupling with a substrate bearing a protic functional group such as NH_2 or OH in aryl halide with aqueous ammonia.[7]

The reaction of phenylethyne (**1a**) with 4-amino-1-iodobenzene (**2a**) was carried out in the presence of 1 mol% of $PdCl_2(PPh_3)_2$, 2 mol% of CuI and 2 equiv of 0.5 M aqueous ammonia. The coupling product **3aa** was obtained in 88% isolated yield after stirring at room temperature for 2 h in THF. On the other hand, no reaction was found to take place in the absence of ammonia suggesting that the presence of



Scheme 1.

Keywords: Azotolane; Aqueous ammonia; Sonogashira; Palladium; Terminal alkynes.
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Table 1. Cross coupling of terminal alkynes, R-C≡CH, with aryl halides bearing a protic functional group[a]

Alkyne (R)	Aryl halide	Time, h	**3**, %Yield
1a (Ph)	I–C_6H_4-2-NH_2 (**2b**)	3.5	**3ab**, 87
	I–C_6H_4-2-OH (**2c**)	4	**3ac**, 97
	I–C_6H_4-4-OH (**2d**)	2	**3ad**, 96
	Br–C_6H_4-4-NH_2 (**2a′**)	12	**3aa**, 86[b]
	Br–C_6H_4-2-NH_2 (**2b′**)	19	**3ab**, 72[b]
	Br–C_6H_4-3-NH_2 (**2e′**)	30	**3ae**, 83[b]
	Br–C_6H_4-4-OH (**2d′**)	17	**3ad**, 80[b]
	Br–C_6H_4-3-OH (**2f′**)	24	**3af**, 77[b]
1b (Me_3Si)	**2a**	2	**3ba**, 86
	2b	3.5	**3bb**, 77
	2c	16	**3bc**, 63
	2d	3	**3bd**, 92

[a] Unless noted, the reaction was carried out with 0.5 mmol aryl halide, 0.6 mmol alkyne, and 1 mL of 0.5 M aq NH_3 in the presence of 1 mol% of $PdCl_2(PPh_3)_2$, 2 mol% of CuI in THF at room temperature.
[b] The reaction was performed at 60 °C with 3 mol% of $PdCl_2(PPh_3)_2$ and 2 mol% of CuI. Instead of aq. NH_3, 0.5 M of aq. 2-ethanolamine (2 equiv) was employed.

the amino group in the aryl halide could not be a surrogate promoter for ammonia as shown in Scheme 1.

Table 1 summarizes the results of the cross-coupling reaction of terminal alkynes with various aryl halides bearing an amino or hydroxy group at room temperature in the presence of 2 equiv of 0.5 M aqueous ammonia. The reaction of **1a** with 2-amino-1-iodobenzene (**2b**) similarly proceeded to give **3ab** in 87%. Use of aryl iodides bearing a hydroxy group, 2-hydroxy-1-iodobenzene (**2c**)[8] and 4-hydroxy-1-iodobenzene (**2d**) also resulted in giving the coupling products **3ac** and **3ad** in 97 and 96% yields, respectively. Aryl bromides bearing an amino (**2a′**, **2b′** and **2e′**) or hydroxy group (**2d′** and **2f′**) effected the reaction, which was carried out at 60 °C using an aqueous solution of 2-ethanolamine instead of ammonia.[9] In addition, the reaction of trimethylsilylethyne (**1b**) with several aryl iodides took place to afford the coupling products in excellent yields.

Studies on the reaction bearing an amino group on the aromatic group of aryl alkynes were then carried out. As summarized in Scheme 2, the reaction of (4-aminophenyl)ethyne (**1c**) with 4-methoxy-1-iodobenzene (**2g**) was found to proceed to give **3cg** in 74% yield after stirring at room temperature for 4 h. The coupling reaction of terminal alkyne **1c** and aryl halide **2a**, both of which possessed an amino group on the aromatic group, proceeded to afford **3ca**.

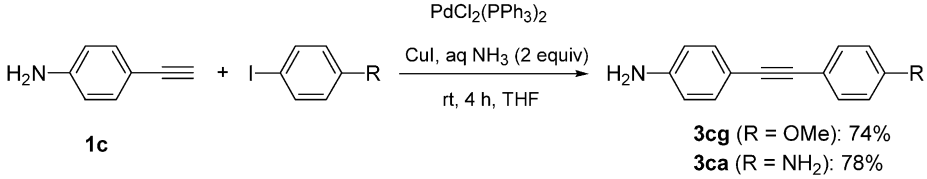
The Sonogashira coupling with aqueous ammonia was applied for the reaction of aryl alkynes **1** and aryl iodide bearing an azo group **4**. As summarized in Table 2, the reaction was found to take place smoothly. With **4a** bearing an *n*-heptyloxy group the coupling reaction of trimethylsilylethyne (**1b**) and (4-cyanophenyl)ethyne (**1d**) afforded the corresponding azotolanes **5ba** and **5da** in 87 and 79% yields, respectively. Worthy of note is that aryl iodide **4b**, which possesses a phenolic hydroxy group as well as an azo group, also undergoes the coupling reaction. Azotolanes bearing a hydroxy group **5bb**, **5eb**, and **5fb** can be converted into various ethers.[10] Subsequently, introduction of an alkyl group of different chain length would be applicable for the library of tail groups.

Scheme 3 represents that azotolanes can be synthesized with different pathways. Treatment of **4a** with **1g** with the palladium/copper catalyst system in the presence of aqueous ammonia afforded azotolane **5ga** in 87% yield after stirring at room temperature for 14 h. On the other hand, azo alkyne **1h** and aryl iodide **2h** also effected the reaction to furnish the identical product with that of the former reaction in 79% yield. These results show that the reaction with aqueous ammonia proceeds by employing terminal alkynes bearing an azo group as well as aryl halides.

It is also remarkable that sila-Sonogashira coupling,[11] which is the reaction of trimethylsilylalkyne with aryl triflate was found to take place. The reaction of **5ba** with 4-cyanobenzene triflate afforded **5da** in 81% yield with the Pd(0)/CuCl catalyst system in DMF at 80 °C (Scheme 4).

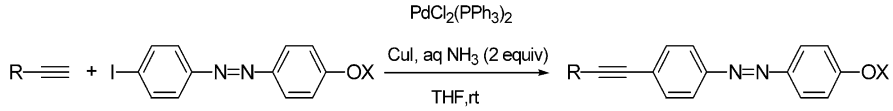
3. Conclusion

Coupling reactions of alkynes with aryl halides, in which an azo group is incorporated in the molecule, produce azotolanes in good to excellent yields. The reaction was also found to be applicable for substrates bearing a protic functional group such as NH_2 or OH on the aromatic ring.



Scheme 2.

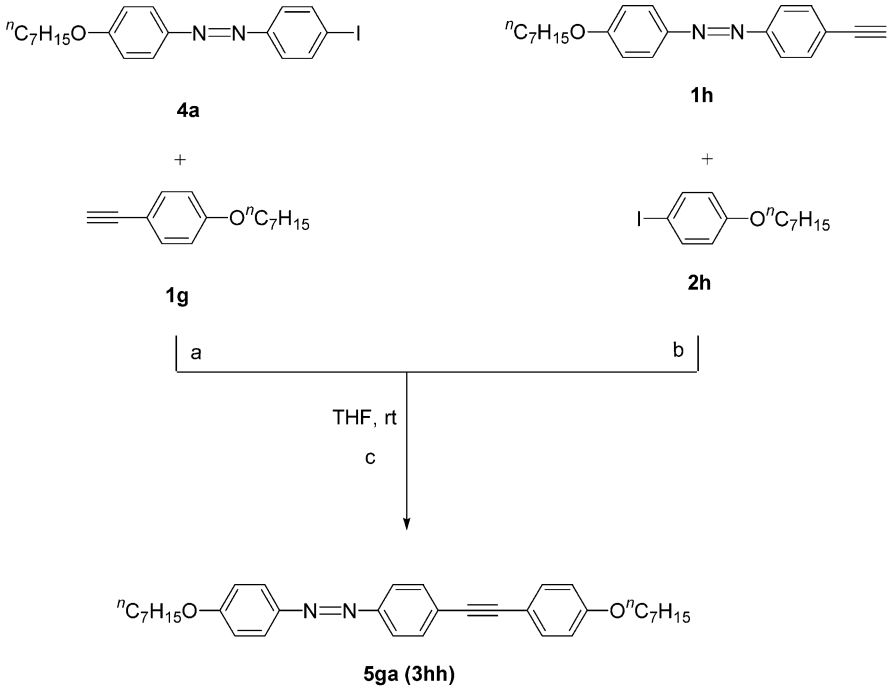
Table 2. Sonogashira coupling of aryl iodide bearing an azo group **4** with aqueous ammonia[a]



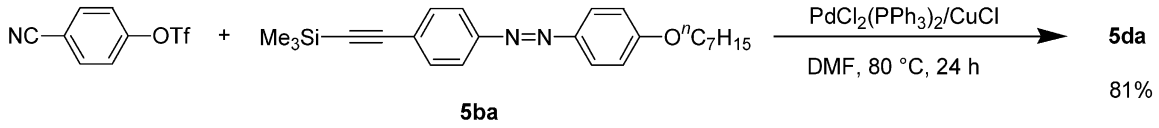
1 **4** **5**

Alkyne (R)	Iodide (X)	Time, h	**5**, %yield
1b (Me_3Si)	**4a** ($^nC_7H_{15}$)	5	**5ba**, 87
1d (4-NC–C_6H_4)	**4a**	16	**5da**, 79
1b	**4b** (H)	3	**5bb**, 90
1e (*t*-Bu)	**4b**	18	**5eb**, 76
1f ($^nC_6H_{13}$)	**4b**	24	**5fb**, 77

[a] The reaction was carried out with 0.5 mmol aryl halide, 0.6 mmol alkyne, and 1 mL of 0.5 M aq. NH_3 in the presence of 1 mol% of $PdCl_2(PPh_3)_2$, 2 mol% of CuI in THF at room temperature.



Scheme 3.



Scheme 4.

Since isolation and purification procedures for the reaction with aqueous ammonia are quite simple compared with those of conventional Sonogashira conditions, the reaction provides a practical azotolane synthesis that enables to design derivatives bearing a wide range of functional groups and alkyl groups with different chain length directed toward holographic materials of high performance.

4. Experimental

4.1. General

All reactions were performed under an atmosphere of argon using standard Schelnk tubes. Melting points were recorded using an Electrothermal melting point apparatus. Infrared

spectra were recorded on Shimadzu FT/IR-8100 spectrometer and presented in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 NMR spectrometer in $CDCl_3$. The ^1H (300 MHz) and ^{13}C (75 MHz) chemical shifts were referenced to residual $CHCl_3$ (δ 7.26 ppm) for ^1H and (77.0 ppm) for ^{13}C. High resolution mass spectra (HRMS) were recorded using JEOL JMS-700 (70 eV). Elemental analyses were carried out at the Elemental Analysis Center of Tokyo Institute of Technology using a Yanaco MT-5 CHN auto recorder and SX-Elements Micro Analyzer.

4.2. General method for the cross coupling of terminal alkynes with aryl halides bearing a protic functional group

To $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol), CuI (1.9 mg, 0.01 mmol), and **2** (0.5 mmol) in 3 mL of THF was added **1** (0.6 mmol) at room temperature. A 0.5 M solution of aqueous ammonia (2 mL, 1 mmol) was then added dropwise and stirring was continued for the period given in Table 1 at room temperature. Two phases of the resulting mixture were separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel (hexanes–ethyl acetate) to furnish the corresponding coupling product in good to excellent yields.

4.2.1. 4-(Phenylethynyl)aniline (3aa).[12] Purified by chromatography on silica gel (30:1 hexanes–ethyl acetate) afforded **3aa** in 88% yield (85 mg, 0.44 mmol).

The following coupling products were obtained in a manner described above: 2-(phenylethynyl)aniline (**3ab**),[13] 2-(phenylethynyl)phenol (**3ac**),[14] 4-(phenylethynyl)phenol (**3ad**),[15] 3-(phenylethynyl)aniline (**3ae**),[7b] 3-(phenylethynyl)-phenol (**3af**),[16] 4-(trimethylsilylethynyl)aniline (**3ba**),[17] 2-(trimethylsilylethynyl)aniline (**3bb**),[18] 2-(trimethylsilyl-ethynyl)phenol (**3bc**),[19] 4-(trimethylsilylethynyl)phenol (**3bd**).[20]

4.3. General procedure for Sonogashira-coupling reaction of 4-aminophenylethyne with aryl iodides

To $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol), CuI (1.9 mg, 0.01 mmol), and **2** (0.5 mmol) in 3 mL of THF was added 4-aminophenylethyne (**1c**) (63.5 mg, 0.5 mmol) at room temperature under an argon atmosphere. A 0.5 M solution of aqueous ammonia (2 mL, 1 mmol) was then added dropwise and stirring was continued for the period given in Scheme 2 at room temperature. Two phases of the resulting mixture were separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel (hexanes–ethyl acetate) to furnish the corresponding coupling product in good yield.

4.3.1. 4-(4-Methoxyphenylethynyl)aniline (3cg). Purified by flash chromatography on silica gel (50:1 hexanes–ethyl acetate) to afford 83 mg of **3cg** (74%) as a white solid. Mp 140–141 °C. IR (KBr) 3447, 3359, 3034, 3011, 2211, 1607 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 3.80–3.83 (br, 2H), 6.63 (d, $J=8.1$ Hz, 2H), 6.86 (d, $J=8.7$ Hz, 2H), 7.32 (d, $J=8.1$ Hz, 2H), 7.43 (d, $J=8.7$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 55.24, 87.11, 88.59, 112.96, 113.90, 114.75, 116.02, 132.74 (br), 146.36, 159.17. HRMS (EI) *m/z* Calcd for $C_{15}H_{13}NO$ 223.0997, found 223.0978.

The following coupling product was obtained in a manner described above: bis-(4-aminophenyl)ethyne (**3ca**).[21]

4.4. (4-Heptyloxyphenyl)-(4-iodophenyl)diazene (4a)

To a solution of KOH (2.94 mmol) and 4-iodoazophenol (1.47 mmol) in 4 mL DMSO was added 1-iodoheptane (2.2 mmol). The resulting mixture was then stirred for 2.5 h at room temperature. After the reaction was complete, the resulting mixture was extracted with chloroform (3× 15 mL) and the combined organic layer was dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography using (10:1 hexanes–ethyl acetate) to afford 551 mg of **4a** (93%) as an orange solid. Mp 112–113 °C. IR (KBr) 2953, 2857, 1605.0, 1584, 1559 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (t, $J=6.9$ Hz, 3H), 1.31–1.50 (m, 8H), 1.79–1.85 (m, 2H), 4.04 (t, $J=6.6$ Hz, 2H), 7.00 (d, $J=9.0$ Hz, 2H), 7.61 (d, $J=9.0$ Hz, 2H), 7.84 (d, $J=9.0$ Hz, 2H), 7.90 (d, $J=9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 14.09, 22.60, 25.95, 29.04, 29.16, 31.75, 68.38, 96.60, 114.75, 124.20, 124.96, 138.22, 146.60, 152.03, 162.05. HRMS (EI) *m/z* Calcd for $C_{14}H_{13}IN_2O$ 422.0855, found 422.0846.

4.5. General procedure for Sonogashira coupling of aryl iodide bearing an azobenzene moiety with aqueous ammonia

To $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol), CuI (1.9 mg, 0.01 mmol), and **4** (0.5 mmol) in 3 mL of THF was added **1** (0.6 mmol) at room temperature. A 0.5 M solution of aqueous ammonia (2 mL, 1 mmol) was then added dropwise and stirring was continued for the period given in Table 2 at room temperature. Two phases of the resulting mixture were separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel (hexanes–ethyl acetate) to furnish the corresponding coupling product in good to excellent yield.

4.5.1. (4-Heptyloxyphenyl)-{(4-trimethylsilylethynyl)-phenyl}diazene (5ba). Purified by chromatography on silica gel (20:1 hexanes–ethyl acetate) to furnish 170.8 mg of **5ba** (87%) as an orange solid. Mp 93–94 °C. IR (KBr) 2955, 2938, 2924, 2867, 2161, 1605, 1584 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.27 (s, 9H), 0.90 (t, $J=6.6$ Hz, 3H), 1.32–1.51 (m, 8H), 1.79–1.86 (m, 2H), 4.04 (t, $J=6.6$ Hz, 2H), 7.00 (d, $J=9.0$ Hz, 2H), 7.58 (d, $J=9.0$ Hz, 2H), 7.81 (d, $J=9.0$ Hz, 2H), 7.90 (d, $J=9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$) −0.08, 14.07, 22.59, 25.95, 29.03, 29.16, 31.75, 68.32, 96.49, 104.83, 114.69, 122.45, 124.89, 132.33, 132.72, 146.82, 152.07, 161.95. HRMS (EI) *m/z* Calcd for $C_{24}H_{32}N_2OSi$ 392.2284, found 392.2280.

4.5.2. 4-[4-(4-Heptyloxyphenylazo)phenylethynyl]benzo-nitrile (5da). Purified by chromatography on silica gel (5:1

hexanes–ethyl acetate) to furnish 110 mg of **5da** (79%) as an orange solid. Mp 171–172 °C. IR (KBr) 2940, 2872, 2855, 2226, 2213, 1601, 1580 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (t, $J=7.2$ Hz, 3H), 1.34–1.51 (m, 8H), 1.79–1.86 (m, 2H), 4.05 (t, $J=6.6$ Hz, 2H), 7.01 (d, $J=9.0$ Hz, 2H), 7.62–7.68 (m, 6H), 7.90 (d, $J=8.4$ Hz, 2H), 7.93 (d, $J=9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 14.06, 22.58, 25.94, 29.01, 29.14, 31.74, 68.39, 89.58, 93.59, 111.65, 114.76, 118.45, 122.69, 123.86, 125.00, 127.97, 132.05, 132.08, 132.60, 146.81, 152.48, 162.14. HRMS (EI) *m/z* Calcd for $C_{28}H_{27}N_3O$ 421.2154, found 421.2142.

4.5.3. 4-[(4-Trimethylsilylethynyl)phenylazo]phenol (5bb). Purified by chromatography on silica gel (10:1 hexanes–ethyl acetate) to furnish 132.4 mg of **5bb** (90%) as an orange solid. Mp 129–130 °C. IR (KBr) 3170 (br), 2957, 2155, 1603, 1593 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.27 (s, 9H), 5.27 (brs, 1H), 6.96 (d, $J=9.0$ Hz, 2H), 7.59 (d, $J=8.1$ Hz, 2H), 7.82 (d, $J=8.1$ Hz, 2H), 7.89 (d, $J=9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$) −0.10, 96.77, 104.77, 115.90, 122.48, 125.16, 132.78, 147.09, 151.91, 158.57. HRMS (EI) *m/z* Calcd for $C_{17}H_{18}N_2OSi$ 294.1188, found 294.1194.

4.5.4. 4-[4-(3,3-Dimethylbut-1-ynyl)phenylazo]phenol (5eb). Purified by chromatography on silica gel (10:1 hexanes–ethyl acetate) to furnish 107 mg of **5eb** (76%) as an orange solid. Mp 154–155 °C. IR (KBr) 3235 (br), 2967, 2929, 2865, 2234, 1593 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.34 (s, 9H), 5.18 (brs, 1H), 6.94 (d, $J=9.0$ Hz, 2H), 7.50 (d, $J=8.7$ Hz, 2H), 7.80 (d, $J=8.7$ Hz, 2H), 7.87 (d, $J=9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 28.08, 30.94, 79.05, 101.15, 115.91, 122.45, 125.02, 126.37, 132.32, 147.04, 151.32, 158.54. HRMS (EI) *m/z* Calcd for $C_{18}H_{18}N_2O$ 278.1419, found 278.1411.

4.5.5. 4-(4-Oct-1-ynylphenylazo)phenol (5fb). Purified by chromatography on silica gel (10:1 hexanes–ethyl acetate) to furnish 118 mg of **5fb** (77%) as an orange solid. Mp 103–104 °C. IR (KBr) 3320 (br), 2957, 2930, 2857, 2226, 1595 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.92 (t, $J=6.6$ Hz, 3H), 1.31–1.66 (m, 8H), 2.44 (t, $J=7.2$ Hz, 2H), 5.38 (brs, 1H), 6.94 (d, $J=8.7$ Hz, 2H), 7.51 (d, $J=8.7$ Hz, 2H), 7.81 (d, $J=8.7$ Hz, 2H), 7.88 (d, $J=8.7$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 14.03, 19.54, 22.52, 28.61 (br), 31.32, 80.55, 93.25, 115.91, 122.48, 125.04, 126.40, 132.31, 147.02, 151.33, 158.54. HRMS (EI) *m/z* Calcd for $C_{20}H_{22}N_2O$ 306.1732, found 306.1729.

4.5.6. (4-Heptyloxyphenylazo)-phenylethyne (1h). To a solution of **5bb** (196 mg, 0.5 mmol) in 3 mL methanol was added K_2CO_3 (26.6 mg, 0.19 mmol). The stirring was continued at room temperature for 40 min. The solvent was then evaporated under reduce pressure and the resulted crude sample subjected to aqueous workup and purified through flash chromatography (hexanes–ethyl acetat 10:1) afforded 134.5 mg of 1 h (84%) as a red solid. Mp 89 °C. IR (KBr) 3285, 2961, 2936, 2924, 2872, 2859, 1603, 1586 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.90 (t, $J=6.9$ Hz, 3H), 1.32–1.48 (m, 8H), 1.83 (quent, $J=8.4$ Hz, 2H), 3.21 (s, 1H), 4.05 (t, $J=6.6$ Hz, 2H), 7.00 (d, $J=9.0$ Hz, 2H), 7.61 (d, $J=8.4$ Hz, 2H), 7.84 (d, $J=8.4$ Hz, 2H), 7.91 (d, $J=9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 14.06, 22.59, 25.95, 29.03, 29.16, 31.75, 68.37, 79.04, 82.96, 114.72, 122.49, 122.61, 123.83, 124.94, 132.90, 146.80, 152.36, 162.02. HRMS (EI) *m/z* Calcd for $C_{21}H_{24}N_2O$ 320.1889, found 320.1892.

4.5.7. (4-Heptyloxyphenyl)-[4-(4-heptyloxyphenylethynyl)phenyl]diazene (5ga). Purified by chromatography on silica gel (20:1 hexanes–ethyl acetate) to furnish 110 mg of **5ga** (86%) as an orange solid. Mp 173–174 °C. IR (KBr) 2953, 2936, 2924, 2872, 2861, 2215, 1603, 1584 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (t, $J=6.6$ Hz, 6H), 1.25–1.51 (m, 16H), 1.74–1.87 (m, 4H), 3.98 (t, $J=6.6$ Hz, 2H), 4.04 (t, $J=6.6$ Hz, 2H), 6.88 (d, $J=9.0$ Hz, 2H), 7.0 (d, $J=9.0$ Hz, 2H), 7.48 (d, $J=8.4$ Hz, 2H), 7.62 (d, $J=8.4$ Hz, 2H), 7.86 (d, $J=9.0$ Hz, 2H), 7.91 (d, $J=9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 14.06, 22.60, 25.98, 29.04, 29.20, 31.77, 68.13, 68.41, 88.07, 91.84, 114.62, 114.76, 114.90, 122.61, 124.84, 125.67, 132.15, 133.13, 146.96, 151.79, 159.47, 161.91. Anal. Calcd for $C_{34}H_{42}N_2O_2$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.56; H, 8.23; N, 5.38.

4.6. Coupling of 5ba with 4-cyanobenzene triflate

To 25 mL Schlenk tube under argon atmosphere were added $PdCl_2(PPh_3)_2$ (17.5 mg, 0.025 mmol), CuCl (4.95 mg, 0.05 mmol), 4-cyanobenzene triflate (125.6 mg, 0.5 mmol), and **5ba** (196.3 mg, 0.5 mmol) in 3 mL of DMF at room temperature. The stirring was continued for 24 h in an oil bath at 80 °C. The resulting mixture was then cooled down and followed the general aqueous workup. The crude product was then purified by chromatography on silica gel (hexanes–ethyl acetate) to furnish 113 mg of **5da** (81%).

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Simple access to 2-methylalk-2-enoates and insect pheromones by zinc-promoted reduction of Baylis–Hillman-derived allylic bromides

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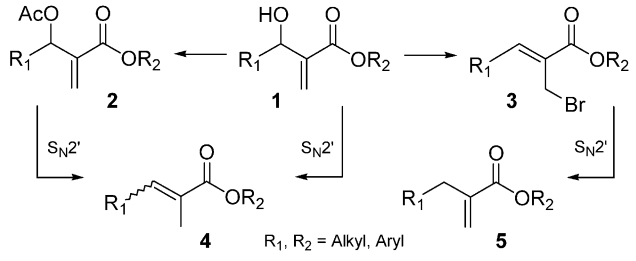
Abstract—(*E*)-2-Methylacrylates are prepared in good yield and high stereoselectivity by zinc-promoted reduction of 2-(bromomethyl) alkenoates derived from Baylis–Hillman adducts. Synthesis of the male ant pheromone (*E*)-2,4-dimethyl-2-hexenoic acid was performed using this simple methodology.

1. Introduction

Many natural products and biologically active compounds contain a trisubstituted alkene as a common structural motif.[1] The physiological properties of these natural substances are often remarkably dependent on the stereochemistry of the double bond.[2] Consequently, over the past decades, a great number of synthetic methodologies have been developed in order to create stereochemically defined trisubstituted olefins.[2–5] The required high control of selectivity, however, has been frequently associated with multi-step transformations and rather complex experimental protocols and reagents.

α-Methylene-β-hydroxy esters **1** are easily prepared by the popular Baylis–Hillman reaction[6] and are well-established as versatile building blocks for the stereoselective construction of natural products, including alkaloids,[7] macrolides,[8] terpenoids[9–11] and pheromones.[12–15] Multifunctional allylic compounds such as **1** and its derivatives **2** and **3** represent powerful scaffolds for the synthesis of trisubstituted olefins of structural complexity, providing that functionality is correctly modulated (Scheme 1). For instance, chemical reductions of **1** and **2** using metal hydrides[11,16–18] or a combination of palladium(II) and formic acid[19] proceed by a S_N2'-type mechanism involving double-bond migration to give the corresponding 2-methylalkenoates **4**. However, some disadvantages are associated with these reaction conditions, including the use of expensive reagents or moderate-to-low yields and double-bond stereoselectivity. Moreover, most methods are not suitable for substrates bearing β-aliphatic groups (R_1 = alkyl) which restrict their use in synthesis. While the reduction of (*Z*)-2-(bromomethyl)alkenoates **3** promoted by metal hydrides[11] can be performed under mild conditions,[20] such transformation also occurs by a related S_N2' mechanism, yielding α-methylenealkanoates **5** rather than the corresponding 2-methylalkenoates **4** (Scheme 1). Therefore, a stereoselective synthesis of (*E*)-2-methylalkenoates **4** by reduction of (*Z*)-2-(bromomethyl)alkenoates **3** should involve an alternative procedure wherein double-bond migration is avoided.

Allylic bromides can be reduced to the corresponding olefins by a number of methods, including simple and inexpensive reaction conditions employing metallic zinc in acidic medium.[21] However, reduction of allylic bromides **3** using zero-valent metals and related synthetic and mechanistic implications have not been reported to date. The need to develop a mild and efficient method to access trisubstituted olefins, together with our recent interest in



Scheme 1.

Keywords: Insect pheromones; Baylis–Hillman; Trisubstituted olefins; 2-Methylalkenoates; Reduction.
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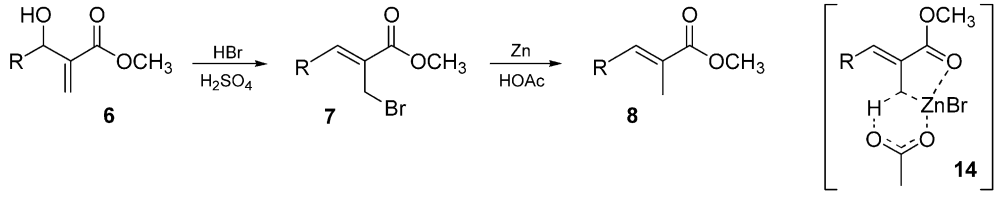
enzymatic resolution of α-methylene-β-hydroxy esters[22] and synthesis of aza-heterocycles[23] from the Baylis–Hillman reaction, motivated a search for a simple protocol for metal-promoted reduction of allylic bromides to olefins. This paper presents a versatile method for the preparation of (*E*)-2-methylacrylates **4** in good yield and high stereoselectivity by reduction of 2-(bromomethyl)alkenoates **3** with zinc–acetic acid. The synthesis of (*E*)-2,4-dimethyl-2-hexenoic acid, a caste-specific substance present in the mandibular glands of male ants in the genus *Camponotus*,[24] was carried out in order to illustrate the synthetic potential of this methodology.

2. Results and discussion

Baylis–Hillman adducts (**6a–f**) were obtained in good to moderate yield by the reaction of the corresponding aldehydes with methyl acrylate in the presence of a catalytic amount of DABCO according to the procedure described in the literature.[6,22] Subsequent transformation to (*Z*)-2-(bromomethyl)alk-2-enoates **7** was readily effected[25] by treating allylic alcohol **6** with a combination of 48% HBr and concentrated H_2SO_4 in CH_2Cl_2 at 0–5 °C (Scheme 2). The reaction shows good tolerance to functional groups and proceeds with clean allylic rearrangement and high stereoselectivity, producing representative bromomethylacrylates **7a–f** in high yield after a quick purification by filtration on a plug of silica gel. The anticipated[25] *Z*-stereochemistry assigned to bromomethylacrylates **7** was based on the characteristic shift of the β-olefinic hydrogen *cis* to the carboxyl group (*δ* 6.5–7.1 for β-alkyl and *δ* 7.5–8.0 for β-aryl, Table 1).[7,26]

Reduction of allylic bromides **7a–f** to the corresponding olefins by means of zinc in acidic medium[27] under different reaction conditions was then investigated. Accordingly, treatment of allylic bromides **7** with 2–4 equiv of zinc dust in dichloromethane for 30 min at ambient temperature followed by quenching with acetic acid provided 2-methyl-3-substituted acrylates **8** in very good yields (Scheme 2). The characteristic ^{1}H NMR downfield signals[26] for β-olefinic hydrogen at *δ* 6.5–7.85 and the appearance of a singlet at *δ* 1.8–2.2 due to the 2-methyl group are diagnostic for the formation of a 2-methyl-3-substituted propenoate with *E*-stereochemistry (Table 1). Piperonyl derivative **8c** (previously described as a thick oil)[16] was obtained as triclinic crystals after careful crystallization in ethyl ether and its structure was determined by X-ray crystallography, unequivocally confirming the expected stereochemistry (Fig. 1). 3-Aryl-2(bromomethyl)acrylates **7a–c**, as well as 3-alkyl derivatives **7e**,**f**, were cleanly reduced to the corresponding methyl acrylates **8**, and no other product was noted in the NMR spectrum of the crude reaction mixture. On the other hand, reaction of nitrophenyl derivative **7d** with Zn–AcOH was not selective, affording an aminophenyl propenoate due to over-reduction of the nitro group, as suggested by IR and NMR spectra. However, attempts to purify and characterize this unstable material were unsuccessful.

Solvent exerts a remarkable influence on the reduction of allylic bromides **7**, dichloromethane being superior by favouring cleaner reactions, while extensive formation of by-products is observed with ethyl ether, THF, or acetic acid. The amount of zinc used in the reaction is also important for a successful transformation. For instance, control experiments involving reduction of bromide **7e** with



Scheme 2.

Table 1. Yields[a] for compounds **7** and **8** and chemical shifts[b] for their β-vinylic hydrogen (*δ* H_β, ppm)

Structure	R	7		8		
		Yield (%)	*δ* H_β (ppm)	Yield with Zn (%)	Yield with Zn/Cu (%)	*δ* H_β (ppm)
A	Phenyl	85	7.79 (s)	80	80	7.69 (s)
B	2-Naphthyl	85	7.99 (s)	85	84	7.85 (m)[c]
C	Piperonyl	60	7.73 (s)	90	88	7.60 (s)
D	4-Nitrophenyl	65	7.83 (s)	(80)[d]	(80)[d]	
E	CH_3	70	7.08 (q)	85	85	6.85 (q)
F	$CH_3CH_2CH_2$	75	6.98 (t)	84	85	6.77 (t)
G	$CH_3CH_2(CH_3)CH$	75	6.75 (d)	88	86	6.53 (d)

[a] After purification by chromatography on silica gel.
[b] Acquired with a 200 MHz ^{1}H NMR spectrometer using $CDCl_3$ as solvent and 1–2% tetramethylsilane as reference.
[c] Expected singlet for H_β was covered by an aromatic multiplet. For detailed descriptions on coupling constant abbreviations and values please refer to Section 4.
[d] Methyl 3-(4-(aminophenyl)-2-methylpropenoate was obtained impure and could not be characterized.

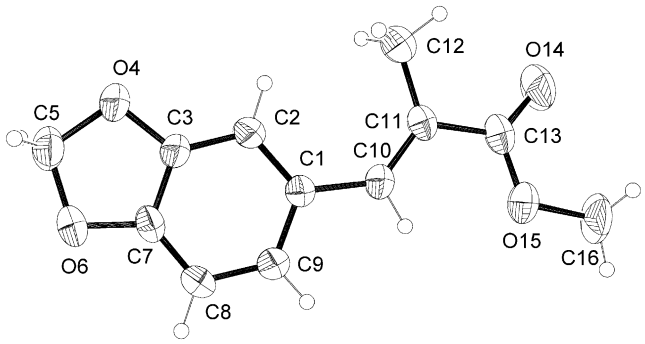
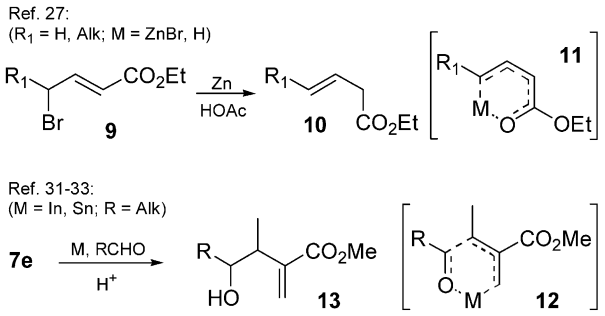


Figure 1. View of the structure of **8c** with labeling scheme and the ellipsoids with 40% of the probability level. Selected bond lenghts (Å) and angles (°): C3–O4 1.375(3), C5–O4 1.417(3), C5–O6 1.429(3), C7–O6 1.372(3), C10–C11 1.339(3), C11–C13 1.475(3), C11–C12 1.493(4), C13–O14 1.202(3), C13–O15 1.335(3), C16–O15 1.451(3), O4–C5–O6 108.1(2), C3–O4–C5 106.0(2), C7–O6–C5 105.77(19), C11–C10–C1 132.9(2), C10–C11–C13 118.7(2), C10–C11–C12 126.4(2), C13–C11–C12 114.9(2), O14–C13–O15 121.8(2), O14–C13–C11 124.0(3), O15–C13–C11 114.2(2), C13–O15–C16 117.6(2).

0.8 and 1.5 equiv of zinc dust under standard conditions resulted in low conversions to 2-methylbutenoate **8e** (42 and 75%, respectively). Consequently, typical reactions were carried out with 2–4 equiv of Zn in order to ensure complete conversions and high yields. The inefficiency of Mg or Sn to transform allylic bromides **7** into the corresponding 2-methylpropenoates **8** without promoting extensive side reactions further emphasizes the distinctive properties of zinc as the reducing agent. On the other hand, the Zn–Cu couple[28,29] presented nearly equivalent results under non-optimized conditions (Table 1). The order in which the reactants are added is also decisive to achieve high yields of **8**. Addition of HOAc to a mixture of **7**/Zn/CH_2Cl_2 was found to be the best condition, while treatment of **7e**/HOAc/CH_2Cl_2 with Zn or addition of **7e** over a Zn/HOAc/CH_2Cl_2 suspension resulted in very low conversions to **8e**. It is important to mention the unique ability of acetic acid to participate as an acidic quencher in this reaction, giving more homogeneous results in comparison to other proton sources tested (H_2O or aqueous NH_4Cl). Representative electrophiles such as aldehydes, acid chlorides, methyl acrylate and acetic anhydride failed to react under these conditions.

The exclusive formation of stereo-defined *E*-alkenes **8** from reduction of *Z*-allylic bromides **7** apparently occurs without involvement of the double bond and is undoubtedly the most striking feature of this transformation, not only because of its synthetic relevance but also from a mechanistic point of view. Related processes such as zinc reduction of representative allylic bromides[27] and metal-mediated coupling of 2-(bromomethyl)alkenoates with electrophiles[30–33] are known to proceed with double-bond shift to form rearranged alkenes (Scheme 3). In these cases, rearrangement might be explained by a direct participation of the allylic moiety in a concerted Transition State (TS). Reduction of 4-bromo-2-alkenoates **9** with Zn–HOAc yielded β,γ-unsaturated esters **10**,[27] probably by initial formation of a transient zinc enolate **11** (M=ZnBr) followed by *O*-protonation (M=H) and enol–keto tautomerization to the correspondent ester **10**.

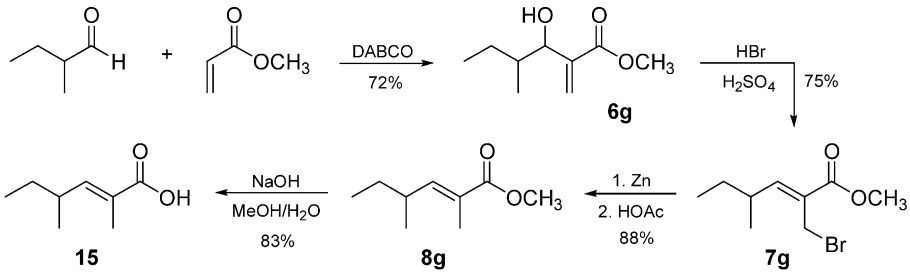


Scheme 3.

The In or Sn mediated allylic addition to aldehydes[31–33] possibly involves[34] a 6-member chelated TS **12** that gives 4-hydroxy-3-methyl-2-methylenealkanoates **13** after acidic quenching. A different scenario is proposed for the present reduction of 2-(bromomethyl)acrylates **7** with Zn–HOAc, in which a 6-membered TS (roughly represented by structure **14** in Scheme 2) is composed of acetic acid, zinc and the terminal carbon of the allylic framework. Therefore, the allyl system behaves as a primary carbanion, maintaining the stabilizing conjugation with the ester carbonyl and retaining the stereochemistry of the double bond. From the limited data available, it is difficult to ascertain whether these simplified models properly explain the details involved in this complex transformation or whether a more detailed mechanistic proposal should be formulated to rationalize the observed stereochemistry.

The simple conditions developed for zinc reduction of allylic bromides **7** and the high (*E*)-selectivity obtained for 2-methylacrylates **8** motivated further studies on the synthetic applicability of this method. (*E*)-2,4-dimethyl-2-hexenoic acid (**15**), an active substance found in the mandibular gland secretions of male ants in the genus *Camponotus*,[24] was selected as the synthetic target mainly due to the presence of a stereodefined (*E*)-geometry which is ultimately responsible for the observed biochemical signalling. Furthermore, the syntheses of **15** already reported are limited by the cost and stability of the reagents or involve multi-step processes with low overall yields and selectivity.[35–41]

Key methyl 3-hydroxy-4-methyl-2-methylenehexenoate (**6g**) was prepared through the Baylis–Hillman reaction of 2-methylbutyraldehyde with methyl acrylate under different conditions (Scheme 4). Reactions performed with catalytic amounts of DABCO (0.3–0.5 equiv) under typical conditions were very slow and furnished **6g** in low yield (45% after 20 days at ambient temperature), as expected for transformations involving an α-branched aldehyde.[6] Application of simple alternative modifications to accelerate the Baylis–Hillman reaction, including DABCO (at low temperatures,[42] with dioxane–water as the solvent,[43] with $Cu(OAc)_2$ as co-catalyst)[44] or aqueous trimethylamine (with or without ethanol as co-solvent)[45,46] as nucleophilic promoters, gave compound **6g** in only 30–50% yield after 15–20 days. However, using a moderate excess of DABCO (2–3 equiv) without any solvent resulted in a satisfactory formation of **6g** as a 1.5:1 inseparable mixture of *syn*/*anti* diastereoisomers (72% combined yield). The assignment of



Scheme 4.

syn (major) and *anti* (minor) stereochemistry in **6g** was based on the typical ^{1}H NMR chemical shifts and coupling constants of the methyne hydrogens[47] (H-3 and H-4, see Section 4).

No particular attempts to separate the diastereomeric mixture were undertaken at this point because the following step involving bromination with HBr–H_2SO_4 would lead to the loss of the stereogenic centre. Accordingly, hydroxy ester **6g** (*syn*/*anti* mixture) underwent smooth allylic rearrangement to 2-(bromomethyl)-4-methyl-2-hexenoate (**7g**), with the expected *Z*-stereochemistry, in 75% yield (Table 1). Subsequent reduction of **7g** with Zn (or Zn–Cu) in CH_2Cl_2 by the conditions outlined above for allylic bromides **7a–f** furnished methyl (*E*)-2,4-dimethyl-2-hexenoate (**8g**), which was hydrolysed[39] to give the target (*E*)-2,4-dimethyl-2-hexenoic acid (**15**) in high overall yield. Unfortunately, the asymmetric preparation of natural (*S*)-acid **15** from (*S*)-2-methylbutyraldehyde[41,48] by this route produced, after four steps, the expected acid **15** in low enantiomeric excess (up to 25%). This drawback is possibly associated with the very slow Baylis–Hillman reaction in the first step, wherein the aldehyde is partly racemized due to the prolonged exposure to DABCO.

3. Conclusion

In summary, (*E*)-α,β-unsaturated esters were prepared in three steps from inexpensive reagents, simple conditions, and good overall yields. β-Alkyl and β-aryl acrylates can be easily accessed by zinc promoted reduction of allylic bromides derived from widely available Baylis–Hillman adducts. This transformation occurs without allylic rearrangement to give reduced products with *E*-stereochemistry. Successful application of this methodology was exemplified by the synthesis of pheromone (*E*)-2,4-dimethyl-2-hexenoic acid (**15**) in four steps and ~40% overall yield. Further investigations dealing with the unusual reactivity of multifunctional allylic compounds and the synthesis of important targets such as insect pheromones and terpenoids are in progress.

4. Experimental

4.1. General considerations

All chemicals were of reagent grade and were used as received. Melting points were determined using a Microquímica MQPF301 apparatus and are uncorrected. Infrared spectra were acquired with a Perkin-Elmer FT-IR 1600 spectrometer using KBr for solids and film for liquid samples (range 4000–400 cm^{-1}). ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz, fully decoupled) spectra were recorded with a Bruker AC-200F spectrometer. Samples were prepared in $CDCl_3$ solution containing 1–2% tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in parts per million (δ) relative to TMS. Coupling constants (J) are measured in Hertz (Hz); coupling patterns are designated as s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); brs (broad singlet). X-ray analysis was carried out with an automatic diffractometer for monocrystals ENRAF NONIUS CAD-4. Elemental analyses were conducted in a CHN Perkin Elmer 2400 by UFSC-Central Analítica, Departamento de Química, Florianópolis, SC, Brazil. Purifications by column chromatography were performed with silica gel (Aldrich, 100–200 mesh particle size). Baylis–Hillman adducts **6a–f**,[6,22] and allylic bromides **7a**, **7d**,[25] **7e**,[8] **7f**,[11] were prepared according to the described methods.

4.2. General procedure for preparation of allylic bromides 7

To a stirred solution of the allylic alcohol **6** (2.5 mmol) in 1.0 mL of CH_2Cl_2 at 0–5 °C was carefully added 0.2 mL (13.3 mmol) of 48% HBr followed by 0.1 mL (6.6 mmol) of 96% H_2SO_4. After the addition is complete, the reaction was allowed to warm to 25 °C and stirring was continued for further 1–3 h. The final mixture was diluted with CH_2Cl_2, washed with H_2O, sat. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by chromatography (hexane/ethyl acetate 9:1) to give the corresponding methyl 2-(bromomethyl)-2-alkenoates **7**.

4.2.1. Methyl (*Z*)-2-(bromomethyl)-3-(2-naphthyl)-2-propenoate (7b). 3 h; clear yellow solid, 85% yield; mp = 88–89 °C; IR (KBr): ν_{max} 3038, 2996, 2848, 1718, 1616 cm^{-1}; ^{1}H NMR: δ 3.91 (s, 3H), 4.48 (s, 2H), 7.55 (m, 2H), 7.62–7.67 (m, 2H), 7.88 (m, 2H), 7.99 (s, 1H), 8.12 (s, 1H); ^{13}C NMR: δ 26.9, 52.4, 126.3–130.0 (7×*C*H), 131.6–133.4 (4×*C*), 143.0, 166.6 Anal. Calcd. for $C_{15}H_{13}BrO_2$ (%): C, 59.03; H, 4.29; Found: C, 59.16; H, 4.38.

4.2.2. Methyl (*Z*)-2-(bromomethyl)-3-(3,4-methylenedioxyphenyl)-2-propenoate (7c). 1 h; yellow solid, 60% yield; mp = 70–71 °C; IR (KBr): ν_{max} 3052, 2905, 1712, 1597, 1483, 1344, 1241, 1149, 1030 cm^{-1}; ^{1}H NMR: δ 3.87 (s, 3H), 4.25 (s, 2H), 6.04 (s, 2H), 6.90 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.5 Hz, 2H), 7.73 (s, 1H); ^{13}C NMR: δ 27.1,

52.3, 101.6, 108.7, 109.4, 125.5, 126.6, 128.1, 142.7, 148.2, 148.9, 166.7 Anal. Calcd. for $C_{12}H_{11}BrO_4$ (%): C, 48.18; H, 3.70; Found: C, 48.42; H, 3.96.

4.2.3. Methyl 3-hydroxy-4-methyl-2-methylene-2-hexenoate (6g). To a mixture containing 2.50 mL (28 mmol) of methyl acrylate and 0.51 mL (4.7 mmol) of 2-methylbutyraldehyde[41,48] at 25 °C was added 0.70 g (6.2 mmol) of DABCO. After stirring for 20 days at ambient temperature, the reaction mixture was diluted with CH_2Cl_2, washed with H_2O and 5% HCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by chromatography (hexane/ethyl acetate 95:5) to give 0.59 g of ester **6g** (clear oil) as an inseparable mixture of *syn*/*anti* isomers (1.5:1; 72% combined yield); IR (neat): ν_{max} 3462, 2964, 2934, 2878, 1718, 1628 cm^{-1}; ^1H NMR: δ 0.80–0.95 (m, 6H), 1.14 (m, 1.2H, *syn*), 1.43 (m, 0.8H, *anti*), 1.71 (m, 1H), 2.30 (d, J=6.5 Hz, 0.6H, *syn*, D_2O-exchange), 2.60 (d, J=8.0 Hz, 0.4H, *anti*, D_2O-exchange), 3.77 (s, 3H), 4.08 (t, J=8.0 Hz, 0.4H, *anti*), 4.30 (t, J=6.5 Hz, 0.6H, *syn*), 5.74 (s, 0.4H, *anti*), 5.79 (s, 0.6H, *syn*), 6.25 (s, 0.4H, *anti*), 6.28 (s, 0.6H, *syn*); ^{13}C NMR: **6g**-*syn* δ 12.2, 13.9, 27.1, 39.4, 52.5, 75.6, 126.3, 142.3, 167.7; **6g**-*anti* δ 11.9, 16.4, 24.9, 39.8, 52.4, 75.5, 127.0, 141.8, 167.7. Anal. Calcd. for $C_9H_{16}O_3$ (%): C, 62.77; H, 9.36; Found: C, 62.53; H, 9.52.

4.2.4. Methyl (*Z*)-2-(bromomethyl)-4-methyl-2-hexenoate (7g). Obtained as a clear yellow oil in 75% yield by brominating alcohol **6g** with HBr/H_2SO_4 for 12 h according to general procedure; IR (neat): ν_{max} 2962, 2930, 2874, 1722, 1642 cm^{-1}; ^1H NMR: δ 0.89 (t, J=7.5 Hz, 3H), 1.04 (d, J=6.5 Hz, 3H), 1.43 (m, 2H), 2.55 (m, 1H), 3.80 (s, 3H), 4.23 (s, 2H), 6.75 (d, J=11.0 Hz, 1H); ^{13}C NMR: δ 11.8, 19.1, 24.3, 29.1, 35.3, 52.0, 127.8, 153.4, 166.1. Anal. Calcd. for $C_9H_{15}BrO_2$ (%): C, 45.98; H, 6.43; Found: C, 46.26; H, 6.55.

4.3. Activation of Zn[49]

Zinc dust was previously treated with 10% aqueous HCl for 5 min, then the dark suspension was filtered, washed with water and acetone, and the collected solid was dried at 50–60 °C for 30 min and stored in desiccator.

4.4. Preparation of Zn–Cu couple using $CuCl_2$[28]

To a stirred suspension of zinc dust (6.5 g) in water (10 mL) was added a 0.15 M solution of $CuCl_2$ in 5% HCl (10 mL). After the evolution of gas ceased, the black solid formed was filtered by suction, washed thoroughly with H_2O and acetone, dried under vacuum at 25 °C and stored in a desiccator.

4.5. General procedure for reduction of allylic bromides 7 with Zn/HOAc

To a stirred solution of the allylic bromide **7a–g** (2.5 mmol) in 1.0 mL of CH_2Cl_2 at 25 °C was added 3–5 equiv of zinc dust[49] or Zn–Cu couple.[28,29] After stirring at 25 °C for 30 min the suspension was cooled with an ice-water bath and 1.0 mL of glacial acetic acid was added slowly. The cooling bath was removed, the final mixture was stirred for further 30 min and then filtered by suction, washing the collected solids thoroughly with H_2O and CH_2Cl_2. The organic phase was separated, washed with H_2O, sat. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by chromatography (hexane/ethyl acetate 9:1) to give the corresponding methyl 2-(bromomethyl)-2-alkenoates **8** (yields are given in Table 1). Esters **8a**,[17,50] **8e**,[50,51] **8f**[11,19] and **8g**[35,39] (clear oils) were previously described and gave spectral characteristics consistent with those reported.

4.5.1. Methyl (*E*)-2-methyl-3-(2-naphthyl)-2-propenoate (8b). Clear yellow solid; mp=55–56 °C; IR (KBr): ν_{max} 3038, 2996, 2848, 1699, 1616 cm^{-1}; ^1H NMR: δ 2.21 (s, 3H), 3.85 (s, 3H), 7.49 (m, 3H), 7.83–7.87 (m, 5H); ^{13}C NMR: δ 14.2, 52.0, 126.4, 126.7, 127.0, 127.6, 127.9, 128.3, 128.5, 129.3, 132.9, 133.0, 133.3, 138.9, 169.1. Anal. Calcd. for $C_{15}H_{14}O_2$ (%): C, 79.62; H, 6.23; Found: C, 79.79; H, 6.61.

4.5.2. Methyl (*E*)-3-(3,4-methylenedioxyphenyl)-2-methyl-2-propenoate (8c). Clear yellow solid; mp=71–72 °C (lit.[16] thick oil); IR (KBr): ν_{max} 2918, 1691, 1620, 1498, 1446, 1280, 1235 cm^{-1}; ^1H NMR: δ 2.12 (s, 3H), 3.80 (s, 3H), 6.00 (s, 2H), 6.81–6.93 (m, 3H), 7.60 (s, 1H); ^{13}C NMR: δ 14.0, 51.8, 101.2, 108.2, 109.4, 124.5, 126.5, 129.8, 138.5, 147.6 (2×*C*), 169.0. Anal. Calcd. for $C_{12}H_{12}O_4$ (%): C, 65.44; H, 5.49; Found: C, 65.19; H, 5.50.

4.6. (*S*)-(*E*)-2,4-Dimethyl-2-hexenoic acid (15)

A mixture containing 0.20 g (1.28 mmol) of methyl (*E*)-2,4-dimethyl-2-hexenoate (**8g**) and 0.20 g (5.0 mmol) of NaOH in 3.0 mL of MeOH was stirred for 12 h at 25 °C. The reaction was then diluted with H_2O and extracted with ethyl ether. The aqueous phase was acidified to pH 1–2 with 10% HCl and extracted twice with ethyl ether. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a colorless oil[35–41] (0.15 g, 83% yield); IR (neat): ν_{max} 3290–2600, 2964, 2929, 2875, 1685, 1641 cm^{-1}; ^1H NMR: δ 0.86 (t, J=7.5 Hz, 3H), 1.01 (d, J=6.5 Hz, 3H), 1.33 (m, 2H), 1.80 (s, 3H), 2.44 (m, 1H), 6.71 (d, J=10.0 Hz, 1H), 10.1 (brs, 1H). Anal. Calcd. for $C_8H_{14}O_2$ (%): C, 67.57; H, 9.92; Found: C, 67.72; H, 10.08.

4.7. Crystal data for 8c

$C_{12}H_{12}O_4$, FW 220.22, Monoclinic, space group $C2/c$, a=14.526(3), b=6.5167(13), c=23.570(5) Å, β=104.77(3)°, Z=8, D_{calc}=1.356 g/cm^3, μ=0.102 mm^{-1}, $F(000)$ 928, 145 refined parameters, R_1=0.0448, wR_2=0.1034 for 1037 observed reflections [$I>2\sigma(I)$] and R_1=0.1121, wR_2=0.1253 for 1887 unique reflections. Intensity data collection was performed with graphite monochromatized Mo Kα radiation (λ=71073 Å) on an Enraf-Nonius CAD4 diffractometer, at ambient temperature. Cell parameters were determined from 25 centered reflections in the θ range 3.70–12.03° using a standard procedure.[52a] All data were corrected for Lorentz, polarization effects.[52b] The structure was solved with SIR97[52c] and refined by full-matrix least-square methods on F^2 using SHELXL97 program.[52d] All

non-H atoms were refined anisotropically and H atoms were placed in the atom list using standard geometric criteria. The thermal ellipsoid plot was performed with ORTEP3 program.[52e]

4.8. Supplementary material

Crystallographic data (atomic coordinates and equivalent isotropic displacement parameters, calculated hydrogen atom parameters, anisotropic thermal parameters and bond lengths and angles) for the structure presented here have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 239498. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.08.018

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New norditerpenoids and a diterpenoid from a sponge that inhibit the lyase activity of DNA polymerase β

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Abstract—Using an assay to detect inhibitors of the lyase activity of DNA polymerase β, bioassay-directed fractionation of a $CHCl_3$ extract of an unidentified sponge of the family Demospongiae resulted in the isolation of the new diterpenoid **1**, the new bis-norditerpenoids **2–3**, and the two known compounds spongia-13(16),14-dien-19-oic acid (**4**), and methylspongia-13(16),14-dien-19-oate (**5**). The structures of the new compounds were established on the basis of extensive 1D and 2D NMR spectroscopic interpretation. All five compounds inhibited the lyase activity of DNA polymerase β.

1. Introduction

In addition to its polymerization activity, the DNA repair enzyme DNA polymerase β (pol β) also has an intrinsic deoxyribose phosphate (dRP) lyase activity which is important to its repair function.[1,2] This second activity constitutes a second target for the discovery of potential anticancer agents, since inhibitors of the lyase activity of pol β should also potentiate the cytotoxicity of DNA-damaging agents. It has already been shown by one of our groups that naturally occurring inhibitors of the polymerization activity of pol β can be found in Nature,[3] and it is thus reasonable to suppose that specific inhibitors of the lyase activity may also exist in Nature. We thus elected to begin a search for naturally occurring inhibitors of pol β lyase as a part of our continuing research to identify novel naturally occurring anticancer agents.[4,5] The assay system used for this purpose has been described previously.[6]

An extract of an unidentified sponge species of the order Dictyoceratida was selected for bioassay-guided fractionation on the basis of its strong activity at 16.2 μg/mL in the pol β lyase assay. Previous studies of sponge species of the order Dictyoceratida have resulted in the isolation of various diterpenoids.[7] Bioassay results for the initial liquid–liquid partition of the crude extract of the sponge indicated that the activity was concentrated in the $CHCl_3$-soluble fraction of a $CHCl_3$/aqueous MeOH partition. The $CHCl_3$-soluble fraction was further separated by chromatography over MCI gel, followed by reversed-phase PTLC and normal phase HPLC to yield the new diterpenoid **1**, the new bis-norditerpenoids **2–3**, and the two known compounds **4–5**. The two known compounds were identified as spongia-13(16),14-dien-19-oic acid (**4**), and methyl spongia-13(16),14-dien-19-oate (**5**) by comparison of their spectroscopic data with literature values.[8,9] Since the ^{13}C NMR spectral data for the known compound methyl spongia-13(16),14-dien-19-oate (**5**) have not been reported in the literature, the chemical shift values were determined on the basis of HMQC and HMBC spectral data and are given in Table 2.

2. Results and discussion

Compound **1** was obtained as an optically active viscous liquid and was shown to have the molecular formula $C_{22}H_{32}O_3$ by HRFABMS, ^{13}C NMR, and APT (Attached Proton Test) spectral data. The mass fragment observed in its EIMS at *m/z* 284 formed by the loss of an AcOH molecule from the molecular ion indicated the presence of an acetoxy group in its structure, which was supported by the absorption band observed at 1723 cm^{-1} in its IR spectrum. The ^1H NMR spectrum showed the presence of three methyl singlets at δ 0.88, 0.97, and 1.19; two broad singlets at δ 7.04 and 7.07, characteristic for the

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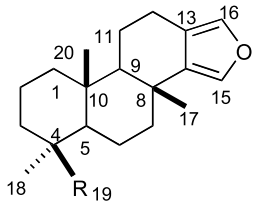
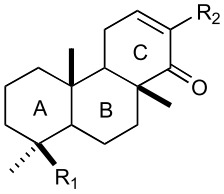
β,β-disubstituted furan moiety;[8] a primary acetate group [δ 4.21 (1H, d, J=10.7 Hz), 3.93 (1H, d, J=10.7 Hz), and 2.04 (s, 3H)]; seven methylenes and two methines between δ 0.88 and 2.74 (Table 1).





1 R = CH_2OAc
4 R = COOH
5 R = $COOCH_3$
6 R = CH_2OH

2 R_1 = $COOCH_3$, R_2 = OH
3 R_1 = COOH, R_2 = OH
7 R_1 = $COOCH_3$, R_2 = OAc

The ^{13}C NMR values for all 22 carbons were assigned on the basis of APT, HMQC and HMBC spectral data (Table 2), which indicated the presence of four sp^3 methyls, eight sp^3 methylenes, two sp^3 methines, three sp^3 quaternary carbons, two sp^2 methine carbons, two sp^2 quaternary carbons, one ester carbonyl group. A search of the literature indicated that the ^1H NMR spectral data of **1** were similar to those of **6**, an alcohol derivative of spongia-13(16),14-diene formed by the reduction of methyl spongia-13(16),14-dien-19-oate (**5**).[8] The only significant difference is the presence an additional primary acetate group in **1**. The basic skeleton of a spongia-13(16),14-diene system in **1** was supported by several key COSY correlations (H-1/H-2; H-2/H-3; H-5/H-6; H-6/H-7; H-9/H-11; H-11/H-12) and HMBC (H-1/C-2, C-3, C-5, C-10; H-5/C-4, C-10, C-18, C-19, C-20; H-7/C-5, C-6, C-8; H-9/C-8, C-10, C-11, C-12; H-15/C-8, C-13, C-14; H-16/C-12, C-13, C-14). In the absence of any other assignable oxygenated carbons, the primary acetate group has been assigned to the C-19 position as in **6**; this was supported by the HMBC correlations H-19/C-4, C-5, C-18, $OCOCH_3$, H-18/C-4, C-5, C-19 and H-5/C-4, C-18, C-19. Since the ^{13}C NMR spectral data for **6** have not been reported in the literature, the carbon values were assigned on the basis of comparison with the ^{13}C NMR values of compounds **1** and **4** and are given in Table 2. The stereochemistry of **1** was considered to be similar to **4** and **6**, on the basis of the almost identical ^{13}C NMR values of their respective carbons, and chemical modification studies of compounds **1** and **5**. Thus, hydrolysis of **1** with 5% methanolic NaOH, and reduction of **5** with LAH furnished the identical known compound **6**, confirming the stereochemistry of **1** as that of compounds **4**–**6**. The structure was further supported by the HMBC correlations shown in Figure 1. On the basis of the above spectral and chemical evidence, **1** was assigned as 19-acetoxyspongia-13(16),14-diene.

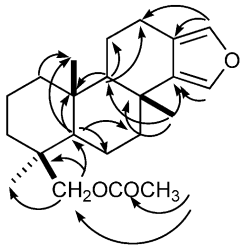


Figure 1. Selected HMBC correlations of **1**.

Compound **2** possesses the molecular formula $C_{19}H_{28}O_4$ based on the number of carbon atoms deduced from its ^{13}C NMR spectrum and HRFABMS, suggesting 6° of unsaturation. The ^1H NMR spectrum of **2** showed the presence of three methyl singlets at δ 0.81, 1.11, and 1.19; an olefinic proton as a multiplet centered at δ 6.06, a methoxy singlet at δ 3.63, a hydroxyl singlet at δ 5.85, and six methylenes and two methines between δ 0.94 and 2.31. The ^{13}C NMR spectrum coupled with APT, HMQC and HMBC spectral data indicated the presence of four sp^3 methyls, six sp^3 methylenes, two sp^3 methines, three sp^3 quaternary carbons, one sp^2 methine carbon, one sp^2 quaternary carbon, and two carbonyl groups. A close comparison of the ^{13}C NMR values of **2** with those of **5** suggested their almost identical value in the ring A, suggesting the presence of a $-COOCH_3$ group at C-19 position. The similar nature of **2** and **5** in ring A was supported by COSY (H-1/H-2; H-2/H-3) and HMBC

Table 1. ^1H NMR data for compounds **1**–**3** ($CDCl_3$)[a]

Position	1	2	3
1	1.72 m, 1.41 m	1.74 m, 1.40 m	1.76 m, 1.46 m
2	1.56 m, 0.98 m	1.56 m, 1.03 m	1.56 m, 1.06 m
3	1.76 m, 0.95 m	1.86 m, 1.01 m	1.92 m, 1.03 m
5	1.07 m	1.06 m	1.05 m
6	1.78 m, 0.88 m	1.92 m, 0.94 m	1.93 m, 0.87 m
7	1.73 m, 1.52 m	2.07 td 13.6, 4.8, 1.48 m	2.06 td 13.4, 4.6, 1.52 m
9	1.22 m	2.14 m	2.17 m
11	2.44 m, 1.48 m	2.31 m, 1.92 m	2.31 m, 1.72 m
12	2.74 dd 16.6, 6.1, 1.76 m	6.06 m	6.07 m
15	7.07 br s		
16	7.04 br s		
17	1.19 s	1.18 s	1.21 s
18	0.97 s		
19	4.21 d 10.7, 3.93 d 10.7	1.11 s	1.12 s
20	0.88 s	0.81 s	0.91 s
OCOMe	2.04 s		
COOMe		3.63 s	
13-OH		5.85	5.87

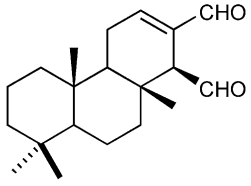
[a] Assignments made on the basis of COSY, HMQC, and HMBC spectral data and in comparison with literature data.[8,9]

Table 2. ^{13}C NMR data for compounds **1–3**, **5–6** ($CDCl_3$)[a]

Carbon	1	2	3	5	6
1	36.5	38.2	37.8	38.2	35.8
2	18.3	18.9	18.9	18.4	18.3
3	41.5	39.8	39.7	41.1	41.6
4	37.5	43.8	43.7	44.0	37.6
5	56.5	56.4	56.4	55.7	56.6
6	18.2	21.0	21.0	20.8	18.2
7	40.0	34.5	34.6	40.3	40.2
8	34.5	44.6	44.7	34.3	34.4
9	57.4	53.6	53.7	57.4	57.5
10	38.8	37.9	38.4	38.0	38.8
11	19.1	19.5	19.5	19.2	19.2
12	20.8	116.6	116.6	20.4	20.8
13	119.8	144.6	144.6	119.8	119.7
14	137.5	201.9	201.9	137.6	137.6
15	135.2			135.1	135.1
16	136.9			136.9	136.8
17	26.2	18.2	18.3	25.9	26.3
18	27.5	28.7	28.8	28.8	27.0
19	67.2	177.7	182.2	178.0	65.6
20	16.8	14.6	14.8	13.9	16.9
O*CO*Me	167.9				
OCO*Me*	21.1				
OCH_3		51.4		51.2	

[a] Assignments made on the basis of COSY, HMQC, and HMBC spectral data and in comparison with literature data.[9]

(H-1/C-2, C-3, C-5, C-10; H-3/C-4, C-18, C-19) correlations. Further, from Table 1, it was observed that the β,β-disubstituted furan moiety observed in **1** and **4–5** was absent in **2**. Assuming a $COOCH_3$ group, a trisubstituted double bond, and a carbonyl group were present, the structure of compound **2** had to have a tricyclic ring system. A search in the literature revealed that diterpenes belonging to the class of *ent*-isocopalanes containing a tricyclic ring system were reported from the sponges of the order Dictyoceratida,[10] which were considered as precursors of spongian diterpenoids. A comparison of the ^1H and ^{13}C NMR values of **2** with those of **5** and of *ent*-isocopal-12-en-15,16-dial (**8**)[10] indicated that compound **2** was identical to **5** in rings A and B and to **8** in ring B, suggesting the presence of a $COOCH_3$ group in ring A. From the molecular formula and the presence of a $COOCH_3$ group, **2** had to have a dinor *ent*-isocopalane skeleton. The presence of the trisubstituted olefinic group, the hydroxy group, and the carbonyl group in the C-ring were assigned at C-12/C-13, C-13, and C-14, respectively, on the basis of the key HMBC correlations: H-9/C-11, C-12; H-12/C-11, C-13, C-14; 13-OH/C-12, C-13, C-14 and H-17/C-8, C-13, C-14. The ^{13}C NMR values for all the carbons were assigned on the basis of HMQC and HMBC spectral and in comparison with **5** and are given in Table 2. Further, the peak observed at δ 5.85 in **2** disappeared after acetylation with Ac_2O/pyridine, which furnished a monoacetate **7**. The stereochemistry at the chiral centers in **2** was established on the basis of ^{13}C NMR values as well as 1D and 2D NOESY studies. The ^{13}C NMR values of **2** in ring A were almost identical to those of **5** suggesting the relative orientation of $COOCH_3$ group at C-19 position. The NOESY spectrum of **2** showed a cross peak between H-18/H-5 suggesting that their relative orientation is as in **5** and **8**. Irradiation of the C-17 methyl group increased the intensity of the C-20 methyl group, whereas irradiation of the C-18 methyl group increased the intensity of the C-5 methine proton. From the above spectral analysis, the stereochemistry at the chiral centers in **2** was considered to be the same as that of **5** and **8**. The structure was supported by the HMBC correlations as shown in Figure 2. Thus, **2** was deduced to be methyl-*ent*-15,16-dinorisocopal-12-en-13-ol-19-oate.



8

The molecular formula of **3** was derived as $C_{18}H_{26}O_4$ on the basis of HRFABMS and ^{13}C NMR spectral data. A comparison of the ^1H and ^{13}C NMR spectral data of **3** with those of **2** (Tables 1 and 2) suggested the identical nature of the two compounds, except for the absence of the methoxyl singlet. From the HRFABMS, the molecular ion was 14 mass units less than that of **2**. The absence of the methoxy singlet and the lesser molecular mass suggested the presence of a carboxylic acid at C-19 position in **3**. Further, methylation of **3** with CH_2N_2 furnished **2**, confirming its structure and stereochemistry. On the basis of above

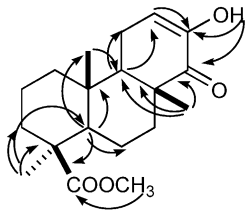


Figure 2. Selected HMBC correlations of **2**.

Table 3. IC_{50} of polymerase β lyase inhibition of compounds isolated from sponge species[a]

Compound	IC_{50} (μM)
1	26.0
2	20.6
3	23.9
4	27.1
5	15.2

[a] Data are the mean of three determinations.

spectral and chemical studies, the structure of **3** was established as *ent*-15,16-dinorisocopal-12-en-13-ol-19-oic acid.

All the isolated compounds were tested for inhibition of DNA polymerase β lyase activity. In Table 3, it is shown that compounds **1**–**5** were all active with IC_{50} values ranging from 15.2 to 27.1 μM, methylspongia-13(16),14-dien-19-oic acid (**5**) having the greatest activity.

3. Experimental

3.1. General experimental procedures

Melting points were recorded with an Thermolyne microscopic apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. IR ($CHCl_3$) and UV (MeOH) spectra were measured on MIDAC M-series FTIR and Shimadzu UV-1201 spectrophotometers, respectively. NMR spectra were obtained on a JEOL Eclipse 500 spectrometer. The HRFABMS were obtained on a JEOL HX-110 instrument. The chemical shifts are given in ppm (δ) with TMS (tetramethylsilane) as an internal reference and coupling constants (J) in Hz.

3.2. Polymerase β lyase bioassay

The assay was performed as previously reported.[6]

3.3. Marine material

The sponge species (Phylum: Porifera, Class: Demospongiae, Order: Dictyoceratida) was collected in Papua New Guinea off the island of Rabaul at 26 m depth on October 11, 1991. The voucher specimen Q66C6047 is deposited at the Queensland Museum in Brisbane, Australia, and photographs of the sponge collection (16047) are available as supporting data. The deep frozen sponge was pulverized at the National Cancer Institute in dry ice by use of a worm-fed grinder (hamburger mill), the powder produced was allowed to stand at −30 °C until the CO_2 sublimed, and the mass was then extracted at 4 °C with de-ionized water (1 L) by stirring (30 rpm) for 30 min. The mixture was centrifuged at RT and the supernatant lyophilized to give the aqueous extract. The insoluble portion from the centrifugation was lyophilized and then statically extracted overnight at RT with 1 L of a 1:1 ratio of MeOH:CH_2Cl_2. The organic phase was filtered off, the pellet washed with a 10% volume of fresh MeOH, and the combined organic phases reduced to dryness at <35 °C by rotary evaporation and then finally dried under high vacuum at RT to give the organic extract as a gum. An extract of this sponge was received from the National Cancer Institute as sample number C009129 (1.0 g).

3.4. Isolation of compounds

The crude extract (0.10 g) was suspended in aqueous MeOH (MeOH–H_2O, 9:1, 50 mL) and extracted with three 50-mL portions of *n*-hexane. The aqueous layer was then diluted to 70% MeOH (v/v) with H_2O and extracted with three 50-mL portions of $CHCl_3$. The $CHCl_3$ extract was found to be more active (0.075 g), and was fractionated over MCI gel using MeOH–H_2O (50:50 → 100:0) to furnish five active fractions (A–E). Fraction A on crystallization yielded the known diterpene spongia-13(16),14-dien-19-oic acid (**4**, 18.5 mg). Fraction B on reversed-phase preparative TLC (MeOH–H_2O, 95:5) afforded **4** (13.8 mg). Fraction C on reversed-phase preparative TLC (MeOH–H_2O, 95:5) yielded the two known diterpenes **4** (3.2 mg) and **5** (4.4 mg). Fractions D on normal phase HPLC with mobile phase $CHCl_3$–MeOH (96:4) furnished the known diterpene **5** (3.4 mg) and the two new diterpenes **1** (3.4 mg) and **2** (2.6 mg). Similarly, fraction E on normal phase HPLC with mobile phase $CHCl_3$–MeOH (100:1) furnished the new diterpene **3** (3.2 mg). The two known compounds **4**–**5** were identified by comparison of their spectral data with literature values.

3.4.1. 19-Acetoxyspongia-13(16),14-diene (1). Colorless viscous liquid; $[\alpha]_D^{25} = -21.6°$ (c 0.0043, $CHCl_3$); UV (MeOH) λ_{max} 204 nm (ε 12,860); IR ($CHCl_3$) ν_{max} 2960, 1723, 1450, 1325, 1125, 1065, 825 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS m/z (rel int.) 344 [M^+] (6), 285 (46), 284 (100), 240 (15), 235 (10), 226 (32), 201 (100), 164 (13), 147 (28), 134 (12), 91 (46); HRFABMS m/z 344.2362 $[M]^+$ (calcd for $C_{22}H_{32}O_3$, 344.2351).

3.4.2. Alkaline hydrolysis of 1. Compound **1** (1.5 mg) was heated at reflux with 5% methanolic NaOH (3 mL) for 1 h. The reaction mixture was treated with 10 mL of H_2O and extracted with three 10-mL portions of $CHCl_3$. The residue obtained after evaporation of the solvent was separated by reversed-phase preparative TLC (MeOH–H_2O, 90:10) affording **6** (0.8 mg).[8]

3.4.3. Reduction of 5. Compound **5** (2.0 mg) in anhydrous diethyl ether (3 ml) was treated with $LiAlH_4$ (15 mg) at room temperature for 18 h. Filtration of the reaction mixture and evaporation of the solvent furnished a residue (1.6 mg), which on purification using reversed-phase preparative TLC (MeOH–H_2O, 85:15) furnished **6** (1.2 mg).[8]

3.4.4. Methyl-*ent*-15,16-dinorisocopal-12-en-13-ol-19-oate (2). Colorless viscous liquid; $[\alpha]_D^{25} = -15.2°$ (c 0.0062, $CHCl_3$); UV (MeOH) λ_{max} 207 (ε 11,640), 265 (ε 11,640) nm; IR ($CHCl_3$) ν_{max} 3450, 2945, 1715, 1445, 1315, 1115, 1052, 820 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; HRFABMS m/z 321.2063 $[M+H]^+$ (calcd for $C_{19}H_{29}O_4$, 321.2066).

3.4.5. Acetylation of 2. Compound **2** (1.5 mg) was dissolved in pyridine (0.2 mL) and acetic anhydride (0.2 mL) and the solution was stirred for 16 h at room

temperature. The product was dried under vacuum and the residue obtained was purified over reversed-phase preparative TLC (MeOH–H_2O, 90:10) to furnish **7** (0.6 mg) as a colorless liquid: $[\alpha]_D^{25} = -11.4°$ (*c* 0.0028, $CHCl_3$); ^1H NMR δ ppm (Hz) $CDCl_3$: 6.45 (^1H, m, H-12), 3.64 (3H, s, $COOCH_3$), 2.19 (3H, s, $OCOCH_3$), 1.18 (3H, s, 17-CH_3), 1.15 (3H, s, 18-CH_3), 0.82 (3H, s, 20-CH_3); HRFABMS *m/z* 363.2160 $[M+H]^+$ (calcd for $C_{21}H_{31}O_5$, 363.2171).

3.4.6. *ent*-15,16-Dinorisocopal-12-en-13-ol-19-oic acid (3). Colorless viscous liquid; $[\alpha]_D^{25} = -31.8°$ (*c* 0.0054, $CHCl_3$); UV (MeOH) λ_{max} 205 (ε 12,240), 266 (ε 10,820) nm; IR ($CHCl_3$) ν_{max} 2950, 1703, 1450, 1325, 1120, 1055, 815 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; HRFABMS *m/z* 307.1902 $[M+H]^+$ (calcd for $C_{18}H_{27}O_4$, 307.1909).

3.4.7. Methylation of 3. To compound **3** (1.2 mg) in diethyl ether (2 mL) was added an excess of freshly prepared diazomethane in diethyl ether and the mixture was kept at 0 °C for 12 h. Concentration of the reaction mixture under vacuum and purification of the residue using reversed-phase preparative TLC (MeOH–H_2O, 95:5) furnished **2** (0.5 mg).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.08.017

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Synthesis of (3′*R*,5′*S*)-3′-hydroxycotinine using 1,3-dipolar cycloaddition of a nitrone

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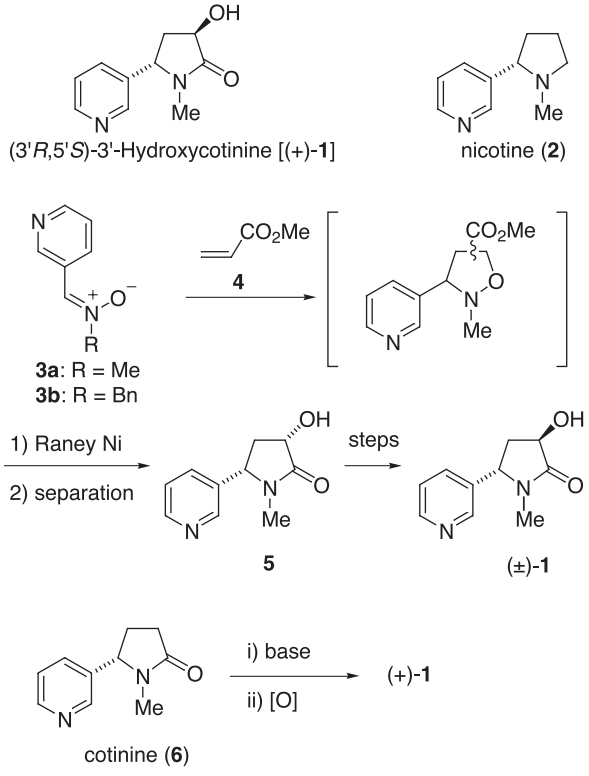
Abstract—To synthesize (3′*R*,5′*S*)-3′-hydroxycotinine [(+)-**1**], the main metabolite of nicotine (**2**), cycloaddition of *C*-(3-pyridyl)nitrones **3a**, **3c**, and **15** with (2*R*)- and (2*S*)-*N*-(acryloyl)bornane-10,2-sultam [(2*R*)- and (2*S*)-**8**] was examined. Among them, L-gulose-derived nitrone **15** underwent stereoselective cycloaddition with (2*S*)-**8** to afford cycloadduct **16**, which was elaborated to (+)-**1**.

1. Introduction

(3′*R*,5′*S*)-3′-Hydroxycotinine [(+)-**1**], which is found in urine of smokers, is one of the main metabolites of nicotine (**2**).[1] Compound (+)-**1** is an important tool for the investigations of the metabolism of nicotine, drug interaction in smokers, and for drug discovery, and many efforts have therefore been made to synthesize (±)-**1** and (+)-**1**, and their derivatives (Scheme 1).[1,2] In 1972, Dagne reported the synthesis of (±)-**1** and revealed that (+)-**1** bears *trans*-stereochemistry.[2a] The synthesis commenced with cycloaddition of nitrone **3a** with methyl acrylate (**4**), which produced a regio- and stereoisomeric mixture of cycloadducts. Hydrogenolysis of the mixture with Raney nickel followed by separation of isomers gave *cis*-hydroxycotinine (**5**), which was elaborated to (±)-**1** in two steps including a Mitsunobu reaction. Since the early 1990s, (3′*R*,5′*S*)-3′-hydroxycotine [(+)-**1**] has been synthesized by using oxidation of natural cotinine (**6**).[2b–e]

Recently, Tejero and co-workers reported reactions of *N*-benzyl-*C*-arylnitrones **7a** and **7b** with (2*R*)-*N*-(acryloyl)-bornane-10,2-sultam [(2*R*)-**8**] (Scheme 2).[3] Thus, *N*-benzyl-*C*-(2-thiazolidinyl)nitrone (**7a**) reacts with (2*R*)-**8** to give only *endo*-addition products **9a** and **10a** with moderate diastereofacial selectivity (78:22) referred to (2*R*)-**8**.[3a] *N*-Benzyl-*C*-(2-furanyl)nitrone (**7b**) also undergoes cycloaddition with (2*R*)-**8** to afford cycloadduct **9b** as the major isomer along with its diastereomer **10b**.[3b] Cycloadditions of acrylate **4** with various *N*-benzyl-*C*-(heteroaryl)nitrones including **3b** and **7b** were also reported.[3c]



Scheme 1.

Keywords: (3′*R*,5′*S*)-3′-Hydroxycotinine; L-Gulose-derived nitrone; Cycloaddition.

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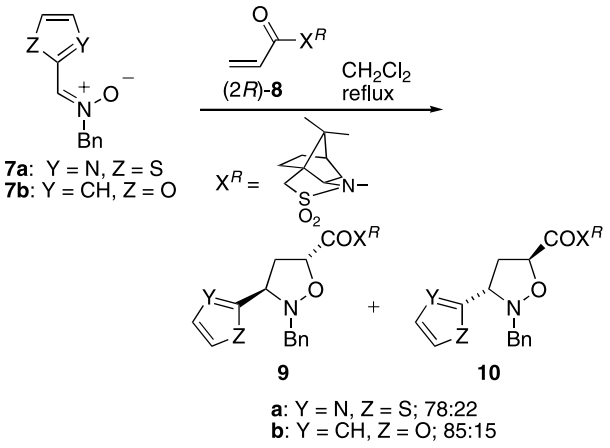


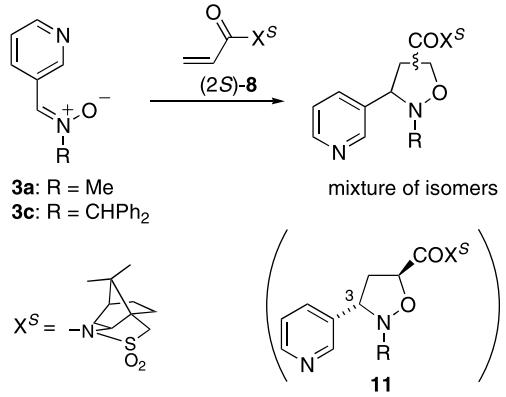
Scheme 2.

To develop chemical synthesis of (+)-**1**, we have examined cycloaddition of *C*-(3-pyridyl)nitrones **3a**, **3c**, and **15** with (2*R*)- and (2*S*)-*N*-(acryloyl)bornane-10,2-sultams [(2*R*)- and (2*S*)-**8**], and report here the synthesis of (3′*R*,5′*S*)-3′-hydroxycotinine [(+)-**1**] by regio and stereoselective cycloaddition of L-gulose-derived nitrone **15** with (2*S*)-**8**.

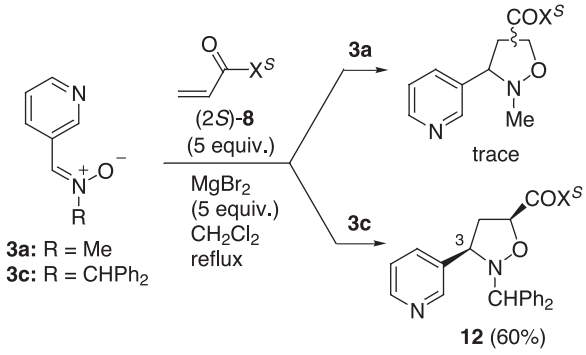
2. Results and discussion

Our investigation began with 1,3-dipolar cycloaddition of *N*-methylnitrone **3a** and *N*-diphenylmethylnitrone **3c** with (2*S*)-**8**,[4] which was expected based on the report by Tejero et al. to afford cycloadduct **11** as the major product having correct stereochemistry at the 3-position of the isoxazolidine ring (Schemes 2 and 3). Nitrone **3a**, on treatment with (2*S*)-**8** in refluxing CH_2Cl_2, underwent 1,3-dipolar cycloaddition to give, however, a complex isomeric mixture of cycloadducts including regio-isomers. Reaction of nitrone **3c** with (2*S*)-**8** again gave a complex mixture of cycloadducts.

These disappointing results prompted us to consider the use of Lewis acid for the cycloaddition (Scheme 4).[4e,5] When *N*-methylnitrone **3a** was heated with (2*S*)-**8** (5 equiv) in the presence of $MgBr_2$ (5 equiv)[6] in refluxing CH_2Cl_2, only trace amounts of cycloadducts were detected. In contrast, reaction of *N*-diphenylmethylnitrone **3b** with (2*S*)-**8** under conditions similar to those for **3a** afforded 60% isolated



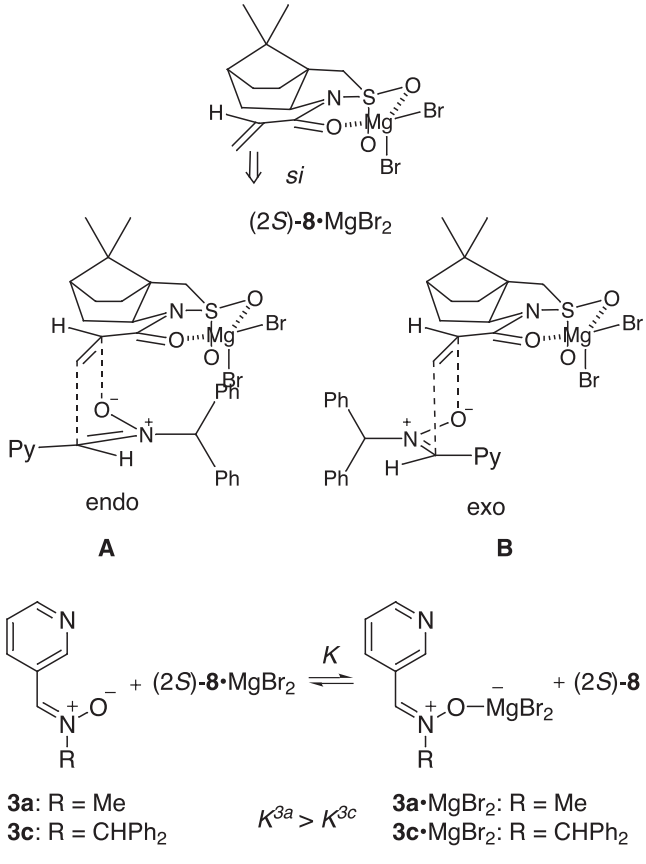
Scheme 3.



Scheme 4.

yield of cycloadduct **12** along with other isomers. The stereochemistry of cycloadduct **12** was determined by X-ray crystallography (Fig. 1),[7] which revealed that cycloadduct **12** had *cis*-relative stereochemistry and (3*R*)-isoxazolidine. To our knowledge, this reaction represents the first example of cycloaddition of *N*-alkyl-*C*-arylnitrone with acryloyl-derivative giving *cis*-isoxazolidine.

Since cycloaddition of nitrones **3a** and **3c** with acrylate-derived dipolarophiles is expected to be controlled by $HOMO_{nitrone}$–$LUMO_{acrylate}$ interaction,[3c] the formation of cycloadduct **12** may involve (2*S*)-**8**·$MgBr_2$ complex having lowered LUMO, which would undergo cycloaddition from the less-hindered *si*-face because of the *s-cis* conformation (Scheme 5).[8,9] Since *endo*-transition state **A** may have severe steric interaction between the bulky diphenylmethyl group and chelated $MgBr_2$, the reaction would mainly



Scheme 5.

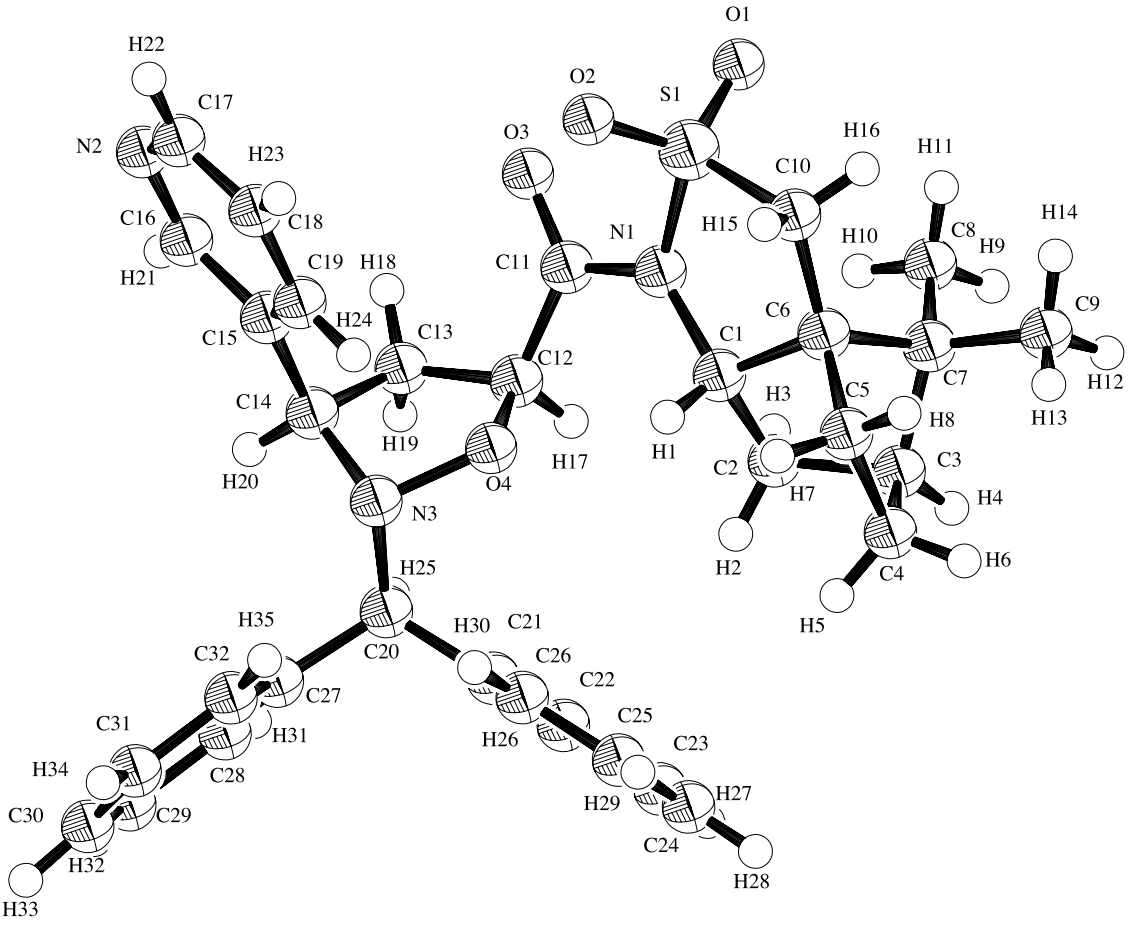


Figure 1. ORTEP drawing of compound **12**.

proceed via *exo*-transition state **B** to afford cycloadduct **12** as the major isomer. The difference in reactivity between nitrones **3a** and **3c** in the presence of $MgBr_2$ may be ascribed to their Lewis basicities. Less bulky nitrone **3a** appears to strongly coordinate with $MgBr_2$ to form non-reactive complex **3a**·$MgBr_2$, whereas sterically more demanding diphenylmethyl group of **3c** would interfere to coordinate with $MgBr_2$. Accordingly, liberated **3b** would react with (2*S*)-**8**·$MgBr_2$ complex to afford adduct **12**.[10]

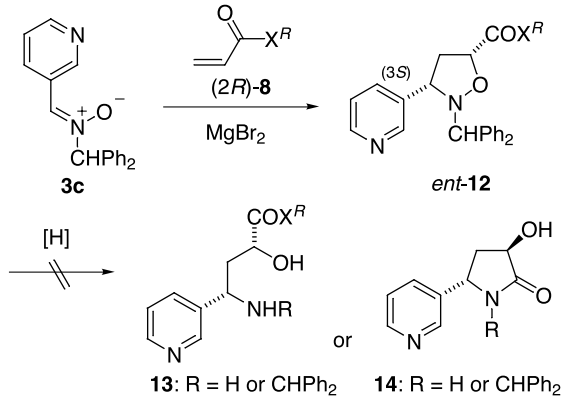
To synthesize (+)-**1** using the present cycloaddition, (3*S*)-isoxazolidine is required. Thus, (3*S*)-isoxazolidine *ent*-**12** was prepared in 58% isolated yield by cycloaddition of nitrone **3c** with (2*R*)-**8** in the presence of $MgBr_2$ (Scheme 6). With *ent*-**12** having correct stereochemistry in hand, we next examined reductive cleavage of the *N–O* bond of *ent*-**12**. However, attempts to obtain 1,3-amino alcohol **13** or lactam **14** by hydrogenolysis of *ent*-**12** with Raney-nickel or 10% Pd–C under various pressures of hydrogen resulted in recovery of *ent*-**12** or a complex mixture probably due to the bulkiness of the diphenylmethyl group of *ent*-**12**.

We then turned our attention to the use of L-gulose-derived nitrone **15**[11–13] because a combination of the chiralities of nitrone **15** and (2*S*)-**8** or (2*R*)-**8** was expected to improve stereoselectivity by double asymmetric induction[14] and because the L-gulosyl group, the chiral auxiliary of nitrone **15**, can be removed under acidic conditions after cycloaddition (Fig. 2).[11] Treatment of nitrone **15** with (2*R*)-**8** in refluxing CH_2Cl_2 caused 1,3-dipolar cycloaddition, however, to give a complex mixture of cycloadducts (Table 1, entry 1). On the other hand, reaction of nitrone **15** with (2*S*)-**8** under conditions similar to those for entry **1** gave cycloadduct **16** as the major product along with small amounts of isomers (entry 2). Moreover, reaction of nitrone **15** with (2*S*)-**8** in refluxing $(CH_2Cl)_2$ still afforded cycloadduct **16** with high selectivity within a shorter reaction time (entry 3).

These results clearly showed a combination of nitrone **15** and (2*R*)-**8** to be a mismatched pair and that of **15** and (2*S*)-**8** to be a matched pair (Scheme 7). In our experience,[11b–e] (*Z*)-*N*-(L-gulosyl)nitrones tend to react from the *si*-face,

Table 1. 1,3-Dipolar cycloaddition of nitrone **15** with (2*R*)- and (2*S*)-**8**

Entry	Dipolarophile	Conditions	Yield (%)	Major product
1	(2*R*)-**8**	CH_2Cl_2 reflux, 9 d	91	Complex mixture of isomers
2	(2*S*)-**8**	CH_2Cl_2 reflux, 7 d	88	**16** (**16**/other isomers=9.3:1)
3	(2*S*)-**8**	$(CH_2Cl)_2$ reflux, 12 h	79	**16** (**16**/other isomers=9.4:1)



Scheme 6.

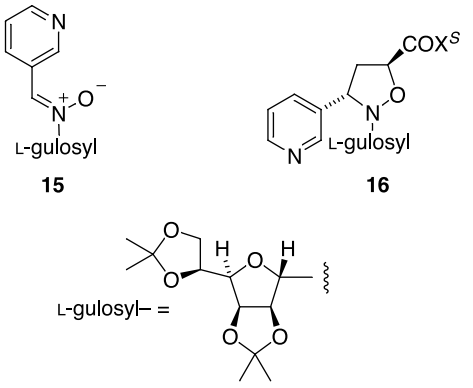
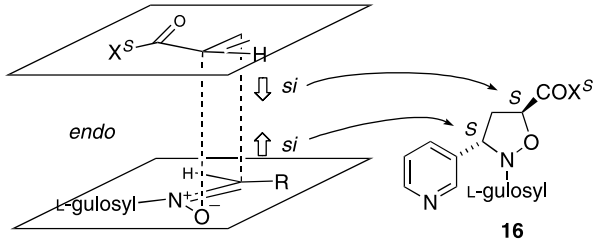


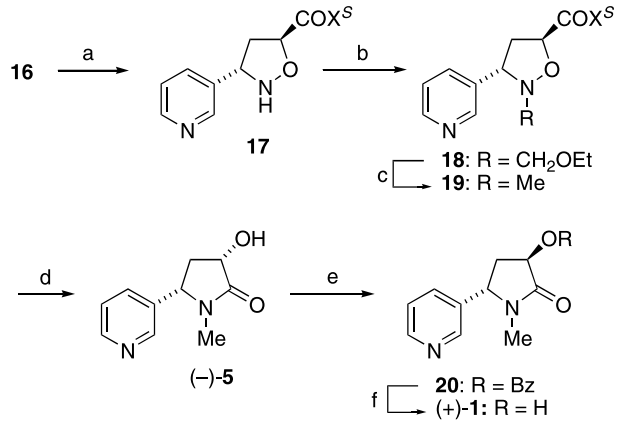
Figure 2. Structures of nitrone **15** and cycloadduct **16**.



Scheme 7.

whereas, as shown in Scheme 2, (2*R*)-**8** reacts mainly from the *e*-face,[9,15] hence of course, (2*S*)-**8** used here should have a tendency to react from the *si*-face. Accordingly, a combination of both selectivities of nitrone **15** and (2*S*)-**8** may exhibit high endo stereoselectivity.

With cycloadduct **16** in hand, we elaborated **16** to (3′*R*,5′*S*)-3′-hydroxycotinine [(+)-**1**] (Scheme 8). As expected, adduct **16** underwent hydrolytic removal of the L-gulosyl group by treatment with hydrochloric acid to give *N*-free isoxazolidine **17** in 76% yield. Isoxazolidine **17** was exposed to formaldehyde in EtOH to give *N*-(ethoxymethyl)isoxazolidine **18**, which, without isolation, was reduced with triethylsilane-trifluoroacetic acid to afford *N*-methylisoxazolidine **19** in 88% yield in two steps.[16] Hydrogenolysis of **19** caused cleavage of the *N–O* bond and lactamization to afford (3′*S*,5′*S*)-3′-hydroxycotinine [(−)-**5**]. Finally,



Scheme 8. Reagents and conditions: (a) HCl–EtOH, rt, 5 h, 76%. (b) HCHO, EtOH, rt, 2 h. (c) Et_3SiH, TFA–CH_2Cl_2, reflux, 0.5 h, 88% in two steps. (d) H_2, 10% Pd/C, 95% EtOH, 1.5 h, 54%. (e) $PhCO_2H$, DEAD, Ph_3P, toluene, rt, 5 min. (f) NaOH, MeOH, rt, 15 min, 88% in two steps.

(3′*R*,5′*S*)-3′-hydroxycotinine [(+)-**1**] was obtained by Mitsunobu reaction of (−)-**5** with benzoic acid followed by alkaline hydrolysis of the benzoate **20**.[2a,17]

3. Conclusions

In conclusion, we have synthesized (3′*R*,5′*S*)-3′-hydroxycotine [(+)-**1**], by using cycloaddition of *N*-(L-gulosyl)-*C*-(3-pyridyl)nitrone **15** with (2*S*)-**8**. Since it is known that control of regio and stereoselectivity is difficult with cycloaddition of *C*-(3-pyridyl)nitrone, the present approach will be useful for cycloaddition of a range of nitrones.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were recorded with a Shimazu FTIR-8100 spectrophotometer for solutions in $CHCl_3$. ^1H NMR and ^{13}C NMR spectra were measured on a JEOL JNM-EX 270 or a JEOL JNM-GSX 500 spectrometer. δ Values quoted are relative to tetramethylsilane. High resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX 102 instrument. Column chromatography was performed on Silica gel 60 PF_{254} (Nacalai Tesque) under pressure. Compounds **3a**[2a], (2*R*)-**8**[18], and (2*S*)-**8**[18] were prepared by previously reported methods.

4.1.1. (*Z*)-*N*-Diphenylmethyl-(3-pyridyl)methylideneamine *N*-oxide, 3c. A mixture of 3-pyridinecarboaldehyde (0.944 mL, 1.0 mmol) and diphenylmethylhydroxylamine[19] (199 mg, 1.0 mmol) in dry benzene (15 mL) was heated at reflux with azeotropic removal of water using a Dean–Stark trap for 4 h. After cooling, the mixture was concentrated under reduced pressure, and crystalline residue was triturated with Et_2O, and **3c** (267 mg, 94%) was collected by filtration: mp 182–184 °C (EtOH); IR ($CHCl_3$) 3000, 1580 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.40 (1H, s), 7.32–7.41 (11H, m), 7.53 (1H, s), 8.60 (1H, m), 8.90 (1H, br s), 9.10 (1H, br d, J=8.3 Hz). Anal. Calcd for $C_{19}H_{16}N_2O$: C, 78.99; H, 5.58; N, 9.75, found: C, 79.14; H, 5.59; N, 9.72.

4.1.2. (2*S*)-*N*-[[(3*R*,5*S*)-2-(Diphenylmethyl)-3-(3-pyridyl)-isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam, 12. To a stirred mixture of (2*S*)-**8** (380 mg, 1.41 mmol) and $MgBr_2$ (318 mg, 1.41 mmol) in CH_2Cl_2 (15 mL) was added nitrone **3c** (80 mg, 0.282 mmol) in CH_2Cl_2 (2 mL), and the mixture was heated at reflux for 3 days. After cooling, the mixture was successively washed with a saturated solution of $NaHCO_3$ and brine, dried (Na_2CO_3), and evaporated under reduced pressure. The residue was chromatographed on silica gel ($CHCl_3$–AcOEt, 30:1) to give **12** (94 mg, 60%) as colorless crystals: mp 224–226 °C (*n*-hexane–AcOEt); $[\alpha]_D^{20}=+89.8$ (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 1700, 1340 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.93 (3H, s), 1.08 (3H, s), 1.1–1.3 (2H, m), 1.75–1.9 (3H, m), 1.9–2.1 (1H, m), 2.1–2.2 (1H, m), 2.7–3.0 (2H, m), 3.35 (1H, d, $J=$ 13.8 Hz), 3.44 (1H, d, $J=13.8$ Hz), 3.76 (1H, br t, $J=$ 6.1 Hz), 3.95 (1H, t, $J=7.9$ Hz), 4.88 (1H, s), 5.01 (1H, br), 7.05–7.10 (3H, m) 7.1–7.35 (6H, m), 7.45 (2H, d, $J=$ 7.2 Hz), 7.90 (1H, br d, $J=7.8$ Hz), 8.23 (1H, br s), 8.39 (1H, dd, $J=4.4$, 1.5 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.4, 21.5, 26.7, 33.3, 38.9, 45.4, 48.1, 49.4, 53.2, 65.2, 65.5, 73.0, 75.4, 77.7, 124.1, 127.8, 127.9, 128.6, 128.7, 128.9, 129.5, 136.1, 136.5, 140.4, 140.7, 149.1, 149.8, 169.8; MS *m*/*z* 557 (M^+); HRMS calcd for $C_{32}H_{35}N_3O_4S$ 557.2349, found: 557.2344.

4.1.3. (2*R*)-*N*-[[(3*S*,5*R*)-2-(Diphenylmethyl)-3-(3-pyridyl) isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam, *ent*-12. Mp 224–226 °C (*n*-hexane–AcOEt); $[\alpha]_D^{20}=-89.8$ (*c* 0.31, $CHCl_3$).

4.1.4. (*Z*)-3-Pyridyl-*N*-(2′,3′:5′,6′-*O*-diisopropylidene-α-L-gulofuranosyl)methylideneamine *N*-oxide, 15. A mixture of 3-pyridinecarbaldehyde (0.70 mL, 8.72 mmol) and 2,3:5,6-*O*-diisopropylidene-L-gulofuranose oxime[11d] (2.00 g, 7.26 mmol) in toluene (30 mL) was heated at reflux with azeotropic removal of water by a Dean–Stark trap for 20 h. After cooling to room temperature, precipitated crystals were collected by filtration to give **15** (1.88 g, 71%). The mother liquor was concentrated to give the residue, which was chromatographed on silica gel (AcOEt) to give additional **15** (611 mg, total 94%): mp 177–180 °C (toluene); $[\alpha]_D^{26}=+42.3$ (*c* 2.37, $CHCl_3$); IR ($CHCl_3$) 2990, 1560 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.41 (3H, s), 1.47 (3H, s), 1.52 (3H, s), 3.74 (1H, dd, $J=8.3$, 7.1 Hz), 4.23 (1H, dd, $J=8.3$, 6.6 Hz), 4.40 (1H, dt, $J=8.3$, 6.6 Hz), 4.60 (1H, dd, $J=8.3$, 4.3 Hz), 4.90 (1H, dd, $J=5.9$, 4.3 Hz), 5.33 (1H, d, $J=5.9$ Hz), 5.60 (1H, s), 7.36 (1H, dd, $J=8.3$, 5.0 Hz), 7.68 (1H, s), 8.63 (1H, dd, $J=4.6$, 1.7 Hz), 8.93 (1H, dt, $J=8.3$, 1.7 Hz), 9.00 (1H, d, $J=2.0$ Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.5, 25.4, 25.9, 26.7, 65.8, 75.8, 80.2, 84.4, 87.6, 103.5, 109.9, 113.5, 123.5, 126.0, 130.7, 134.8, 150.1, 151.1. Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69, found: C, 59.61; H, 6.77; N, 7.51.

4.1.5. (2*S*)-*N*-[[(3*S*,5*S*)-2-(2′,3′:5′,6′-*O*-Diisopropylidene-α-L-gulofuranosyl)-3-(3-pyridyl)isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam, 16. (a) (Table 1, entry 2). A solution of (2*S*)-**8** (269 mg, 1.00 mmol) and **15** (73 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was heated at reflux for 7 days. After concentration of the mixture, the residue was chromatographed on silica gel ($CHCl_3$–AcOEt, 30:1) to give a 9.3:1 mixture (111.5 mg) of **16** and other isomers. The mixture was subjected to preparative TLC on silica gel (Et_2O–AcOEt, 10:1) to give **16** (101 mg, 80%): mp 85–88 °C; $[\alpha]_D^{26}=+72.3$ (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 1700, 1340 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, s), 1.19 (3H, s), 127 (3H, s), 1.28 (3H, s), 1.32 (3H, s), 1.44 (3H, s), 1.2–1.3 (2H, m), 1.8–2.15 (4H, m), 2.24–2.26 (1H, m), 2.70 (1H, ddd, $J=12.7$, 8.3, 4.4 Hz), 3.02 (1H, dt, $J=$ 12.7, 6.4 Hz), 3.43 (1H, d, $J=13.7$ Hz), 3.52 (1H, d, $J=$ 13.7 Hz), 3.61 (1H, dd, $J=8.3$, 6.4 Hz), 3.86 (1H, dd, $J=$ 8.3, 4.4 Hz), 3.92 (1H, dd, $J=7.8$, 4.9 Hz), 4.13 (1H, dd, $J=8.3$, 6.4 Hz), 4.26 (1H, dt, $J=8.3$, 6.8 Hz), 4.66 (1H, dd, $J=6.4$, 4.4 Hz), 4.85 (1H, dd, $J=6.9$, 4.4 Hz), 4.86 (1H, s), 5.06 (1H, d, $J=6.4$ Hz), 5.15 (1H, dd, $J=8.3$, 6.4 Hz), 7.24 (1H, dd, $J=7.8$, 4.9 Hz), 7.71 (1H, br d, $J=7.8$ Hz), 8.50 (1H, br d, $J=4.9$ Hz), 8.61 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.8, 20.9, 24.8, 25.2, 26.0, 26.426.6, 32.9, 38.1, 39.4, 44.7, 47.8, 48.9, 53.0, 62.8, 65.5, 65.8, 75.6, 76.6, 80.2, 83.8, 84.2, 97.3, 109.5, 112.5, 123.4, 134.3, 135.8, 148.7, 148.8, 170.1. HRMS (EI) *m*/*z* Calcd for $C_{31}H_{43}N_3O_9S$ 633.2720, found: 633.2717. (b) (Table 1, entry 3). A solution of (2*S*)-**8** (185 mg, 0.686 mmol) and **15** (50.0 mg, 0.137 mmol) in $(CH_2Cl)_2$ (5 mL) was heated at reflux for 12 h. A work-up similar to that for the reaction in CH_2Cl_2 gave **16** (61.2 mg, 71%) and a mixture of isomers (6.7 mg, 7.7%)

4.1.6. (2*S*)-*N*-[[(3*S*,5*S*)-3-(3-Pyridyl)isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam, 17. A solution of **16** (39.9 mg, 63.0 μmol) in concentrated HCl–EtOH (1:6, 1 mL) was stirred at room temperature for 5 h. After concentration, the residue was diluted with $CHCl_3$, washed with a saturated solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel ($CHCl_3$–AcOEt, 20:1) to give **17** (18.7 mg, 76%): mp 218–219 °C (AcOEt–MeOH); $[\alpha]_D^{25}=+175.2$ (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 1690, 1340 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.18 (3H, s), 1.3–1.5 (2H, m), 1.8–2.0 (3H, m), 2.0–2.3 (2H, m), 2.6–2.8 (1H, m), 2.95 (ddd, $J=13.2$, 8.8, 4.4 Hz), 3.44 (1H, d, $J=13.8$ Hz), 3.53 (1H, d, $J=13.8$ Hz), 3.90 (1H, dd, $J=7.8$, 4.9 Hz), 4.73 (1H, m), 5.26 (1H, dd, $J=8.3$, 4.4 Hz), 7.26 (1H, m), 6.60 (1H, br), 7.76 (1H, d, $J=7.8$ Hz), 8.50 (1H, d, $J=$ 4.9 Hz), 8.59 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.8, 20.8, 26.3, 32.8, 38.2, 38.4, 42.8, 44.4, 44.6, 47.8, 49.0, 53.0, 60.0, 65.1, 123.4, 133.8, 148.2, 148.5, 172.4; HRMS (EI) *m*/*z* Calcd for $C_{19}H_{25}N_3O_4S$ 391.1566, found: 391.1557. Anal. Calcd for $C_{19}H_{15}NO_2$: C, 58.29; H, 6.44; N, 10.73, found: C, 58.03; H, 6.39; N, 10.66.

4.1.7. (2*S*)-*N*-[[(3*S*,5*S*)-2-Methyl-3-(3-pyridyl)isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam, 19. A mixture of **17** (10.8 mg, 27.6 μmol) and a 36% aqueous solution of formaldehyde (0.07 mL) in EtOH (1.5 mL) was stirred at room temperature for 2 h, and then the mixture was concentrated to give crude (2*S*)-*N*-[[(3*S*,5*S*)-2-ethoxymethyl-3-(2-pyridyl)isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam (**18**). The crude **18** was diluted with a 1:1 mixture of CF_3CO_2H and CH_2Cl_2 (3 mL). To the solution was added Et_3SiH (36 μL, 0.41 mmol), and the mixture was heated at reflux for 30 min. After concentration, the residue was diluted with $CHCl_3$, washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (AcOEt–MeOH,

30:1) to give **19** (9.3 mg, 83%): mp 44–47 °C; $[\alpha]_D^{25}=+39.0$ (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 1700, 1340 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, s), 1.18 (3H, s), 1.30–1.45 (2H, m), 1.90–1.92 (3H, m), 2.10–2.20 (2H, m), 2.63–2.72 (1H, m), 2.71 (3H, s), 2.73–2.90 (1H, m), 3.42 (1H, d, $J=13.8$ Hz), 3.52 (1H, d, $J=13.8$ Hz), 3.90 (1H, br), 3.94 (1H, dd, $J=7.8$, 4.9 Hz), 5.21 (1H, dd, $J=8.8$, 4.4 Hz), 7.28 (1H, dd, $J=8.0$, 4.5 Hz), 7.75 (1H, br d, $J=7.8$ Hz), 8.54 (1H, br d, $J=2.9$ Hz), 8.57 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.9, 20.8, 26.4, 32.9, 38.3, 43.6, 44.7, 47.8, 49.0, 53.0, 65.5, 69.2, 75.5, 123.7, 134.0, 134.1, 149.4, 149.5, 170.3; HRMS (EI) *m/z* Calcd for $C_{20}H_{27}N_3O_4S$ 405.1723, found: 405.1720.

4.1.8. (3′*S*,5′*S*)-3′-Hydroxycotinine, (−)-5. A mixture of **19** (19.0 mg, 46.9 μmol) and 10% Pd–C (30 mg) in 95% EtOH (2 mL) was stirred under a hydrogen atmosphere for 1.5 h. After filtration through a pad of Celite®, the filtrate was concentrated and the residue was chromatographed on silica gel ($CHCl_3$–MeOH, 10:1) to give (−)-**5** (5.8 mg, 54%) and (2*S*)-bornane-2,10-sultam (5.8 mg, 64%). (−)-**5**: mp 134–136 °C (acetone); $[\alpha]_D^{25}=-21.8$ (*c* 0.13, MeOH); IR (CHCl3) 1692 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.92 (1H, dt, $J=13.2$, 7.9 Hz), 2.66 (3H, s), 2.90 (1H, ddd, $J=13.2$, 8.3, 7.3 Hz), 4.23 (1H, br), 4.46 (1H, t, $J=7.6$ Hz), 4.50 (1H, t, $J=8.6$ Hz), 7.37 (1H, dd, $J=7.9$, 4.6 Hz), 7.68, (1H, dt, $J=7.9$, 1.8 Hz), 8.56 (1H, d, $J=2.3$ Hz), 8.63 (1H, dd, $J=4.6$, 1.8 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.4, 37.6, 58.9, 69.5, 124.2, 134.6, 135.1, 149.1, 150.2, 175.4. Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57, found: C, 62.53; H, 6.32; N, 14.44

4.1.9. (3′*R*,5′*S*)-3′-Hydroxycotinine, (+)-1. To a stirred solution of (−)-**5** (7.0 mg, 36 μmol), Ph_3P (12.4 mg, 47 μmol), and benzoic acid (8.5 mg, 47 μmol) in toluene (2 mL) was added a 40% solution of DEAD (19 μL, 85 μmol) at room temperature. After 5 min, the mixture was diluted with $CHCl_3$ (20 mL), washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was purified by preparative TLC on silica gel ($CHCl_3$–MeOH, 10:1) to give (3*R*,5*S*)-1-methyl-3-(benzoyl)oxy-5-(3-pyridyl)pyrrolidin-2-one (**20**); IR ($CHCl_3$) 1710, 1270 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.55 (1H, ddd, $J=12.2$, 8.3, 4.0 Hz), 2.61 (1H, ddd, $J=12.2$, 8.3, 6.9 Hz), 2.83 (3H, s), 4.75 (1H, dd, $J=8.3$, 4.0 Hz), 5.70 (1H, dd, $J=8.3$, 6.9 Hz), 7.36–7.62 (5H, m), 8.07 (1H, d, $J=1.7$ Hz), 8.10 (1H, br s), 8.54 (1H, br s), 8.63 (1H, br d, $J=3.3$ Hz). This material was used for the next step without further purification. Compound **20** was dissolved in 10% NaOH–MeOH (1:10, 1 mL), and the solution was stirred at room temperature for 15 min. After concentration, the residue was purified by preparative TLC on silica gel ($CHCl_3$–MeOH, 5:1) to give (+)-**1** (6.0 mg, 88%): mp 108–110 °C (acetone) [lit.[2c] mp 107–108 °C (acetone)]; $[\alpha]_D^{26}=+38.2$ (*c* 0.40, MeOH) [lit.[2d] $[\alpha]_D=+39$ (*c* 0.48, MeOH); IR ($CHCl_3$) 1694 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.34 (1H, ddd, $J=13.2$, 8.2, 3.0 Hz), 2.52 (1H, ddd, $J=13.2$, 8.6, 7.5 Hz), 2.78 (3H, s), 4.59 (1H, br t, $J=7.7$ Hz), 4.66 (1H, dd, $J=8.6$, 3.0 Hz), 5.51 (1H, br), 7.35 (1H, dd, $J=7.9$, 4.6 Hz), 7.46 (1H, br d, $J=8.3$ Hz), 8.49 (1H, d, $J=2.0$ Hz), 8.60 (1H, dd, $J=5.0$, 1.3 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.4, 37.1, 59.6, 68.2, 123.9, 133.6, 135.8, 148.1, 149.5, 175.4.

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References and notes

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Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 246606. 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).

8. Although coordination of $MgBr_2$ with nitrogen-atom of the pyridine ring cannot be ruled out,[6d] the coordination would not be crucial for the present cycloadditions. If it were crucial, reaction of **3c** should give a result similar to that of **3a**. In fact, however, cycloaddition of **3c** afforded adduct **12** with a moderate selectivity whereas that of **3a** gave only a trace amount of the product.
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Cobalt-catalyzed cyclotrimerization of diynes with norbornenes in one efficient step

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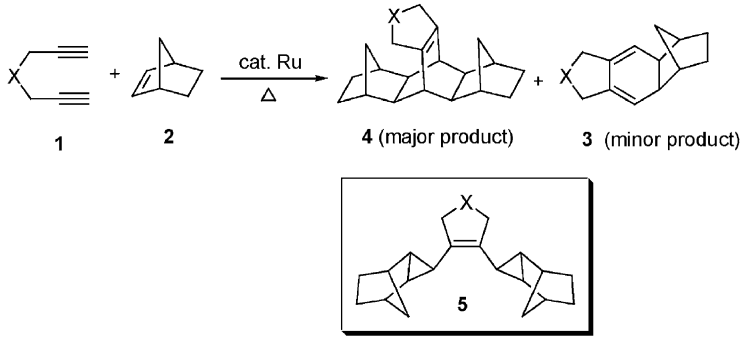
Abstract—An efficient cobalt-catalyzed [2+2+2] cyclotrimerization of diynes and norbornene is described. Treatment of diyne with norbornene in the presence of $CoI_2(PPh_3)_2$ and zinc powder in 1,2-dichloroethane at 80 °C for 12 h afforded [2+2+2] cyclotrimerization adduct exclusively in good yields. These cobalt-catalyzed results are in contrast to the ruthenium-catalyzed reaction of diyne with norbornene reported previously.

1. Introduction

Transition metal catalyzed [2+2+2] cocyclotrimerization of alkynes is an efficient route for the construction of polysubstituted benzene derivatives.[1,2] The cocyclotrimerization of two alkynes and an alkene catalyzed by transition metal complexes is also a potential strategy for the synthesis of cyclohexadiene system,[3] which is an important component for the Diels–Alder reactions.[4]

Recently, Itoh et al. initially reported the reaction of diyne and norbornene catalyzed by ruthenium complex (10.0 mol%) to give a [2+2+2]/[4+2] adduct **4** and a minor [2+2+2] cyclotrimerization product **3** (Scheme 1).[5] The structure of **4** was latter characterized to be an unusual cyclopropanation product **5** by the same authors.[6] This ruthenium-catalyzed reaction requires a large excess of norbornene (20.00 mmol) relative to diynes (1.00 mmol) and a large volume of solvent (20.0 mL).

We were interested in nickel-catalyzed [2+2+2] cyclotrimerization of alkynes or diynes with alkenes.[7,8] A variety of alkenes such as α,β-unsaturated ketones,[7a] 7-oxabenzonorbornadienes,[7b,c] fullerenes[7d] and more recently allenes[7e,f] were found to undergo this [2+2+2] cyclotrimerization. However, there appears no efficient [2+2+2] cyclotrimerization involving norbornenes and diynes as substrates to date. The unusual results of the ruthenium-catalyzed cyclotrimerization of diynes with norbornenes strongly encouraged us to investigate the reaction catalyzed by other metal complexes. Herein, we wish to report that cobalt complexes catalyze the [2+2+2] cyclotrimerization of



Scheme 1.

Keywords: Cyclotrimerization; Cobalt catalysis; Norbornene; Diynes.
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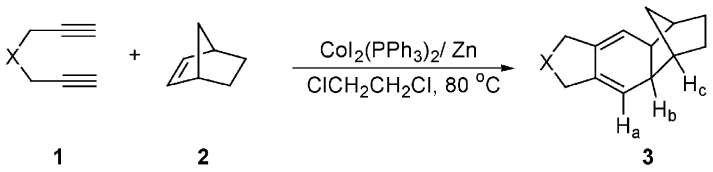


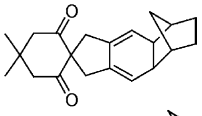
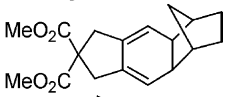
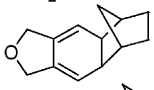
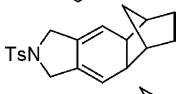
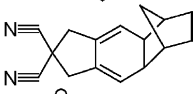
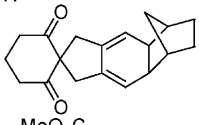
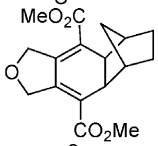
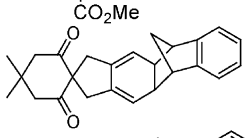
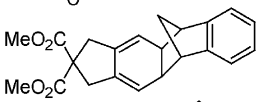
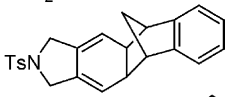
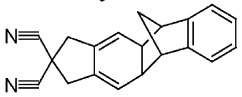
Scheme 2.

diynes and norbornenes to afford multiple rings with cyclohexadiene functionality in good yields under mild conditions (Scheme 2) in contrast to the results reported by Itoh's group.

2. Results and discussion

Diynes **1** undergo [2+2+2] cyclotrimerization readily with norbornenes in the presence of cobalt phosphine complex and zinc metal powder. Thus, treatment of diyne **1a** (1.00 mmol), norbornene (**2a**) (4.00 mmol), zinc (2.00 mmol) and 10.0 mol% $CoI_2(PPh_3)_2$ in $ClCH_2CH_2Cl$ (2.0 mL) at 80 °C for 12 h afforded [2+2+2] cycloadduct in 81% isolated yield (Scheme 2 and Table 1, entry 1). The structure of **3a** was confirmed by ^1H, ^{13}C NMR and by its high-resolution mass. No trace of diyne dimerization was observed in the ^1H NMR of the crude reaction mixture. In

Table 1. Results of cobalt-catalyzed cyclotrimerization of diynes with norbornenes[a]

Entry	1	2	Product		Yield (%)[b]	Dimer **6** (%)[c]
1	**1a**	**2a**		**3a**	81 (86)	0
2	**1b**	**2a**		**3b**	70	8
3	**1c**	**2a**		**3c**	46	11
4	**1d**	**2a**		**3d**	75	9
5	**1e**	**2a**		**3e**	73	0
6	**1f**	**2a**		**3f**	31	0
7	**1g**	**2a**		**3g**	83	0
8	**1a**	**2b**		**3h**	61	12
9	**1b**	**2b**		**3i**	63	15
10[d]	**1d**	**2b**		**3j**	34	11
11	**1e**	**2b**		**3k**	43	18

[a] Unless stated otherwise, all reactions were carried out using a $CoI_2(PPh_3)_2$ (0.10 mmol, 10.0 mol%), Zn (2.00 mmol), diyne (1) (1.00 mmol), norbornene (2) (4.00 mmol) in 1,2-dichloroethane (2.0 mL) at 80 °C under N_2 for 12 h.
[b] Isolated yields were based on diyne used; yields in the parenthesis were determined by ^1H NMR using mesitylene as an internal method.
[c] Yields of diyne dimerization product (a trace of diyne trimer was observed in few cases).
[d] 40% of diyne was recovered.

the ^{1}H NMR of **3a**, the characteristic peaks appear at following positions. The cyclohexadiene protons H_a appears at δ 5.18, the ring junction protons H_b at δ 2.40 and the bridge head protons H_c at δ 1.95.

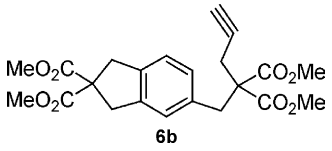
The present catalytic reaction is greatly influenced by the ligand and solvent used. The effects of reaction conditions were studied on the reaction of **1a** with **2a**. No reaction was observed in the absence of a cobalt complex or zinc metal powder (Table 2). Only trace amount of **3a** was formed by the use of $Co(acac)_3$ while no product was formed with $CpCo(CO)_2$ as catalyst. Similarly, no formation of **3a** was observed, when bidentate phosphine ligand such as CoI_2(dppe) was used. Simple CoI_2 afforded **3a** in 28% yield. $CoI_2(PPh_3)_2$ appears to be the best catalyst for this cyclotrimerization reaction furnishing **3a** in 86% yield. The addition of extra PPh_3 inhibited the reaction completely. The solvent used is critical for the present catalytic reaction. The use of THF, CH_3CN and toluene afforded **3a** in 2, 15, and 5% yields, respectively whereas no **3a** was observed in DMF. 1,2-Dichloroethane appears to be the best solvent for this [2+2+2] reaction giving **3a** in the maximum yield. Interestingly, we find that nickel complexes that are efficient catalysts for [2+2+2] cyclotrimerization in our previous reactions[7a–f] were much less effective. The use of $NiCl_2(PPh_3)_2$ in 1,2-dichloroethane and toluene afforded **3a** in 3 and 23% yields, respectively (entries 14 and 15).

Table 2. Effect of cobalt-complex and solvent on the [2+2+2] cocyclotrimerization of diyne (**1a**) with norbornene (**2a**)[a]

Entry	Catalyst	Solvent	**3a** Yield (%)[b]
1	—	$ClCH_2CH_2Cl$	—
2	$CoI_2(PPh_3)_2$	$ClCH_2CH_2Cl$	—
3	Zn	$ClCH_2CH_2Cl$	—
4	$Co(acac)_3$/Zn	$ClCH_2CH_2Cl$	Trace
5	$CpCo(CO)_2$	$ClCH_2CH_2Cl$	0
6	CoI_2(dppe)/Zn	$ClCH_2CH_2Cl$	0
7	$CoI_2(PPh_3)_2$/Zn	$ClCH_2CH_2Cl$	86
8	CoI_2/Zn	$ClCH_2CH_2Cl$	28
9[c]	$CoI_2(PPh_3)_2$/ $2PPh_3$/Zn	$ClCH_2CH_2Cl$	0
10	$CoI_2(PPh_3)_2$/Zn	THF	2
11	$CoI_2(PPh_3)_2$/Zn	CH_3CN	15
12	$CoI_2(PPh_3)_2$/Zn	DMF	Trace
13	$CoI_2(PPh_3)_2$/Zn	Toluene	5
14	$NiCl_2(PPh_3)_2$/ Zn	$ClCH_2CH_2Cl$	3
15[c]	$NiCl_2(PPh_3)_2$/ $8PPh_3$/Zn	Toluene	23

[a] Unless stated otherwise, all reactions were carried out using a Co complex or nickel complex (0.10 mmol), Zn (2.00 mmol), diyne (**1a**) (1.00 mmol), norbornene (**2a**) (4.00 mmol) and solvent (2.0 mL) at 80 °C under N_2 for 12 h.
[b] Yields were determined by ^{1}H NMR using mesitylene as an internal method.
[c] Extra PPh_3 was added in the reaction.

Under similar reaction conditions, the [2+2+2] cyclotrimerization reaction can be extended to various diynes and the results are summarized in Table 1. Thus, diyne **1b** reacted with norbornene (**2a**) to produce the desired [2+2+2] adduct **3b** in 70% yield (Table 1, entry 2). However, in this reaction the dimerization product of diyne **6b** was isolated in 8% yield. Similarly, diynes having a heteroatom at the 4-position **1c** and **1d** underwent cyclotrimerization with norbornene smoothly to afford the desired adducts **3c** and **3d** in 46 and 75% yields, respectively. A small amount of dimerization product of diyne was also observed in each case (Table 1, entries 3 and 4).



6b

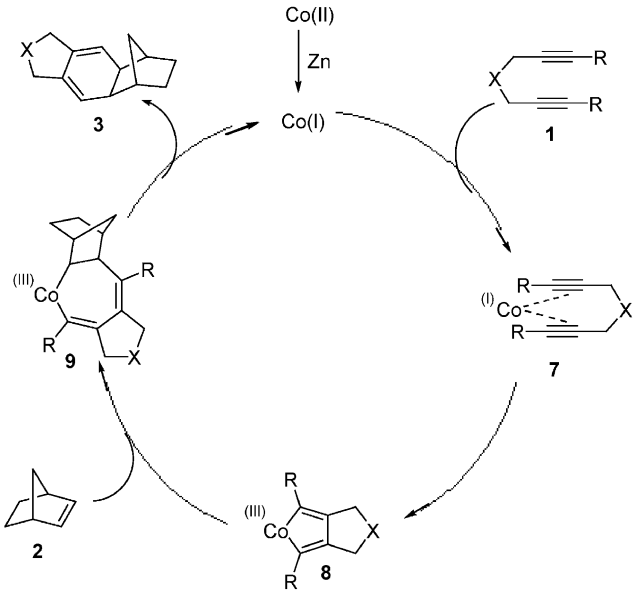
It is interesting to compare the reaction of **1d** with **2a** under ruthenium-catalyzed[5] and cobalt-catalyzed conditions. The former produced cyclopropanation product **5d** in 36% yield with a trace amount of [2+2+2] adduct was observed, whereas the latter afforded the [2+2+2] adduct **3d** in 75% yield. Similar observation was also found in the case of malononitrile diyne derivative **1e**. Diyne **1e** reacted with **2a** to furnish [2+2+2] adduct **3e** in 73% yield with no corresponding diyne dimerization product.

Cyclohexanedione diyne derivative **1f** gave **3f** albeit lower yield (entry 6). Diyne **1g** possessing two electron-withdrawing ester groups on the triple bonds underwent cyclotrimerization smoothly to produce the [2+2+2] adduct **3g** in a high yield of 83%. Probably the presence of electron-withdrawing groups on the triple bonds facilitates the cyclotrimerization process. Similar results were observed for the nickel-catalyzed [2+2+2] cyclotrimerization of diynes with allenes.[7e,f]

The cobalt-catalyzed [2+2+2] cyclotrimerization was successfully implemented to benzonorbornadiene, although, in moderate yields. Entry 8 demonstrates the reaction of diyne (**1a**) with benzonorbornadiene (**2b**) to give the desired product **3h** in 61% yield. In a similar fashion, **2b** reacts with diynes **1b**, **1d** and **1e** to furnish cycloadduct **3i–k** in 63, 34 and 43% yields, respectively. It is noteworthy that the ruthenium-catalyzed reaction of benzonorbornadiene (**2b**) with diyne failed to give either the [2+2+2] cyclotrimerization product or cyclopropanation product, instead afforded only the diyne dimerization and trimerization products.

Overall, the ruthenium-catalyzed reaction reported by Itoh's group generally prefers to form the cyclopropanation product with small amount of [2+2+2] adducts whereas the present cobalt-catalyzed method provides exclusively [2+2+2] adducts and no other tandem adducts. In addition, the ruthenium-catalyzed reaction involve a large excess of norbornene (20.00 mmol) relative to diynes (1.00 mmol) and a large volume of solvent (20.0 mL), but the present cobalt-catalyzed [2+2+2] cyclotrimerization requires less norbornene (4.00 mmol) and solvent (2.0 mL), thus, making it very practical. The difference of these two transition-metal catalyzed methods in the reactivity and product formation is interesting; however the exact explanation for this observation is not yet clear.

Based on the known organometallic chemistry of cobalt and



Scheme 3.

the observed product formation, a probable mechanism for the cobalt-catalyzed reaction of diyne **1** with norbornene **2** is depicted in Scheme 3. The reduction of Co(II) species to Co(I) species by zinc metal likely initiates the catalytic reaction. Coordination of diyne **1** to the cobalt center followed by cyclometalation gives cobaltacyclopentadiene intermediate **8**.[9,10] Exo coordination and subsequent insertion of norbornene into a Co(III)–carbon bond produces cobaltacycloheptadiene intermediate **9**. Further reductive elimination of **9** affords product **3** and regenerates the Co(I) catalyst. The formation of dimer of diyne **1** can be explained by the competitive insertion of one triple bond of **1** in to intermediate **8**, leading to the formation of cobaltacycloheptatriene. Reductive elimination of the latter furnishes **6**.

3. Conclusion

In conclusion, we have developed an efficient and selective cobalt-catalyzed [2+2+2] cyclotrimerization of diynes with norbornenes. This reaction offers a very convenient and mild method for the synthesis of various multiple rings containing a cyclohexadiene moiety in good yields. It is applicable to a broad class of substrates and is complementary to the reported ruthenium-catalyzed reaction.

4. Experimental

4.1. General procedure for the [2+2+2] cyclotrimerization of 1,6-heptadiynes with norbornenes

$CoI_2(PPh_3)_2$ (84 mg, 0.10 mmol, 10.0 mol%) and Zn (2.00 mmol) were placed in a screw-capped vessel. The vial was sealed with septum and flushed several times with nitrogen. Diyne (1.00 mmol), norbornene (4.00 mmol) and 1,2-dichloroethane (2.0 mL) were sequentially injected into the reaction mixture via a syringe. The septum was removed, and the vial was sealed with a screw cap quickly under nitrogen. The reaction mixture was stirred at 80 °C for 12 h. The crude reaction mixture was diluted with CH_2Cl_2, filtered through a thin Celite pad, and concentrated in vacuo. The residue was chromatographed on a silica gel column (hexane/EtOAc=19/1) to give the desired pure product. Products **3a–k** were obtained according to this procedure. The spectral data of all compounds are as follows.

4.1.1. Compound 3a. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.97 (6H, s), 1.13 (1H, dt, J_1=1.5 Hz, J_2=9.5 Hz), 1.29–1.31 (2H, m), 1.47–1.50 (2H, m), 1.56 (1H, dt, J_1=1.5 Hz, J_2=9.5 Hz), 1.95 (2H, t, J=1.5 Hz), 2.40 (2H, s), 2.57 (4H, s), 2.69 (4H, s), 5.18 (2H, s); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ=28.4, 30.3, 30.7, 34.5, 37.5, 43.7, 45.7, 51.7, 51.8, 69.1, 119.3, 133.8, 207.3, 207.5; IR (KBr): 2951, 1723, 1694 cm^{-1}; HRMS (*m*/*e*): calcd for $C_{21}H_{26}O_2$ 310.1933, found 310.1937.

4.1.2. Compound 3b. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.13 (1H, dt, J_1=1.2 Hz, J_2=9.6 Hz), 1.30–1.33 (2H, m), 1.48–1.52 (2H, m), 1.54 (1H, dt, J_1=1.2 Hz, J_2=9.6 Hz), 1.95 (2H, t, J=2.0 Hz), 2.41 (2H, s), 2.82 (4H, s), 3.69 (3H, s), 3.70 (3H, s), 5.20 (2H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=30.2, 34.4, 38.9, 43.7, 45.7, 52.7, 58.2, 119.5, 133.6, 171.9; HRMS (*m*/*e*): calcd for $C_{18}H_{22}O_4$ 302.1518, found 302.1521.

4.1.3. Compound 3c. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.19 (1H, dt, J_1=1.6 Hz, J_2=9.6 Hz), 1.34–1.36 (2H, m), 1.52–1.56 (2H, m), 1.62 (1H, dt, J_1=1.6 Hz, J_2=9.6 Hz), 2.00 (2H, t, J=2.0 Hz), 2.49 (2H, s), 4.30 (4H, s), 5.21 (2H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=30.4, 34.6, 43.7, 45.7, 70.5, 116.2, 134.3; HRMS (*m*/*e*): calcd for $C_{13}H_{16}O$ 188.1201, found 188.1207.

4.1.4. Compound 3d. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.13 (1H, dt, J_1=1.2 Hz, J_2=9.6 Hz), 1.29–1.33 (2H, m), 1.44 (1H, dt, J_1=1.2 Hz, J_2=9.6 Hz), 1.49–1.52 (2H, m),1.95 (2H, t, J=1.2 Hz), 2.40 (5H, s), 3.75 (2H, d, J=13.6 Hz), 3.83 (2H, d, J=13.6 Hz), 5.18 (2H, s), 7.29 (2H, d, J=8.8 Hz), 7.67 (2H, d, J=8.8 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=21.5, 30.2, 34.6, 43.4, 45.6, 51.1, 119.0, 127.9, 129.6, 131.0, 133.0, 143.6; HRMS (*m*/*e*): calcd for $C_{20}H_{23}O_2NS$ 341.1449, found 341.1455.

4.1.5. Compound 3e. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.20 (1H, dt, J_1=1.2 Hz, J_2=10.0 Hz), 1.34–1.37 (2H, m), 1.54–1.57 (3H, m), 2.03 (2H, t, J=1.6 Hz), 2.49 (2H, s), 2.95 (2H, d, J=15.6 Hz), 3.01 (2H, d, J=15.6 Hz), 5.42 (2H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=30.2, 32.3, 34.7, 42.9, 43.7, 45.5, 115.8, 123.2, 129.2; HRMS (*m*/*e*): calcd for $C_{16}H_{16}N_2$ 236.1313, found 236.1310.

4.1.6. Compound 3f. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.14 (1H, dt, J_1=1.2 Hz, J_2=9.6 Hz), 1.29–1.33 (2H, m), 1.49–1.55 (2H, m), 1.57 (1H, dt, J_1=1.2 Hz, J_2=9.6 Hz), 1.92–1.97 (4H, m), 2.41 (2H, s), 2.65 (4H, t, J=6.8 Hz), 2.71 (4H, s), 5.19 (2H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=17.9, 30.3, 34.5, 37.5, 37.8, 37.9, 43.7, 45.8, 70.5, 119.4, 133.9, 207.6, 207.9; IR (KBr): 2948, 1727, 1696 cm^{-1}; HRMS (*m*/*e*): calcd for $C_{19}H_{22}O_2$ 282.1620, found 282.1622.

4.1.7. Compound 3g. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.17

(1H, dt, $J_1=1.2$ Hz, $J_2=9.6$ Hz), 1.45 (1H, dt, $J_1=1.2$ Hz, $J_2=9.6$ Hz), 1.52–1.56 (2H, m), 1.58–1.62 (2H, m), 2.22 (2H, t, $J=1.6$ Hz), 2.98 (2H, s), 3.75 (3H, s), 3.80 (3H, s), 4.69 (2H, d, $J=16.4$ Hz), 4.81 (2H, d, $J=16.4$ Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta=30.5$, 33.9, 44.7, 46.1, 51.7, 72.1, 123.2, 146.7, 167.1; IR (KBr): 2947, 1704, 1673, 1254 cm^{-1}; HRMS (*m*/*e*): calcd for $C_{17}H_{20}O_5$ 304.1311, found 304.1310.

4.1.8. Compound 3h. ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 0.99 (6H, s), 1.69 (1H, dt, $J_1=1.6$ Hz, $J_2=9.2$ Hz), 1.92 (1H, dt, $J_1=1.6$ Hz, $J_2=9.2$ Hz), 2.45 (2H, s), 2.60 (4H, s), 2.75 (2H, d, $J=16.4$ Hz), 2.81 (2H, d, $J=16.4$ Hz), 3.11 (2H, s), 5.43 (2H, s), 7.04–7.06 (2H, m), 7.13–7.15 (2H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta=28.4$, 30.7, 37.5, 41.7, 45.0, 51.7, 51.8, 53.1, 69.4, 119.1, 120.6, 125.7, 135.3, 148.8, 207.3; IR (KBr): 2935, 1721, 1691 cm^{-1}; HRMS (*m*/*e*): calcd for $C_{25}H_{26}O_2$ 358.1933, found 358.1938.

4.1.9. Compound 3i. ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.68$ (1H, dt, $J_1=1.6$ Hz, $J_2=9.2$ Hz), 1.88 (1H, dt, $J_1=1.6$ Hz, $J_2=9.2$ Hz), 2.45 (2H, s), 2.92 (4H, s), 3.11 (2H, s), 3.72 (6H, s), 5.46 (2H, s), 7.04–7.06 (2H, m), 7.13–7.15 (2H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta=38.9$, 41.6, 44.9, 52.8, 53.0, 58.5, 119.3, 120.6, 125.7, 135.1, 148.7, 171.8, 171.9; IR (KBr): 2957, 1735 cm^{-1}; HRMS (*m*/*e*): calcd for $C_{22}H_{22}O_4$ 350.1518, found 350.1528.

4.1.10. Compound 3j. ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.66 (1H, dt, $J_1=1.2$ Hz, $J_2=9.2$ Hz), 1.77 (1H, dt, $J_1=$ 1.2 Hz, $J_2=9.2$ Hz), 2.40 (3H, s), 2.45 (2H, s), 3.11 (2H, s), 3.85 (2H, d, $J=13.6$ Hz), 3.92 (2H, d, $J=13.6$ Hz), 5.45 (2H, s), 7.04–7.06 (2H, m), 7.12–7.14 (2H, m), 7.31 (2H, d, $J=8.0$ Hz), 7.70 (2H, d, $J=8.0$ Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta=21.5$, 41.5, 45.0, 51.1, 52.9, 118.8, 120.7, 126.0, 127.9, 129.7, 132.4, 132.9, 143.7, 148.4; IR (KBr): 2948, 1347, 1163 cm^{-1}; HRMS (*m*/*e*): calcd for $C_{24}H_{23}NO_2S$ 389.1449, found 389.1456.

4.1.11. Compound 3k. ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.75 (1H, dt, $J_1=1.2$ Hz, $J_2=9.2$ Hz), 1.90 (1H, dt, $J_1=$ 1.2 Hz, $J_2=9.2$ Hz), 2.54 (2H, s), 3.08 (2H, d, $J=16.0$ Hz), 3.09 (2H, d, $J=16.0$ Hz), 3.19 (2H, s), 5.68 (2H, s), 7.07–7.09 (2H, m), 7.16–7.18 (2H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta=32.6$, 41.7, 42.8, 45.0, 52.8, 115.6, 115.7, 120.8, 122.9, 126.1, 130.5, 148.2; IR (KBr): 2958, 2247 cm^{-1}; HRMS (*m*/*e*): calcd for $C_{20}H_{16}N_2$ 284.1313, found 284.1310.

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Extended mesoionic systems: synthesis and characterization of monocyclic, polycyclic and macrocyclic pyrimidinium-olate derivatives and their photochemical behavior

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Abstract—Mesoionic pyrimidinium-olate derivatives have been known to undergo photoreactions upon irradiation with UV light to form bis(beta-lactame) structures for about two decades. Here, new mono-, poly- and macrocyclic mesoions were prepared and their photochemical rearrangement behavior was investigated. The synthesized compounds were characterized by NMR, IR, UV/Vis spectroscopy, elemental analysis and mass spectrometry. The extension of the aromatic core leads to a significant red-shift of the absorption maximum from ~380 to ~430 nm, indicating a strong electronic coupling of the mesoionic base chromophore with the annellated aromatic subunit. The rigidity of the extended aromatic system prevents polycyclic mesoions from shifting to their bis(beta-lactame) isomers, while the alkyl bridge of the 16-membered macrocycle in an ansa-mesoion does not inhibit photochemical rearrangement.

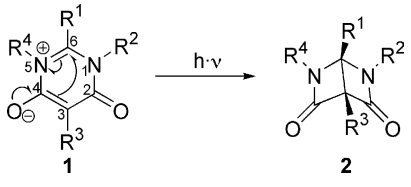
1. Introduction

Since the discovery of the five-membered Sydnone system[1] there has been growing interest in mesoions as heterocyclic compounds and in their reactions. Six-membered mesoionic ring systems are known that undergo various 1,4-dipolar cycloaddition reactions, for example, with alkenes, ketones and singulet oxygen.[2–6] Mesoionic 6-oxo-1,6-dihydropyrimidin-3-ium-4-olates (**1**) are cross-conjugated mesomeric betaines whose positive and negative charges are exclusively restricted to separate parts of the molecules' π-electron system. Their irradiation with UV light irreversibly results in the formation of the much less polar bis(beta-lactames) (**2**), as shown in Scheme 1. The bis(beta-lactame) structure of the photo products was first reported by Gotthardt et al.[3] in 1986 and is consistent with the ^{13}C NMR spectroscopic data (particularly for the C–C bridge across the 3.6-positions).

Since such mesoions are photoactive compounds with interesting physical properties, such as photoinduced change of polarity, refractive index, and density, new polymeric materials have been synthesized that contain mesoions either in the side chains or in the backbone.[7,8] Unfortunately, reversible photoswitching has not yet been reported with this class of compounds, and little is known about the photoreactivity of polycyclic and macrocyclic mesoionic compounds. In this paper, we present the synthesis and photochemical behavior of mesoionic structures with an extended conjugated π-system and carbon framework.

2. Results and discussion

Monocyclic mesoions **5a** and **5b** were synthesized starting from 1,3-diphenylthiourea (**3**) and pentyl bromide, using a modified literature procedure.[9] The resulting *N*,*N*′-disubstituted amidine *S*-pentyl-1,3-diphenylisothiourea **4** was reacted with substituted malonic acid (R = methyl, butyl) and dicyclohexylcarbodiimide (DCC) as a condensing agent at room temperature (Scheme 2) to yield the mesoionic structures **5**. As **5b** resembles the cleaved macrocyclic



Scheme 1. Photochemical conversion of mesoionic 6-oxo-1,6-dihydropyrimidin-3-ium-4-olates **1** to bis(beta-lactames) **2**.

Keywords: Polycyclic mesoions; Pyrimidinium-olates; Photocyclization reaction.

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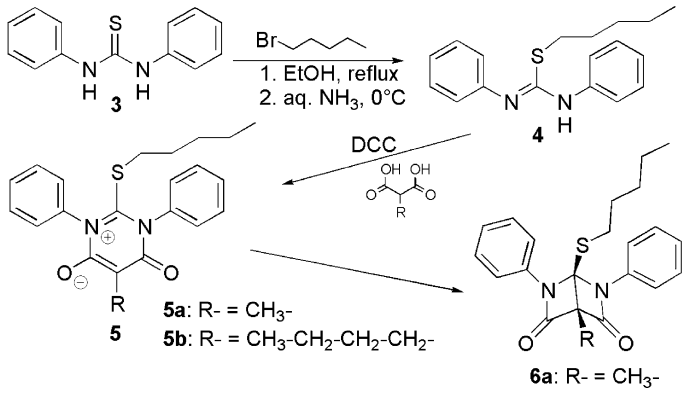
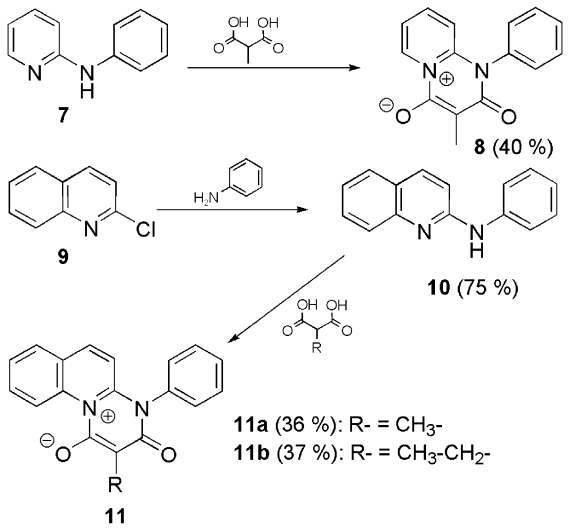


Scheme 2. Synthesis of monocyclic mesoions **5**.

structure **21** with a symmetrically broken ansa ring, it can be regarded as a model structure for the synthetic incorporation of the photoactive substance into a macrocyclic system at the 3- and 6-position, which is discussed further below. Irradiation of **5a** in dichloromethane at 365 nm gave the colorless photoproduct **6a** as an oil, although the substituent lengths at the 3- and 6-position should give rise to crystalline bis(beta-lactame) derivatives after the photoreaction.[3]

The routes to polycyclic mesoions are based on the same strategy via *N*,*N*′-disubstituted amidines **7** and **10** (Scheme 3). The latter was synthesized from 2-chloroquinone and aniline by nucleophilic aromatic substitution according to a literature procedure.[11]

Less polar solvents are better suited for the photocyclization reaction of mesoions **5** (solubility provided), due to their ability to stabilize the transition states to the much less polar bis(beta-lactames).[10] In fact, the absorption maxima in acetonitrile solution are shifted to shorter wavelengths as compared to those in dichloromethane. This indicates negative solvatochromism because the energy difference between ground state and excited state (HOMO–LUMO), which is correlated to the activation energy, is inversely proportional to the absorption wavelength. The larger



Scheme 3. Synthesis of polycyclic mesoions **8** and **11**.

activation energy barrier in acetonitrile compared to dichloromethane also accounts for the longer photoreaction times required in acetonitrile.

Alcohols are not appropriate as solvents for the photocyclization reaction, since product decomposition is observed by thin layer chromatography.[10] With different substitution patterns of the mesoionic systems, it can be shown that the long wavelength absorption maximum strongly depends on the number of rings in the aromatic core and weakly on the alkyl chain length at positions 3 and 6. The corresponding UV/Vis spectra from 10^{-4} mol l^{-1} dichloromethane solutions and compound colors are shown in Figure 1.

Due to the fact that the desired photochemical back reaction from the bis(beta-lactame) **2** to the pyrimidinium-olate **1** is not observed in conventional monocyclic mesoions, polycyclic compounds with extended aromatic systems were synthesized and their switching behavior was investigated. These investigations should address the question whether the extension of the aromatic system can lead to a reversible photoreaction. The long wavelength UV/Vis absorption maximum of the mesoions shows a significant red-shift with increasing ring number of the aromatic core, which indicates an enlarged delocalization of the mesoionic aromatic system. The reason for the bathochromic shift from ~380 to ~430 nm of **11** compared to the simple mesoions **5** can be found in the electronic coupling of the mesoionic base chromophore with the formal styrene subunit leading to a new extended orbital structure. The coupling of the aromatic cores is substantially higher than in the mesoion **5** with a principally isoelectronic pi-electron system including the phenyl substituent and free sulfur electron pair. Additionally, alkyl chain extension at the 3- and 6-position of the mesoionic core also leads to a weak bathochromic shift due to changes of the polarity in the vicinity of the mesoionic core similar to a solvent effect (compare in Fig. 1 compounds **5a**: 3-methyl, **5b**: 3-butyl, and **21**: 3,6-undecamethylene bridge; or **11a**: 3-methyl, and **11b**: 3-ethyl).

The UV spectra of the polycyclic mesoions show specific new features that can be attributed to the *N*,*N*′-disubstituted amidine substructure: a strong absorption band at 290–300 nm, and a double band at 320–330 nm for the two-ring

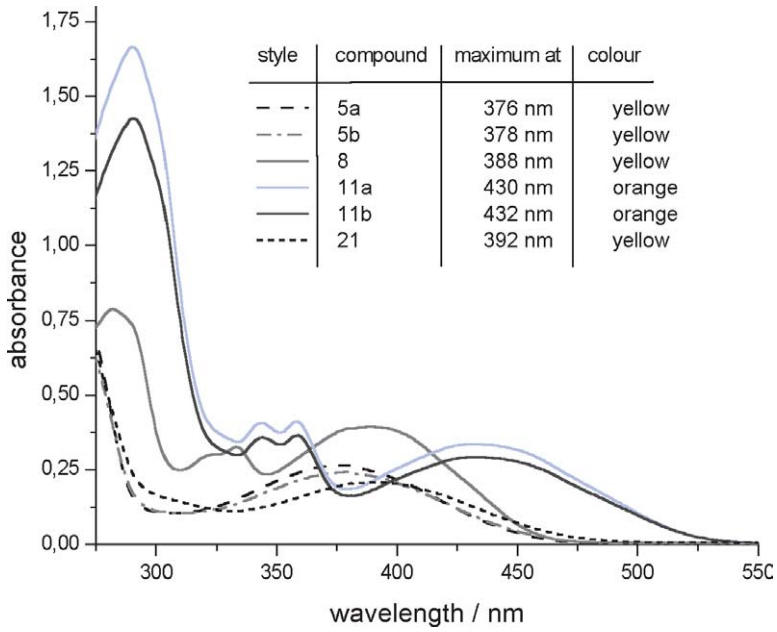
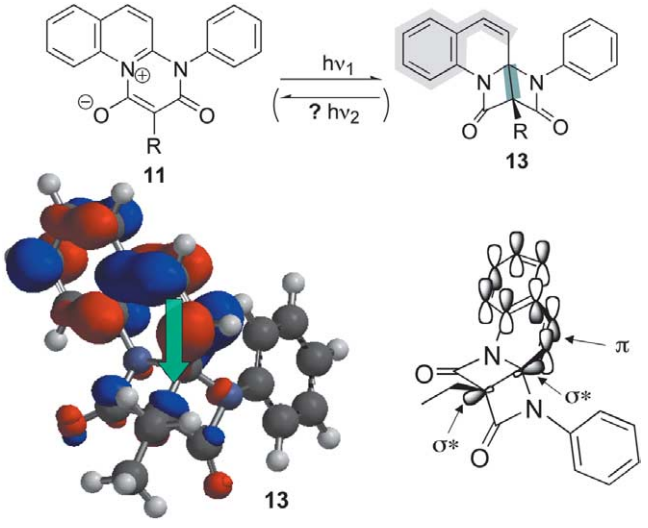


Figure 1. UV/Vis-spectra with the long wavelength absorption maxima of all synthesized mesoionic systems (10^{-4} mol l^{-1} in dichloromethane solution).

system **8** and even more distinct at 340–360 nm for the three-ring system **11**, respectively.

It was speculated that a photochemical ring opening of the hypothetical bis(beta-lactame) **13** might take place based on the fact, that the *ortho*-amino styrene fragment in **13** can be in hyperconjugation with the highly strained transannular σ-bond of the bis(beta-lactame) substructure. This hypothesis is supported by the structure of the LUMO of **11** (calculated by semiempirical PM3) which shows high orbital coefficients in the styrene subunit and a lobe at the carbon in position 3 (Scheme 4). This LUMO orbital should primarily control the course of the reaction upon photoexcitation. Thus, the styrene fragment, which is the largest chromophore in **13**, should be selectively excited by irradiation at



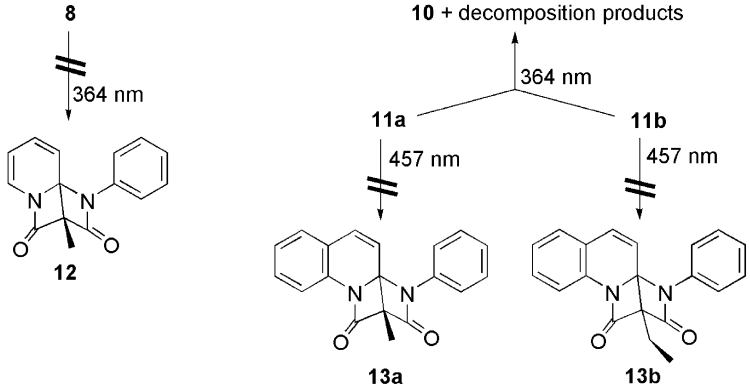
Scheme 4. Top: hypothetical photoreaction of **11** to **13** (with styrene subunit in light grey and transannular σ-bond in dark green). Bottom: left: LUMO of bis(beta-lactame) **13b** with the transannular σ-bond marked with an arrow; right: LUMO of **13b** with skeched π-orbitals of aromatic subunit and σ^*-orbitals of transannular σ-bond.

the longest energy absorption in **13**. The excited π-system could then directly interact with the almost parallely oriented antibonding orbital of the transannular σ-bond to break this bond and again form the polycyclic mesoion.

Surprisingly, none of the three annulated compounds formed the bis(beta-lactame) isomer upon irradiation in degassed dichloromethane solution (Scheme 5). Laser irradiation of **8** at 364 nm and of **11** at 457 nm led to very slow decomposition, whereas the starting compound **10** could be re-isolated after irradiation and fragmentation of **11** at the shorter wavelength absorption of 364 nm (double band feature in Fig. 1).

The major structural differences of polycyclic mesoions compared to simple mesoions are provided by the forced planarity of the molecular framework in contrast to the possible phenyl ring rotation in **5**. In addition, the conjugation pathways between the phenyl ring and the 6-position of the mesoion core (for numbering refer to Scheme 1) are different. As discussed before, the conjugation pathway in the annulated derivatives leads to a new orbital structure with longer wavelength absorption, but photoexcitation of the mesoionic core is still possible. What is to be held responsible for the lacking photorearrangement of the annulated systems **8** and **11** is the rigidity of the aromatic scaffold, which sterically hinders the photocyclization reaction in contrast to monocyclic systems, thus preventing the excited planar mesoionic core to convert to the roof-shaped photoproduct.

Ansa-bridged macrocyclic mesoions are not known from literature, so there is no data available addressing a possible hindrance of photocyclization due to the attachment of an alkyl bridge between the 3- and 6-position (designated R^1 and R^3 in Scheme 1). Synthesis of the macrocycle **21** was performed in 7 steps, as shown in Scheme 6.[12] ω-Bromoundecanol **14**, whose alcohol functionality was protected by 3,4-dihydro-2*H*-pyran (**15**),[13] was coupled with malonic acid di-*tert*-butyl ester using basic conditions.



Scheme 5. Results of the laser irradiation experiments with **8** and **11** in solution.

After acidic deprotection of the alcohol group[13] the resulting alcohol **17** was tosylated using 4-methyl-benzenesulfonyl chloride and pyridine in dichloromethane. Alkylation of 1,3-diphenylthiourea by the tosylate **18** leads to the formation of the corresponding isothiourea **19**. The soft nucleophilic sulphur makes 1,3-diphenylthiourea a good candidate for the reaction with soft electrophiles such as alkyl halogenides and sulphonates. The rather polar solvent *tert*-butyl alcohol stabilizes the intermediate *S*-alkyl-thiouronium salt. Basic workup yielded the desired diester **19**.

Basic saponification reactions for transforming **19** to **20** are not applicable here since the isothiourea functionality would decompose to 1,3-diphenylurea and the corresponding thiol.[14] Acidic deprotection of **19** with trifluoroacetic acid in dichloromethane was successful and led to complete conversion of the *tert*-butyl diester to the free carboxylic diacid after a few hours. Cyclization of **20** to the mesoionic macrocycle **21** was achieved using pseudo-dilution conditions with DCC in dichloromethane.

Irradiation of **21** in degassed dichloromethane gave the bis(beta-lactame) macrocycle **22**. The uniformity of the photocyclization process is proven by the isosbestic points in the UV/Vis spectra of Figure 2 and the detection of only one new spot by TLC.

3. Conclusion

Mesoions with an extended aromatic core show a shifted absorption maximum to longer wavelength compared to the 6-membered parent derivatives, but the stiffness of the molecular framework in such annulated systems prevents photochemical rearrangement to the roof-shaped bis(beta-lactames). This leaves the question if bis(beta-lactames) with extended aromatic systems in principle show a photochemical back reaction to their corresponding mesoions. This has to be investigated further, for example, by modifying the aromatic backbone.

In contrast, the long alkyl bridge of a macrocyclic ansa-

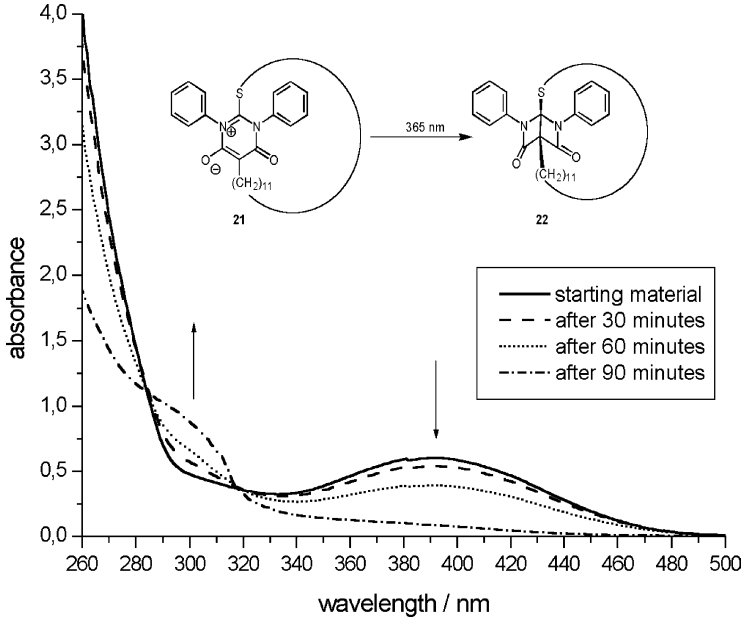
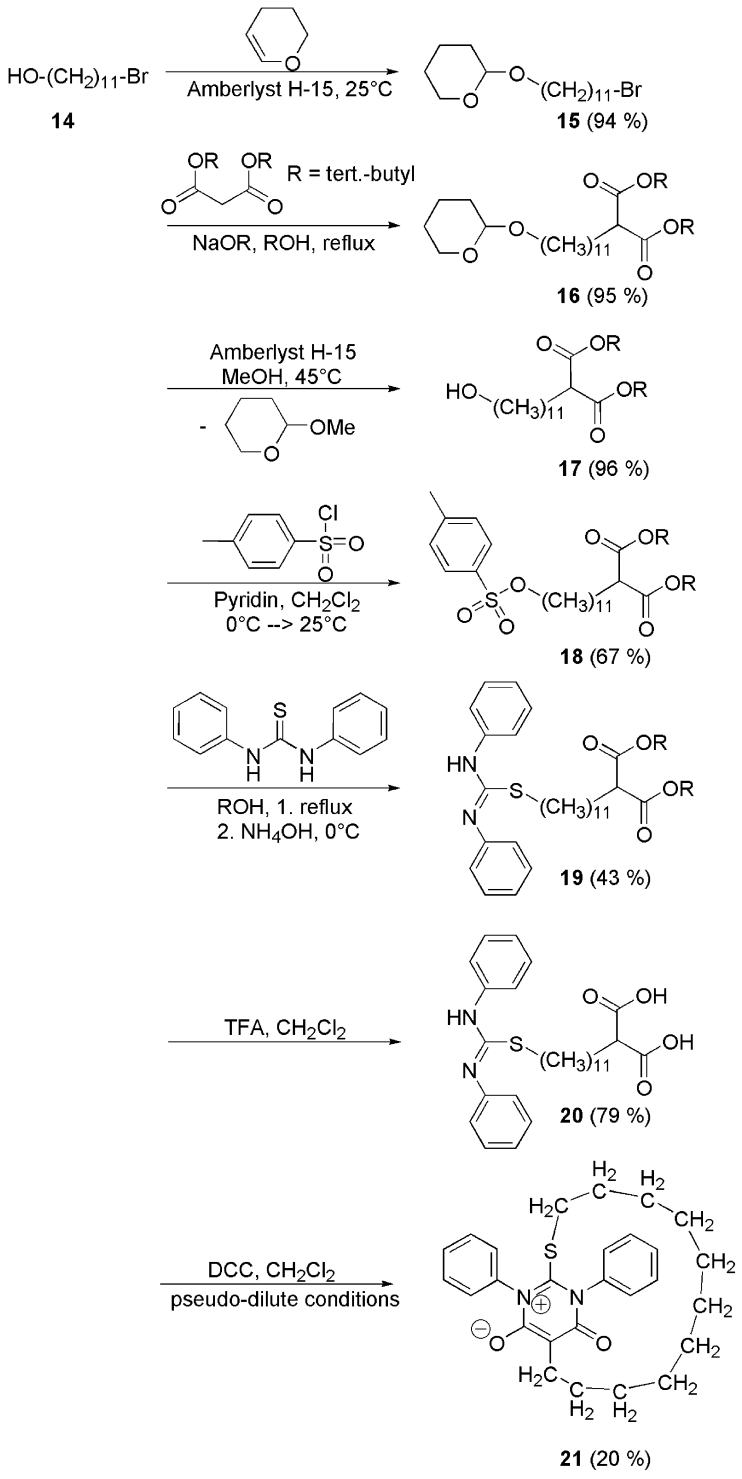


Figure 2. UV/Vis-spectra for the irradiation experiment of **21** (irradion with a UVP UV crosslinker consisting of 5 Sylvania lamps F8W/BL350 8 W each at 350 nm maximum, 10^{-4} mol l^{-1} in dichloromethane solution, Argon atmosphere).



Scheme 6. Synthetic route to the macrocyclic mesoion **21**.

mesoion does not markedly change intramolecular strain nor the electronic system, hence the photochemical rearrangement process is unhindered. This provides the possibility to incorporate the mesoionic function into flexible macrocyclic systems as a photosensitive unit, which may lead to interesting new material properties for macrocyclic systems, such as catenanes and cyclic ligands for biomolecular binding studies.

4. Experimental

4.1. General

All NMR spectra were acquired on Bruker Spectrospin 250 and AMX 500 spectrometers with the corresponding deuterated solvents as internal standard, IR spectra were measured on a Perkin Elmer Paragon 1000, EI- and FD-MS

spectra on a TRIO-2000 and ZAB 2-SE-FPD by VG-Instruments, UV/Vis spectra on a Perkin–Elmer Lambda 2 using 1×10^{-4} mol dichloromethane solutions of the respective substances. Melting points were measured on a Büchi B-545 apparatus and are uncorrected. **5a** was irradiated with a 600 W medium pressure mercury lamp with pyrex glass filter. **8**, **11a** and **11b** were irradiated using an Ar-Laser at 364 nm (0.25 W) and 457 nm (1.00 W), **21** using a UV crosslinker by UVP with 5 lamps (Sylvania F8W/BL350, 8 W each). Irradiation experiments were performed at 10^{-3} mol/l in degassed and argon-flushed dichloromethane.

Chemicals were purchased from ABCR, Merck and Sigma-Aldrich and were used without further purification. Solvents were dried with standard methods and stored over molecular sieve (4 Å).

S-Pentyl-1,3-diphenyl-isothiourea **4**. Pentyl bromide (15.10 g, 100 mmol, 1.4 equiv) was slowly added to a stirred suspension of **3** (16.34 g, 71.6 mmol) in ethanol (60 ml). The mixture was heated to reflux while the thiourea dissolved completely. After 25 h the reaction mixture was cooled and poured into aqueous ammonium hydroxide solution (220 ml, 2%) at 0 °C with rigorous stirring. The aqueous phase was decanted from the oil and extracted with diethyl ether, the combined organic phases were dried and concentrated. The crude product was purified by MPLC over silica (petrol ether/acetone 5:1) yielding a pale yellow waxy solid (12.76 g, 60%). TLC R_F 0.64 (petrol ether/acetone 5:1). IR (neat) 3383, 3057, 3028, 2956, 2929, 2858, 1624, 1586 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, $J=7$ Hz, 3H), 1.31–1.36 (m, 4H), 1.63 (quint., $J=7.2$ Hz, 2H), 2.73 (t, $J=6.9$ Hz, 2H), 6.41 (s, br, 1H), 7.12 (t, $J=7.2$ Hz, 2H), 7.28 (d, $J=7.2$ Hz, 4H), 7.36 (t, $J=7.2$ Hz, 4H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.9, 22.1, 29.2, 30.8, 31.7, 121.5, 123.6, 129.0, 143.8. MS (FD) *m/z* 298 $[M]^+$.

Preparation of mesoions **5**, **8**, and **11**. A typical procedure is exemplified for 5-methyl-6-oxo-1,3-diphenyl-2-pentylthio-pyrimidinium-4-olate **5a** as follows. To a stirred suspension of **4** (770 mg, 2.6 mmol) and methylmalonic acid (305 mg, 2.6 mmol) in dichloromethane (3 ml), DCC (1065 mg, 5.2 mmol) in dichloromethane (3 ml) was added with a syringe while the temperature was maintained at about 20 °C by water cooling. The mixture turned yellow and 1,3-dicyclohexylurea precipitated, showing the reaction progress. After stirring for another 3.5 h at ambient temperature the urea was filtered off and washed with dichloromethane. The filtrate was evaporated to dryness, dissolved in the minimum amount of toluene to which a 20-fold excess of hexane was slowly added. The product precipitated, was filtered and washed with hexane to yield yellow plates (770 mg, 78%), mp 174–175 °C. TLC R_F 0.63 (dichloromethane/methanol 20:1). IR (KBr) 3059, 3036, 2961, 2922, 2857, 1648, 1590 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 0.75 (t, $J=7$ Hz, 3H), 0.87–1.00 (m, 2H), 1.01–1.12 (m, 2H), 1.14–1.26 (m, 2H),1.95 (t, $J=7.9$ Hz, 2H), 1.96 (s, 3H), 7.30–7.34 (m, 4H), 7.46–7.49 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.6, 13.6, 21.7, 28.9, 30.1, 36.0, 92.5, 128.3, 129.3, 129.6, 137.3, 159.5, 159.6. UV (CH_2Cl_2) 226 (3.22), 376 (0.22) nm (log *e*). MS (EI) *m/z* 380 $[M]^+$, 294, 119, 91, 83, 77, 71, 69, 59, 56, 55. $C_{22}H_{24}N_2O_2S$ (380.50): calcd C 69.44 H 6.36 N 7.36; found C 69.31 H 6.51 N 7.46.

The other compounds were prepared in a similar manner. If necessary, purification was performed with chromatographic standard methods, using the TLC solvents.

4.1.1. 5-Butyl-6-oxo-1,3-diphenyl-2-pentylthio-pyrimidinium-4-olate 5b. Yellow solid, mp 108–109 °C. TLC R_F 0.89 (dichloromethane/methanol 20:1). IR (KBr) 3063, 3050, 2955, 2928, 2857, 1648, 1594 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) $\delta=0.74$ (t, $J=7.1$ Hz, 3H), 0.85 (t, $J=7.3$ Hz, 3H), 0.87–1.00 (m, 2H), 1.01–1.12 (m, 2H), 1.14–1.26 (m, 2H), 1.26–1.40 (m, 2H), 1.41–1.58 (m, 2H), 1.95 (t, $J=7.4$ Hz, 2H), 2.44 (t, $J=7.7$ Hz, 2H), 7.31–7.34 (m, 4H), 7.44–7.49 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.6, 13.9, 21.6, 22.9, 24.5, 28.8, 30.0, 30.1, 36.0, 97.2, 128.3, 129.2, 129.5, 137.3, 159.5, 159.7. UV (CH_2Cl_2) 234 (1.38), 383 (0.15) nm (log *e*). MS (FD) *m/z* 422 $[M]^+$. $C_{25}H_{30}N_2O_2S$ (422.58): calcd C 71.06 H 7.16 N 6.63; found C 70.70 H 7.02 N 7.03.

4.1.2. 3-Methyl-2-oxo-1-phenyl-1,2-dihydropyrido[1,2-*a*]pyrimidin-5-ium-4-olate 8. Yellow solid, mp ca. 290 °C (dec.). TLC R_F 0.12 (petrol ether/acetone 5:1). IR (KBr) 3110, 3070, 2926, 2854, 1638, 1627, 1586 cm^{-1}. ^1H NMR (250 MHz, d_6-DMSO) δ 1.92 (s, 3H), 6.73 (d, $J=8.85$ Hz, 1H), 7.39–7.49 (m, 3H), 7.53–7.66 (m, 3H), 8.04 (ddd, $J=1.58$, 1.90, 8.85 Hz, 1H), 9.22 (dd, $J=1.26$, 6.95 Hz, 1H). ^{13}C NMR (63 MHz, d_6-DMSO) δ 10.3, 87.8, 114.6, 116.2, 129.2, 129.3, 130.0, 130.1, 136.3, 142.2, 146.5, 153.8, 159.7. UV (CH_2Cl_2) 234 (1.74), 282 (0.40), 332 (0.17), 388 (0.20) nm (log *e*). MS (FD) *m/z* 253 $[M+H]^+$. $C_{15}H_{12}N_2O_2$ (252.27): calcd C 71.42 H 4.79 N 11.10; found C 71.16 H 5.25 N 11.00.

4.1.3. 2-Methyl-3-oxo-4-phenyl-3,4-dihydropyrimido[1,2-*a*]chinolin-11-ium-1-olate 11a. Orange solid, mp 232 °C (dec.). TLC R_F 0.27 (ethyl acetate). IR (KBr) 3323, 3150, 3047, 2921, 2854, 1685, 1636, 1610, 1561, 1518 cm^{-1}. ^1H NMR (250 MHz, d_6-DMSO) δ 1.94 (s, 3H), 6.70 (d, $J=9.5$ Hz, 1H), 7.44–7.48 (m, 2H), 7.58–7.70 (m, 4H), 7.82 (ddd, $J=1.58$, 1.90, 8.85 Hz, 1H,), 8.00 (dd, $J=1.58$, 7.9 Hz, 1H); 8.30 (d, $J=9.48$ Hz, 1H), 9.64 (d, $J=8.85$ Hz, 1H). ^{13}C NMR (63 MHz, d_6-DMSO) δ 10.6, 90.1, 114.0, 122.3, 124.1, 126.8, 129.0, 129.4, 130.0, 130.9, 134.4, 136.8, 141.5, 148.2, 158.5, 159.4. UV (CH_2Cl_2) 240 (2.45), 288 (1.12), 342 (0.25), 358 (0.25), 430 (0.20) nm (log *e*). MS (EI) *m/z* 302 $[M]^+$, 274, 273, 245, 219, 218, 128, 83, 77. $C_{19}H_{14}N_2O_2$ (302.33): calcd C 75.48 H 4.67 N 9.27; found C 75.22 H 4.77 N 9.15.

4.1.4. 2-Ethyl-3-oxo-4-phenyl-3,4-dihydropyrimido[1,2-*a*]chinolin-11-ium-1-olate 11b. Orange solid, mp 217–218 °C (dec.). TLC R_F 0.49 (ethyl acetate). IR (KBr) 3321, 3144, 3020, 2950, 2923, 2859, 1682, 1633, 1617, 1560, 1518 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.21 (t, $J=7.27$, 7.58 Hz, 3H), 2.68 (q, $J=7.27$, 7.58 Hz, 2H), 6.75 (d, $J=9.5$ Hz, 1H), 7.29–7.33 (m, 2H), 7.55–7.65 (m, 4H), 7.74–7.82 (m, 2H), 7.93 (d, $J=9.5$ Hz, 1H), 9.77 (d, $J=8.9$ Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.8, 18.8, 99.5, 113.1, 123.5, 124.3, 127.3, 128.67, 128.73, 129.9, 130.6, 131.7, 135.2, 136.5, 141.2, 147.9, 158.9, 159.9. UV (CH_2Cl_2) 240

(2.85), 290 (1.12), 344 (0.28), 358 (0.28), 432 (0.23) nm (log *e*). MS (FD) *m/z* 317 $[M+H]^+$. $C_{20}H_{16}N_2O_2$ (316.35): calcd C 75.93 H 5.10 N 8.86; found C 75.77 H 5.12 N 8.90.

4.1.5. 4-Methyl-1-pentylsulfanyl-2,6-diphenyl-2,6-diaza-bicyclo[2.2.0]hexane-3,5-dione 6a. 76 mg (0.2 mmol) **5a** were dissolved in degassed dichloromethane (200 ml) and irradiated for 3.5 h with a medium pressure mercury lamp (600 W) through a pyrex glass filter. The solvent was removed in vacuo and the crude product purified by preparative TLC (petrol ether/acetone 5:1) to yield a colorless oil. TLC R_F 0.38 (petrol ether/acetone 5:1). IR (neat): 3065, 2958, 2930, 2859, 1782, 1750, 1599, 753, 691 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (t, $J=7$ Hz, 3 H), 1.20–1.36 (m, 4H), 1.53–1.65 (m, 2H), 1.73 (s, 3H), 2.68 (t, $J=7.2$ Hz, 2H), 7.12–7.18 (m, 2H), 7.26–7.33 (m, 4H), 7.56 (d, $J=7.9$ Hz, 4H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 7.0, 13.8, 22.0, 28.4, 30.4, 30.8, 79.5, 85.5, 119.7, 125.9, 129.2, 136.2, 162.7. UV (CH_2Cl_2) 232 (2.06) nm (log *e*). MS (FD) *m/z* 398 $[M+H_2O]^+$, 133.

4.1.6. 2-(11-Bromo-undecyloxy)-tetrahydro-pyran 15. To a stirred suspension of 11-bromo-1-undecanol (15.07 g, 60 mmol) and 3,4-dihydro-2*H*-pyrane (6.06 g, 72 mmol) in cyclohexane (30 ml) amberlyst H-15 (1.50 g, 10 mequiv) was added. After stirring for 4.5 h at ambient temperature the residue was filtered off and the solvent removed in vacuo. The crude product was purified by distillation (a small piece of potassium hydroxide was added to the flask), yielding **15** as a colorless oil (18.92 g, 94%), bp 145–150 °C, 0.15 mbar. TLC R_F 0.66 (petrol ether/acetone 50:1). IR (neat) 2930, 2854 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.25–1.87 (series of m, 24H), 3.37 (t, $J=6.9$ Hz, 2H), 3.30–3.88 (series of m, 4H), 4.54 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.7, 25.5, 26.2, 28.1, 28.7, 29.4, 29.5, 29.7, 30.8, 32.8, 33.9, 62.3, 67.6, 98.8. MS (EI) *m/z* 337/335 $[M]^+$, 85 $[THP]^+$.

4.1.7. 2-[11-(Tetrahydro-pyran-2-yloxy)-undecyl]-malonic acid di-*tert*-butyl ester 16. 0.57 g sodium metal was dissolved in 20 ml *tert*-butanol at elevated temperature. Malonic acid di-*tert*-butyl ester (5.36 g, 24.8 mmol) and **15** (7.51 g, 23.6 mmol) were added successively with a syringe. The reaction mixture was refluxed overnight, until **15** was no longer detected by TLC. After removing most of the solvent in vacuo water was added to the cold reaction mixture to dissolve the sodium bromide precipitate. The aqueous phase was decanted and extracted twice with diethyl ether, dried and concentrated to yield 10.56 g (95%) of the product as a colorless viscous oil. TLC R_F 0.72 (petrol ether/acetone 5:1). IR (neat) 2977, 2928, 2855, 1748, 1729 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.16–1.32 (m, 16H), 1.41 (s, 18H), 1.42–1.53 (m, 6H), 1.65–1.82 (m, 4H), 3.05 (t, 1H), 3.28–3.37 (m, 1H), 3.42–3.46 (m, 1H), 3.63–3.72 (m, 1H), 3.78–3.85 (m, 1H), 4.54 (s, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.6, 25.4, 26.2, 27.1, 27.9, 28.5, 29.2, 29.3, 29.4, 29.5, 29.5, 29.7, 30.7, 53.9, 62.2, 67.6, 81.0, 98.7, 169.0. MS (EI) *m/z* 472 $[M+1]^+$.

4.1.8. 2-(11-Hydroxy-undecyl)-malonic acid di-*tert*-butyl ester 17. Amberlyst H-15 (674 mg, 10 mequiv) was added to a solution of **16** (10.56 g, 22.4 mmol) in methanol (40 ml) and the mixture was stirred at 45 °C for 10 h until **16** could no longer be traced by TLC. The residue was filtered off and the solvent removed in vacuo to yield 8.34 g (96%) of the crude product as colorless oil. TLC R_F 0.18 (petrol ether/acetone 5:1). IR (neat) 3414, 2978, 2921, 2855, 1742, 1725 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.13–1.35 (m, 16H), 1.39 (s, 18H), 1.45–1.57 (m, 2H), 1.65–1.78 (m, 2H), 2.49 (s, 1H), 3.04 (t, $J=7.6$ Hz, 1H), 3.56 (t, $J=6.6$ Hz, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.6, 27.1, 27.8, 28.5, 29.1, 29.2, 29.3, 29.4, 29.4, 29.5, 32.6, 53.9, 62.8, 81.1, 169.0. MS (FD) *m/z* 387 $[M]^+$.

4.1.9. 2-[11-(Toluene-4-sulfonyloxy)-undecyl]-malonic acid di-*tert*-butyl ester 18. 17 (8.16 g, 21.1 mmol) and pyridine (3.34 g, 42.2 mmol) were dissolved in dichloromethane (90 ml) and cooled to 0 °C in an ice-bath. *p*-Toluenesulfonic acid chloride (4.02 g, 21.1 mmol) was slowly added and the mixture stirred for 3 days at ambient temperature. After washing with water the organic phase was concentrated and the crude product purified by column chromatography on silica (petrol ether/acetone 5:1), yielding a colorless oil (7.59 g, 67%). TLC R_F 0.32 (petrol ether/acetone 5:1). IR (neat) 3072, 2977, 2928, 2855, 1742, 1727, 1598, 1367, 1177, 816 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.16–1.24 (m, 16H), 1.41 (s, 18H), 1.53–1.64 (m, 2H), 1.67–1.80 (m, 2H), 2.41 (s, 3H), 3.06 (t, $J=7.6$ Hz, 1H), 3.97 (t, $J=6.5$ Hz, 2H), 7.30 (d, $J=8.2$ Hz, 2H), 7.75 (d, $J=8.2$ Hz, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.6, 25.2, 27.1, 27.9, 28.5, 28.7, 28.8, 29.2, 29.2, 29.3, 29.3, 29.4, 53.9, 70.6, 81.1, 127.8, 129.7, 133.2, 144.5, 169.0. MS (FD) *m/z* 541 $[M]^+$, 206, 172 $[tosyl\text{-}OH]^+$.

4.1.10. 2-[11-(*N*,*N*′-Diphenyl-carbamimidoylsulfanyl)-undecyl]-malonic acid di-*tert*-butyl ester 19. A solution of **18** (7.30 g, 13.5 mmol) and **3** (3.08 g, 13.5 mmol) in *tert*-butanol (20 ml) was refluxed while the thiourea completely dissolved. After 16 h most of the solvent was removed in vacuo and ethanol (20 ml) was added to the brownish reaction mixture. Then the mixture was poured into an aqueous ammonium hydroxide solution (41 ml, 2%) at 0 °C with rigorous stirring. The aqueous phase was decanted from the oil and the remaining water was distilled off as an azeotrope with chloroform. The crude product was purified by MPLC over silica (petrol ether/acetone 5:1) yielding a waxy solid that was recrystallized from hexane to give a pale yellow solid (3.49 g, 43%), mp 80–81 °C. TLC R_F 0.40 (petrol ether/acetone 5:1). IR (KBr) 3362, 3057, 3030, 2977, 2927, 2854, 1737, 1727, 1626, 1588, 1368, 755, 694 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.13–1.32 (m, 16H), 1.40 (s, 18H), 1.47–1.52 (m, 2H), 1.62–1.76 (m, 2H), 2.61 (t, br, $J=$ 7.1 Hz, 2H), 3.06 (t, $J=7.6$ Hz, 1H), 5.90 (s, br, 1H), 7.02 (t, $J=7.2$ Hz, 2H), 7.18 (d, $J=7.2$ Hz, 4H), 7.25 (t, $J=7.2$ Hz, 4H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.1, 27.9, 28.5, 28.6, 29.0, 29.2, 29.2, 29.3, 29.4, 29.5, 31.7, 53.9, 81.1, 121.6, 123.7, 129.0, 169.0. MS (FD) *m/z* 596 $[M]^+$.

4.1.11. 2-[11-(*N*,*N*′-Diphenyl-carbamimidoylsulfanyl)-undecyl]-malonic acid 20. 19 (500 mg, 0.84 mmol) and trifluoroacetic acid (1.91 g, 16.8 mmol, 20 equiv) were dissolved in dichloromethane (10 ml) and stirred for 10 h at ambient temperature. After the volatile part was removed in vacuo, the product was used without further purification. Colorless oil (320 mg, 79%). TLC R_F 0.30 (dichloromethane/methanol/25%NH_3 in water 13:6:1). IR (neat)

3207, 2980, 2929, 2857, 1722, 1605, 1573, 1172, 759, 693 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.10–1.40 (m, 16H), 1.46–1.60 (m, 2H), 1.85–1.95 (m, 2H), 3.02 (t, br, 2H), 3.40 (t, $J=7.2$ Hz, 1H), 5.90 (s, br, 1H),7.29–7.44 (m, 10H), 9.74 (s, br, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 26.9, 27.7, 28.3, 28.6, 28.9, 29.0, 30.9, 32.1, 51.2, 126.0, 129.7, 130.2, 133.7, 174.9. MS (FD) *m/z* 485 $[M]^+$, 441 $[M-CO_2]^+$.

4.1.12. 16-Aza-17-azonia-16,17-diphenyl-18-oxido-15-oxo-2-thia-bicyclo-[11.2.2]octadeca-1(17),14(18)-diene 21. DCC (87 mg, 0.42 mmol) in dichloromethane (50 ml) was added to a stirred solution of **20** (100 mg, 0.21 mmol) in dichloromethane (150 ml) with a syringe while the temperature was maintained at about 20 °C by water cooling. The mixture turned yellow and 1,3-dicyclohexylurea precipitated, showing the progress of the reaction. After stirring overnight at ambient temperature the urea was filtered off and washed with dichloromethane. The filtrate was concentrated and the crude product purified by preparative TLC (petrol ether/acetone 5:1) yielding a yellow solid (19 mg, 20%), mp 171 °C. IR (KBr) 2926, 2854, 1649, 1358, 1244 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.25–1.65 (m, 18H), 2.20 (t, $J=6$ Hz, 2H), 2.58 (t, $J=6$ Hz, 2H), 7.27–7.58 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.1, 25.9, 26.8, 26.9, 27.1, 27.8, 28.6, 30.6, 36.1, 97.8, 128.4, 128.9, 129.2, 129.8, 137.5, 159.6. UV (CH_2Cl_2) 392 (0.60) nm (log *e*). MS (FD) *m/z* 531, 448 $[M]^+$. HRMS found M^+ 448.2190. $C_{27}H_{32}N_2O_2S$ requires 448.2185.

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Synthesis of chromeno[4,3,2-*cd*]isoindolin-2-ones and chromeno[4,3,2-*de*]isoquinolin-3-ones. Electrophilic versus anionic cyclization of carbamates

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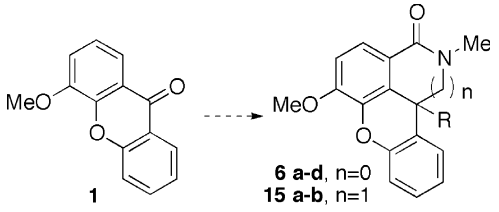
Abstract—The total synthesis of chromeno[4,3,2-*cd*]isoindolin-2-ones **6a–d** and chromeno[4,3,2-*de*]isoquinolin-3-ones **15a–b** from 4-methoxy-9*H*-xanthen-9-one is reported. The construction of the nitrogenated ring was attempted by both intramolecular electrophilic and anionic cyclizations of the corresponding carbamate precursors. Only anionic cyclization was possible for isoindolinones, but for isoquinolinones the electrophilic and anionic routes both afforded excellent yields.

1. Introduction

Xanthenes are among the oldest classical pigments,[1] are used as linkers in solid phase peptide synthesis[2] and as protectors of the 5′-OH of nucleosides,[3] and in many cases have interesting biological effects[4] such as inhibition of gastric secretion,[5] and antitumoral,[6] opiaceous[7] or cytotoxic activity.[8] Benzolactams such as isoindolinones[9] and isoquinolinones[10] have also been reported to have a broad spectrum of pharmacological activities. In particular, in the recent patent literature there are claims that unsubstituted chromeno[4,3,2-*cd*]isoindolin-1-one and isoquinolin-3-one are poly(ADP ribose) polymerase inhibitors that are useful for treating neural and cardiovascular tissue damage.[11] In this paper we report our approach to the synthesis of chromenoisoindolinones **6a–d** and chromenoisoquinolinones **15a–b** by construction of the nitrogenated ring on the skeleton of 4-methoxyxanthone **1** by either electrophilic or anionic annelating (Scheme 1).



Scheme 1.

2. Results and discussion

We first planned to synthesize isoindolone **6a** by the classical approach, electrophilic cyclization of the corresponding carbamate **4** (Scheme 2). The intramolecular arylation of carbamates (Banwell's cyclization)[12] is a well established procedure for the synthesis of isoquinolinones,[13] but we know of no reports of its use for the synthesis of isoindolinones. The required carbamate was prepared straightforwardly from starting 4-methoxyxanthone (Scheme 2). Reduction of xanthone **1**[7] with zinc powder in alkaline ethanol gave a 92% yield of xanthydrol **2**,[6] which was then aminated to the *N*-xanthen-9-yl derivative **3** with ethyl carbamate in acetic acid/ethanol (91%). Alkylation of **3** by treatment with NaH in DMF followed by addition of methyl iodide gave the tertiary carbamate **4** in 90% yield. However, reaction of **4** under Banwell's conditions[12] (with Tf_2O (5 equiv) and DMAP (3 equiv) in CH_2Cl_2) afforded a quantitative yield of the dimethylamine pyridinium salt resulting from nucleophilic displacement of the urethane. Other attempts at cyclization included the treatment of **4** with PPA at 70 °C,[14] which led to slow oxidation to the xanthone **1**, or with refluxing $POCl_3$,[15] which afforded a complex mixture with no cyclized compounds.

The failure of **4** to undergo cyclization was ascribed to the

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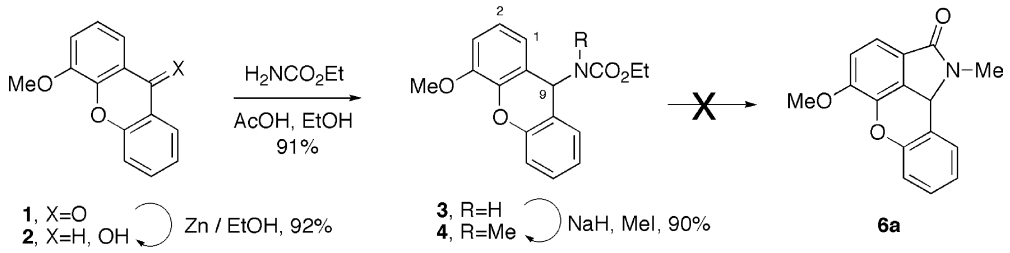
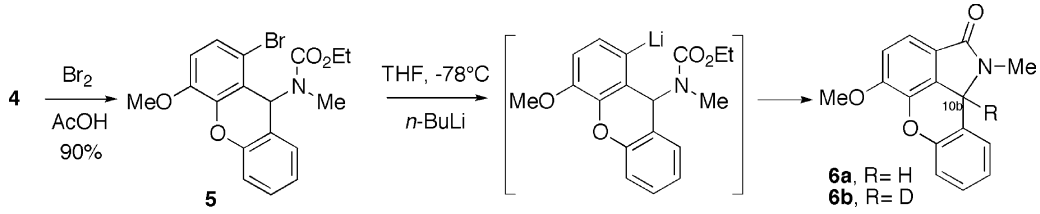


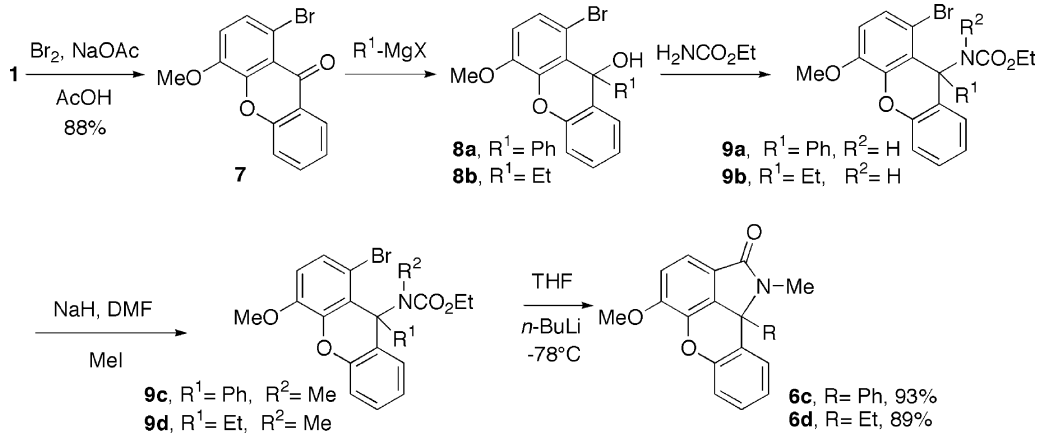
Scheme 2.



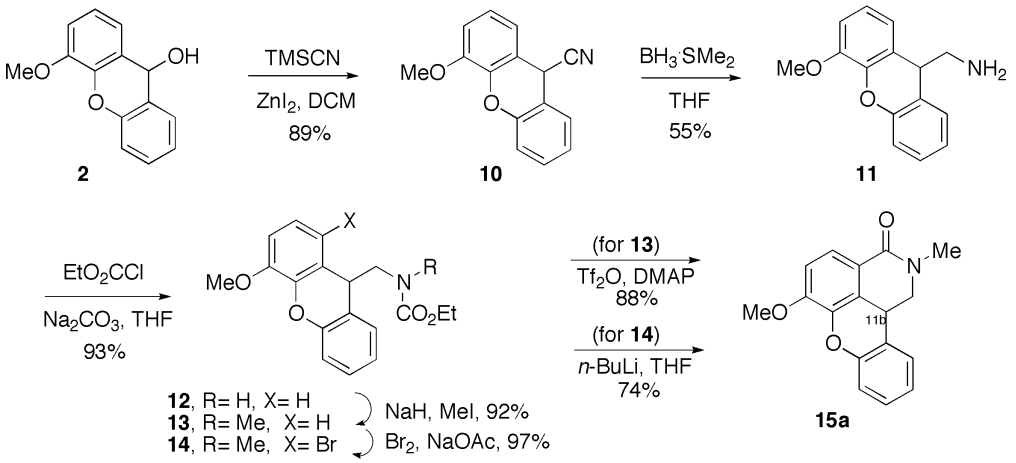
Scheme 3.

instability of the carbamate group at the very reactive 9-position of the xanthene nucleus under the harsh conditions required for its activation. We therefore, decided to try to construct the fused five membered lactam ring by means of the anionic cyclization mechanism that we had previously used for the synthesis of benzofused γ-lactones,[16] and which appears to have been applied to isoindolinones only in the case of a synthesis of dibenz[*cd*, *f*]indolones described in the patent literature.[17] For this we needed to metalate the aromatic ring *para* to the methoxy group in **4** so as to acylate it intramolecularly with the carbamate.[18] To be able to carry out the metalation by halogen–metal exchange, we treated the carbamate **4** with bromine in acetic acid in the presence of sodium acetate, which regioselectively afforded the required brominated compound **5** in high yield (Scheme 3). Treatment of **5** with an equimolecular amount of *n*-BuLi at −78 °C (Method A in Section 3) then provided the intermediate lithiated derivative that evolved to a mixture of the desired cyclized compound **6a** (54%) and debrominated **4** (39%). To clarify whether the latter one was produced by protonation of the intermediate aryl-lithium derivative during work-up or previously, we repeated the reaction and quenched it with methanol-d_1 (Method B); the finding that the resulted lactam **6b** had deuterium at C10b while the accompanying compound **4** had none suggests that the isoindolone product acts as a proton source for the organometallic intermediate. In keeping with this, the yield of **6** increased to 65% when 2 equiv of *n*-BuLi were used, and to 80% when the carbamate was added to a solution of 3 equiv of *n*-BuLi (Method C). Adding the carbamate to the base instead of the other way round favors deprotonation at position 10b of the isoindolinone by the excess of base, which both forestalls its deprotonation by the aryl-lithium intermediate (which thus survives to be cyclized) and prevents nucleophilic addition of *n*-BuLi to the carbonyl of the cyclized product.

The applicability of the above cyclization procedure to the synthesis of 10b-substituted isoindolinones was verified by preparing **6c** and **6d** by anionic cyclization of the 9-substituted bromocarbamates **9c** and **9d**. Although bromination of the corresponding 9-substituted analogues of **4** did not occur at position 1 but at position 2, which was ascribed to steric hindrance by C9 substituents, this problem was circumvented by brominating the starting xanthone (Scheme 4): regioselective bromination of **1** to **7** followed by reaction with phenylmagnesium chloride or ethylmagnesium bromide gave the tertiary xanthydrols **8a** and



Scheme 4.



Scheme 5.

8b in high yields, and reaction of the latter ones with ethyl carbamate followed by *N*-methylation as before led to the required 9-substituted bromocarbamates **9c** and **9d**. Treatment of these intermediates with an equimolecular amount of *n*-BuLi in THF at −78 °C (Method A) led to bromine–lithium exchange, and the resulting aryl-lithiated derivatives were successfully trapped by the internal acylating carbamate in an anionic cyclization step which proceeded in very good yield for both **6c** and **6d**.

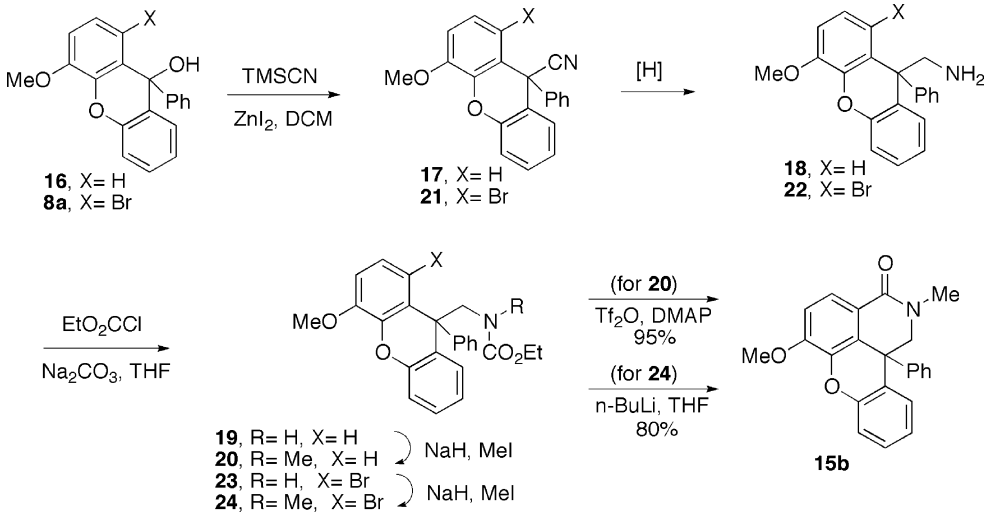
We next addressed the preparation of six-membered lactams. The carbamate necessary for electrophilic cyclization, **13**, was prepared starting from xanthydrol **2** by cyanation with TMSCN, followed by reduction with borane to the aminomethyl xanthene **11**, which was then reacted with ethyl chloroformate and finally *N*-methylated (Scheme 5). Gratifyingly, submitting carbamate **13** to electrophilic cyclization conditions (treatment with Tf_2O and DMAP) provided the desired isoquinolinone **15a** in excellent yield. This result contrasts sharply with the failure of this procedure in the case of the lower homologue **4**; it seems likely that carbamate **13** is more stable, surviving the reactions conditions without decomposition.

The alternative anionic cyclization also proved successful. The first ones to apply this method to the synthesis of δ-benzolactams were Comins et al., who after considerable experimentation obtained a 26% optimized yield in the assembly of the 6-membered lactam ring of the protoberberine alkaloid (−)-xylopinine.[19] Recent findings by Orito et al. suggest that these low yields are due to the organometallic reagent reacting with the benzolactam product faster than with the substrate.[20] Thus, for this cyclization to be successful it would appear that the substrate must be such that bromine–lithium exchange and subsequent entrapment by the carbamate group are so fast that no organometallic is left when the lactam is formed by internal acylation. Fortunately this proved to be the case with the bromocarbamate **14**, which was prepared straightforwardly by almost quantitative bromination of **13** (Scheme 5). Upon treatment of **14** with an equimolecular amount of *n*-BuLi the isoquinolinone **15a** was formed in 74%. In contrast with the lower homolog **6**, the yield of cyclization of **14** drastically drops to 14 and 11% when using 2 or 3 equiv of *n*-BuLi respectively. The deleterious effect of excess base, which contrasts with its increasing the yield of isoindolone **6**, is due to the acidity of proton 11b of the isoquinolinone **15a**, abstraction of which by the *n*-BuLi promotes the alkylation of this position by *n*-BuBr formed during the bromine–lithium exchange (as was deduced from the isolation of significant amounts of the corresponding 11b-butylisoquinolinone when 2 equiv of *n*-BuLi were used); with 3 equiv of *n*-BuLi this process was followed by nucleophilic addition to the carbonyl of the lactam, affording an 3,11b-dibutylisoquinolinium derivative as major product.

Thus both cyclization procedures are effective for the synthesis of chromenoisoquinolinone **15a**, although the electrophilic mechanism provides the shorter and higher yielding route.

As in the case of isoindolinones, we also synthetized the 11b-phenylated analogue (Scheme 6). Carbamate **20** was prepared from 9-phenylxanthydrol **16** by conversion of the latter to cyanide **17** (by treatment with TMSCN and ZnI_2), reduction of **17** to amine **18** (best achieved by $NaBH_4/NiCl_2$ in EtOH), carboxylation of **18** to carbamate **19**, and final *N*-methylation. Upon treatment with triflic anhydride and DMAP the electrophilic cyclization of **20** to **15b** occurred in an excellent 95% yield. Carbamate **24**, required for the anionic cyclization, was prepared from bromophenylxanthydrol **8a**, regioselectivity problems precluding its preparation by direct bromination of **20**. Compound **8a** was converted to the cyanide **21**, following which reduction with borane, acylation and *N*-methylation gave the required bromocarbamate **24**. Finally, addition of an equimolar amount of *n*-BuLi promoted anionic cyclization, affording **15b** in 80% yield.

In summary, we have evaluated both electrophilic and anionic cyclization protocols for the annelation of lactams in xantheno derivatives. The more classical electrophilic cyclization of carbamates was only useful for the synthesis of isoquinolinones, while the less known anionic cyclization proved to be efficient for the assembling of both five and six-membered lactams.



Scheme 6.

3. Experimental

3.1. General procedures

The solvent for NMR was $CDCl_3$ (unless otherwise stated), with TMS as internal reference. Coupling constants (J) are in Hertz. Most of the ^1H (250.13 MHz) and ^{13}C NMR (62.83 MHz) signals of the tertiary carbamates are doubled as a consequence of their existence as mixtures of rotamers. All new compounds were determined to be more than 95% pure by ^1H and ^{13}C NMR. All chemicals were purchased from Aldrich.

3.2. Synthesis of chromeno[4,3,2-*cd*]isoindolin-2-ones (6a–d)

3.2.1. 4-Methoxy-9*H*-xanthen-9-ol (2). A suspension of 4-methoxy-9*H*-xanthen-9-one (**1**)[7] (20 g, 0.088 mol), Zn (8.68 g, 0.133 mol) and NaOH (21.2 g, 0.53 mol) in 96% ethanol (220 mL) was heated at 90 °C for 2 h. The solid was removed by filtration, associated product was recovered by washing with ethanol, and the pooled washings and filtrate condensed to dryness. Water was added to the residue and the precipitated 4-methoxy-9*H*-xanthen-9-ol was filtered out and washed with more water affording a white solid (18.6 g, 92%). Mp 124 °C; lit.[6] 125–128 °C. ^1H NMR: 7.60 (dd, J=7.6, 1.6 Hz, 1H), 7.35–7.08 (m, 5H), 6.92 (dd, J=7.9, 1.6 Hz, 1H), 5.82 (d, J=8.6 Hz, 1H), 3.94 (s, 3H), 2.15 (d, J=8.6 Hz, 1H).

3.2.2. *N*-(4-Methoxy-9*H*-xanthen-9-yl)carbamic acid ethyl ester (3). A solution of urethane (1.56 g, 17.5 mmol) in acetic acid/ethanol (5 mL/5 mL) was added to a solution of 4-methoxy-9*H*-xanthen-9-ol (4 g, 17.5 mmol) in acetic acid (7 mL) and ethanol (7 mL). After stirring for 12 h at rt, water was added and a white solid was filtered out and washed with water and cold methanol (4.7 g, 91%). Mp 142 °C. IR (KBr): 3308 (NH), 1681 (CO) cm^{-1}. ^1H NMR: 7.53 (d, J=7.4 Hz, 1H), 7.31–7.22 (m, 2H), 7.16–7.03 (m, 3H), 6.89 (dd, J=7.7, 1.7 Hz, 1H), 6.20 (d, J=9.6 Hz, 1H), 5.33 (d, J=9.6 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 3.95 (s, 3H, OMe), 1.26 (t, J=7.1 Hz, 3H). ^{13}C/DEPT: 156.7 (CO), 151.2 (C), 148.0 (C), 141.2 (C), 129.8 (CH), 129.5 (CH), 124.0 (CH), 123.4 (CH), 122.5 (C), 121.5 (C), 121.2 (CH), 117.2 (CH), 111.3 (CH), 61.5 (OCH_2), 56.5 (OCH_3), 46.2 (CH), 15.0 (CH_3). EI-MS: m/z (%) 299 (M^+, 49), 270 (74), 211 (100). HRMS: Calcd for $C_{17}H_{17}NO_4$: 299.115758; found: 299.115593.

3.2.3. *N*-(4-Methoxy-9*H*-xanthen-9-yl)-*N*-methylcarbamic acid ethyl ester (4). Sodium hydride (1.19 g, 80% in mineral oil, 39.6 mmol) was washed twice with THF, DMF (3 mL) was added and this suspension was first deoxygenated by passing a stream of argon through it, and then cooled to 0 °C before a solution of carbamate **3** (3.94 g, 13.1 mmol) in deoxygenated DMF (24 mL) was added. After 30 min at 0 °C, methyl iodide (1.64 mL, 26 mmol) was added, and after a further 30 min at rt water was added, the mixture was extracted with CH_2Cl_2, the organic extract was washed with saturated aqueous NaCl solution (3× 100 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (1:4 EtOAc/hexane), giving **4** as a colourless oil (3.94 g, 90%). IR (NaCl): 1695 (CO) cm^{-1}. ^1H NMR: 7.40–7.22 (m, 3H), 7.14–6.86 (m, 4H), 6.82 and 6.63 (both s, 1H), 4.35 and 4.26 (both q, J=7.1 Hz, 2H), 3.93 (s, 3H), 2.45 and 2.40 (both s, 3H), 1.39 and 1.31 (both t, J=7.1 Hz, 3H). ^{13}C/DEPT: 157.9 (CO), 156.6 (CO), 152.2 (C), 151.9 (C), 148.1 (C), 148.0 (C), 142.2 (C), 142.0 (C), 129.6 (CH), 129.5 (CH), 129.1 (CH), 124.1 (CH), 123.4 (CH), 121.0 (CH), 120.5 (CH), 120.4 (CH), 120.1 (CH), 119.4 (C), 119.1 (C), 117.3 (CH), 117.2 (CH), 111.3 (CH), 62.1 (OCH_2), 62.0 (OCH_2), 56.4 (OCH_3), 50.8 (CH), 50.6 (CH), 29.4 (NCH_3), 28.9 (NCH_3), 15.3 (CH_3), 15.1 (CH_3). EI-MS: m/z (%) 313 (M^+, 12), 211 (100). HRMS: Calcd for $C_{18}H_{19}NO_4$: 313.131408; found: 313.131961.

3.2.4. *N*-(1-Bromo-4-methoxy-9*H*-xanthen-9-yl)-*N*-methylcarbamic acid ethyl ester (5). The carbamate **4** (3.2 g, 10.3 mmol) and NaOAc (1.26 g, 15.4 mmol) were dissolved in AcOH (30 mL), bromine (0.63 mL, 12.2 mmol) was added, and the solution was stirred for 12 h. Sodium thiosulphate solution was added and the mixture was extracted with CH_2Cl_2, the organic layer washed with aqueous NaCl, dried with Na_2SO_4 and filtered, and the

solvent was removed under reduced pressure. The residue was purified by flash chromatography (3:1 CH_2Cl_2/hexane), affording 3.6 g (90%) of **5**, which was recrystallized from CH_2Cl_2/hexane. Mp 130 °C. IR (NaCl): 1696 (CO) cm^{-1}. ^1H NMR: 7.68 and 7.31 (both d, $J=7.1$, 8.7 Hz, 1H), 7.27–7.12 (m, 4H), 6.83 and 6.63 (both s, 1H), 6.79 (d, $J=5.7$ Hz, 1H), 4.36–4.19 (m, 2H), 3.95 (s, 3H), 2.37 and 2.35 (both s, 3H), 1.43 and 1.27 (both t, $J=7.1$ Hz, 3H). ^{13}C/DEPT: 156.9 (CO), 156.0 (CO), 151.7 (C), 147.8 (C), 144.4 (C), 144.2 (C), 130.1 (CH), 129.7 (CH), 129.6 (CH), 129.5 (CH), 127.2 (CH), 127.1 (CH), 124.7 (CH), 124.6 (CH), 120.6 (C), 120.1 (C), 119.6 (C), 119.4 (C), 116.8 (CH), 116.6 (CH), 115.0 (C), 114.9 (C), 112.7 (CH), 112.6 (CH), 62.2 (OCH_2), 62.0 (OCH_2), 56.6 (OCH_3), 51.8 (CH), 51.6 (CH), 29.2 (NCH_3), 28.8 (NCH_3), 15.4 (CH_3), 15.2 (CH_3). EI-MS: *m/z* (%) 393 [$(M+2)^+$, 1], 391 (M^+, 1), 312 (M−Br, 87), 291 (M−$NMeCO_2Et$+2, 99), 289 (M−$NMeCO_2Et$, 100). HRMS: Calcd for $C_{18}H_{18}BrNO_4$: 391.041919; found: 391.041090.

3.3. Anionic cyclization of carbamate 5

3.3.1. 5-Methoxy-1-methyl-2,10b-dihydro-1*H*-chromeno[4,3,2*cd*]isoindolin-2-one (6a). *Method A* (*Quenching with NH_4Cl*). A solution of carbamate **5** (100 mg, 0.25 mmol) in THF (4 mL) was cooled to −80 °C and *n*-BuLi (175 μL 1.6 M, 0.28 mmol) was added. After 30 min a saturated aqueous NH_4Cl solution (0.1 mL) was added to the cooled solution and the solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2, and the organic extract was washed with water, dried over Na_2SO_4 and concentrated. Separation of the products by flash chromatography (99:1 CH_2Cl_2/MeOH) afforded carbamate **4** (31 mg, 39%) and isoindolinone **6a** (37 mg, 54%). Mp 118 °C (dec). IR (NaCl): 1693 (CO). ^1H NMR: 7.59–7.54 (m, 1H), 7.54 (d, $J=8.1$ Hz, 1H), 7.38–7.19 (m, 3H), 7.02 (d, $J=8.1$ Hz, 1H), 5.24 (s, 1H), 4.02 (s, 3H), 3.52 (s, 3H). ^{13}C/DEPT (DMSO-d_6): 169.6 (CO), 153.2 (C), 150.4 (C), 138.6 (C), 131.6 (C), 129.1 (CH), 126.1 (CH), 125.2 (CH), 123.6 (C), 122.8 (C), 119.9 (CH), 118.2 (CH), 114.1 (CH), 56.9 (OCH_3), 54.5 (CH), 31.8 (CH_3). EI-MS: *m/z* (%) 267 (M^+, 41), 266 (100). HRMS: Calcd for $C_{16}H_{13}NO_3$: 267.089543; found: 267.088436.

3.3.2. 10b-Deutero-5-methoxy-1-methyl-2,10b-dihydro-1*H*-chromeno[4,3,2-*c*,*d*]isoindolin-2-one (6b). *Method B* (*Quenching with MeOD*). Carbamate **5** (100 mg, 0.25 mmol) was treated as before except that MeOD (0.1 mL) was added for quenching instead of aqueous NH_4Cl. Work-up as before afforded carbamate **4** (27 mg, 34%) and deuterated **6b** (35 mg, 52%): IR (KBr): 1694 (CO) cm^{-1}. ^1H NMR: 7.59–7.54 (m. 1H), 7.56 (d, $J=$ 8.1 Hz, 1H), 7.40–7.18 (m, 3H), 7.03 (d, $J=8.1$ Hz, 1H), 4.02 (s, 3H), 3.54 (s, 3H). ^{13}C/DEPT: 170.6 (CO), 153.9 (C), 150.9 (C), 139.4 (C), 131.4 (C), 129.1 (CH), 125.6 (CH), 124.9 (CH), 123.5 (C), 123.3 (C), 120.3 (CH), 118.7 (CH), 113.6 (CH), 57.1 (OCH_3), 32.2 (NCH_3). EI-MS: *m/z* (%) 268 (M^+, 40), 267 (30), 266 (100). HRMS: Calcd for $C_{16}H_{12}DNO_3$: 268.095820; found: 268.094551.

3.3.3. 5-Methoxy-1-methyl-2,10b-dihydro-1*H*-chromeno[4,3,2-*cd*]isoindolin-2-one (6a). *Method C (Inverse addition)*. A solution of the bromocarbamate **5** (100 mg, 0.25 mmol) in THF (4 mL) was added to *n*-BuLi (478 μL 1.6 M, 0.76 mmol) in THF (1 mL) at −80 °C. After 30 min, aqueous NH_4Cl was added to the cooled reaction mixture and the solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2, and the extract was washed with water, dried over Na_2SO_4 and concentrated. Flash chromatography (99:1 CH_2Cl_2/MeOH) afforded solid **6a** (54 mg, 80%).

3.3.4. 1-Bromo-4-methoxy-9*H*-xanthen-9-one (7). Bromine (1.37 mL, 26.6 mmol) was added to a suspension of 4-methoxy-9*H*-xanthen-9-one (**1**, 4 g, 17.7 mmol) and sodium acetate (2.9 g, 35.4 mmol) in AcOH (65 mL). The mixture was heated at 60 °C and another three doses of bromine (each 0.45 mL, 8.8 mmol) and NaOAc (each 0.73 g, 8.8 mmol) were added over 2 days. H_2O (750 mL) was added and the precipitate (4.75 g) was filtered out, washed with water, loaded onto SiO_2 and purified by flash chromatography (3:1 CH_2Cl_2/hexane) affording brominated xanthone **7** as a solid (4.32 g, 88%). Mp 208 °C. IR (KBr): 1669 (CO) cm^{-1}. ^1H NMR: 8.31 (dd, $J=7.9$, 1.6 Hz, 1H), 7.76–7.70 (m, 1H), 7.54 (d, $J=8.6$ Hz, 2H), 7.39 (apparent t, $J=7.6$ Hz, 1H), 7.06 (d, $J=8.6$ Hz, 1H), 4.03 (s, 3H). ^{13}C/DEPT: 176.3 (CO), 155.2 (C), 148.9 (C), 148.4 (C), 135.2 (CH), 129.9 (CH), 127.3 (CH), 124.8 (CH), 122.4 (C), 120.1 (C), 118.2 (CH), 115.6 (CH), 110.8 (C), 56.9 (OCH_3). EI-MS: *m/z* (%) 306 [$(M+2)^+$, 100], 304 (M^+, 100), 291 [(M−Me)+2, 92], 289 (M−Me, 92). HRMS: Calcd for $C_{14}H_9BrO_3$: 303.973503; found: 303.973552.

3.3.5. 1-Bromo-4-methoxy-9-phenyl-9*H*-xanthen-9-ol (8a). A suspension of **7** (2 g, 6.55 mmol) in THF (40 mL) was cooled to 0 °C, phenylmagnesium chloride (3.93 mL 2 M, 7.86 mmol) was added and the solution was stirred for 2 h at rt. Aqueous NH_4Cl was added, and the solvent was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and water, the organic layer was washed with water and dried, and the solvent was evaporated. The crude was taken into ether/hexane and **8a** (2.23 g, 89%) was filtered out. Mp 229 °C (dec). IR (KBr): 3481, 1600 cm^{-1}. ^1H NMR: 7.73 (d, $J=7.8$ Hz, 1H), 7.38–7.17 (m, 8H), 7.07–7.01 (m, 1H), 6.83 (d, $J=8.7$ Hz, 1H), 4.15 (s, 1H, OH), 3.99 (s, 3H, OMe). ^{13}C/DEPT: 148.2 (C), 147.7 (C), 146.9 (C), 141.5 (C), 129.1 (CH), 128.7 (CH), 128.4 (CH), 128.1 (2×CH), 126.6 (CH), 125.8 (2×CH), 125.3 (C), 124.7 (C), 123.8 (CH), 116.3 (CH), 112.7 (C), 111.9 (CH), 71.8 (C), 56.4 (OCH_3). EI-MS: *m/z* (%) 384 [$(M+2)^+$, 3], 382 (M^+, 3), 307 [(M−Ph)+2, 99], 305 (M−Ph, 100). HRMS: Calcd for $C_{20}H_{15}BrO_3$: 382.020456; found: 382.020758.

3.3.6. 1-Bromo-9-ethyl-4-methoxy-9*H*-xanthen-9-ol (8b). A suspension of **7** (3 g, 9.83 mmol) in THF (50 mL) was cooled to 0 °C, ethylmagnesium bromide (4.1 mL 3 M, 12.3 mmol) was added and the solution was stirred at rt for 2 h. After the same work up as for **8a** flash chromatography (1:1 CH_2Cl_2/hexane) afforded **8b** as a colourless oil (1.94 g, 93%). IR (KBr): 3351 (OH), 1621 cm^{-1}. ^1H NMR: 7.73 (dd, $J=8.1$, 1.4 Hz, 1H), 7.32–7.18 (m, 3H), 7.32 (d, $J=$ 8.7 Hz, 1H), 6.78 (d, $J=8.7$ Hz, 1H), 3.94 (s, 3H, OMe), 3.67 (s, 1H), 2.69 (dq, $J=15.0$, 7.5 Hz, 1H), 1.97 (dq, $J=$ 15.0, 7.5 Hz, 1H), 0.44 (t, $J=7.5$ Hz, 3H). ^{13}C/DEPT: 149.3 (C), 148.1 (C), 142.0 (C), 129.1 (2×CH), 127.3 (CH), 125.6

(C), 124.2 (CH), 123.9 (C), 116.0 (CH), 112.0 (CH), 111.1 (C), 72.3 (C), 56.7 (OCH_3), 37.7 (CH_2), 9.3 (CH_3). EI-MS: *m/z* (%) 336 [$(M+2)^+$, 1], 334 (M^+, 1), 335 (3), 333 (3), 307 [(M−Et)+2, 100), 305 (M−Et, 98). HRMS: Calcd for $C_{16}H_{15}BrO_3$: 334.020456; found: 334.020223.

3.3.7. *N*-(1-Bromo-4-methoxy-9-phenyl-9*H*-xanthen-9-yl)carbamic acid ethyl ester (9a). Phenylxanthydrol **8a** (800 mg, 3.09 mmol), urethane (372 mg, 4.17 mmol) and AcOH (16 mL) were heated at 110 °C for 15 h. The solvent was evaporated, the residue was partitioned between CH_2Cl_2 and water, and the organic layer was washed with water, dried and filtered. Flash chromatography (1:9 EtOAc/hexane) afforded recovered **8a** (343 mg, 43%) and **9a** (400 mg, 43%), the latter of which was recrystallized from CH_2Cl_2/hexane as a white solid. Mp 181 °C. IR (KBr): 3440, 3419, 1730 cm^{-1}. ^1H NMR: 7.37 (d, $J=7.7$ Hz, 1H), 7.33–7.12 (m, 8H), 6.93 (m, 1H), 6.78 (m, 2H), 3.97 (s, 3H, OMe), 3.89 (q, $J=7.0$ Hz, 2H), 1.04 (bs, 3H). ^{13}C/DEPT: 155.2 (CO), 148.1 (C), 147.4 (C), 146.4 (C), 142.8 (C), 128.7 (2×CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 126.9 (CH), 125.5 (2×CH), 124.7 (C), 123.4 (C), 123.3 (CH), 116.1 (CH), 112.5 (C), 111.8 (CH), 60.8 (OCH_2), 58.4 (C), 56.3 (OCH_3), 14.2 (CH_3). EI-MS: *m/z* (%) 374 (M^+−Br, 96), 301 (100). CI-MS: *m/z* (%) 456 [$(M+2)+H^+$, 5), 455 (M+2, 14), 454 ($M+H^+$, 6), 453 (M, 13). C I-HRMS: Calcd for $C_{23}H_{21}BrNO_4$: 454.065395; found: 454.063410.

3.3.8. *N*-(1-Bromo-9-ethyl-4-methoxy-9*H*-xanthen-9-yl)carbamic acid ethyl ester (9b). Sodium hydride (880 mg, 60% in mineral oil, 22 mmol) was washed twice with CH_2Cl_2 and a solution of urethane (1.17 g, 13 mmol) in methylene chloride (20 mL) was added, The mixture was stirred for 15 min and cooled to 0 °C. In another flask $HClO_4$ (260 μL, 3 mmol) was added to a solution of **8b** (1.0 g, 2.99 mmol) in CH_2Cl_2 (40 mL). After 1 min this solution was added over the first, and the mixture was stirred for 1 h at 0 °C and then extracted with CH_2Cl_2. The extract was washed with water, dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (1:4 EtOAc/hexane) giving the secondary carbamate **9b** (400 mg, 33%). Mp 169 °C. IR (KBr): 3349 (NH), 1647 (CO) cm^{-1}. ^1H NMR: 7.46 (dd, $J=7.8$, 1.5 Hz, 1H), 7.29–7.09 (m, 4H), 6.74 (d, $J=8.6$ Hz, 1H), 5.89 (bs, 1H, NH), 3.94–3.92 (bs, 5H, OCH_3 and OCH_2), 2.71–2.67 (m, 1H), 1.87–1.75 (m, 1H), 1.33–1.13 (broad, 3H), 0.41 (t, $J=7.4$ Hz, 3H). ^{13}C/DEPT: 154.2 (CO), 149.7 (C), 147.5 (C), 142.5 (C), 128.5 (CH), 128.2 (CH), 125.6 (CH), 124.2 (C), 123.5 (CH), 121.5 (C), 115.7 (CH), 111.5 (CH), 110.2 (C), 60.6 (OCH_2), 56.6 (C), 56.2 (OCH_3), 35.9 (CH_2), 14.5 (CH_3), 8.1 (CH_3). CI-MS: *m/z* (%) 407 [$(M+2)^+$, 19], 405 (M^+, 19), 378 [(M−Et)+2, 26], 376 (M−Et, 26), 326 (M−Br, 49), 319 [(M−$NHCO_2Et$)+2, 97], 317 (M−$NHCO_2Et$, 100). HRMS: Calcd for $C_{19}H_{20}BrNO_4$: 405.05757; found: 405.056955.

3.3.9. *N*-(1-Bromo-4-methoxy-9-phenyl-9*H*-xanthen-9-yl)-*N*-methylcarbamic acid ethyl ester (9c). Sodium hydride (274 mg, 60% in mineral oil, 6.9 mmol) was washed twice with THF, and DMF (3 mL) was added. The resulting suspension was cooled to 0 °C and a solution of **9a** (1.0 g, 2.2 mmol) in DMF (12 mL) was added. After 30 min at 0 °C methyl iodide (274 μL, 4.4 mmol) was added, and after a further 30 min at rt water was added, the mixture was extracted with CH_2Cl_2, the organic extract was washed with saturated aqueous NaCl solution (3×10 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (1:4 EtOAc/hexane) giving **9c** (768 mg, 75%) as a solid that was recrystallized from CH_2Cl_2/hexane. Mp 130 °C. IR (NaCl): 1701 cm^{-1}. ^1H NMR: 7.44–7.29 (m, 2H), 7.40 (d, $J=8.8$ Hz, 1H), 7.24–7.14 (m, 5H), 7.01–6.97 (m, 2H), 6.74 (d, $J=8.8$ Hz, 1H), 3.93–3.88 (m, 5H, OMe, OCH_2), 2.87 (s, 3H), 0.88–0.80 (m, 3H). ^{13}C/DEPT: 156.6 (CO), 150.5 (C), 148.7 (C), 142.3 (C), 140.8 (C), 130.1 (CH), 129.5 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 125.8 (CH), 123.7 (CH), 118.9 (C), 117.1 (CH), 111.5 (CH), 110.6 (C), 66.3 (C), 61.7 (OCH_2). 56.6 (OCH_3), 36.4 (NCH_3), 14.6 (CH_3). EI-MS *m/z* (%): 469 [$(M+2)^+$, 1], 467 (M^+, 1), 440 [(M−Et)+2, 2), 438 (M−Et, 2), 388 (M−Br, 100), 367 [(M−$NMeCO_2Et$)+2, 74), 365 (M−$NMeCO_2Et$, 74). HRMS: Calcd for $C_{24}H_{22}BrNO_4$: 467.073220; found: 467.073871.

3.3.10. *N*-(1-Bromo-9-ethyl-4-methoxy-9*H*-xanthen-9-yl)-*N*-methylcarbamic acid ethyl ester (9d). Sodium hydride (230 mg, 60% in mineral oil, 5.8 mmol) in DMF (2 mL), a solution of **9b** (781 mg, 1.92 mmol) in DMF (6 mL) and methyl iodide (239 μL, 3.8 mmol) were used as described in the preparation of **9c**. After work up the residue was purified by flash chromatography (1:9 EtOAc/hexane) giving **9d** (751 mg, 93%) as a solid that was recrystallized from ether/hexane. Mp 120 °C. IR(NaCl): 1701, 1689 cm^{-1}. ^1H NMR (345 K): 7.26–7.02 (m, 5H), 6.71 (d, $J=8.7$ Hz, 1H), 3.90 (s, 3H, OMe), 3.76 (broad, 2H), 3.30 (broad, 3H), 2.87–2.74 (m, 1H), 2.13 (broad, 1H), 0.80 (broad, 3H), 0.46–0.40 (m, 3H). ^{13}C/DEPT: 156.7 (CO), 155.9 (CO), 149.9 (C), 149.4 (C), 147.5 (C), 142.5 (C), 142.2 (C), 128.7 (CH), 128.5 (CH), 127.7 (C), 125.5 (C), 124.8 (CH), 124.0 (CH), 123.6 (C), 122.9 (C), 116.2 (C), 115.8 (CH), 115.5 (CH), 111.5 (C), 111.4 (CH), 110.2 (C), 61.3 (OCH_2), 56.7 (OCH_3), 56.5 (O CH_3), 37.7 (C), 34.2 (NCH_3), 34.0 (CH_2), 33.6 (C), 15.1 (CH_3), 13.7 (CH_3), 9.5 (CH_3). EI-MS *m/z* (%): 340 (M−Br, 42), 319 [(M−$NMeCO_2Et$)+2, 100], 317 (M−$NMeCO_2Et$, 100). FAB-MS: 422 [$(M+2)+H^+$, 6], 421 (9), 420 ($M+H^+$, 7), 419 (8). HRMS: Calcd for $C_{20}H_{22}BrNO_4$: 419.073220, found: 419.073112.

3.3.11. 5-Methoxy-1-methyl-10b-phenyl-2,10b-dihydro-1*H*-chromeno[4,3,2-*cd*]isoindolin-2-one (6c). A solution of carbamate **9c** (100 mg, 0.21 mmol) in THF (4 mL) was cooled to −80 °C and treated with *n*-BuLi (133 μL, 0.21 mmol) (Method A). After 30 min, work-up, purification by flash chromatography (1:4 EtOAc/hexane) and stirring with hexane afforded isoindolinone **6c** as a solid (68 mg, 93%). Mp 213 °C. IR (KBr): 1686 cm^{-1}. ^1H NMR: 7.68–7.64 (m, 1H), 7.64 (d, $J=8.0$ Hz, 1H), 7.43–7.16 (m, 6H), 7.02 (d, $J=8.0$ Hz, 1H), 6.72–6.67 (m, 2H), 3.97 (s, 3H), 3.16 (s, 3H). ^{13}C/DEPT: 170.6 (CO), 155.5 (C), 151.4 (C), 139.9 (C), 139.6 (C), 137.2 (C), 129.6 (CH), 129.3 (2×CH), 128.6 (CH), 127.4 (2×CH), 126.5 (CH), 125.9 (C), 125.3 (CH), 122.7 (C), 120.6 (CH), 118.8 (CH), 113.6 (CH), 64.7 (C), 57.3 (OCH_3), 30.0 (CH_3). EI-MS: *m/z* (%) 343 (M^+, 10), 266 (M−Ph, 100). HRMS: Calcd for $C_{22}H_{17}NO_3$: 343.120844; found: 343.121832.

3.3.12. 10b-Ethyl-5-methoxy-1-methyl-2,10b-dihydro-1*H*-chromeno[4,3,2-*cd*]isoindolin-2-one (6d). A solution of carbamate **9d** (100 mg, 0.24 mmol) in THF (2 mL) was cooled to −80 °C and treated with *n*-BuLi (149 μL, 0.24 mmol) (Method A). After 30 min, work-up and purification by flash chromatography (1:4 EtOAc/hexane) afforded isoindolinone **6d** as a solid (62 mg, 89%), that was recrystallized from ether/hexane. Mp 143 °C. IR (NaCl): 1693 (CO) cm^{-1}. ^1H NMR: 7.57 (d, $J=8.1$ Hz, 1H), 7.51–7.30 (m, 3H), 7.19 (dt, $J=7.6$, 1.2 Hz, 1H), 7.02 (d, $J=8.1$ Hz, 1H), 4.03 (s, 3H, OMe), 3.41 (s, 3H, NMe), 2.05 (dq, $J=14.6$, 7.3 Hz, 1H), 1.86 (dq, $J=14.6$, 7.3 Hz, 1H), 0.48 (t, $J=7.3$ Hz, 3H), ^{13}C/DEPT: 169.8 (CO), 153.8 (C), 150.8 (C), 139.2 (C), 134.8 (C), 128.7 (CH), 125.0 (CH), 124.5 (CH), 123.7 (C), 119.9 (CH), 118.6 (CH), 113.0 (CH), 62.1 (C), 57.1 (OCH_3), 33.4 (CH_2), 28.8 (NCH_3), 7.9 (CH_3). EI-MS: *m/z* (%) 266 (M^+-Et, 100). CI-MS: *m/z* (%) 296 ($M+H^+$, 100). CI-HRMS: Calcd for $C_{18}H_{18}NO_3$: 296.128669; found: 296.129638.

3.4. Synthesis of chromeno[4,3,2-*de*]isoquinolin-3-ones (15a–b)

3.4.1. 4-Methoxy-9*H*-xanthene-9-carbonitrile (10). Zinc iodide (350 mg, 1 mmol) and trimethylsilyl cyanide (7.7 mL, 59.6 mmol) in dry CH_2Cl_2 (20 mL) were cooled to 0 °C and a solution of xanthydrol **2** (7.0 g, 30.7 mmol) in CH_2Cl_2 (90 mL) was added dropwise over 2 h. After 1 h aqueous $NaHCO_3$ was added, the mixture was extracted with CH_2Cl_2, the extract was washed with water, dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude was recrystallized in CH_2Cl_2/hexane, affording cyanide **10** (6.48 g, 89%). Mp 140 °C. IR (KBr): 2237 (CN) cm^{-1}. ^1H NMR: 7.50 (d, $J=7.7$ Hz, 1H), 7.41–7.01 (m, 5H), 6.95 (dd, $J=7.1$ Hz, 2.2, 1H), 5.38 (s, 1H), 3.96 (s, 3H, OMe). ^{13}C/DEPT: 150.9 (C), 148.8 (C), 140.9 (C), 130.5 (CH), 128.8 (CH), 124.6 (CH), 124.1 (CH), 120.2 (CH), 119.3 (C), 118.0 (CH), 115.7 (C), 114.8 (C), 112.5 (CH), 56.7 (OCH_3), 30.7 (CH). EI-MS: *m/z* (%) 237 (M^+, 100). HRMS: Calcd for $C_{15}H_{11}NO_2$: 237.078979; found: 237.078912.

3.4.2. (4-Methoxy-9*H*-xanthen-9-yl)methylamine (11). Borane dimethylsulphide (3.3 mL, 34.79 mmol) was added to a solution of **10** (4.0 g, 16.9 mmol) in THF (40 mL) and the mixture was refluxed for 2 h. The solution was cooled to 0 °C, water (13 mL) and 20% KOH (13 mL) were added, and refluxing was continued for a further 2 h. The solvents were evaporated, the residue was partitioned between CH_2Cl_2 and water, and the organic layer was washed with water, dried with Na_2SO_4, filtered and concentrated. Purification by flash chromatography (95:5 CH_2Cl_2/MeOH) gave the amine as a solid (2.23 g, 55%). Mp 89 °C. IR (NaCl): 1579 cm^{-1}. ^1H NMR 7.25–6.83 (m, 7H), 3.99 (t, $J=5.2$ Hz, 1H), 3.95 (s, 3H, OMe), 2.96 (d, $J=5.1$ Hz, 2H), 1.31 (broad, 2H, NH_2). ^{13}C/DEPT: 152.6 (C), 148.3 (C), 142.3 (C), 128.9 (CH), 128.4 (CH), 124.3 (C), 123.9 (CH), 123.4 (CH), 123.2 (C), 120.7 (CH), 117.2 (CH), 110.8 (CH), 56.5 (OCH_3), 51.3 (CH_2), 43.9 (CH).CI-MS: *m/z* (%) 242 ($M+H^+$, 71). HRMS: Calcd for $C_{15}H_{16}NO_2$: 242.118104; found: 242.118175.

3.4.3. *N*-[(4-Methoxy-9*H*-xanthen-9-yl)methyl]carbamic acid ethyl ester (12). Na_2CO_3 (880 mg, 8.3 mmol) and ethyl chloroformate (0.48 mL, 5 mmol) were added to a solution of the amine **11** (1.0 g, 4.15 mmol) in THF (14 mL) and the mixture was stirred at rt for 1 h. A pH 7 aqueous solution of KH_2PO_4 (50 mL 0.1 M) and NaOH (29 mL 0.1 M) was added, the mixture was extracted with CH_2Cl_2, and the organic extract was washed with water, dried with Na_2SO_4, filtered, concentrated in vacuo and purified by flash chromatography (2:3 EtOAc/hexane) affording carbamate **12** as a foam (1.20 g, 93%). IR (NaCl): 3345 (NH), 1706 (CO) cm^{-1}. ^1H NMR: 7.32–7.22 (m, 3H), 7.14–7.01 (m, 2H), 6.94–6.85 (m, 2H), 4.68 (broad, 1H, NH), 4.18–4.00 (m, 3H, C9-H and OCH_2), 3.94 (s, 3H, OMe), 3.39–3.37 (m, 2H), 1.27–1.19 (m, 3H). ^{13}C/DEPT: 156.9 (CO), 152.3 (C), 148.3 (C), 141.9 (C), 129.3 (CH), 128.5 (CH), 124.1 (C), 123.8 (CH), 123.4 (CH), 123.0 (C), 120.9 (CH), 117.1 (CH), 110.9 (CH), 61.1 (OCH_2), 56.3 (OCH_3), 49.3 (CH_2), 39.7 (CH), 15.0 (CH_3). CI-MS: *m/z* (%) 314 ($M+H^+$, 37), 268 ($M-OEt$, 22), 225 ($M-NHCO_2Et$, 12). CI-HRMS: Calcd for $C_{18}H_{20}NO_4$: 314.139233; found: 314.140003.

3.4.4. *N*-[(4-Methoxy-9*H*-xanthen-9-yl)methyl]-*N*-methylcarbamic acid ethyl ester (13). Sodium hydride (268 mg, 60% in mineral oil, 6.7 mmol) in DMF (1 mL), a solution of **12** (700 mg, 2.23 mmol) in deoxygenated DMF (7 mL) and methyl iodide (278 μL, 4.34 mmol) were used as described in the preparation of **4**. After work-up the residue was purified by flash chromatography (1:4 EtOAc/hexane) giving **13** as an oil (673 mg, 92%). IR (NaCl): 1697 (CO) cm^{-1}. ^1H NMR: 7.22–6.69 (m, 7H), 4.36–4.04 (m, 2H, OCH_2), 3.88 (s, 3H, OMe), 3.90–3.82 (m, 1H), 3.38–3.23 (m, 2H), 2.73 and 2.44 (both s, 3H, NCH_3), 1.29 and 1.02 (both t, 3H). ^{13}C/DEPT: 156.8 (CO), 156.6 (CO), 152.4 (C), 148.3 (C), 142.0 (C), 129.3 (CH), 129.0 (CH), 128.4 (CH), 127.1 (C), 126.3 (C), 124.8 (CH), 124.4 (C), 123.8 (CH), 123.4 (CH), 121.0 (CH), 120.8 (CH), 116.9 (CH), 110.9 (CH), 61.5 (OCH_2), 60.6 (OCH_2), 58.4 (CH_2), 57.1 (CH_2), 56.3 (OCH_3), 38.9 (CH), 38.5 (CH), 36.8 (NCH_3), 35.9 (NCH_3), 15.2 (CH_3), 14.8 (CH_3). MS-FAB: *m/z* (%) 328 ($M+H^+$, 97). HRMS: Calcd for $C_{19}H_{22}NO_4$: 328.154883; found: 328.154347.

3.4.5. *N*-[(1-Bromo-4-methoxy-9*H*-xanthen-9-yl)-methyl]-*N*-methylcarbamic acid ethyl ester (14). Bromine in AcOH (1.5 mL 1 M, 1.46 mmol) was added to a solution of **13** (400 mg, 1.22 mmol) and NaOAc (200 mg, 2.44 mmol) in AcOH (6 mL). After 3 h, work-up as in the preparation of **5** led to a residue that upon flash chromatography (1:4 EtOAc/hexane) afforded carbamate **14** (482 mg, 97%), which was recrystallized from ether/hexane. Mp 91 °C. IR (NaCl): 1700 (CO) cm^{-1}. ^1H NMR: 7.36–7.05 (m, 5H), 6.69 (d, $J=8.8$ Hz, 1H), 4.60–4.35 (m, 1H), 4.12–3.62 (m, 2H, OCH_2), 3.87 (s, 3H, OMe), 3.46–3.25 (m, 2H), 2.79 and 2.53 (both s, 3H, NMe), 1.22 and 0.87 (both t, $J=7.0$ Hz, 3H). ^{13}C/DEPT: 156.6 (CO), 152.4 (C), 152.2 (C), 148.0 (C), 143.4 (C), 131.0 (C), 129.1 (CH), 128.6 (CH), 126.8 (CH), 124.7 (C), 124.1 (CH), 123.5 (C), 123.2 (C), 116.5 (CH), 113.9 (C), 113.7 (C), 112.0 (CH), 61.4 (OCH_2), 56.5 (OCH_3), 55.4 (CH_2), 54.1 (CH_2), 39.2 (CH), 39.1 (CH), 36.0 (NCH_3), 35.5 (NCH_3), 15.2 (CH_3), 14.7 (CH_3). CI-MS: *m/z* (%) 408 [$(M+2)+H^+$, 22), 406 ($M+H^+$, 22). CI-HRMS: Calcd for $C_{19}H_{21}BrNO_4$: 406.065395; found: 406.064411.

3.4.6. Isoquinolinone 15a by electrophilic cyclization. Triflic anhydride (1.05 mL, 6.12 mmol) was added to a solution of carbamate **13** (400 mg, 1.22 mmol) and DMAP (453 mg, 3.67 mmol) in methylene chloride (20 mL) at 0 °C. After 4 h. of stirring at 0 °C, 15 mL of 1 M NaOH was added and the mixture was extracted with CH_2Cl_2. The extract was washed with water, dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography (1:1 EtOAc/hexane) gave 6-methoxy-2-methyl-1,2,3,11b-tetrahydrochromeno[4,3,2-*de*]isoquinolin-3-one (**15a**, 303 mg, 88%), which was recrystallized from ether/hexane. Mp 171 °C. IR (NaCl): 1649 (CO) cm^{-1}. ^1H NMR: 7.82 (d, $J=8.6$ Hz, 1H), 7.32–7.20 (m, 3H), 7.12 (td, $J=8.0$, 1.7 Hz, 1H), 6.93 (d, $J=8.6$ Hz, 1H), 4.50 (dd, $J=12.7$, 5.7 Hz, 1H), 3.99 (s, 3H, OMe), 3.96 (dd, $J=11.9$, 5.7 Hz, 1H), 3.79 (apparent t, $J=12.3$ Hz, 1H), 3.25 (s, 3H, NMe). ^{13}C/DEPT: 164.7 (CO), 151.7 (C), 150.7 (C), 139.0 (C), 129.1 (CH), 126.1 (CH), 124.1 (CH), 124.0 (CH), 122.4 (C), 121.3 (C), 120.0 (C), 117.8 (CH), 110.7 (CH), 56.5 (OCH_3), 52.9 (CH_2), 35.8 (CH), 30.2 (NCH_3). EI-MS: *m*/*z* (%) 281 (M^+, 15), 238 (38), 210 (100). HRMS: Calcd for $C_{17}H_{15}NO_3$: 281.105194; found: 281.104917.

3.4.7. Isoquinolinone 15a by anionic cyclization. A solution of bromocarbamate **14** (50 mg, 0.12 mmol) in THF (3 mL) and *n*-BuLi (81 μL 1.6 M, 0.13 mmol) were used as described in Method A. The product was purified by flash chromatography, affording **15a** (25 mg, 74%).

3.4.8. 4-Methoxy-9-phenyl-9*H*-xanthen-9-ol (16). Phenylmagnesium bromide (7.1 mL 2 M, 14.2 mmol) was added to a suspension of xanthone **1** (3 g, 13.2 mmol) in THF (90 mL) at 0 °C and the solution was stirred for 2 h. After work up as for **8a**, the residue was purified by stirring in ether/hexane (3.75 g, 93%). Mp 167 °C. IR (KBr): 3488 (OH), 1576 cm^{-1}. ^1H NMR: 7.41–6.93 (m, 10H), 7.17 (t, $J=7.2$ Hz, 1H), 6.87 (dd, $J=7.3$, 2.1 Hz, 1H), 3.98 (s, 3H, OMe), 2.63 (s, 1H, OH). ^{13}C/DEPT: 149.8 (C), 148.4 (C), 147.9 (C), 140.1 (C), 129.4 (CH), 129.3 (CH), 128.3 (2×CH), 127.3 (C), 127.1 (CH), 126.6 (2×CH), 124.1 (CH), 123.4 (CH), 120.7 (CH), 117.1 (CH), 111.0 (CH), 70.7 (C), 56.6 (OCH_3). EI-MS: *m*/*z* (%) 304 (M^+, 10), 227 (M−Ph, 100). HRMS: Calcd for $C_{20}H_{16}O_3$: 304.10994; found: 304.109937.

3.4.9. 4-Methoxy-9-phenyl-9*H*-xanthene-9-carbonitrile (17). A solution of 4-methoxy-9-phenyl-9*H*-xanthen-9-ol (**16**, 2 g, 6.58 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 2 h to a suspension of zinc iodide (70 mg, 0.22 mmol) and trimethylsilyl cyanide (1.2 mL, 9.59 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After 1 h aqueous $NaHCO_3$ was added, the mixture was extracted with CH_2Cl_2, the extract was washed with water, dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Compound **17** was recrystallized from CH_2Cl_2/hexane (1.84 g, 90%). Mp 147 °C. IR (NaCl): 2238 (CN), 1602 cm^{-1}. ^1H NMR: 7.39–7.21 (m, 8H), 7.14–7.09 (m, 1H), 7.05 (t, $J=8.0$ Hz, 1H), 6.97–6.90 (m, 2H), 3.97 (s, 3H, OMe). ^{13}C/DEPT: 149.7 (C), 148.6 (C), 143.4 (C), 139.9 (C), 130.4 (CH), 129.6 (CH), 129.4 (2×CH), 128.4 (CH), 126.8 (2×CH), 124.8 (CH), 124.2 (CH), 121.7 (C), 121.1 (C), 120.9 (CH), 120.7 (C), 117.9 (CH), 112.0 (CH), 56.7 (OCH_3), 46.3 (C). EI-MS: *m*/*z* (%) 313 (M^+, 23), 236 (M−Ph, 100). HRMS: Calcd for $C_{21}H_{15}NO_2$: 313.110279; found: 313.109484.

3.4.10. (4-Methoxy-9-phenyl-9*H*-xanthen-9-yl)methylamine (18). A mixture of **17** (400 mg, 1.28 mmol) and $NiCl_2$ (170 mg, 1.29 mmol) in ethanol (45 mL) was heated at 60 °C and $NaBH_4$ (230 mg, 5.9 mmol) was added. After 3 h the mixture was filtered through celite, the solvent was evaporated, the residue was partitioned between CH_2Cl_2 and water, and the organic phase was washed with water, dried with Na_2SO_4, filtered and concentrated. The product was purified by flash chromatography (97:3 CH_2Cl_2/MeOH) and recrystallized from ether/hexane (332 mg, 82%). Mp 134 °C. IR (NaCl): 3382 and 3350 (NH_2), 1573 cm^{-1}. ^1H NMR: 7.28–7.15 (m, 7H), 6.97–6.77 (m, 4H), 6.41 (dd, $J=7.8$, 1.6 Hz, 1H), 3.94 (s, 3H, OMe), 3.47 (s, 2H), 0.80 (bs, 2H, NH_2). ^{13}C/DEPT: 151.9 (C), 148.4 (C), 148.2 (C), 142.1 (C), 129.9 (C), 129.6 (2×CH), 128.9 (2×CH), 128.6 (CH), 127.4 (C), 127.2 (CH), 126.4 (C), 124.2 (CH), 123.4 (CH), 121.4 (CH), 117.2 (CH), 110.5 (CH), 56.8 (OCH_3), 54.3 (CH_2), 50.7 (C). MS-FAB: *m*/*z* (%) 318 ($M+H^+$, 100). HRMS-*FAB*: Calcd for $C_{21}H_{20}NO_2$: 318.149404, found: 318.149563.

3.4.11. *N*-[(4-Methoxy-9-phenyl-9*H*-xanthen-9-yl)-methyl]carbamic acid ethyl ester (19). Na_2CO_3 (215 mg, 2 mmol) and ethyl chloroformate (117 μL, 1.2 mmol) were added to a solution of amine **18** (320 mg, 1 mmol) in THF (8 mL) and the mixture was stirred at rt for 30 min. Work up as described for **12** gave a residue of carbamate **19**, which was recrystallized from CH_2Cl_2/hexane (353 mg, 90%). Mp 160 °C. IR (NaCl): 3440 (NH), 1720 (CO) cm^{-1}. ^1H NMR: 7.35–7.18 (m, 7H), 7.01–6.80 (m, 4H), 6.50 (d, $J=7.5$ Hz, 1H), 4.46 (broad, 1H, NH), 4.10 (d, $J=6.0$ Hz, 2H), 3.95 (s, 3H, OMe), 3.91 (q, $J=7.1$ Hz, 2H, OCH_2), 1.06 (t, $J=7.1$ Hz, 3H). ^{13}C/DEPT: 156.7 (CO), 151.4 (C), 148.0 (C), 146.9 (C), 141.6 (C), 129.6 (CH), 128.9 (2×CH), 128.7 (2×CH), 128.6 (CH), 127.1 (CH), 126.6 (C), 125.5 (C), 123.9 (CH), 123.2 (CH), 121.2 (CH), 117.0 (CH), 110.6 (CH), 61.2 (OCH_2), 56.6 (OCH_3), 51.2 (NCH_2), 48.1 (C), 14.8 (CH_3). MS-FAB: *m*/*z* (%) 390 ($M+H^+$, 28). HRMS-FAB: Calcd for $C_{24}H_{24}NO_4$: 390.170534; found: 390.170889.

3.4.12. *N*-[(4-Methoxy-9-phenyl-9*H*-xanthen-9-yl)-methyl]-*N*-methylcarbamic acid ethyl ester (20). Sodium hydride (123 mg, 60% in mineral oil, 3 mmol) in DMF (0.5 mL), a solution of **19** (300 mg, 0.77 mmol) in DMF (2.5 mL) and methyl iodide (96 μL, 1.54 mmol) were used as described in the preparation of **9c**. After work-up the residue was purified by flash chromatography (1:3 EtOAc/hexane), giving carbamate **20** as a foam (286 mg, 92%). IR (KBr): 1700 (CO) cm^{-1}. ^1H NMR: 7.31–7.12 (m, 7H), 6.90–6.75 (m, 4H), 6.47–6.38 (m, 1H), 4.30 and 4.24 (both s, 2H), 3.92 (s, 3H, OMe), 3.82 and 3.55 (both m, 2H, OCH_2), 2.23 (s, 3H, NMe), 0.99–0.93 (m, 3H). ^{13}C/DEPT: 156.5 (CO), 156.4 (CO), 151.1 (C), 148.1 (2×C), 147.3 (C), 147.0 (C), 141.5 (C), 141.3 (C), 130.5 (CH), 130.3 (CH), 128.6 (2×CH), 128.0 (2×CH), 127.7 (CH), 126.6 (C), 126.3 (CH), 125.5 (C), 122.8 (CH), 122.1 (CH), 121.9 (CH), 116.3 (CH), 115.9 (CH), 109.8 (CH), 109.6 (CH), 60.9 (CH_2), 60.8 (CH_2), 56.0 (OCH_3), 47.6 (C), 36.0 (NCH_3),

35.4 (NCH_3), 14.3 (CH_3), 14.2 (CH_3). CI-MS: *m/z* (%) 404 ($M+H^+$, 100). CI-HRMS: Calcd for $C_{25}H_{26}NO_4$: 404.186184; found: 404.188140.

3.4.13. 1-Bromo-4-methoxy-9-phenyl-9*H*-xanthene-9-carbonitrile (21). A solution of xanthydrol **8a** (1.5 g, 3.9 mmol) in CH_2Cl_2 (90 mL) was added dropwise over 2 h to a suspension of zinc iodide (100 mg, 0.31 mmol) and trimethylsilyl cyanide (0.98 mL, 7.8 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After 1 h aqueous $NaHCO_3$ was added, the mixture was extracted with CH_2Cl_2, the organic layer was washed with water, dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure, leaving a residue that was stirred with ether/hexane (1.48 g, 96%). Mp 245 °C. IR (KBr): 2232 (CN), 1570 cm^{-1}. ^{1}H: 7.46–7.01 (m, 10H), 6.88 (d, $J=8.8$ Hz, 1H), 3.99 (s, 3H, OMe). ^{13}C/DEPT: 148.3 (C), 146.9 (C), 143.2 (C), 141.7 (C), 130.3 (CH), 130.1 (CH), 129.2 (CH), 129.1 (2×CH), 128.0 (CH), 127.3 (2×CH), 124.9 (CH), 120.8 (C), 120.2 (C), 118.5 (C), 117.5 (CH), 114.8 (C), 113.6 (CH), 58.6 (OCH_3), 46.9 (C). EI-MS: *m/z* (%) 393 [$(M+2)^+$, 36], 391 (M^+, 36), 316 [$(M-Ph)+2$, 100], 314 (M−Ph, 99). HRMS: Calcd for $C_{21}H_{14}BrNO_2$: 391.020790; found: 391.019766.

3.4.14. (1-Bromo-4-methoxy-9-phenyl-9*H*-xanthen-9-yl)methylamine (22). Borane dimethylsulphide (0.7 mL, 7.38 mmol) was added to a solution of nitrile **21** (1.48 g, 3.78 mmol) in THF (80 mL) and the mixture was refluxed for 2 h. The solution was cooled to 0 °C, water (13 mL) and 20% KOH (13 mL) were added, and refluxing was continued for a further 2 h. The solvents were evaporated, the residue was partitioned between CH_2Cl_2 and water, and the organic layer was washed with water, dried with Na_2SO_4, filtered and concentrated. Purification by flash chromatography (96:4 CH_2Cl_2/MeOH) gave the amine as a solid (900 mg, 60%). Mp 184 °C. IR (NaCl): 3387 (NH), 1570 cm^{-1}. ^{1}H NMR: 7.29–6.86 (m, 10H), 6.76 (d, $J=8.7$ Hz, 1H), 4.20 (d, $J=12.9$ Hz, 1H), 3.97 (s, 3H, OMe), 3.54 (d, $J=12.9$ Hz, 1H). ^{13}C/DEPT: 149.4 (C), 148.4 (C), 147.9 (C), 143.8 (C), 129.8 (CH), 129.5 (CH), 129.2 (2×CH), 128.5 (2×CH), 128.0 (CH), 126.4 (CH), 126.0 (C), 124.2 (CH), 123.5 (C), 116.3 (CH), 114.0 (C), 112.0 (CH), 56.6 (OCH_3), 51.8 (C), 51.1 (CH_2). MS-FAB: *m/z* (%) 398 [$(M+2)+H^+$, 23], 396 ($M+H^+$, 24). HRMS-FAB: Calcd for $C_{21}H_{19}BrNO_2$: 396.059915; found: 396.059797.

3.4.15. *N*-[(1-Bromo-4-methoxy-9-phenyl-9*H*-xanthen-9-yl)methyl]carbamic acid ethyl ester (23). Na_2CO_3 (429 mg, 4 mmol) and ethyl chloroformate (0.23 mL, 2.43 mmol) were added to a solution of amine **22** (800 mg, 2 mmol) in THF (55 mL), and the mixture was stirred at rt for 1 h. After work-up as described for **12** the residue was purified by flash chromatography (1:3 EtOAc/hexane) affording carbamate **23** (756 mg, 80%). Mp 147 °C. IR(KBr): 3332 (NH), 1720, 1693 cm^{-1}. ^{1}H NMR: 7.30–7.08 (m, 8H), 6.89–6.90 (m, 2H), 6.73 (d, $J=8.7$ Hz, 1H), 4.78 (dd, $J=12.7$, 5.8 Hz, 1H), 4.33 (dd, $J=6.5$, 5.8 Hz, 1H, NH), 4.22 (dd, $J=12.7$, 6.5 Hz, 1H), 3.93 (s, 3H, OMe), 3.85 (q, $J=7.0$ Hz, 2H), 1.01 (t, $J=7.0$ Hz, 3H). ^{13}C/DEPT: 156.7 (CO), 148.9 (C), 147.9 (C), 147.6 (C), 143.4 (C), 130.2 (CH), 129.5 (CH), 128.9 (2×CH), 128.7 (2×CH), 128.3 (CH), 126.7 (CH), 125.3 (C), 124.1 (CH), 122.9 (C), 116.3 (CH), 114.6 (C), 112.3 (CH), 61.1 (OCH_2), 56.7 (OCH_3), 49.5 (CH_2), 49.4 (C), 14.8 (CH_3). MS-FAB: *m/z* 470 [$(M+2)+H^+$, 37), 468 ($M+H^+$, 37). HRMS-FAB: Calcd for $C_{24}H_{23}BrNO_4$: 468.081045; found: 468.079173.

3.4.16. *N*-[(1-Bromo-4-methoxy-9-phenyl-9*H*-xanthen-9-yl)methyl]-*N*-methylcarbamic acid ethyl ester (24). Sodium hydride (183 mg, 60% in mineral oil, 4.58 mmol) in DMF (0.2 mL), a solution of **23** (700 mg, 1.49 mmol) in DMF (8 mL) and methyl iodide (180 μL, 2.89 mmol) were used as described in the preparation of **9c**. After work-up, flash chromatography of the residue (1:4 EtOAc/hexane) gave carbamate **24** (286 mg, 92%), which was recrystallized from ether/hexane. Mp 120 °C. IR (NaCl): 1697 (CO) cm^{-1}. ^{1}H NMR: 7.31–6.84 (m, 10H), 6.72 (d, $J=8.7$ Hz, 1H), 4.90–4.85 (m, 1H), 4.41–4.18 (m, 1H), 3.91 (s, 3H, OMe), 3.80–3.61 (m, 2H), 2.25 (s, 3H, NMe), 1.00 (t, $J=7.1$ Hz, 3H). ^{13}C/DEPT: 157.3 (CO), 149.4 (C), 148.6 (C), 148.1 (C), 143.9 (C), 131.1 (CH), 129.0 (2×CH), 128.6 (2×CH), 128.3 (CH), 128.1 (CH), 126.5 (CH), 126.3 (C), 124.0 (C), 123.6 (CH), 116.5 (CH), 115.8 (C), 112.1 (CH), 61.6 (OCH_2), 57.9 (OCH_2), 56.7 (OCH_3), 49.5 (C), 36.9 (NCH_3), 36.3 (NCH_3), 14.9 (CH_3). MS-FAB: *m/z* (%) 484 [$(M+2)+H^+$, 66), 482 ($M+H^+$, 68). HRMS-FAB: Calcd for $C_{25}H_{25}BrNO_4$: 482.096695; found: 482.095358.

3.4.17. Isoquinolinone 15b by electrophilic cyclization. Triflic anhydride (213 μL, 1.24 mmol) was added to a solution of carbamate **20** (100 mg, 0.25 mmol) and DMAP (92 mg, 0.76 mmol) in methylene chloride (5 mL) at 0 °C. After 4 h of stirring at 0 °C, 5 mL of 1 M NaOH was added, the mixture was extracted with CH_2Cl_2, the organic phase was washed with water, dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography (1:1 EtOAc/hexane) gave 6-methoxy-2-methyl-11b-phenyl-1,2,3,11b-tetrahydrochromeno[4,3,2-*de*]isoquinolin-3-one (**15b**, 84 mg, 95%), which was recrystallized from ether/hexane. Mp 219 °C. IR (NaCl): 1649 (CO) cm^{-1}. ^{1}H NMR: 7.92 (d, $J=8.6$ Hz, 1H), 7.42 (d, $J=8.6$ Hz, 1H), 7.25–7.02 (m, 9H), 4.36 (d, $J=12.4$ Hz, 1H), 4.28 (d, $J=12.4$ Hz, 1H), 4.03 (s, 3H, OMe), 3.10 (s, 3H, NMe). ^{13}C/DEPT: 164.3 (CO), 151.7 (C), 151.1 (C), 144.0 (C), 140.3 (C), 129.1 (2×CH), 128.9 (CH), 127.3 (CH), 126.4 (2×CH), 126.3 (C), 126.1 (C), 125.6 (CH), 124.7 (CH), 124.5 (CH), 121.5 (C), 118.1 (CH), 111.1 (CH), 57.9 (CH_2), 56.6 (OCH_3), 40.8 (C), 35.9 (NCH_3). EI-MS: *m/z* (%) 357 (M^+, 8), 314 (100), 299 (89). HRMS: Calcd for $C_{23}H_{19}NO_3$: 357.136494; found: 357.137727.

3.5. Isoquinolinone 15b by anionic cyclization

A solution of bromocarbamate **24** (100 mg, 0.20 mmol) in THF (5 mL) and *n*-BuLi (130 μL 1.6 M, 0.20 mmol) were used as described in Method A. The product was purified by flash chromatography, affording **15b** (59 mg, 80%).

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Double versus single helical structures of oligopyridine-dicarboxamide strands. Part 1: Effect of oligomer length

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Abstract—Oligoamides of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid were previously shown to fold into single helical monomers and to hybridize into double helical dimers. A new series of these oligomers comprising 5 to 15 pyridine units, 4-decyloxy residues, and benzylcarbamate end groups were synthesized using a new convergent scheme that involves an early disymmetrization of the diamine and of the diacid. The hybridization of these compounds into double helices was studied by ^{1}H NMR spectroscopy in chloroform solutions at various temperatures. Somewhat unexpectedly, these studies revealed that dimerization increases with oligomer length up to a certain point, and then decreases down to undetectable levels for the longest strands. NMR studies show that both double helices and single helices become more stable when strand length increases. The measured values of enthalpy and entropy of hybridization for oligomers of various length show that the enthalpic gain constantly decreases with strand length. This can be interpreted as being the result of an increasing enthalpic price of the spring-like extension that the strand undergoes upon hybridization as its length increases. On the other hand, the entropic loss of hybridization also constantly decreases with strand length. Presumably, the helical preorganization of the monomers increases with strand length, which allows the longer strands to hybridize with a minimal loss of motional freedom, that is to say at a low entropic price. The competiton between these two factors results in a maximum of hybridization for the strands having an intermediate length.

1. Introduction

In recent years, much effort has been devoted to the design and characterization of artificial oligomers capable of pairing into duplexes through multiple cooperative and selective interactions.[1] These structures are useful tools for the orchestration of self-assembly and self-organization at a nanometer level. They also give new insights on the functions of strand pairing as it occurs in biological systems as, for example, the duplication of information coded in a molecular strand through the template directed growth of a complementary strand.

Artificial molecular duplexes may be stabilized by (self)-complementary hydrogen bond arrays. They can be directly inspired by natural hybridization motifs as, for example, the pairing of nucleobases[1–3] or the double stranded β-barrel of the bacterial peptide Gramicidin D[4] which both give rise to double helical architectures. Several non-natural hydrogen bond arrays have also been designed.[1,5–12] The three dimensional structures of these molecular duplexes have not always been characterized in detail but the two strands are most often supposed to adopt a ladder (or zipper) like linear conformation. Another common way to direct the assembly of a molecular duplex or triplex is to use metal ions[1,13] or anions[14] as templates around which two or three strands wind upon establishing selective interactions. This leads to doubly or triply stranded helical architectures termed helicates. Less commonly, artificial duplexes based on inter-strand aromatic–aromatic interactions have also been described.[15]

Oligoamide strands derived from 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid (AOA's) belong to the wider class of aromatic oligoamides which adopt well-defined folded conformations.[16–20] AOA's self-organize into single helical conformers stabilized by both attractive and repulsive interactions involving either the amide hydrogen or oxygen on the one hand, and the adjacent pyridine nitrogen and protons on the other hand (Fig. 1). Additionally, the helices gain stability from intramolecular aromatic–aromatic interaction.[16,18] Remarkably, in non polar solvents, the single helices of AOA's can extend like springs and reversibly assemble, giving rise to double-helical dimeric complexes (Fig. 1).[19,20] These artificial molecular

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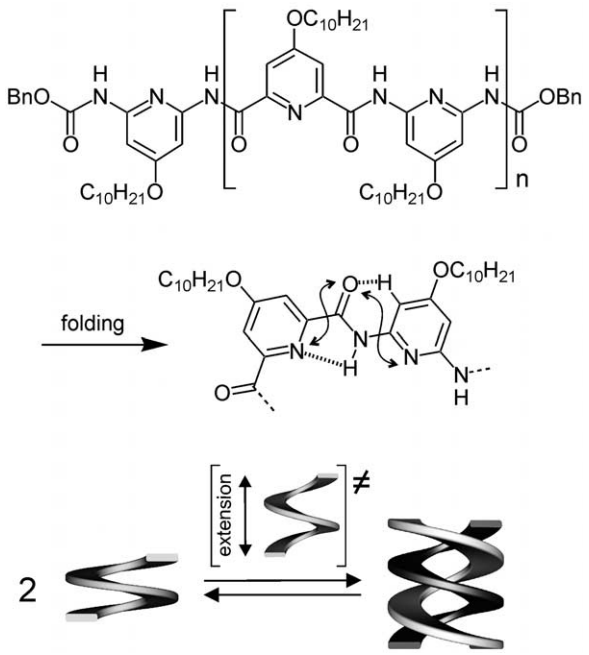


Figure 1. Intramolecular hydrogen bonds involved in helical conformations of pyridine oligoamides and schematic representation of single helix/double helix equilibrium implying a spring like extension/compression of the strands. The double headed arrows indicate electrostatic repulsions.

duplexes represent an original example of double helices stabilized by direct interactions between the strands following a non-natural hybridization motif. In contrast with helicates,[13,14] their winding into double helices takes place without the help of a template. The double helices of AOA's involve extensive interstrand aromatic–aromatic interactions,[19,20] unlike natural double helices, for example, DNA or Gramicidine D, and their synthetic analogs,[2–4] which are based on interstrand hydrogen bonding.

Short double helices of AOA's comprising five or seven pyridine units per strand were previously characterized in solution by ^{1}H NMR spectroscopy, in the solid state by X-ray crystallography, and by molecular modeling studies.[19,20] In this report, we present the synthesis of much longer chloroform soluble strands and show that, somewhat counter intuitively, dimerization of AOA's into double helices increases with strand length to reach a maximum and then decreases down to undetectable levels for the longest strands. This can be interpreted as being the result of two competing factors: the enthalpic gain of hybridization decreases as strand length increases, but the entropic loss of hybridization also decreases as strand length increases.

2. Results and discussion

2.1. Synthesis

A series of oligomers was prepared according to a new scheme that avoids the low yielding late disymmetrization steps involved in the previous syntheses.[18,19] Using a convergent strategy, we could produce molecular strands up to twice as long as the longest chloroform soluble oligomers that we described previously. In the following, oligomers are labeled according to the number of pyridine rings that they contain. Thus, diester **1a** and diamine **1b** are efficiently disymmetrized at an early stage of the synthesis (Scheme 1). Diester **1a** is monosaponified with 1 equiv of NaOH in 85% yield. Diamine **1b** is deprotonated and converted to its mono-amine mono-benzylcarbamate **1d** in 67% yield. This compound can be coupled to 4-decyloxy-2,6-pyridine dicarbonyl chloride or to the acid chloride of **1c** to give protected diamine **3a** and protected aminoacid **2a**, respectively. These products are quantitatively deprotected at the N terminus using hydrogenation on Pd/C, and at the C terminus using NaOH. Trimer **3b** can also be prepared by directly reacting the anion of diamine **1b** and diester **1a**. Cycles of deprotection, activation via the acid chloride and coupling, allow to convert **2a** into tetrameric strand **4b** and hexameric strand **6b** (Scheme 2). Finally, two dimeric, tetrameric or hexameric acid chloride units can be attached to a monomeric or trimeric diamine core to give oligomers **5**–**15** in moderate yield (Scheme 3).

2.2. Dimerization constants as a function of strand length

The alkoxy chains in position 4 of the pyridines diverge from the helices and confer all oligomers with high solubility in chlorinated, aromatic, and alkane solvents. The ability of strands **5**–**15** to dimerize was investigated in $CDCl_3$ (Fig. 2). As shown by the ^{1}H NMR spectra, single and double helices undergo slow exchange and give rise to different signals. The coalescence between these signals is not reached below the boiling point of chloroform for all these compounds except **5** for which most of the signals coalesce between 25 and 35 °C.

The NMR signals can easily be assigned to the single and double helices according to the variation of their relative intensity upon changing temperature or concentration: the proportion of single helix increases upon heating and upon diluting. The assignment of the signals can also be deduced from the fact that single and double helices do not have the

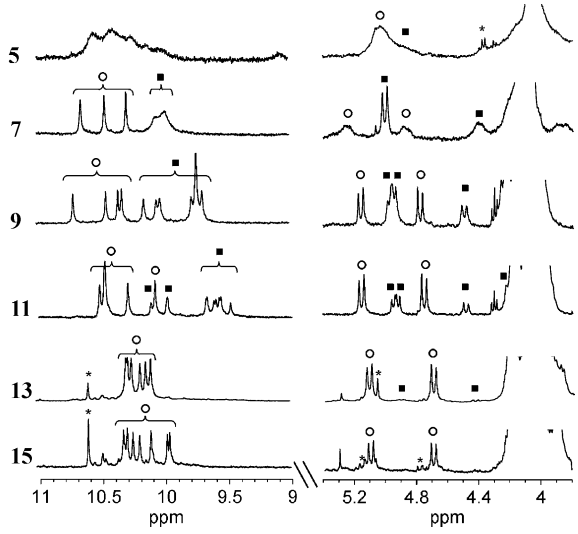
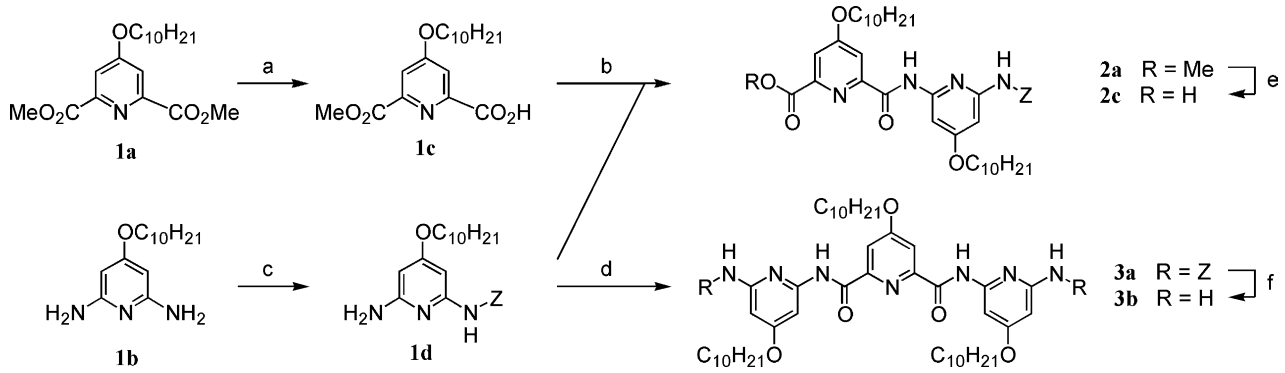


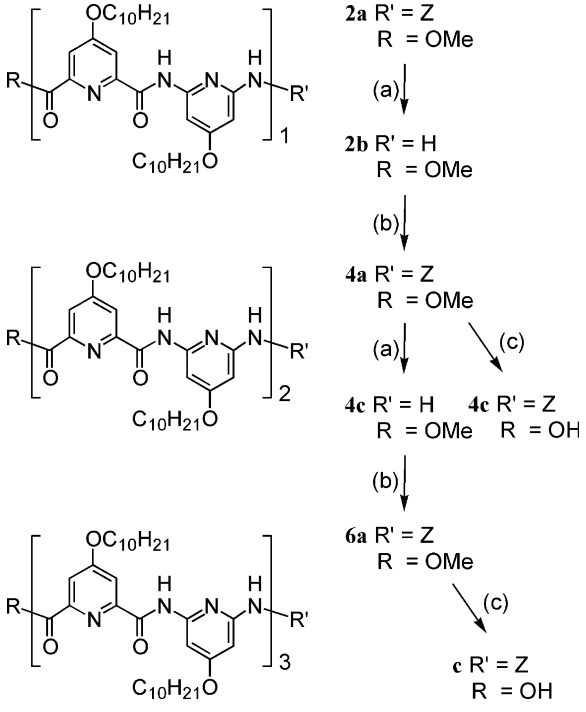
Figure 2. Part of the ^{1}H 400 MHz NMR spectra of compound **5**–**15** at 25 °C, C=1 mM in $CDCl_3$, showing the resonances of the amides (11–9 ppm) and the resonnances of the benzylic methylenes (5.4–4.4 ppm). Signals assigned to single and double helices, and to impurities[21] are labelled by circles, squares, and asterisks respectively.



Scheme 1. Reagents and conditions: (a) MeOH–dioxane, 0 °C, NaOH (1 equiv), 85% yield; (b) $SOCl_2$, reflux, then **1d**, toluene, iPr$_2$EtN, RT, 90% yield; (c) THF, −78 °C, n-BuLi (1 equiv), $ClCO_2Bn$ (1 equiv), 67% yield; (d) toluene, 4-decyloxypyridine 2,6-dicarbonylchloride (0.45 equiv), iPr$_2$EtN, RT, 83% yield; (e) H_2O–dioxane, 25 °C, NaOH (2 equiv), quant. yield; (f) ethyl acetate/AcOH, RT, H_2/Pd–C, quant. yield.

same symmetry. The single helices possess a C_2 symmetry axis perpendicular to the helical axis. Each signal is therefore degenerate and corresponds to the two protons occupying equivalent positions at each end of the strand. This symmetry is lost in the double helices in which the two strands are equivalent, but the extremities of each strand are in different environments. A double helix thus gives rise to twice as many signals as the corresponding single helix (see the spectra of **9**–**15** in Fig. 2). However, this only holds below a certain temperature. Sliding motions within the double helix allow the exchange between the different environments of each strand. When this becomes fast on the NMR timescale, a coalescence takes place and the NMR spectrum of an on-average C_2 symmetrical double helix is seen (see the spectrum of **7** in Fig. 2).

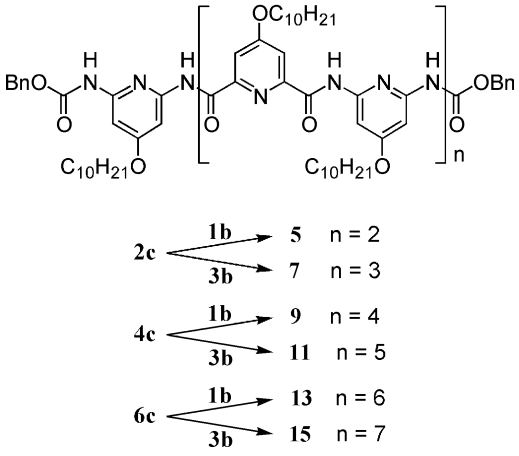
The considerable size of these synthetic double helices should be emphasized. Dimer $(\mathbf{13})_2$, for example, spans over three double-helical turns and is more than 2 nm long with a molecular weigh of 7700 g mol^{-1}.



Scheme 2. Reagents and conditions: (a) DMF/MeOH, RT, H_2/Pd–C, quant. yield; (b) acid chloride of **2c**, toluene, iPr$_2$EtN, RT, 60–80% yield; (c) H_2O–dioxane, NaOH (2 equiv), RT, quant. Yield.

Dimerization constants at various temperatures were calculated by non linear regression analysis of the proportions of monomer and dimer measured from NMR signals at different concentrations. The values reported in Table 1 show that dimerization increases with strand length to reach a maximum value and that, somewhat counter-intuitively, it decreases for longer strands. At 25 °C, the value of K_{dim} increases with strand length from five to nine pyridine rings (up to 5200 L mol^{-1} for **9**), and decreases by 4 orders of magnitude for longer strands down to undetectable levels for **15**. This trend is even more pronounced at −19 °C where dimerization is strongly enhanced (Table 1): K_{dim} then reaches a maximum of 120,000 L mol^{-1} for compound **7**, and dramatically decreases for longer strands. The effect is still observed, though less intense, at 49 °C where dimerization is significantly lowered (Table 1).

These results are surprising because the number of stabilizing inter-strand interactions, and thus the stability of the double helices were expected to increase with increasing strand length. Indeed, oligomers often exhibit positive cooperativity upon hybridizing: not only the overall binding free energy ($-\Delta G^{\circ}$) increases with strand length,



Scheme 3. Reagents and conditions: $SOCl_2$, reflux, then **1b** or **3b**, toluene, iPr$_2$EtN, RT, 20–40% yield.

Table 1. Values of K_{dim} (M^{-1})at various temperatures in $CDCl_3$

Entry	5	7	9	11	13	15
25 °C	210	1500	5200	650	65	—[a]
−19 °C	1900	120,000	42,800	920	180	—[a]
49 °C	—[b]	170	750	500	45	—[a]

[a] Signal intensity too low.
[b] Broad signals.

but also the binding free energy per monomer ($-\Delta G°/n$). For instance, this is the case in nucleic acids double helices and their analogs, and in several synthetic oligomers based on hydrogen bonding.[5,7,11]

To explain these results, we first hypothesized that the attractive interactions leading to duplex formation in oligopyridine dicarboxamides may not match over long strands. However, molecular models of long double helices built on the basis of the crystal structures of short double helices[19] show no alteration of the double helical motif (Fig. 3). Moreover even if the longer strands did not match over their entire length, they should still match along part of their length in the way short strands do and lead to some dimerization.

2.3. Stability of double helices and stability of single helices

The value of K_{dim} depends on the free energy difference between the double and the single helix. A drop in K_{dim} does not necessarily reflect a destabilization of the double helix. It may also result from a more important stabilization of the single helix. We thus sought for data indicating the effect of strand length on single helix stability on the one hand, and on double helix stability on the other hand.

Two independent indicators of single helix stability were followed by measuring ^{1}H NMR spectra of **5**–**15** at different temperatures: first, the extent of ring current effects on the protons belonging to the terminal units which can be deduced from the amplitude of the upfield shifts of their signals; and second the rate of inversion of the helix which is correlated to the temperature of coalescence of diastereopic patterns in the spectra.

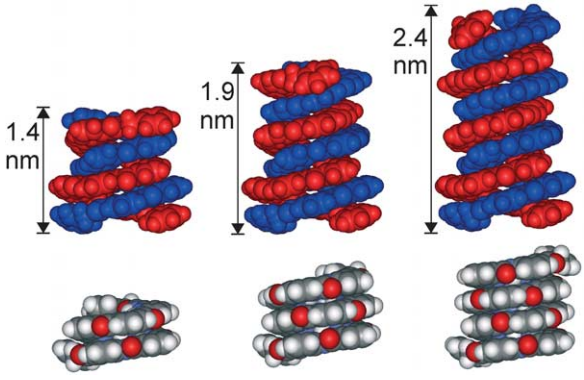


Figure 3. Molecular models of the double (top) and single (bottom) helices of compounds **7**, **11**, and **15**, obtained by prolongation of the patterns found in the crystal structures of previously described single and double helices,[18,19] followed by energy minimization (MM3). Alkoxy chains have been replaced by hydrogens for clarity.

In single helices, the environment of the protons belonging to the terminal units of the strand is not expected to depend much on the length of the strand beyond one helical turn. However, we observe that the signals of these protons undergo an upfield shift as strand length increases. For the signals of benzylic protons, the upfield shift is of almost 0.2 ppm between **7** and **15** (δ in Table 2). Similar shifts are observed for amide (Fig. 2) and aromatic (not shown) resonances. This reflects an increase of the ring current effects in the folded helical conformations and shows that short helices apparently spend more time in an extended form, whereas long helices apparently remain completely folded.

In the single helices, the terminal benzylic methylene protons give rise to two diastereotopic ^{1}H NMR signals which appear as doublets at ca. 4.8 and 5.2 ppm. Upon increasing temperature, these signals coalesce as the inversion of helix handedness becomes rapid on the NMR timescale (Fig. 4). The temperatures of coalescence recorded for **5**–**15** are reported in Table 2 (T_{inv}). The values of T_{inv} increase very rapidly with strand length: about +25° for every two pyridine rings added to the strand. For pentamer **5**, helix inversion becomes rapid on the NMR timescale above 10 °C. T_{inv} is found above the boiling point of $CDCl_3$ for nonamer **9** and undecamer **11** and even close to the boiling point of $C_2D_2Cl_4$ for the longest strands. Thus, these data give a qualitative but clear indication that the stability of the single helices with respect to unfolded states increases rapidly as oligomer length increases.

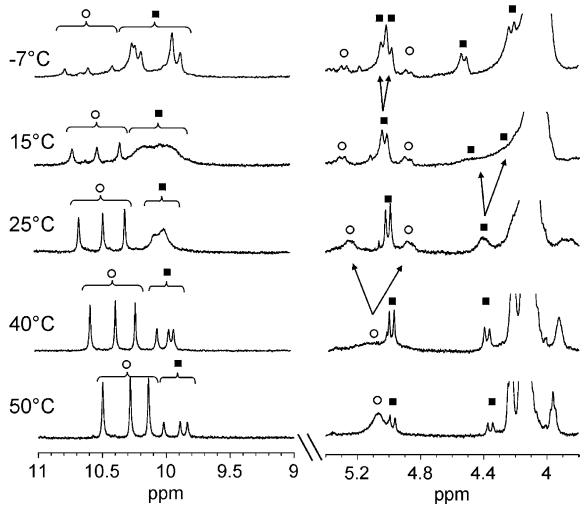


Figure 4. Part of the ^{1}H 400 MHz NMR spectra of compound **7**, $C=1$ mM in $CDCl_3$ at various temperatures, showing the resonances of the amides (11–9 ppm) and the resonnances of the benzylic methylenes (5.4–4.4 ppm). Some signals assigned to single helices and to the double helices are labelled by circles and squares respectively. Arrows indicate coalescences.

Table 2. Physical data for **5**–**15** in $CDCl_3$: chemical shift of one benzylic signal of the single helices (δ); temperatures of coalescence of 400 MHz ^1H NMR signals of diastereotopic protons of the single helice (T_{inv}) and of both ends of each strand in dissymmetrical degenerate double helices (T_{deg}); and estimated surfaces of the strands involved in π–π overlap in double helices (S_{dh} per strand) and single helices (S_{sh})

Compound	δ (ppm)	T_{inv}[a] (°C)	T_{deg}[b] (°C)	S_{dh} (Å^2)	S_{sh} (Å^2)	$\Delta = S_{dh} - S_{sh}$ (Å^2)
5	—[c]	10	36	500	200	300
7	4.86	43	3	760	450	310
9	4.78	65[d]	49	1020	710	310
11	4.75	90[d]	>55	1290	980	310
13	4.71	>120[d]	—[e]	1550	1230	320
15	4.69	>120[d]	—[e]	1820	1500	320

[a] Coalescence of benzylic protons at 5.2 and 4.8 ppm.
[b] Coalescence of benzylic protons at 4.95 and 4.93 ppm.
[c] Broad signal.
[d] In CD_2Cl_4.
[e] Signal intensity too low.

Two indicators of the stability of the double helices were also found. We initially expected to be able to measure the temperature of coalescence between the ^1H NMR signals of the single helix and the signals of the double helix. This temperature is close to room temperature for pentamer **5**, but it increases so rapidly with strand length that we could not access to this data for any other strand but heptamer **7** for which it was measured above 100 °C. The coalescence temperatures of longer strands are above the temperatures that one can reach with a standard NMR spectrometer. This result is corroborated by molecular dynamics simulations that we reported previously[19] that suggest that the rate of duplex dissociation is higher for shorter strands than for longer strands.

We also assessed the stability of the double helices by monitoring the sliding motion of the strands relative to one another within the duplex.[19] In double helices, the extremities of each strand are in a different environment, and the terminal benzylic methylene protons are not equivalent and give rise to two pairs of doublets between 5.2 and 4.4 ppm (Figs. 2 and 4). These four doublets are the signals of two pairs of diastereotopic protons which, in principle, can exchange upon inversion of the double helices. However, since the inversion of the double helix handedness requires dissociation of the strands, the coalescence between the diastereotopic signals of the double helix could not be observed in $CDCl_3$ (except for **5**, see above). Nevertheless, an equilibrium takes place between two degenerate states of the double helix allowing an exchange between the different environments of the strands.[19] When this equilibrium is fast on the NMR timescale, only two diastereotopic doublets are observed for the benzylic methylenes protons (Figs. 2 and 4). The temperatures of coalescence between the signals of these degenerate double helices (T_{deg} in Table 2) thus reflect the rate of an internal motion within the duplex. These temperatures also increase regularly with strand length from −36 °C for pentamer **5a** to over 55 °C for undecamer **11a**. For longer strands, T_{deg} could not be measured because the amount of double helix at high temperature is too low to be detected. This indicates slower dynamics in longer double helices, suggesting that the duplexes become more stable and that they do hybridize over their entire length.

In summary of this section, NMR data qualitatively show that, as could be expected, both double and single helices increase in stability as their length become longer. This arises from an increase of stabilizing interactions in both single and double helices, and results in a better helical organization and a decrease of the rates of dynamic motions as the length increases. However, these data alone give no hint why the variation of K_{dim} as a function of strand length goes through a maximum instead of following a monotonous increase or a monotonous decrease.

2.4. Enthalpic and entropic factors

Previous studies on the dimerization of oligopyridine dicarboxamides suggest that the main driving force of hybridization is interstrand π–π stacking.[19,20] The increase of stability of both single and double helices with increasing chain length presumably arises from an increase of intramolecular π–π overlap in the single helices (S_{sh} in Table 2) and of intermolecular π–π overlap in the double helices (S_{dh} in Table 2). In order to estimate S_{sh} and S_{dh}, we calculated the energy-minimized conformations of the single and double helices (Fig. 3), and compared the solvent accessible surfaces of these folded structures with those of linearly extended strands. As could be expected, the surface involved in π–π overlap increases linearly with strand length both in the single (S_{sh}) and in the double (S_{dh}) helices. However, the difference between S_{dh} and S_{sh} does not depend upon chain length and remains constant at ca. 300 Å^2, which is roughly the surface of the cross-section of one helix.[22] This result suggests that, in first approximation, the enthalpic gain of hybridization associated with π–π interactions is independent of strand length. One may argue that the nature of the stacked π-systems differ in the single and in the double helices,[23] and that the overall enthalpic gain may vary with strand length even though the surface involved in π-stacking does not increase. But the data show that this effect, if it exists, is not significant.

On the other hand, hybridization has an enthalpic cost associated with the extension of the strand and the doubling of the pitch (Fig. 1) that implies an increase of dihedral angles and a lengthening of the NH···N intramolecular hydrogen bonds within each strand of the duplex. This cost is directly proportional to the number of dihedral angles of the strand, and therefore increases linearly with strand length. The sum of an enthalpic cost that increases linearly with strand length and of an enthalpic gain that does not depend on strand length should lead to an overall decrease of the enthalpy of double helix formation as strand length increases.

We calculated the enthalpy of dimerization from van't Hoff plots for compounds **7**, **9** and **11**, for which K_{dim} can reliably be measured over a large temperature range. The results shown in Table 3 indeed show that the enthalpy of hybridization constantly decreases as the length of the oligomer increases. The enthaplic term is very strong for heptamer **7** ($\Delta H = -64 \pm 3$ kJ mol^{-1}) as the increase of the surface involved in π–π overlap from single to double helix is large relative to the overall surface of the strand. For nonamer **9**, the enthalpic gain of dimerization is smaller ($\Delta H = -42 \pm 4$ kJ mol^{-1}). For compound **11**, the enthalpic term reaches very low levels ($\Delta H = -5.8 \pm 0.4$ kJ mol^{-1}) which reflects the fact the gain in π–π overlap upon dimerization is largely compensated by the cost of helix extension.

From these results, it seems reasonable to propose that the drop of K_{dim} for longer oligomers results from a drop of the enthalpic gain of hybridization. It remains to explain why K_{dim} goes through a maximum and does not follow a monotonous decrease. The van't Hoff plots for compounds **7**, **9** and **11** show that the entropy of hybridization follows a trend opposite to that of the enthalpy. The large ΔH for **7** is compensated by a large negative entropic term ($\Delta S = -154 \pm 9$ J K^{-1} mol^{-1}). The entropic loss during hybridization is smaller for **9** ($\Delta S = -74 \pm 14$ J K^{-1} mol^{-1}), and even has a (small) positive value ($\Delta S = 34 \pm 1$ J K^{-1} mol^{-1}) for **11**. This trend of the entropy of hybridization as a function of length presumably reflects that the helical preorganization of the monomers increases with strand length, which allows the longer strands to hybridize with a minimal loss of motional freedom, that is to say at a low entropic price. The positive value of ΔS for **11** suggests that other factors are at play, possibly desolvation, which may contribute favorably to dimerization.

It is worth noting that the large value of ΔS for **7** results in a strong temperature dependence of K_{dim}: by up to three orders of magnitude over a range of 75° (Table 3 and Fig. 4). On the other hand, dimerization of the longer strands show very little temperature dependence (Table 3): only a factor of 2 over a range of 75°.

The hybridization behavior of AOA's contrasts with that of most artificial and natural oligomers. The major difference is that not only the dimers of AOA's fold into well organized structures, but also the monomers. For instance, single stranded DNA, does not generally adopt a stable and well-defined conformation. However, when this is possible as, for example, in hairpins or in G-quartets, hybridization into double helices is impeded.[24] A few artificial oligomers capable of pairing into duplexes reported in the literature also form stable single stranded structures, and it will be interesting to see whether these oligomers keep their ability to hybridize as the strands get longer.

3. Conclusion

In summary, we have presented a new synthetic scheme for the preparation of AOA's and studied their hybridization into double helices as a function of strand length. The fact that the enthalpic price of spring-like extension that a strand must undergo during the formation of a double helix is not compensated by intermolecular π–π interactions explains that dimerization of AOA's decreases for longer oligomers. That K_{dim} goes through a maximum before decreasing results from entropic effects that partially compensate for the decreasing enthalpy of hybridization. These results suggest that a subtle destabilization of the single helical monomers might enhance their hybridization into double helices. Studies on these effects and also on the role of the side chains, and of terminal residues, are currently underway and will be reported in due course.

4. Experimental

4.1. General

Solvents (THF, toluene, CH_2Cl_2) were dried by filtration over activated alumina on a commercially available setup. FTIR spectra were recorded on a Brucker IFS 55 FT-IR Spectrometer 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra were recorded on a Bruker 400 Ultrashield spectrometer. The chemical shifts are expressed in parts per million (ppm) using the residual solvent peak as an internal standard. The following notations are used for the ^{1}H NMR spectral splitting patterns: singlet (s), doublet (d), triplet (t), multiplet (m), borad (br). Melting points are uncorrected. Diester **1a** and diamine **1b** were prepared as described previously.

4.1.1. 4-Decyloxy-2,6-pyridinedicarboxylic acid monomethyl ester (1c). Dimethyl 4-decyloxy-2,6-pyridinedicarboxylate[19] (2.1 g, 6 mmol) was dissolved in 1,4-dioxane (32 mL) and methanol (8 mL) and the solution was cooled to 0 °C. Sodium hydroxide (0.24 g, 6 mmol) was added and the mixture was stirred at 0 °C for 2 h and another 2 h at ambient temperature. The solution was neutralized with acetic acid and poured into water (100 mL). The product was extracted with CH_2Cl_2 (2×50 mL). The organic phase was evaporated and dried under vacuum. The product contaminated with small amounts of starting diester was used without further purification. Yield 1.7 g (85%) of a white solid. Mp: 91–92 °C. ^{1}H NMR ($CDCl_3$), δ 7.84 (1H, s), 7,80 (1H, s), 4.15 (2H, t, J=6.7 Hz), 4.01 (3H, s), 1.84 (2H, m), 1.47 (2H, m), 1,27 (15H, m). TOF-MS (*m/z*): 338.37 $[M+H]^+$ (Calcd for $C_{18}H_{28}NO_5$: 338.20).

4.1.2. (6-Amino-4-decyloxy-pyridin-2-yl)-carbamic acid benzyl ester (1d). To a solution of 4-decyloxy-2,6-diaminopyridine **1b**[19] (1.5 g, 5.65 mmol) in anhydrous

Table 3. Values of K_{dim} (M^{-1}) at various temperatures for and values of ΔH and ΔS **7**, **9** and **11**

Compound	T (°C)							ΔH (kJ mol^{-1})	ΔS (J K^{-1} mol^{-1})
	−19	−4	10	25	36	−49	55		
7	120,000	22,000	12,000	1500	710	170	140	−64±3	−154±9
9	42,800	23,200	10,300	5200	2500	750	400	−42±4	−74±14
11	920	750	710	650	560	500	480	−5.8±0.4	34±1

THF at −78 °C (60 mL) was slowly added a 2 M solution of *n*-butyllithium in hexane (2.7 mL, 1 equiv) After 15 min, benzyl chloroformate (934 μL, 1 equiv) was added at once. The mixture was stirred at −78 °C for 5 h, then at room temperature for 12 h. The reaction was quenched with a small amount of water. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2. This solution was washed with water, dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with CH_2Cl_2/AcOEt. Yield 1.5 g (67%) of an off-white solid. Mp: 85–87 °C. ^{1}H NMR ($CDCl_3$) δ 7.56 (1H, s), 7.36 (5H, m), 6.97 (1H, s), 5.69(1H, s), 5.87 (2H, s), 4.21 (2H, s), 3.95 (2H, t, J=6.8 Hz), 1.74 (2H, m), 1.27 (14H, m), 0.89 (3H, t, J=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ 168.65, 158.51, 153.08, 151.57, 135.86, 128.51, 128.25, 128.16, 89.86, 89.22, 67.89, 66.85, 31.85, 29.50, 29.27, 28.94, 25.88, 22.64, 14.08. IR (liquid layer) ν (cm^{-1}): 3450, 3343, 3258, 3208, 3201, 2957, 2942, 2920, 2873, 2852, 1743, 1718, 1658, 1611, 1578, 1562, 1468, 1454, 1444, 1440, 1405, 1332, 1321, 1313, 1291, 1241, 1226, 1190, 810, 753, 731. TOF-MS (*m*/*z*): 400.35 $[M+H]^+$ (Calcd for $C_{23}H_{34}N_3O_3$: 400.26).

4.1.3. Trimeric diamine 3b. To a solution of 4-decyloxy-2,6-diaminopyridine (0.5 g, 1.88 mmol) in anhydrous THF (4 mL) at −78 °C, was added *n*-butyllithium (2.1 M, 0.942 mL, 1.05 equiv). The mixture was allowed to stand at −78 °C for 15 min. A solution of dimethyl 4-decyloxy-2,6-pyridinedicarboxylate (0.278 g, 0.79 mmol, 0.42 equiv) in THF (3 mL) was added using a canula. The mixture was stirred at −78 °C for 4 h, then at ambient temperature for 24 h. The reaction was quenched with acetic acid (1.2 equiv) and then evaporated to dryness. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/cyclohexane 2:1 vol/vol, to afford **3b**. Yield 259 mg (40% from the diester) of a yellow wax. ^{1}H NMR ($CDCl_3$, ppm) δ 9.99 (2H, s), 7.86 (2H, s), 7.35 (2H, s), 5.66 (2H, s), 5.27 (4H, br), 4.10 (2H, t, J=6,7 Hz), 3.86 (4H, t, J=6.7 Hz), 1.70 (6H, m), 1.28 (42H, m), 0.89 (9H, m). ^{13}C NMR ($CDCl_3$): 168.72, 168.15, 161.38, 158.42, 150.27, 111.52, 91.58, 90.12, 69.16, 68.07, 52.74, 31.87, 29.67, 29.56, 29.38, 29.27, 29.00, 25.91, 25.80, 22.65, 14.08. IR (liquid layer) ν (cm^{-1}): 3361, 2924, 2854, 1694, 1613, 1578, 1535, 1448, 1378, 1344, 1175, 1048.

4.2. Synthesis of 2a, 4a and 6a. General method for coupling a monoacid and a monoamine

Under an anhydrous atmosphere, a solution of acid **1c** or **2c** (1 mmol) in thionyl chloride (5 mL) was heated to reflux till evolvement of gas stopped (ca 30–60 min). The excess thionyl chloride was distilled under reduced pressure, and azeotroped with dry toluene. The residue was dissolved in dry toluene (10 mL). To this solution at 0 °C was added a solution of amine **1d**, **2b** or **4b** (0.9 equiv) in dry toluene (10 mL), followed by distilled *N*,*N*-diisopropylethylamine (5 equiv). The mixture was allowed to warm to ambient temperature and stirred overnight. The solvent was removed and the residue was purified by flash chromatography on silica gel.

4.2.1. Dimer 2a. From acid **1c** (2.026 g, 6.0 mmol) and amine **1d** (2 g, 5.0 mmol). The residue was purified by flash chromatography on silica gel eluting with cyclohexane/EtOAc 10:1 vol/vol. Yield 2.63 g (73%) of a white solid. Mp: 107–109 °C ^{1}H NMR ($CDCl_3$), δ 10.19 (1H, s), 7.91 (1H, d, J=2.8 Hz), 7.75 (1H, d, J=2 Hz), 7.68 (1H, d, J=2 Hz), 7.32 (6H, m), 5.22 (2H, s), 4.15 (2H, t, J=6 Hz), 4.07 (2H, t, J=6.8 Hz), 4.02 (3H, s), 1.82 (4H, m), 1.28 (28H, m), 0.88 (6H, t, J=6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 169.00, 167.64, 165.01, 161.74, 152.84, 151.27, 150.99, 150.19, 148.45, 135.78, 128.58, 128.11, 111.01, 95.88, 94.84, 69.14, 68.43, 67.08, 52.97, 31.85, 29.48, 29.30, 29, 28.94, 28.68, 25.89, 25.80, 22.65, 14.09. IR (KBr) ν (cm^{-1}) 3363, 2919, 2852, 1732, 1713, 1695, 1602, 1580, 1537, 1509, 1444, 1354, 1332, 1262, 1215, 1172, 1151, 1092, 1042. TOF-MS (*m*/*z*): TOF-MS 719.46 $[M+H]^+$ (Calcd for $C_{41}H_{59}N_4O_7$: 719.44), 741.45 $[M+Na]^+$, 757.42 $[M+K]^+$.

4.2.2. Tetramer 4a. From acid **2c** (1.44 g, 2.0 mmol) and amine **2b** (1.0 g, 1.7 mmol). The residue was purified by flash chromatography on silica gel eluting with cyclohexane/EtOAc 10:1 vol/vol. Yield 1.78 g (82%) of a white wax. ^{1}H NMR ($CDCl_3$) δ 10.60 (1H, s), 10.52 (1H, s), 10.50 (1H, s), 8.42 (1H, br), 7.83 (1H, d, J=2 Hz), 7.77 (1H, d, J=2 Hz), 7.75 (1H, d, J=2 Hz), 7.64 (1H, s), 7.57 (2H, m), 7.40 (1H, d, J=2 Hz), 7.11 (5H, m), 7.01 (1H, d, J=3 Hz), 4.85 (2H, s), 4.15 (2H, t, J=6.8 Hz), 4.04 (4H, t, J=6 Hz), 3.97 (2H, t, J=6.4 Hz), 3.67 (3H, s), 1.82 (8H, m), 1.30 (56H, m), 0.89 (12H, t, J=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ 168.92, 168.14, 167.40, 164.61, 161.74, 161.56, 152.91, 151.30, 150.56, 150.47, 150.27, 147.52, 135.51, 128.22, 127.83, 127.35, 114.75, 111.60, 110.90, 97.21, 96.77, 96.05, 95.16, 69.22, 69.08, 68.54, 68.42, 66.62, 52.83, 31.90, 29.58, 29.55, 29.31, 29.00, 28.78, 25.94, 25.84, 22.68, 14.11. IR (KBr) ν (cm^{-1}): 2924, 2854, 1736, 1699, 1580, 1522, 1438, 1338, 1218, 1173, 1108, 1088, 1046, 1018. TOF-MS (*m*/*z*): 1271.76 $[M+H]^+$ (Calcd for $C_{73}H_{107}N_8O_{11}$: 1271.81).

4.2.3. Hexamer 6a. From acid **2c** (0.26 g, 0.37 mmol) and amine **4b** (0.35 g, 0.31 mmol). The residue was purified by flash chromatography on silica gel eluting with toluene/EtOAc 95:5 vol/vol. Yield 390 mg (69%) of a white wax. ^{1}H NMR ($CDCl_3$, 36 °C, 1 mM) δ 10.86 (1H, s), 10.70 (1H, s), 10.46 (1H, s), 10.26 (1H, s), 10.08 (1H, s), 7.94 (1H, br), 7.89 (1H, br), 7.78 (1H, br), 7.80 (1H, br), 7.72 (2H, br), 7.52 (1H, br), 7.43 (1H, br), 7.34 (3H, br), 7.14 (5H, br), 7.00 (2H, br), 5.10 (2H, s), 4.16 (24H, m), 3.64 (3H, s), 1.88 (6H, br), 1.33 (84H, m), 0.91 (12H, s). ^{13}C NMR ($CDCl_3$) δ 168.80, 168.00, 167.78, 167.43, 166.95, 164.5, 164.30, 161.39, 160.62, 151.28, 150.27, 150.18, 149.86, 149.44, 135,51, 134.97, 128.83, 128.15, 127.65, 127.18, 114.88, 114.20, 11.49, 111.22, 111.00, 110.36, 110.11, 97.39, 96.64, 96.56, 95.09, 94.70, 69.10, 68.63, 68.01, 66.10, 52.86, 52.48, 31.95, 29.68, 29.42, 29.06, 25.93, 22.71, 14.13. IR (KBr) ν (cm^{-1}): 3372, 2924, 2854, 1735, 1696, 1583, 1523, 1438, 1339, 1218, 1174, 1121, 1046, 849. TOF-MS (*m*/*z*): 1824.06 $[M+H]^+$ (Calcd for $C_{105}H_{155}N_{12}O_{15}$: 1824.17).

4.3. Synthesis of 2b and 4b. General hydrogenation procedure

A mixture of benzylcarbamate **2a** or **4a** (1 mmol) dissolved in DMF (10 mL) and methyl alcohol (10 mL), and of 10% Pd/C (10% weigh) was stirred overnight under hydrogen at

atmospheric pressure The mixture was filtered through Celite. The solvents were removed under reduced pressure to give the product, which was used without further purification.

4.3.1. Synthesis of dimer amine 2b. From dimer **2a** (1 g, 1.39 mmol) and 10% Pd/C (100 mg). Yield 810 mg (quantitative) of **2b** as an off-white solid. Mp: 160–161 °C. ^{1}H NMR ($CDCl_3$) δ 10.15 (1H, s), 7.92 (1H, d, J=2.8 Hz), 7.74 (1H, d, J=2 Hz), 7.46 (1H,d, J=2 Hz), 5.83 (1H, d, J=2 Hz), 4.32 (2H, s), 4.14 (2H,t, J=6.8 Hz), 4.02 (5H, m), 1.82 (4H, m), 1.28 (28H, m), 0.88 (6H, t, J=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ 168.61, 167.61, 165.01, 158.84, 151.61, 150.62, 148.10, 114.91, 110.82, 91.36, 90.32, 69.10, 68.00, 52.90, 31.85, 29.54, 29.49, 29.28, 29.02, 28.70, 25.93, 25.80, 22.64, 14.09. IR (KBr) ν (cm^{-1}): 3404, 3343, 2920, 2851, 1723, 1702, 1658, 1614, 1597, 1532, 1464, 1382, 1347, 1294, 1254, 1165, 1107, 1040. TOF-MS (*m*/*z*): 585.49 $[M+H]^+$ (Calcd for $C_{33}H_{53}N_4O_5$: 585.40).

4.3.2. Synthesis of tetramer amine 4b. From tetramer **4a** (0.95 g) and 10% Pd/C (80 mg). Yield 850 mg (quantitative) of **4b** as an off-white wax. ^{1}H NMR ($CDCl_3$) δ 10.61 (1H, s), 10.47(1H, s), 10.39 (1H, s), 7.91 (4H, m), 7.73 (1H, s), 7.70 (1H, s), 7.51(1H, s), 5.81 (1H, s), 4.16 (6H, m), 4.01(2H, t, J=6 Hz), 3.95 (2H, s), 3.50 (3H, s), 1.84 (8H, m), 1.29 (56H, m), 0.89 (12H, t, J=7.4 Hz). TOF-MS (*m*/*z*): 1137.87 (Calcd for $C_{65}H_{101}N_8O_9$: 1137.77).

4.4. General method for the saponification of methyl esters

To a solution of ester **2a**, **4a**, or **6a** (1.39 mmol) in 1,4-dioxane (20 mL) and water (2 mL), was added sodium hydroxide (111.2 mg; 2 equiv). The resulting solution was stirred for 2 h at 25 °C, and then neutralized with an excess of AcOH. The solution was extracted with dichloromethane (40 mL). The organic phase was washed with water, dried over $MgSO_4$, filtered and evaporated, to yield the corresponding acid which was used without further purification. Following this procedure, dimer acid **2c**, tetramer acid **4c** and hexamer acid **6c** were obtained as off-white solids in quantitative yield. Dimer **2c** could be characterized by ^{1}H NMR but **4c** and **6c** show very broad spectra due to the single helix-double helix equilibrium and non-specific aggregation involving the carboxylic acid group. Complete conversion was confirmed by thin layer chromatography and the absence of methyl ester signal on the NMR spectra.

4.4.1. Dimer 2c. Mp: 176–177 °C. ^{1}H NMR ($CDCl_3$) δ 10.76 (1H, s), 8.03 (1H, s), 7.96 (1H, d, J=2.7 Hz), 7.90 (1H, d, J=2.7 Hz), 7.78 (1H, d, J=2 Hz), 7.41 (6H, m), 5.25 (2H, s), 4.16 (2H, dd, J_1=6.7 Hz, J_2=6 Hz), 4.09 (2H, dd, J_1=6.7 Hz, J_2=6 Hz), 1.83 (4H, m), 1.46 (4H, m), 1.28 (24H, s), 0.88 (6H, m). HR TOF-MS (*m*/*z*): 705.54 $[M+H]^+$ (Calcd for $C_{40}H_{57}N_4O_7$: 705.42).

4.5. Synthesis of oligomers 5, 7, 9, 11, 13 and 15. General method coupling an acid and a diamine

The procedure is the same as for coupling a monoacid and a monoamine (see Section 4.2), except that only 0.4 equiv of diamine were used. All products were purified by flash chromatography on silica gel eluting with cyclohexane/EtOAc 95/5 vol:vol.

4.5.1. Pentamer 5. From diameric acid **2c** (300 mg, 0.42 mmol)) and monomeric diamine **1b** (47 mg, 0.18 mmol). Yield 69 mg (25%) of a white wax. ^{1}H NMR ($CDCl_3$, 36 °C, 1 mM, signals of the single helix) δ 10.35 (4H, br), 7.85 (4H, br), 7.03 (2H, br, m), 7.15 (10H, br, m), 7.03 (6H, br, m), 5.03 (4H, br, m), 4.08 (10H, br, m), 1.86 (10H, br, m), 1.31 (70H, br, m), 0.91 (15H, br, m). IR (KBr) ν (cm^{-1}): 2924, 2854, 1697, 1586, 1533, 1453, 1339, 1217, 1175, 1045. HR TOF-MS (*m*/*z*): 1639.04 $[M+H]^+$ (Calcd for $C_{95}H_{136}N_{11}O_{13}$: 1639.03).

4.5.2. Heptamer 7. From dimeric acid **2c** (72 mg, 0.1 mmol) and trimeric diamine **3b** (36.5 mg, 0.045 mmol). Yield 34.21 mg (35%) of a white wax. ^{1}H NMR ($CDCl_3$, 36 °C, 1 mM, signals of the single helix) δ 10.60 (2H, s), 10.41 (2H, s), 10.25 (2H, s), 7.88 (2H, s), 7.79 (2H, s), 7.65 (2H, s), 7.49 (2H, s), 7.32 (2H, s), 7.13 (7H, m), 7.03 (7H, m), 7.00 (2H, s), 5.23 (2H, br), 4.89 (2H, br), 4.22 (2H, br), 4.14 (12H, br), 1.88 (14H, br), 1.34 (98H, br, m), 0.91 (21H, br, m). ^{13}C NMR ($CDCl_3$) δ 169.25, 168.92, 168.11, 167.91, 167.41, 167.31, 163.82, 161.41, 161.05, 160.92, 151.66, 150.22, 150.06, 149.77, 149.46, 148.79, 135.44, 130.86, 128.78, 128.21, 127.74, 127.17, 126.77, 111.65, 111.41, 111.26, 110.93, 96.96, 96.75, 96.28, 95.63, 94.06, 69.22, 68.07, 66.31, 37.39, 33.68, 32.75, 31.93, 30.17, 29.68, 29.40, 29.05, 27.30, 26.05, 25.93, 22.71, 19.73, 14.13. IR (liquid layer) ν (cm^{-1}): 3313, 2957, 2924, 2853, 1735, 1700, 1648, 1616, 1585, 1579, 1560, 1540, 1523, 1458, 1430, 1377, 1349, 1339, 1261, 1218, 1176, 1092, 1052, 1020. TOF-MS (*m*/*z*): 2191.27 $[M+H]^+$ (Calcd for $C_{127}H_{184}N_{15}O_{17}$: 2191.40).

4.5.3. Nonamer 9. From tetrameric acid **4c** (103 mg, 0.082 mmol) and monomeric diamine **1b** (8.68 mg, 0.033 mmol). Yield 19.2 mg (21%) of a white wax. ^{1}H NMR ($CDCl_3$, 36 °C, 1 mM, signals of the single helix) δ 10.65 (2H, s), 10.40 (2H, s), 10.34 (2H, s), 10.32 (2H, s), 7.90 (2H, d, J=2 Hz), 7.62 (4H, d, J=2 Hz), 7.59 (4H, d, J=2 Hz), 7.54 (2H, d, J=2 Hz), 7.58 (2H, s), 7.44 (2H, d, J=2 Hz), 7.18 (2H, d, J=2 Hz), 7.10 (10H, br), 6.87 (2H, d, J=2 Hz), 5.18 (2H, d, J=12.8 Hz), 4.79 (2H, d, J=12.8 Hz), 4.10 (18H, br, m), 1.93 (18H, br, m), 1.33 (126H, br, m), 0.91 (27H, br, m). ^{13}C NMR ($CDCl_3$) δ 168.08, 167.91, 167.72, 167.17, 161.18, 160.77, 160.70, 151.55, 150.17, 149.85, 149.67, 149.36, 128.16, 127.71, 127.17, 111.30, 111.11, 95.95, 95.60, 94.20, 69.17, 68.03, 31.92, 29.73, 29.68, 29.35, 29.06, 28.87, 26.11, 25.97, 22.68, 14.13. IR (liquid layer) ν (cm^{-1}): 2956, 2923, 2853, 1740, 1699, 1613, 1585, 1523, 1439, 1389, 1261, 1217, 1176, 1092, 1046. HR TOF-MS (*m*/*z*): 2744.03 $[M+H]^+$ (Calcd for $C_{160}H_{233}N_{18}O_{21}$: 2742.77).

4.5.4. Undecamer 11. From tetrameric acid **4c** (55 mg, 0.044 mmol) and trimeric diamine **3b** (17 mg, 0.021 mmol). Yield 23.4 mg (34%) of a white wax. ^{1}H NMR ($CDCl_3$, 36 °C, 1 mM, single helix, ppm) δ 10.45 (4H, s), 10.40 (2H, s), 10.20 (2H, s), 10.07 (2H, s), 7.80 (2H, d, J=2 Hz), 7.63 (2H, d, J=2 Hz), 7.57 (2H, s), 7.55 (2H, d, J=2 Hz), 7.45 (2H, d, J=2 Hz), 7.33 (2H, d, J=2 Hz), 7.28 (5H, br), 7.20

(5H, br), 7.14 (2H, d, $J=2$ Hz), 7.04 (2H, s), 7.02 (2H, s), 6.95 (2H, s), 6.93(2H, s), 6.81 (2H, s), 5.17 (2H, d, $J=$ 12 Hz), 4.76 (2H, d, $J=12.8$ Hz), 4.12 (22H, br, m), 1.91 (22H, br, m), 1.34 (154H, br, m), 0.93 (33H, br, m). ^{13}C NMR ($CDCl_3$) δ 168.03, 167.85, 167.64, 167.55, 167.13, 167.04, 161.24, 161.06, 160.61, 160.52, 151.05, 150.14, 149.94, 149.56, 149.34, 149.24, 149.12, 148.82, 148.61, 135.51, 135.33, 130.92, 128.83, 128.15, 127.70, 127.17, 111.65, 111.46, 111.13, 110.82, 95.93, 95.76, 95.51, 69.11, 67.88, 66.52, 66.05, 32.08, 31.90, 30.12, 29.65, 29.40, 29.33, 29.05, 25.99, 25.80, 22.80, 22.711, 14.14. IR (liquid layer) ν (cm^{-1}): 2924, 2854, 1702, 1611, 1581, 1517, 1438, 1339, 1216, 1175, 1048. TOF-MS (*m/z*): 3113.38 $[M+H-2(C_7H_8)]^+$, 3136.24 $[M+Na-2(C_7H_8)]^+$, 3152.24 $[M+K-2(C_7H_8)]^+$ (Calcd for $C_{177}H_{266}N_{23}O_{25}$: 3114.03).

4.5.5. Tridecamer 13. From hexameric acid **6c** (128 mg) and monomeric diamine **1b** (7.0 mg). Yield 31.5 mg (31%) of a white wax. ^{1}H NMR ($CDCl_3$, 25 °C, 1 mM, signals of the single helix) δ 10.29 (2H, s), 10.28 (2H, s), 10.25 (2H, s), 10.18 (2H, s), 10.14 (2H, s), 10.10 (2H, s), 7.79 (2H, s), 7.47 (2H, s), 7.39 (2H, s), 7.37 (2H, s), 7.17 (10H, br, m), 7.02 (4H, s), 6.98 (4H, br, m), 6.96 (2H, s), 6.88 (2H, s), 6.86 (2H, s), 6.84 (2H, s), 6.77 (2H, s), 5.13 (2H, d, $J=12.8$ Hz), 4.72 (2H, d, $J=12.8$ Hz), 4.08 (26H, br, m), 1.96 (26H, br, m), 1.35 (182H, br, m), 0.92 (33H, br, m). ^{13}C NMR ($CDCl_3$) δ 168.86, 168.56, 168.02, 167.62, 167.23, 166.99, 166.90, 161.21, 160.83, 160.62, 160.41, 159.26, 153.74, 151.54, 150.09, 149.86, 149.77, 149.53, 149.40, 149.17, 149.00, 148.66, 148.55, 148.34, 135.68, 135.32, 128.10, 127.91, 127.65, 127.17, 126.53, 111.58, 111.38, 111.11, 110.96, 110.86, 96.55, 95.88, 95.70, 95.568, 95.46, 69.07, 68.50, 67.94, 67.82, 66.46, 31.95, 30.15, 29.82, 29.67, 29.56, 29.41, 29.11, 26.05, 22.73, 14.14. IR (liquid layer) ν (cm^{-1}): 2924, 2854, 1700, 1615, 1585, 1524, 1439, 1389, 1339, 1216, 1175, 1046. TOF-MS (*m/z*): 3666.66 $[M+H-2(C_7H_8)]^+$, 3688.45 $[M+Na-2(C_7H_8)]^+$ (Calcd for $C_{209}H_{314}N_{27}O_{29}$: 3666.39).

4.5.6. Pentadecamer 15. From hexameric acid **6c** (90 mg) and trimeric diamine **3b** (16.3 mg). Yield 1.9 mg (2.2%) as a white wax. ^{1}H NMR ($CDCl_3$, 25 °C, 1 mM, signals of the single helix) δ 10.32 (2H, s), 10.29 (2H, s), 10.25 (2H, s), 10.20 (2H, s), 10.11 (2H, s), 9.98 (2H, s), 9.96 (2H, s), 7.76 (2H, s), 7.46 (2H, s), 7.36 (2H, s), 7.34 (2H, s), 7.20 (5H, s), 7.17 (2H, s), 7.13 (2H, s), 7.08 (5H, s), 7.06 (2H, s), 7.02 (2H, s), 7.00 (2H, s), 6.98 (2H, s), 6.95 (2H, s), 6.88 (4H, br), 6.85 (2H, s), 6.79 (2H, s), 6.75 (2H, s), 5.12 (2H, d, $J=$ 12.8 Hz), 4.71 (2H, d, $J=12.8$ Hz), 4.06 (30H, br, m), 1.86 (30H, br, m), 1.35 (210H, br, m), 0.92 (45H, br, m), IR (liquid layer) ν (cm^{-1}): 2923, 2853, 1701, 1585, 1524, 1439, 1340, 1045. TOF-MS (*m/z*): 4228.65 $[M+H-2(C_7H_8)]^+$, 4240.07 $[M+Na-2(C_7H_8)]^+$, 4256.03 $[M+K-2(C_7H_8)]^+$ (Calcd for $C_{241}H_{362}N_{31}O_{33}$: 4218.76).

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21. Final products were purified by chromatography at least three times on TLC or radial chromatography prior to NMR studies. The impurities can be characterized as such and not as being other conformations/aggregates of the oligomers because: (i) TLC reveals their presence; (ii) the line shape of their signals remains sharp at any temperature even when the rest of the spectrum broadens due to coalescence phenomena; (iii) when the concentration is varied, the proportions of single and double helices varies but the quantity of 'impurity' is proportional to neither of them: it remains proportional to the total concentration of single and double helices.
22. The surface involved in π–π stacking in a double helical dimer is similar to that involved in two stacked single helical monomers. It differs from the surface involved in π–π stacking in two dissociated monomers by twice the cross-section of the helix.
23. Crystal structures show that pyridine rings are sandwiched between amide functions in the single helices, whereas they are sandwiched between other pyridine rings in the double helices, see Ref. 19.
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Mild and selective deprotection of carbamates with Bu_4NF

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Abstract—A new mild method allowing the removal of carbamates using TBAF in THF is reported. Reactions were performed on indole, indoline, *N*-methyl aniline, aniline and tryptamine derivatives. The observed selectivity according to the carbamates or the substrates is discussed. A mechanism is postulated.

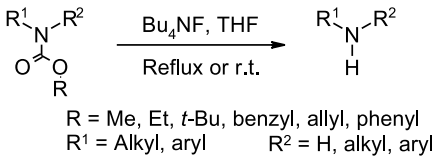
1. Introduction

The selection of a protective group is often a crucial step in organic synthesis;[1] the development of new protective groups and novel efficient methods for their introduction or cleavage remains of prime importance in synthetic methodology.

Many protective groups have been developed for the amino functionality, in peptide, protein, and nucleotide syntheses as well as in heterocyclic chemistry. Among them, may be the most useful and popular are the carbamates. Actually, carbamates are not only used as protective but also as efficient directing metallation groups.[2] Carbamates are generally obtained from an amine by reaction with the adequate chloroformate or anhydride. It is of prime interest to dispose of a wide range of methods allowing the selective cleavage of a definite protective group on a given nitrogen atom in the presence of other *N*-protected sites.[3,4] There are a lot of conditions allowing the recovery of the free amino group; catalytic hydrogenolysis, acidic or basic[3] treatments are generally appropriate to remove most of the different carbamates used in organic synthesis. Nevertheless several drawbacks constitute sometimes a limitation of the efficiency of these methods. For instance, the presence of a sulfur atom is commonly incompatible with a catalytic hydrogenolysis.[5] The acidic cleavage of a Boc group can generate *t*-butyl cations and in some cases, scavengers have to be used to prevent undesirable alkylation or electrophilic additions.[6] The unwanted formation of heterocycles by an intramolecular cyclisation has been as well reported in the course of reactions involving methyl and ethyl carbamates.[7,8] In some instance cleavage of phenyl carbamates led also to undesired side-products.[9–12]

Tetra-*n*-butylammonium fluoride (Bu_4NF) is a versatile and popular reagent widely used in organic chemistry[13–17] for most fluoride-assisted reactions (deprotection of silyl groups,[3] desilylation,[18] fluorination)[19] and used as a base in a variety of base-catalysed reactions.[20–24] In particular the hydrolysis of aliphatic esters[25] with aqueous TBAF and the cleavage of *N*-mesyl[22] or *N*-benzenesulfonyl groups[26,27] have been reported. Recently, Yasuhara prepared 2-substituted indole from 2-ethynyl anilines with TBAF[22,28,29] and observed a partial or total *N*-dealkoxycarbonylation during the cyclisation process. For our part we have previously reported our own preliminary results concerning the mild deprotection of *tert*-butyl carbamates (Boc) on heteroaromatics using TBAF in refluxing THF.[30]

Herein we wish to extend the scope of our method to the cleavage of various aliphatic (*t*-Bu, Me, Et), allylic (alloc), benzylic (Z) and phenyl carbamates protecting different kinds of nitrogens (Scheme 1).



Scheme 1. General scheme for Bu_4NF cleavage of carbamate protective groups in THF.

2. Results and discussion

All the studied carbamates were prepared using classical

Keywords: Carbamates; Deprotection; Bu_4NF; Protective groups.
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conditions as indicated in the captions of Figures 1–4. The same typical procedure was used for all deprotection assays: the *N*-protected derivative was dissolved in dry THF under argon, then the adapted amount of a 1 M solution of Bu_4NF in THF was added; the reaction was performed at rt or in refluxing THF for the appropriate duration.

2.1. Cleavage of *N*-indolyl protected carbamates

We have recently reported[30] the deprotection of *tert*-butyl carbamate groups on pyrrole, carbazole and indole **7**. The latter was fully deprotected by Bu_4NF (5 equiv) in refluxing THF for 8 h (Table 1, entry 6a). Decreasing the amount of the reagent affected the yield of deprotected indole but the starting material was always recovered.[30] In order to complete these preliminary studies we prepared the other indolyl carbamates **2–6** (Fig. 1) and examined their behavior towards Bu_4NF in different experimental conditions (Table 1).

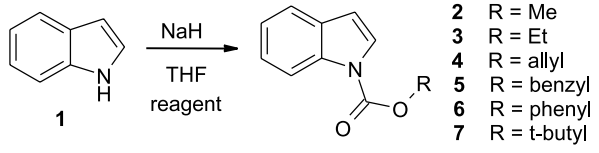


Figure 1. MeOCOCl 1.5 equiv, NaH 2 equiv, DMF, rt, 1 h, quant.; **3** EtOCOCl 1.5 equiv, NaH 2 equiv, THF, rt, 2 h, 95%; **4** AllylOCOCl 1.5 equiv, NaH 2 equiv, THF, rt, 12 h, 76%; **5** NaH 1.3 equiv, $PhCH_2$-OCOCl 3 equiv, DMF, rt, 30 min, 83%; **6** PhOCOCl 3 equiv, NaOH 3 equiv, Bu_4NBr 0.03 equiv, CH_2Cl_2, rt, 1 h, quant. **7** Boc_2O 2 equiv, 4-DMAP 1.5 equiv, THF, rt, 2 h, quant.

At rt, with 5 equiv of Bu_4NF, a rapid reaction occurred in the case of the phenyl carbamate **6**[31] and **1** was obtained in 30 min (entry 5b). In these conditions, the deprotection was effective after a much longer reaction time for all the other carbamate protective groups (entries 1b–4b). By performing the reaction in refluxing THF, however, all the carbamates were cleaved after 1.5 h (entries 1a–5a). Allyl and phenyl derivatives **4** and **6** were particularly sensitive and were cleaved in only 20 and 15 min respectively (entries 3a, 5a). In the cases of compounds **5** and **6**, were also detected benzyl alcohol **8** and phenol **9** along with indole **1**. Decreasing the amount of reagent Bu_4NF to 1.2 equiv (instead of 5 equiv) and performing the reaction at reflux, slowed down the rate of cleavage (entries 1c–5c), but the order of sensitivity of the different carbamates remained unchanged: phenyl, allyl > benzyl, Me, Et > *t*-Bu.

The phenyl carbamate was nearly totally cleaved in 24 h at rt, using 1.2 equiv of TBAF (entry 5d), whereas in the same conditions the deprotection was partial with the other derivatives, but starting material was always recovered (entries 1d–4d, 6d).

2.2. Cleavage of amines carbamates

2.2.1. Primary and secondary aromatic amines. Carbamates **14–28** were prepared from indoline **11**, *N*-methylaniline **12** and aniline **13** using standard procedures (Fig. 2). The Boc carbamates **18**, **23**[32] and **28**[33] were first submitted to the action of TBAF (5 equiv) in refluxing THF for 8 h (Table 2). While the protection of the secondary amines remained intact, the Boc derivative **28** was quantitatively deprotected (entry 10).

The indoline derivatives **14**[34]–**16**,[35] **17** were then submitted to TBAF (5 equiv) in the same conditions. After hydrolysis, deprotected indoline **11** was generally isolated in low yield and the starting material was recovered; no significant

Table 1. Reactions performed on *N*-indolic protected compounds **2–7**

Entry	Reactant	Bu_4NF (equiv)	Time	*T* (°C)	Products (yield, %)[a]
1a	**2**	5.0	40 min	Reflux	**1** (97)
b		5.0	8 h.	rt	**1** (90)
c		1.2	2 h 15	Reflux	**1** (98)
d		1.2	24 h	rt	**1**(54), **2** (14)
2a	**3**	5.0	1 h 30	Reflux	**1** (97)
b		5.0	8 h	rt	**1** (70), **3** (26)
c		1.2	4 h 30	Reflux	**1** (97)
d		1.2	24 h	rt	**1** (30), **3** (66)
3a	**4**	5.0	20 min	Reflux	**1** (97)
b		5.0	6 h 45	rt	**1** (84), **4** (11)
c		1.2	2 h	Reflux	**1** (87), **4** (10)
d		1.2	8 h	rt	**1** (34), **4** (62)
4a	**5**	5.0	1 h 30	Reflux	**1** (75),[b] **8** (ND)[c]
b		5.0	3 h	rt	**1** (76),[b] **8** (ND)[c]
c		1.2	8 h	Reflux	**1** (98),[b] **8** (ND)[c]
d		1.2	8 h	rt	**1** (64), **5** (36), **8** (ND)[c]
5a	**6**	5.0	15 min	Reflux	**1** (82)[b,c]
b		5.0	30 min	rt	**1** (78),[b] **9** (ND)[c]
c		1.2	15 min	Reflux	**1** (77),[b] **9** (ND)[c]
d		1.2	24 h	rt	**1** (78), **6** (5), **9** (ND)[c]
6a	**7**	5.0	8 h	Reflux	**1** (98)
b		5.0	24 h	rt	**7** (99)
c		2	24 h	Reflux	**1** (81), **7** (7)
d		1.2	24 h	rt	**1** (39), **7**(51)

ND—not determined.
[a] Yield given after flash chromatography.
[b] Quantitative on TLC.
[c] ^1H NMR of the crude mixture shows an equimolar composition of compound **1** and of the liberated benzyl alcool **8** or phenol **9**.

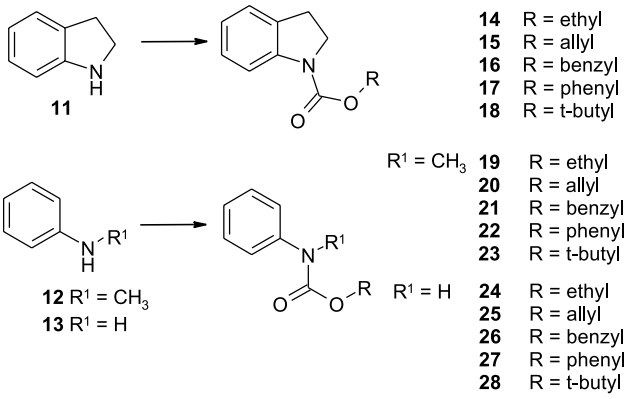


Figure 2. **14** EtOCOCl 1.2 equiv, NaH 1.5 equiv, THF, rt, 1 h, 88%; **15** AllylOCOCl 1.5 equiv, NaH 1.2 equiv, THF, rt, 1 h, quant.; **16** $PhCH_2OCOCl$ 1.2 equiv, NaH 1.5 equiv, DMF, rt, 2 h, 30%; **17** PhOCOCl 1.2 equiv, NaH 1.1 equiv, DMF, rt, 2 h, 72%; **20** AllylOCOCl 1.2 equiv, NaH 1.5 equiv, THF, rt, 1 h, quant.; **21** $PhCH_2OCOCl$ 1.2 equiv, NaH 1.5 equiv, DMF, rt, 18 h, 72%; **22** PhOCOCl 1.2 equiv, NaH 1.1 equiv, DMF, 0 °C to rt, 2 h, 83%; **23** Boc_2O 1.5 equiv, 4-DMAP 1 equiv, NEt_3 1.5 equiv, THF, rt, 5 h, 95%; **24** EtOCOCl 1.2 equiv, NaH 1.4 equiv, THF, rt, 2 h, quant.; **25** AllylOCOCl 1.2 equiv, NaH 1.5 equiv, THF, rt, 6 h, 21%; **26** $PhCH_2OCOCl$ 1.2 equiv, NaH 1.5 equiv, DMF, rt, 18 h, 55%; **27** PhOCOCl 1.1 equiv, NEt_3 1.2 equiv, CH_2Cl_2, 3 h, quant.; **18**, **19**, **28** commercially available.

difference was observed between allyl, benzyl or ethyl carbamates (entries 1–3). One more time the phenyl carbamate **17** was highly sensitive and the indoline was isolated in 68% yield (entry 4). In the case of carbamates **19**, **20**,[36] **21**,[36] **22**[36] and **23**[32] obtained from an other secondary amine, no cleavage was observed. On the other hand, as expected, all the carbamates **24**[37]–**26**,[38]**27**,[39] **28**[33] prepared from aniline were cleaved in no more than 8 h (entries 6–8). The primary amine was always recovered in a quantitative yield. The cleavage of the phenyl carbamate **27** was extremely easy and was effective at rt, in the presence of only 1.2 equiv of TBAF (entry 9).

The degree of substitution of the nitrogen atom of the aromatic amine seems to be determinant. One more time the carbamates rank in the order: phenyl > benzyl > allyl > ethyl > *t*-Bu.

2.2.2. Aliphatic amine. The phenyl and *t*-butyl carbamates **30** and **31** were obtained from 2,3-dichlorophenylethylamine **29**, a primary amine chosen as a model compound. (Fig. 3).

When treated in refluxing THF, with 10 equiv of TBAF, for 8 h, compound **31** was only partially cleaved; the primary amine **29** was isolated in 54% yield with recovery of the starting material **31** in 44% yield. As expected, the phenyl carbamate **30** was more reactive and completely cleaved after 5 min, in refluxing THF, in the presence of 5 equiv of TBAF.

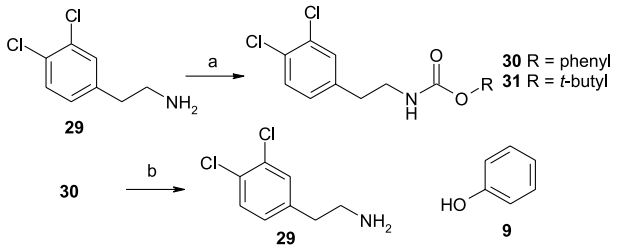


Figure 3. (a) For **30** NEt_3, 1.05 equiv, PhOCOCl 1.05 equiv CH_2Cl_2, rt, 30 min 85%; for **31**, Boc_2O 1.2 equiv, 4-DMAP 1.05 equiv, CH_3CN, rt, 4 h, quant. (b) Bu_4NF, THF, see text.

Decreasing the amount of TBAF to 1.2 equiv just resulted in increasing the reaction duration to 15 min. In the two cases the primary amine **29** was quantitatively recovered from **30**.

2.3. Tryptamine

The obvious contrast between the sensitivity of indolic carbamates and primary amino carbamates led us to search for conditions allowing the selective cleavage of a protective group on a molecule bearing two protected nitrogen atoms. Tryptamine was a good candidate for such a study. We prepared three protected compounds (Table 3), bearing the most sensitive (phenyl), an intermediate (benzyl) and the less (*t*-Bu) reactive carbamate as leaving groups.[39–42] The selectivity of deprotection was studied with:

- the first one, **32**, bearing the same Boc group on the two nitrogen atoms.
- the second one, **33** bearing a phenyl carbamate on the indolic nitrogen atom and a Boc group, on the other one.
- the third one, **34**, bearing a *t*-Boc group on the indolic nitrogen atom and a phenylcarbamate protection on the primary amine. The most representative assays are reported in Table 3.

Even when a large excess of TBAF (10 equiv) was used, the deprotection of **32** was not complete after 8 h in refluxing THF. The cleavage occurred without surprise preferentially on the *N*-indolic atom (entry 1). As expected, the phenyl

Table 2. Deprotection of aniline and indoline *N*-carbamates

Entry	Reactant	Bu_4NF (equiv)	Time	*T* (°C)	Products (%)
1	**14**	5.0	8 h	Reflux	**11** (18), **14** (79)
2	**15**	5.0	8 h	Reflux	**11** (16), **15** (57)
3	**16**	5.0	8 h	Reflux	**11** (22), **16** (74)
4	**17**	5.0	8 h	Reflux	**11** (68), **17** (35)
5	**18**	5.0	8 h	Reflux	No reaction
6	**24**	5.0	6 h	Reflux	**13** (quant.)[a]
7	**25**	5.0	3 h	Reflux	**13** (quant.)[a]
8	**26**	5.0	2.5 h	Reflux	**13** (quant.)[a]
9	**27**	1.2	5 min	rt	**13** (quant.)[a]
10	**28**	5.0	8 h	Reflux	**13** (quant.)[a]

[a] Quantitative yield in TLC and ^1H NMR.

carbamate **33** (entry 2) was fully and selectively deprotected on the *N*-indolic atom affording the monoprotected derivative **35**.[43]

In the presence of 1.2 equiv of TBAF, at rt, compound **34** was also completely and selectively deprotected on the amino position affording **36**[44] in 83% yield. Surprisingly when this reaction was conducted in the presence of a large excess of TBAF, we observed the formation of an urea, compound **37**, in 25% yield, and compound **36** in 39% yield.

2.4. Other results

We showed in our previous investigations[30] that aromatic esters, aldehydes and maleimides were not affected by the presence of a large excess of Bu_4NF in anhydrous conditions even in refluxing THF. We observed that, under the same conditions, *t*-butyl and ethyl esters on pyrrole or indole moieties were neither affected. Even the methyl ester **46**[45] was selectively transformed into the *N*-deprotected ester **47** in good yield (88%) (Fig. 4, assay 4).

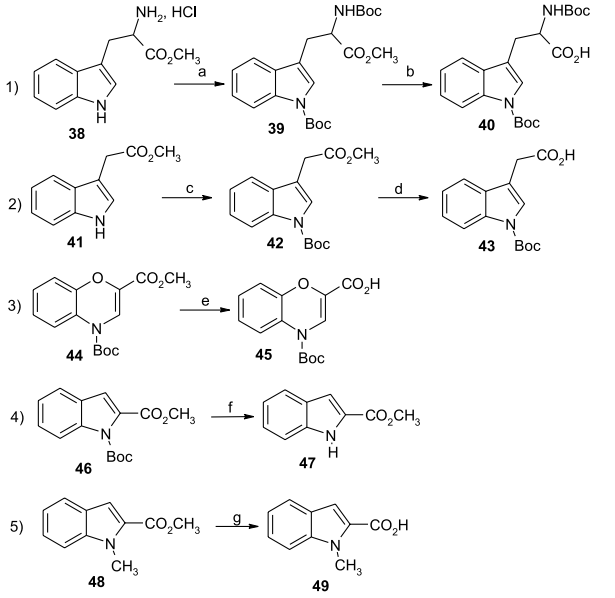


Figure 4. (a) Boc_2O 2.0 equiv, NEt_3 1 equiv, 4-DMAP 1.5 equiv, THF, rt, 12 h, 90%; (b) Bu_4NF 10 equiv, THF, reflux, 6 h, quant.; (c) Boc_2O 1.5 equiv, 4-DMAP 10%, THF, rt, 4 h, 83%; (d) Bu_4NF 5 equiv, THF, reflux, 7 h, quant. in TLC; (e) Bu_4NF 5 equiv, THF, reflux, 5 h, quant.; (f) Bu_4NF 5 equiv, THF, reflux, 6 h, 88%; (g) Bu_4NF 5 equiv, THF, reflux, 7 h, quant.

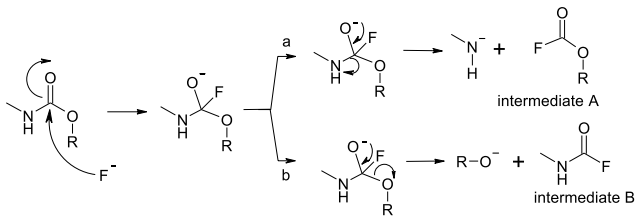
On another hand, the hydrolysis of amino acid esters in the presence of Bu_4NF in aqueous conditions has previously been reported.[25]

We prepared derivatives **39**,[41] **42**,[46] and **44**[47] bearing both a Boc protecting group and a methyl ester in view to examine their behavior towards TBAF (Fig. 4). The different experiments performed show that, actually, TBAF can be reactive towards both carbamates and methyl esters. The observed results are greatly dependent upon the relative reactivities of the carbamates and the methyl esters considered. Treated with an excess of TBAF (5 or 10 equiv) in refluxing THF, in anhydrous conditions, the three esters led, after work-up, to the corresponding acids **40**,[48] **43**,[49] **45** in quantitative yields. In these cases, the Boc protections were never affected although TBAF was present in large excess. These issues are in contradiction with the result observed for **46**. In order to propose an acceptable explanation, we treated the methyl ester **48**[50] (Fig. 4, entry 5) in refluxing THF (5 equiv) for 7 h. This time, we isolated quantitatively the corresponding acid **49**. In fact, it seems that the possible formation of an ammonium salt in the medium after the first reaction of TBAF on a functional group may induce a partial or total inhibition of the reactivity of TBAF on a second less sensitive group. For instance, the cleavage of a Boc group which is relatively easy on an indole moiety (Table 1, entry 6a), is notably slackened in the case of the tryptamine derivative **32** (Table 3, entry 1).

2.5. Mechanism

Initially we attempted this deprotection reaction on Boc protected substrates. In this case, several proposals were possible to explain the observed reactivity. Our investigations prompted us to consider the fluoride anion as a nucleophile agent,[24] which directly added on the carbonyl group. A second possibility was a β-elimination. Considering the present study on carbamates, the second proposal could be rejected because several substrates do not contain any proton susceptible to give elimination.

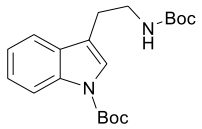
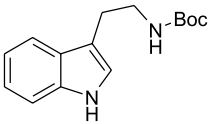
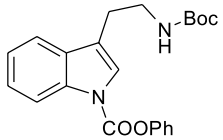
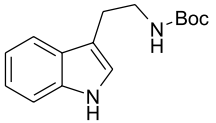
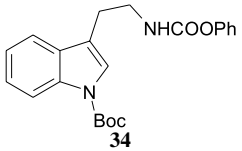
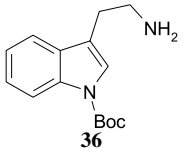
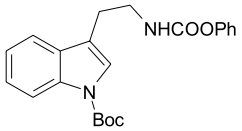
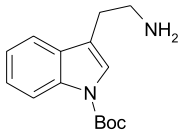
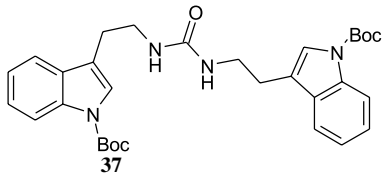
A fluoride attack on the carboxyl group (Scheme 2), generated a tetrahedral intermediate which could evolve according two 2 ways: (a), the amide was considered as the leaving group with formation of an alkyl fluorocarbonate (intermediate A); (b) an alcoolate is generated as the leaving group with formation of a fluorocarbamate (intermediate B). The formation of the urea **37** during the deprotection of **34** (Table 3) could give some insights on the mechanism.



Scheme 2. Postulated mechanism.

The intermediate amide postulated in route (a) could react with the starting material **34** to give the symmetrical urea **37**; but we could not reject route (b) where the intermediate B might react with the deprotected amine **36**. In order to choose between these two hypotheses, the phenyl carbamate **34** was reacted with Bu_4NF in the presence of the primary amine **29**, which could immediately scavenge the high reactive fluoroformate intermediate A or the carbamyl intermediate B (Fig. 5). In this aim, compound **34** was also reacted with 5 equiv Bu_4NF at rt. After 5 min the phenyl carbamate **34** completely disappeared (TLC) and the amine **29** was added (Fig. 5).

Table 3. Reaction of tryptamine derivatives

Entry	Reactant	Conditions	Products (yield % after purification)	
1	 **32**	Bu_4NF, 10 equiv, THF, reflux, 8 h	**35** (67), **32** (30)	 **35**
2	 **33**	Bu_4NF, 1.2 equiv, THF, reflux, 50 min	**35** (quant.)	 **35**
3	 **34**	Bu_4NF, 1.2 equiv, THF, rt, 30 min	**36** (83)[a,b]	 **36**
4	 **34**	Bu_4NF, 5 equiv, THF, rt, 5 min	**36** (39),[a,b] **37** (25)[b]	 **36**  **37**

[a] No degradation.
[b] Total conversion of starting material.

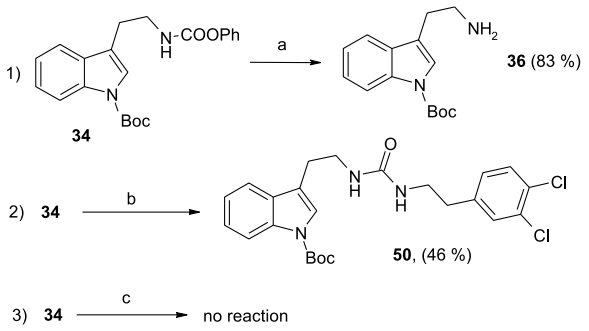


Figure 5. Deprotection of the phenyl carbamate **34** at rt; (a) Bu_4NF, 1.2 equiv 30 min; (b) Bu_4NF 5 equiv, rt, 5 min then **29** 1.0 equiv; (c) **29**, 1.0 equiv, THF, rt, 24 h.

According to route (a) compound **29** reacted with intermediate A giving **30** or following route (b) intermediate B gave access to the dissymmetrical urea **50**. Since compound **50** was effectively obtained in 46% yield, this was in favour of the route (b) (in the absence of TBAF, compounds **34** and **29** did not react after 24 h in refluxing THF).

In the case of indolic nitrogen carbamates, the amide generated according to route (a) was stabilized and could be considered as a good leaving group; this hypothesis explains that the reactions with indolic compounds were the fastest. Depending on the substrate, ways (a) and (b) could (co)exist. The combination of faster leaving alcoolate group $PhO^- > PhCH_2O^- > allylO^- > EtO^- > t\text{-}BuO^-$ and leaving amide anion (aromatic > benzylic > aliphatic) influence certainly the way the reaction occurs.

3. Conclusion

In this paper, we have studied the cleavage of various aromatic and aliphatic carbamates. Whatever the amino function (aliphatic, aromatic), the phenyl carbamate is very easily cleaved except for secondary aromatic amine. *N*-protected indolic compounds were always cleaved in the order phenyl, allyl > benzyl, Me, Et > *t*-Bu. The presence of an aliphatic or vinylic methyl ester seems to inhibit the previous reaction and aliphatic methyl esters were hydrolyzed to the corresponding acids without affecting the protective group. All these results are useful to easily remove various carbamates on substrates, which contain other organic functions not compatible with acidic, basic or catalyzed deprotections generally described in the literature.

4. Experimental

4.1. Chemistry

^1H and ^{13}C NMR spectra were recorded on a Bruker 250 instrument using $CDCl_3$ or DMSO-d_6. The chemical shifts are reported in ppm (δ scale) and all J values are in Hz. Melting points are uncorrected. IR absorption spectra were recorded on a Perkin Elmer PARAGON 1000 PC and values were reported in cm^{-1}. LRMS spectra (Ion Spray) were performed on a Perkin Elmer Sciex PI 300. HRMS were performed by the Centre Régional de Mesures Physiques de l'Ouest. Analyses using Electronic Impact were performed on a High Resolution Mass Spectrometer with double focalisation Varian Mat 311. Analyses using Electrospray Ionisation were performed on a Micromass MS/MS ZAB Spec TOF with an EBE TOF geometry. Monitoring of the reactions was performed using silica gel TLC plates silica Merck 60 F_{254}). Spots were visualized by UV light at 254 and 356 nm. Column chromatographies were performed using silica gel 60 (0.063–0.200 mm, Merck). Only the non-available products are described (not found CAS-online).

4.1.1. 2,3-Dihydro-indole-1-carboxylic acid allyl ester (15). A solution of indoline **11** (1 g, 8.39 mmol) in dry THF (15 mL) was stirred under argon at 0 °C. NaH (242 mg, 10.07 mmol, 60% in oil) was added by portion. After 30 min, allyl chloroformate (1.5 g, 12.59 mmol) was added and the reaction mixture was stirred at rt. After 1 h, water (20 mL) was added and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc 8/2) to afford compound **15** as a solid (1.703 g, quant.). Mp 50 °C; R_f petroleum ether/EtOAc 8/2):0.45; IR (KBr, cm^{-1}) ν 3080, 3052, 2976, 2914, 1696, 1652, 1491, 1420, 1334, 1150, 1058; ($CDCl_3$) δ: ^1H NMR ($CDCl_3$) δ: 3.02 (t, 2H, J= 8.8 Hz), 3.94 (t, 2H, J=8.6 Hz), 4.68 (s, 2H), 5.21–5.38 (m, 2H), 5.92–6.03 (m, 1H), 6.90 (t, 1H, J=7.32 Hz), 7.07–7.16 (m, 2H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 27.5 (CH_2), 47.3 (CH_2), 65.8 (CH_2), 114.8 (CH), 117.7 (CH_2), 122.6 (CH), 124.7 (CH), 127.5 (CH), 131.0 (Cq), 132.8 (CH), 142.6 (Cq), 152.8 (Cq); MS (IS) 204 $(M+H)^+$. HRMS-EI (M^+): 203.09463 calcd for $C_{12}H_{13}NO_2$, found 203.0935.

4.1.2. 2,3-Dihydro-indole-1-carboxylic acid phenyl ester (17). A solution of indoline **11** (1 g, 8.39 mmol) in dry DMF (15 mL) was stirred under argon at 0 °C. NaH (369 mg, 9.23 mmol, 60% in oil) was added by portion. After 30 min phenyl chloroformate (1.5 g, 12.59 mmol) was added and the reaction mixture was stirred at rt. After 2 h, water (20 mL) was added and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude residue was triturated with petroleum ether to afford compound **17** as a white solid (1.4 g, 72%). Mp 135 °C; R_f (petroleum ether /EtOAc 7/3):0.75; IR (KBr, cm^{-1}) ν 3058, 2982, 2916, 1717, 1600, 1487, 1459, 1408, 1336, 1225; ^1H NMR ($CDCl_3$) δ: 3.22 (t, 2H, J=8.1 Hz), 4.24 (t, 2H, J=7.2 Hz), 7.01 (dd, 1H, J= J'=7.5 Hz), 7.21–7.27 (m, 5H), 7.41 (dd, 2H, J=7.5, J'= 8 Hz), 7.88 (bd, 1H, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 27.5 (CH_2), 47.7 (CH_2), 115.0 (CH), 121.6 (2CH), 123.0 (CH), 124.6 (CH), 125.5 (CH), 127.5 (CH), 129.2 (2CH), 130.9 (Cq), 142.1 (Cq), 150.7 (Cq), 151.1 (Cq); MS (IS) 240 $(M+H)^+$, 262 $(M+Na)^+$. HRMS-EI (M^+): 239.09463 calcd for $C_{15}H_{13}NO_2$, found 239.0932.

4.1.3. [2-(3,4-Dichloro-phenyl)-ethyl]-carbamic acid phenyl ester (30). A solution of 3,4-dichlorophenylethylamine **29** (500 mg, 2.64 mmol), NEt_3 (385 μL 2.76 mmol) and phenyl chloroformate (347 μL, 3.16 mmol) in CH_2Cl_2 (10 mL) was stirred at rt under argon. After 30 min, water

(20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc 8/2) to afford compound **30** as a white solid (698 mg, 85%). Mp 74 °C; R_f (petroleum ether/EtOAc 8/2): 0.15; IR (KBr, cm^{-1}) ν 3321, 3050, 2950, 2882, 1707, 1537, 1493, 1292, 1249, 1205; ^1H NMR ($CDCl_3$) δ 2.85 (t, 2H, J=7 Hz), 3.52 (q, 2H, J=6.5 Hz), 5.1 (bs, 1H), 7.04–7.41 (m, 8H); ^{13}C NMR ($CDCl_3$) δ?35.1 (CH_2), 42.0 (CH_2), 121.5 (2CH), 125.4 (CH), 128.2 (CH), 129.3 (2CH), 130.6 (CH), 130.7 (CH), 132.5 (Cq), 138.8 (Cq), 150.8 (Cq), 154.5 (Cq); MS (IS) 310/312 $(M+H)^+$, 332/334 $(M+Na)^+$. HRMS-EI (M^+): 309.03233 calcd for $C_{15}H_{13}Cl_2NO_2$, found 309.0318.

4.1.4. [2-(3,4-Dichloro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (31). A solution of 3,4-dichlorophenylethylamine **29** (500 mg, 2.64 mmol), 4-DMAP (322 mg 2.64 mmol) and Boc_2O (690 mg, 3.16 mmol) in acetonitrile (15 mL) was stirred at rt under argon. After 4 h, water (20 mL) was added and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether then petroleum ether/ EtOAc 6/4) to afford compound **31** as white solid (762 mg, quant.). Mp 86 °C. R_f (petroleum ether/EtOAc 5/5): 0.54; IR (KBr, cm^{-1}) ν 3338, 2979, 2925, 1687, 1534, 1283, 1168; ^1H NMR ($CDCl_3$) δ: 1.44 (s, 9H), 2.79 (t, 2H, J=6.7 Hz), 3.39 (m, 2H), 4.57 (s, 1H), 7.02 (d, 1H, J=8.3 Hz), 7.29 (s, 1H), 7.36 (d, 1H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 28.7 (CH_3), 35.7 (CH_2), 41.8 (CH_2), 79.9 (Cq), 128.6 (CH), 130.8 (CH), 131.2 (CH), 132.8 (Cq), 139.6 (Cq), 156.2 (Cq); MS (IS) 290/292 $(M+H)^+$. HRMS-ESI ($M+Na^+$): 312.05340 calcd for $C_{13}H_{17}NO_2Cl_2Na$, found 312.0539.

4.1.5. 3-(2-*tert*-Butoxycarbonylamino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester (32). A solution of tryptamine hydrochloride (1.38 g, 7.57 mmol), 4-DMAP (1.11 g, 9.08 mmol) and Boc_2O (3.46 g, 15.89 mmol) in acetonitrile (20 mL) was stirred at rt under argon. After 12 h, water (50 mL) was added and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether then petroleum ether/ EtOAc 8/2) to afford compound **32** as a waxy solid (2.45 g, 90%). R_f (petroleum ether/EtOAc 9/1): 0.24; IR (KBr, cm^{-1}) ν 3374, 2976, 2930, 1724, 1722, 1545, 1254, 1160, 1091; ^1H NMR ($CDCl_3$) δ: 1.44 (s, 9H), 1.66 (s, 9H), 2.89 (t, 2H, J=7.0 Hz), 3.46 (m, 2H), 4.63 (s, 1H), 7.23 (m, 2H), 7.41 (s, 1H), 7.53 (d, 1H, J=7.8 Hz), 8.13 (d, 1H, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 26.0 (CH_2), 28.6 (CH_3), 28.8 (CH_3), 40.7 (CH_2), 79.5 (Cq), 83.8 (CH_3), 115.7 (CH), 118.2 (Cq), 119.4 (CH), 122.8 (CH), 123.5 (CH), 124.8 (CH), 130.8 (Cq), 135.9 (Cq), 150.1 (Cq), 156.4 (Cq); MS (IS) 361 $(M+H)^+$. HRMS-ESI ($M+Na^+$): 383.19468 calcd for $C_{20}H_{28}N_2O_4Na$, found 383.1948.

4.1.6. 3-(2-*tert*-Butoxycarbonylamino-ethyl)-indole-1-carboxylic acid phenyl ester (33). A solution of compound **35**[43] (559 mg, 2.15 mmol), phenyl chloroformate (0.432 mL, 3.44 mmol) in CH_2Cl_2 containing NaOH (258 mg, 6.45 mmol) and a catalytic amount of tetrabutyl ammonium bromide (21 mg, 0.06 mmol) was stirred at rt under argon. After 12 h water (20 mL) was added and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether then petroleum ether/EtOAc 8/2) to afford compound **33** as a white solid (579 mg, 71%). Mp 132 °C; R_f (petroleum ether/EtOAc 7/3):0.68; IR (KBr, cm^{-1}) ν 3306, 3053, 3004, 2977, 2899, 1754, 1692, 1535, 1457, 1383; ^1H NMR ($CDCl_3$) δ: 1.44 (s, 9H), 2.92 (t, 2H, J=6.6 Hz), 3.48 (q, 2H, J=6.3 Hz), 4.76 (bs, 1H), 7.23–7.47 (m, 6H), 7.57–7.59 (m, 2H), 8.22 (bd, 1H, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ: 25.6 (CH_2), 28.3 ($3CH_3$), 40.0 (CH_2), 79.2 (Cq), 115.3 (CH), 119.1 (CH), 119.5 (Cq), 121.4 (2CH), 122.6 (CH), 123.2 (CH), 125.0 (CH), 126.3 (CH), 129.5 (2CH), 130.6 (Cq), 135.7 (Cq), 149.0 (Cq), 150.2 (Cq), 155.8 (Cq); MS (IS) 281 $(M+H-Boc)^+$, 381 $(M+H)^+$, 398 $(M+NH_4)^+$. HRMS-ESI ($M+Na^+$): 403.16338 calcd for $C_{22}H_{24}N_2O_4Na$, found 403.1635.

4.1.7. 3-(2-Phenoxycarbonylamino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester (34). A solution of 3-(2-phenoxycarbonylamino-ethyl)-indole[40] (150 mg, 0.53 mmol) in a mixture of THF (2 mL) and DMF (2 mL) was treated with 4-(dimethylamino)pyridine (6 mg, 0.05 mmol), triethylamine (74 μL, 0.53 mmol) and di-*tert*-butyl dicarbonate (128 mg, 0.59 mmol). Stirring was continued overnight. After addition of water (20 mL), the crude product was extracted with ethyl acetate (2×10 mL). The combined organic layers were then washed twice with brine. Purification of the crude product by flash chromatography (petroleum ether/EtOAc 8/2) afforded compound **34** (104 mg, 51%). Colorless oil; R_f (petroleum ether/EtOAc 6/4):0.88; IR (NaCl, cm^{-1}) ν 3355, 2974, 2940, 1731, 1527, 1491, 1454, 1256, 1207, 1159, 1091; ^1H NMR ($CDCl_3$) δ: 1.67 (s, 9H), 2.99 (t, 2H, J=6.8 Hz), 3.60 (q, 2H, J=6.6 Hz), 5.14 (bs, 1H), 7.09–7.38 (m, 6H), 7.46 (s, 1H), 7.58 (d, 1H, J=7.6 Hz), 8.14 (bd, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 25.0 (CH_2), 27.8 (CH_3×3), 40.6 (CH_2), 83.2 (Cq), 115.0 (CH), 117.3 (Cq), 118.7 (CH), 121.3 (CH×2), 122.2 (CH), 122.8 (CH), 124.2 (CH), 124.9 (CH), 128.9 (CH×2), 130.1 (Cq), 135.2 (Cq), 149.4 (Cq), 150.8 (Cq), 154.5 (Cq); MS (IS) 381 $(M+H)^+$, 403 $(M+Na)^+$. HRMS-ESI ($M+Na^+$): 403.16338 calcd for $C_{22}H_{24}N_2O_4Na$, found 403.1635.

4.1.8. 3-(2-Amino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester (36). A solution of **34** (89 mg, 0.234 mmol) and TBAF (0.28 mL, 1 M in THF, 0.281 mmol) in dry THF (2.5 mL) was stirred under argon at rt. After 30 min water (5 mL) was added and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 9/1) to afford compound **36** as colorless oil (50 mg, 83%). R_f (CH_2Cl_2/MeOH 9/1): 0.22; IR (NaCl, cm^{-1}) ν 3404, 2976, 2922, 1731, 1454, 1369, 1250, 1157; ^1H NMR ($CDCl_3$) δ: 1.66 (s, 9H), 2.62 (bs, 2H), 2.89 (t, 2H, J=6.4 Hz), 3.07 (bs, 2H), 7.23 (dd,

1H, $J=J'=7.3$ Hz), 7.32 (dd, 1H, $J=J'=7.3$ Hz), 7.44 (s, 1H), 7.53 (d, 1H, $J=7.0$ Hz), 8.13 (bd, 1H, $J=7.6$ Hz); ^{13}C NMR ($CDCl_3$) δ: 28.3 ($3CH_3$), 29.8 (CH_2), 41.3 (CH_2), 83.6 (Cq), 115.4 (CH), 117.9 (Cq), 119.1 (CH), 122.6 (CH), 123.4 (CH), 124.5 (CH), 129.8 (Cq), 135.5 (Cq), 149.7 (Cq); MS (IS) 261 $(M+H)^+$, 161 $(M+H-Boc)^+$. HRMS-ESI ($M+H^+$): 261.16030 calcd for $C_{15}H_{21}N_2O_2$, found 261.1611.

4.1.9. 1,3-Bis-[2-(1*H*-indol-1- carboxylic acid *tert*-butyl ester-3-yl)-ethyl]-urea (37). A solution of **34** (202 mg, 0.53 mmol) and TBAF (2.65 mL, 1 M in THF, 0.265 mmol) in dry THF (5 mL) was stirred under argon at rt. After 5 min water (5 mL) was added and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using petroleum ether/EtOAc 5/5 to afford compound **37** (36 mg, 25%) as yellow oil and MeOH to afford compound **36** (54 mg, 39%). R_f (petroleum ether/EtOAc 5/5):0.46; IR (NaCl, cm^{-1}) ν 3319, 3046, 1716, 1599, 1532, 1491, 1443, 1318, 1224, 1202, 1023; ^{1}H NMR ($CDCl_3$) δ: 1.64 (s, 18H), 2.86 (t, 4H, $J=6.5$ Hz), 3.47 (q, 4H, $J=6.5$ Hz), 4.42 (t, 2H, $J=5.8$ Hz), 7.16–7.33 (m, 4H), 7.39 (s, 2H), 7.50 (d, 2H, $J=7.6$ Hz), 8.10 (d, 2H, $J=7.9$ Hz); ^{13}C NMR ($CDCl_3$) δ: 25.8 (CH_2), 28.1 ($3CH_3$), 40.0 (CH_2), 83.5 (Cq), 115.2 (CH), 117.9 (Cq), 118.9 (CH), 122.4 (CH), 123.0 (CH), 124.4 (CH), 130.4 (Cq), 135.4 (Cq), 149.6 (Cq), 158.1 (Cq); MS (IS) 547.5 $(M+H)^+$. HRMS-ESI ($M+Na^+$): 569.27399 calcd for $C_{31}H_{38}N_4O_5Na$, found 569.2743.

4.1.10. 4-(*tert*-Butoxy-hydroxy-methyl)-4*H*-benzo[1,4] oxazine-2-carboxylic acid (45). A solution of compound **44**[47] (110 mg, 0.36 mmol) in dry THF (4 mL) was stirred at rt under argon. Bu_4NF (1.8 mL, 1 M in THF) was added and the reaction mixture was refluxed for 5 h. After cooling, a solution of NH_4Cl satd. (10 mL) was added and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Compound **45** was obtained as a white solid (99 mg, quant.). Mp 184 °C dec. R_f (CH_2Cl_2/MeOH 9/1): 0.12; IR (KBr, cm^{-1}) ν 3386, 2975, 2771, 1581, 1731, 1682, 1495, 1151, 755; ^{1}H NMR ($CDCl_3$) δ: 1.51 (s, 9H), 6.84 (m, 3H), 7.27 (s, 1H), 7.83 (d, 1H, $J=8.3$ Hz), 10.3 (s, 1H, exchange D_2O); ^{13}C NMR ($CDCl_3$) δ 28.6 (CH_3), 83.1 (Cq), 116.9 (CH), 117.2 (CH), 119.7 (CH), 121.1 (CH), 127.2 (CH), 134.6 (Cq), 147.9 (Cq) 150.2 (Cq), 164.6 (Cq); MS (IS) 278 $(M+H)^+$. HRMS-ESI ($M-H+2Na^+$): 322.06674 calcd for $C_{14}H_{14}NO_5Na_2$, found 322.0669.

4.1.11. 3-(2-{3-[2-(3,4-Dichloro-phenyl)-ethyl]-ureido}-ethyl)-indole-1-carboxylic acid *tert*-butyl ester (50). A solution of **34** (173 mg, 0.455 mmol) and TBAF (2.27 mL, 1 M in THF, 0.265 mmol) in dry THF (5 mL), amine **29** (86 mg, 0.455 mmol) was stirred under argon at rt for 5 min. Water (5 mL) was added and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl (5 mL) and dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc 55/45) to afford compound **48** (105 mg, 48%) as a pale yellow oil. R_f (CH_2Cl_2/MeOH 9/1): 0.78; IR (NaCl, cm^{-1}) ν 3334, 2977, 2933, 1731, 1634, 1573, 1474, 1453, 1380, 1256; ^{1}H NMR ($CDCl_3$) δ: 1.66 (s, 9H), 2.71 (t, 2H, $J=6.8$ Hz), 2.88 (t, 2H, $J=6.5$ Hz), 3.35 (q, 2H, $J=6.6$ Hz), 3.48 (q, 2H, $J=6.4$ Hz), 4.35 (t, 1H, $J=5.8$ Hz), 4.45 (t, 1H, $J=5.7$ Hz), 6.97 (dd, 1H, $J=8.2$, $J'=2$ Hz), 7.19–7.35 (m, 4H), 7.41 (s, 1H), 7.52 (d, 1H, $J=7.1$ Hz), 8.10 (d, 1H, $J=8.0$ Hz); ^{13}C NMR ($CDCl_3$) δ: 25.8 (CH_2), 28.1 ($3CH_3$), 35.5 (CH_2), 39.9 (CH_2), 41.1 (CH_2), 83.6 (Cq), 115.2 (CH), 117.9 (Cq), 118.9 (CH), 122.4 (CH), 123.0 (CH), 124.4 (CH), 128.2 (CH), 130.1 (Cq), 130.3 (CH), 130.4 (Cq), 130.6 (CH), 132.2 (Cq), 135.4 (Cq), 139.5 (Cq), 149.7 (Cq), 158.2 (Cq); MS (IS) 476/478 $(M+H)^+$, 376/378 $(M+H-Boc)^+$. HRMS-ESI ($M+Na^+$): 498.13272 calcd for $C_{24}H_{27}N_3O_3Cl_2Na$, found 498.1328.

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Design and synthesis of a Mn(III)-porphyrin steroid conjugate used as a new cleavable affinity label: on the road to semi-synthetic catalytic antibodies

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Abstract—We here report the synthesis of a novel porphyrin-steroid conjugate which was designed for the site-specific incorporation of a non-natural heme cofactor at the binding site of an *anti*-estradiol antibody, in order to get a semi-synthetic catalytic antibody with a monooxygenase-like activity. The general strategy involved a coupling reaction between a testosterone modified by an arm bearing a cleavable disulfide bridge and a *meso*-tetraarylporphyrin bearing two successive *meso-ortho*-substituted-phenyl rings, α,α-5,10-bis-[{*o*-(2-carboxyethyl)carboxamido}phenyl]-15,20-diphenyl-porphyrin. The final porphyrin-steroid conjugate was successfully purified and fully characterized, and was subsequently metalated with manganese acetate. The metalloporphyrin moiety will be used to be coupled with the antibody to generate a new biocatalyst with monooxygenase-like activities.

1. Introduction

Recent advances in the field of protein and enzyme engineering have revealed that the combination of the 20 natural amino acids cannot always satisfy the chemical reactivity needed in living systems. Therefore, the presence of other nonproteineous components such as organic and inorganic cofactors, metal ions or complexes is required. Consequently the addition of non-natural cofactors, in particular in a covalent way may represent a powerful methodology to introduce new activities into proteins. The association of molecules produced by organic synthesis with proteins provides an enormous variability for the design of new catalysts with a wide range of enzyme-like properties.[1–4]

With the advent of catalytic antibodies, the field of cofactor-dependent catalytic antibodies has been explored for the engineering of new biocatalysts. Because raising antibodies against transition state analogues in order to induce a catalytic activity in antibodies[5–7] cannot provide all the known enzymatic activities, design efforts have also focused on alternative strategies: antibodies have been associated with catalytically active groups, in particular with the use of semisynthetic methods.[8–10] In this case, a monoclonal antibody, which has initially been designed to bind a molecule in its ground state plays the role of the apoprotein: it specifically binds the substrate and controls its position with respect to the cofactor then influencing the regio- and stereoselectivity of the reaction.

According to this approach, the association of an antibody with a metalloporphyrin cofactor seems to be a promising alternative for the obtention of a new generation of artificial hemoproteins that can exhibit, under mild conditions, efficiencies and selectivities that are comparable to those exhibited by natural enzymes such as cytochrome P450 dependent monooxygenases or peroxidases. Several strategies to produce metalloporphyrin-dependent catalytic antibodies can be envisioned. The first one that has already been used consists in the generation of an antibody directed toward a specific metalloporphyrin cofactor hapten.[11–13] In this strategy, the antibodies are designed either to bring into close proximity the cofactor and the substrate, or to bind tightly the cofactor to enhance its reactivity. The second one is an unprecedent method still in development and consists in the introduction by chemical engineering of a reactive group responsible for the catalysis, next to the Ab-binding

Keywords: Porphyrin-steroid conjugate; Catalytic antibodies; Artificial metalloprotein.

Abbreviations: Ab, Antibody; BSA, bovine serum albumine; E_2, 17β-estradiol; $TPPH_2$, tetraphenylporphyrin free-base; T-3-CMO, testo-3-carboxymethyloxime.

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site. In our case, the chimerical construct resulting from the covalent attachment of a metalloporphyrin close to the Ab-binding site would represent a promising route to semi-synthetic biocatalysts tailored for the regioselective oxidation of small molecules by oxygen donors such as PhI=O or H_2O_2 similar to those performed by cytochrome P450 dependent monooxygenases.

We here report a strategy which provides an alternative for the problems of selectivity encountered in the case of catalytic antibodies, which is based on the recognition of a modified hapten by the antibody and could be extended to other antibodies.

1.1. Strategy for the incorporation of non-natural porphyrin cofactors into native immunoglobulins

One strategy has been developed recently by Meares et al.[14] to attach covalently a metal cofactor inside the binding pocket of an *anti*-chelate monoclonal antibody which has been raised against (*S*)-benzyl-EDTA-indium chelate. This strategy involved 2 steps. First, a serine residue S95 located in the binding pocket, close to the binding site of the hapten, was mutated to replace it by a nucleophilic cysteine. Second, the recombinant protein was incubated with (*S*)-benzyl-EDTA-indium or -iron chelate modified on the benzyl group by a bromo- or chloro-acetamido reactive function. Nucleophilic substitution of the chlorine or the bromine by the cysteine at position 95 afforded the antibody bearing the Fe- or In-chelate covalently attached inside the binding pocket. These complexes could have many applications in biology and medicine. Since this strategy led to a complex in which the binding site was occupied by the metal chelate and since it requiered the modification of the protein by site directed mutagenesis, we prefered to develop a strategy which only involved chemical steps and afforded an antibody labelled by a metalloporphyrin close to, but outside, the binding pocket for the hapten. We then developed a strategy which has been inspired from that described by Pollack et al.[15] These authors have selectively modified the combining site of a natural antibody which binds dinitrophenyl ligands with a group inducing a novel chemical functionality. Using affinity labels including a cleavable disulfide bridge, they have introduced a nucleophilic thiol in the combining site of their antibody and therefore have enhanced its ester-thiolysis activity. The thiol could also act as a handle whereby additionnal functional groups could be attached, in order to develop a catalytic antibody with other activities. It came to our attention that this methodology might be exploited for the site-directed linkage of another type of catalytic group, a metallo-tetraarylporphyrin cofactor on an *anti*-estradiol antibody. In our case, the cofactor would be introduced before the cleavage of a disulfide bridge, in the vicinity of the active site of the antibody. The labile linkage would then be used for the release of the Ab-combining site and would lead to an artificial hemoprotein susceptible to oxidize substrates such as steroids or aromatic compounds in the presence of an oxene donor.

We therefore propose the synthesis of a new cleavable affinity label including the potential catalytic unit in order to apply the following strategy which involves four key steps (Fig. 1): (a) the incubation of the antibody with the cleavable affinity label; (b) the chemical reaction between the side-chain (A) of a targeted aminoacid of the protein and the terminal reactive group of the compound (B); (c) the cleavage of the labile linkage (disulfide bridge) which leads to the semisynthetic Ab of interest; (d) the release of the modified antigen by dialysis.

1.2. Design considerations

To fulfill the requirements of the strategy, it is necessary to synthesize a molecule which presents: (i) an antigenic pattern that can be recognized by the antibody; (ii) a catalytic cofactor bearing an arm ending in a suitable reactive group for the selective coupling with the protein; (iii) an arm binding the antigenic pattern to the catalytic group including a labile linkage, a disulfide bridge, that would permit the release of the modified hapten after cleavage.

A steroid metalloporphyrin conjugate which fullfils these requirements was chosen to modify selectively an *anti*-estradiol antibody by chemical engineering.

The active site-directed incorporation of the potential catalytic group is based on the antibody-antigen recognition, since it is the antigenic pattern that will permit to direct selectively the synthetic cofactor in vicinity of the Ab-binding site. Consequently, an essential point in designing the antigen-porphyrin conjugate to target the Ab-binding site was to identify a parent estradiol molecule that could be recognized by the antibody but that has not enough affinity to be easily removed by dialysis. The substrate chosen for the investigation was the testosterone which has less affinity for the antibody ($Kd=1.7\times10^{-7}$ M) than the estradiol ($Kd=9.5\times10^{-10}$ M) has[16] and it could be easily removed by extensive dialysis.

Another aspect concerns the porphyrin moiety. It should be analog to the prosthetic group of heme-containing enzymes which selectively catalyze various oxidation reactions.[17] Many chemical model systems of these enzymes are based on *meso*-arylporphyrins for several reasons. First, thanks to the aryl substituents in *meso*-positions, such porphyrins are protected from hydroxylations occuring at these positions, which lead to the macrocycle opening.[18] Second, *meso*-susbtituted porphyrins can easily be synthetized from the condensation of pyrrole with an arylaldehyde.[19] Third, metal complexes are efficient catalysts for the oxidation of substrates such as alkanes and alkenes.[20,21]

The last point of this approach is the selective modification of the protein. The coupling chemistry chosen for the preparation of our semisynthetic antibody is based on the use of peptidic linkage which is a stable covalent attachment at pH 7.4.[22] As this type of linkage comes from the reaction between a primary amine and an activated carboxylic acid, it is important to choose an aminoacid with this kind of reactive side chain. If the label reacts with more than one type of amino acid residue, this can be advantageous for optimizing the probability for successful coupling. But on the other hand, it minimizes the selectivity of modification site of the antibody. Ideally, a unique residue should be

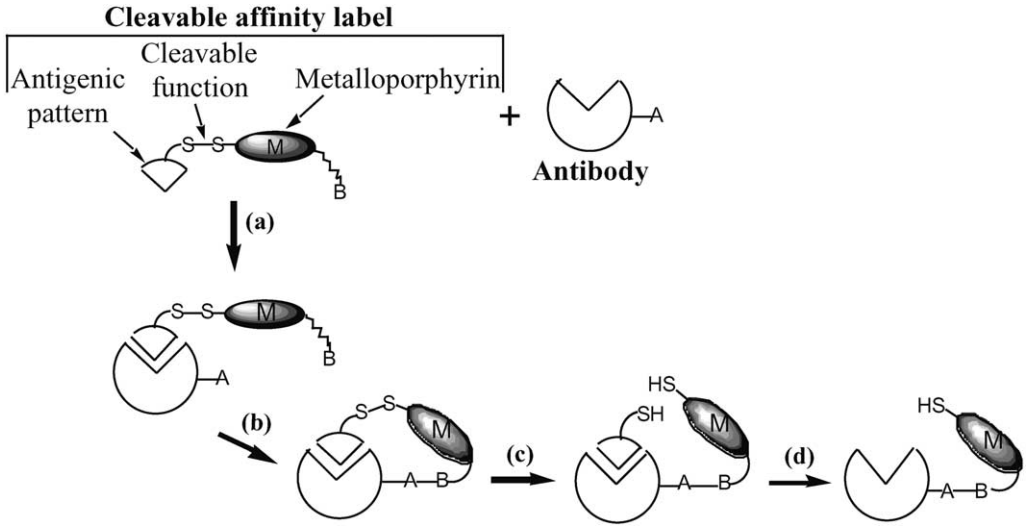


Figure 1. Strategy for the production of a semi-synthetic antibody able to catalyze the selective oxidation of steroids.

modified to give a homogeneous adduct. Consequently, we selected the only aminoacid which presents at the end of its side chain a reactive group that is a primary amine. Several reasons are in favor of such a choice. First, this type of residue has been already used by Pollack and co-authors for the obtention of semi-synthetic antibodies.[23] Second, although the structure of the crystallized antibody is not achieved, the presence of available lysyl residues have been highlighted by several methods. A fluorimetric method[24] has allowed to quantify free amino-groups and the antibody combining site has been characterized by amino acid sequencing and 3D modelling of the variable regions, in order to confirm the presence of suitable lysines for the derivatization.

In this paper, we report then the multistep synthesis of a testosterone-Mn(III) porphyrin conjugate, that could be linked in an irreversible and specific way to an *anti*-estradiol Ab.

2. Results

2.1. Synthesis of the disuccinylated porphyrin

The porphyrin moiety of the conjugate derived from the α,α atropoisomer of 5,10-di(*ortho*-aminophenyl)-15,20-diphenylporphyrin (1) (Scheme 2). This compound was obtained according to the methods of Little et al.[25] and Collman et al.[26] which consists in the condensation of *o*-nitrobenzaldehyde, benzaldehyde and pyrrole in refluxing propionic acid, leading to a mixture of nitro-porphyrins. The *ortho*-nitro substituents were then reduced with stannous chloride in acidic medium. The neutralization step was not performed as described by Collman but with KOH pellets as described by Ruzié et al.[26] which is an easier procedure for the neutralization.

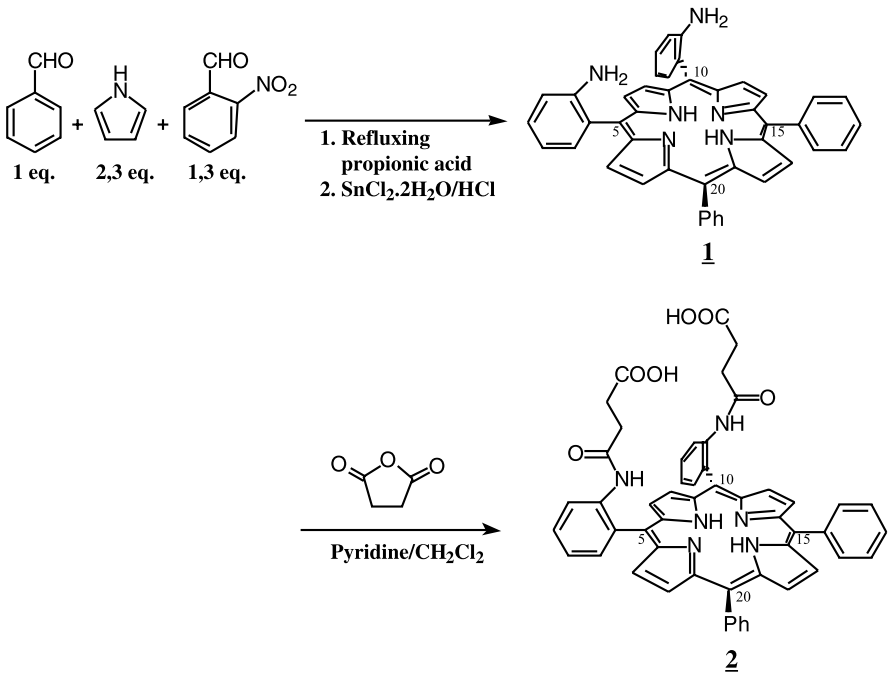
The resulting crude product consists of a mixture of aminoporphyrins and a TLC analysis of the reaction mixture on silica gel (CH_2Cl_2, cyclohexane 9:1 (v/v)) revealed the presence of several porphyrins: $TPPH_2$ (R_f=0.90), *meso*-mono(*o*-aminophenyl)triphenylporphyrin (R_f=0.74), di(*o*-aminophenyl)isomers and other minor more polar tri- and tetrakis-*ortho*-aminophenyl-substituted porphyrins. The atropoisomers of di(*o*-aminophenyl) porphyrin were identified as follows. The α,α-isomers which have their 2-aminophenyl substituents above the same face of the porphyrin are more retained on the silica gel than the α,β-isomers which have their 2-aminophenyl substituents above the two opposite faces of the porphyrin. In addition, the 5,10-isomers which have their 2-aminophenyl substituents on two adjacents *meso*-aryl substituents are slightly more retained than the 5,15-isomers. As a result of the combination of these two effects, the α,α-5,10-isomer (R_f= 0.14) is more polar than the α,α-5,15-isomer (R_f=0.18) and than the α,β-5,10-isomer (R_f=0.60).

The porphyrin of interest, the α,α-5,10-isomer (**1**) was isolated after multiple chromatographic purification steps and characterized by ^1H and ^{13}C NMR, mass spectroscopies and elemental analysis (see Section 4).

For the preparation of the testosterone-porphyrin conjugate, the α,α-5,10-diamino atropoisomer (**1**) was first converted to a suitable reactive derivative. The successful reaction of $BADPPH_2$ with succinic anhydride in presence of pyridine, used as amidation catalyst, led to the tetraarylporphyrin (**2**) bearing two four-atom arms in *ortho* position of two successive *meso*-phenyl substituents in a cofacial conformation. This step also allowed the introduction of two carboxylic acid functional groups. The succinylated porphyrin was isolated by column chromatography in order to fully remove the unreacted succinic anhydride (Scheme 1).

2.2. Synthesis of the testosterone derivative

In parallel, the strategy of T-3-CMO cystamine (**7**) synthesis involves first (Scheme 2) the introduction of a carboxymethyloxime group at the C3 position of the testosterone and the further addition of a spacer arm with a disulfide bridge ending in an amino group able to react with one of the terminal carboxylic acid of (**2**). Among the wide range of various reaction types applicable for derivatizing the 3-position of testosterone, we chose the most commonly



Scheme 1. Synthesis of the tetraaryl porphyrin bearing two arms in the *ortho* position of two consecutive *meso*-phenyl substituents.

used 3-O-carboxymethyl-oxime derivative according to a modification of a previously reported method.[28] Testosterone reacted with carboxymethoxylamine in ethanol for 36 h at room temperature, leading to a mixture of *Z*- and *E*-isomers of (**3**). From the relative intensities of the 4-H signal in ^{1}H NMR at δ 5.76 (*E*) and 6.42 (*Z*) the ratio of *E*/*Z*-isomers was 60:40. The mixture of stereoisomers was used as it was for the following reactions.

The disulfide bridge was then introduced by coupling with cystamine protected at one side by a BOC-group (**4**) in order to allow only a monoaddition.

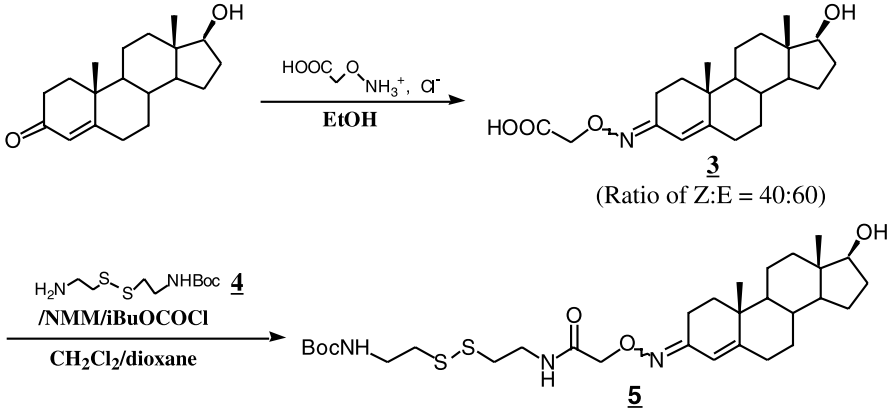
The BOC-protecting group of **5** was then removed using TFA in water in order to obtain the free terminal amino-group able to react with the diacid porphyrin **2**.

2.3. Synthesis of the steroid free-base porphyrin conjugate

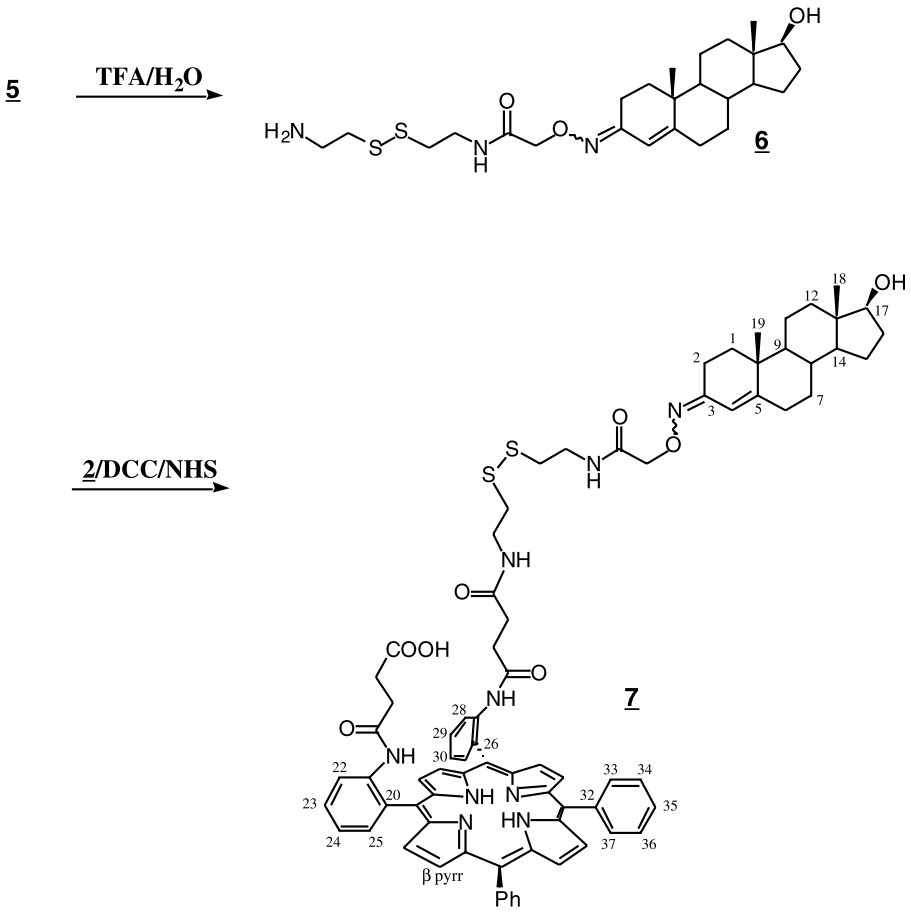
Since the T-3-CMO cystamine (6) resulting from the deprotecting reaction was unstable, it was purified immediately before the use for the coupling reaction by column chromatography, to remove all residual protected compound (5) and degradation products. A DCC-mediated coupling of the succinylated $BADPPH_2$ (2) with *N*-hydroxysuccinimide produced an activated ester which reacted then with the deprotected compound (6) (Scheme 3). The resulting crude product was a mixture of two diastereoisomers of the testosterone-porphyrin conjugate (7) that were undistinguished by TLC or ^{1}H NMR. The structure of this porphyrin derivative was unambiguously proven by uv–vis, IR, ^{1}H NMR and mass spectroscopies (see experimental procedures).

2.4. Metallation of the porphyrin with manganese

The insertion of the manganese was carried out according to the adapted method described by Buchler.[29] The porphyrin free-base was treated with a large excess of $Mn(OAc)_2.4H_2O$ in a mixture of $MeOH/CHCl_3$ at room temperature, leading to the final steroid-acetato-manganese(III)-tetraphenylporphyrin conjugate **8**. This complex was



Scheme 2. Two-step modification of testosterone with an arm including a disulfide bridge and ended by a protected amino group.



Scheme 3. Synthesis of the testosterone porphyrine conjugate after removal of the protecting group of the testosterone derivative.

characterized by its UV–vis spectrum in CH_2Cl_2 which showed maxima of absorption at 376, 401, 474, 578 and 609 nm which were characteristic of a high spin manganese(III) complex[29] and by its MALDI-TOF mass spectrum which showed a peak at $m/z = 1375.36$ (M+1, 100%) which was due to the incorporation of a Mn atom into the porphyrin cycle of compound **7**.

3. Discussion

3.1. Investigations of porphyrin synthesis

meso-Tetraarylporphyrins with *ortho*-substituted *meso*-aryl groups have already been utilized as building bases for modeling hemoprotein active sites and developing biomimetic catalysts, taking advantage of the ability of the *ortho* functionalities to link structures over the porphyrin plane.[20,30] Indeed, free rotation of the *meso*-phenyl rings around the aryl-porphyrin bond in such systems is restricted[31] and substituents introduced in the *ortho*-positions of the phenyl groups diminished the possibility of thermal isomerization of α,α-atropoisomer into α,β-atropoisomer.[32] Consequently, the atropoisomers of the *ortho*-substituted derivative could be observed and then separately obtained. Afterwards, each isomer could be further manipulated to yield the compound of interest and to place appendages on one side or the other of the plane of the porphyrin. Moreover, it has been demonstrated that the presence of substituents at *ortho*-positions increases the efficiency of the catalytic process, preventing autoxidative reactions and the aggregation of the catalyst.[33] Accordingly, such tetraarylporphyrins appeared to be attractive for the building purposes of our model. The strategy we therefore developed was based on the preparation of a tetraarylporphyrin embellished on one face with two *ortho* amino groups suitable for the tight linking of the native antibody on one hand, and, on the other hand, of the modified testosterone in a cofacial conformation. We have assumed that this conformation could be the best to target lysyl residues in the direct vicinity of the combining site of the antibody.

The synthesis of porphyrins with appendages are generally accomplished by pre-synthesizing a porphyrin bearing appropriate reactive functional groups to which an arm can subsequently be attached. This approach was used in the present study, which led us to choose the preparation of the symmetric α,α-atropoisomer of the 5,10-bis(aminophenyl)-15,20-diphenylporphyrin (**1**). Although the already described syntheses of many *o*-diamino-porphyrin systems are based on 5,15-diarylporphyrins,[34,35] there has been no report on the formation of the 5,10-isomer which was chosen as starting material for our synthesis. We decided then to adopt a procedure based on the method described by Collman et al.[26] which easily afforded the stable α,α-5,10-isomer.

3.2. The antigenic pattern

It was important to select a potential position on the ring-core where an appendage (porphyrin) could be attached without seriously compromising antigen-Ab recognition. The specificity of the *anti*-steroid antibody is introduced by the position where the coupling of the steroid hapten to the carrier protein is made and which also determines the cross-reactivity of the Ab. The most favorable position should be similar to the one used in the preparation of the immunogen E_2-3-CM-BSA,[16] that means in C-3 position. Moreover recent modelling studies of the antibody revealed that whereas the steroid was buried inside the protein, the 3-hydroxyl group of E_2 was solvent-exposed. These results suggested that the C-3 position would be an excellent point of attachment for porphyrin derivatives. Since testosterone contains a functional keto-group in 3-position, it provides an ideal reactive site for chemical modification of testosterone without any side reaction.

Although the double bond of the carboxymethyloxime derivatives can cause steric hindrances (no free rotations) and give rise to a mixture of *Z*- and *E*-isomers, this chemical approach appeared as the simplest procedure to obtain, in an one pot reaction, a steroidal precursor for a following conjugation. As already reported,[16,36–39] steroidal-(O-carboxymethyl)oximes have been widely used for the preparation of immunogens and enzyme-conjugates for immunoassay, without separating the geometrical isomers. Furthermore, the CMO-derivatives are susceptible to racemize under mild conditions specially in presence of methanol.[40] It is then very difficult to keep the isomeric purity during work-up. Therefore, the crude product of the two isomers synthesized were not separated in the successive reactions.

3.3. Synthetic approaches of the spacer group

In our effort to construct orientation specific groups appended to hemes, we also explored the use of linking units and labile bond between the porphyrin moiety and the steroid. The affinity label should be designed with a cleavable function in order to release the combining site of the antibody for following catalytic assays, after site-specific incorporation of the catalytic unit.

We have first hypothesized that placing the porphyrin away from the 3 position of testosterone via a long arm might not impair the antibody-recognition seriously and implicate a larger range of lysyl residues. The spacer group should have a flexible structure, in order to allow an effective linkage of the affinity label. We have therefore adopted a linear chain. We have secondly chosen a synthesis which could present several advantages. First, it could bring in a one step reaction arms ended by reactive groups able to react directly with lysine. Second, it should afford an easy way to vary the length of the spacer group, in order to optimize incorporation of label into the protein. The use of cyclic anhydride appeared as a promising alternative for this new requirement. Succinic anhydride appeared to be a good candidate for our first try because it provided an optimal chain length for our studies. Even if such compounds provide in our case symmetric molecules (**2**), the variability of length between the two arms could be achieved by the steroid derivative including the labile linkage.

Another key to this approach was the introduction of a cleavable function into the spacer group. The design considerations led us to choose a disulfide bridge because of its ease of reduction under mild conditions without reducing the buried protein disulfides.[41] Moreover the free thiol group released after cleavage could be selectively modified via disulfide exchange or a reaction with an electrophile in order to attach a fifth ligand of the metal ion introduced in the porphyrin ring. We have then chosen to bring the disulfide bridge by using a difunctionalized commercial molecule, cystamine which moreover afforded two suitable amino-groups for the coupling on one hand with the T-3-CMO (**3**) and on the other hand with the succinylated porphyrin (**2**).

3.4. Final coupling before metallation

The coupling between the disuccinylated porphyrin **2** and the steroid derivative **6** was a delicate step of the synthesis. Since the porphyrin construct presented two carboxylic acid groups with equal reactivity, it was theoretically possible to attach two molecules of Tcyst on it. In order to minimize a multi-coupling reaction, several precautions were taken. First, the disuccynilated porphyrin was activated with only 1.1 equiv. of DCC to favour the formation of the mono-DCC-intermediate. Second, to react slowly enough and thus to lead to a mono-coupling reaction, the testosterone derivative was engaged in conditions favouring the formation of the desired mono-coupled product. The Tcyst **6** was added dropwise, in order to insure that the porphyrin moiety is always in excess in the reaction mixture and then to favour the monoaddition. At last, high dilution and low reaction temperature provide favorable conditions for the desired coupling reaction.

3.5. Metallation with manganese

Iron and manganese complexes of porphyrins have been extensively used as effective catalysts for the oxidation of various substrates in analogy to a similar chemistry performed by cytochromes P450.[42] Indeed, in the presence of oxidants such as iodosobenzene or peroxides, these metals can lead to high-valent metal-oxo species,[43,44] which are very reactive and sensitive to substituent effects on the *meso*-aryl and β-pyrrole carbon atoms. We first tried to insert into the macrocycle, an iron atom which is the one present in the natural cofactor of heme-enzymes. The incorporation of this metal was performed using $FeCl_2$ in refluxing DMF, according to the method described by Adler et al.[45] Unfortunately, this method led to a mixture of degradation products highlighted by TLC or mass spectrometry. In particular, it appeared that, under those conditions, the S–S bridge was broken during this reaction. This could be due to a reduction of the disulfide bridge, either by the excess of ferrous ion present in the reaction mixture or by the iron(II)-porphyrin complex formed. Subsequently, we decided to incorporate the manganese(III) ion which required mild reaction conditions, preventing the atropo-isomerization and the degradation of the molecule. Since the manganese(III)-complex was a paramagnetic compound, it

was difficult to characterize by NMR spectroscopy. Therefore, this metallation was achieved at the very last step of the synthesis, after all diamagnetic intermediates had fully been characterized by NMR spectroscopy as well as mass spectroscopy and elemental analysis.

As a conclusion, the aforementioned results describe an original method which led to the successful preparation of a new steroid-tetraaryl-metalloporphyrin conjugate which possesses all the elements that are necessary to build up a semi-synthetic catalytic antibody with a monooxygenase-like activity: (i) a testosterone moiety that can be recognized by an *anti*-estradiol antibody; (ii) a catalytic Mn(III)-tetraaryl-porphyrin cofactor bearing an arm ending in a carboxylic acid group for the selective coupling with a lysine of the antibody protein; (iii) an arm linking the testosterone moiety to the Mn(III)-tetraaryl-porphyrin cofactor, which includes a labile linkage, a disulfide bridge, that will permit the release of the modified testosterone after reductive cleavage. A direct application of this described material will be reported elsewhere.

This method could constitute a starting point for a general strategy aiming at preparing semi-synthetic antibodies that are able to perform the catalytic oxidation of substrates since: (i) it can be adapted to modify any kind of monoclonal antibody raised against a substrate molecule that can be chemically modified to anchor a cleavable arm, (ii) it can be general for any kind of metal cofactor which possesses a catalytic activity in oxidation reactions, (iii) the length of the arms can be adapted for an optimal positioning of the cofactor with respect to the substrate binding site since it directly derives from the opening of an anhydride by an amine group.

4. Experimental

4.1. General

All reagents (used at their commercial purity) were purchased from Acros and solvents from Prolabo. CH_2Cl_2 was distilled immediately before use and anhydrous solvents were distilled under Argon. Silica gel 60 (70–200 mesh, Merck) was used for column chromatography. Analytical thin layer chromatography (TLC) was performed using SDS 60 F254 silica gel (precoated sheets, 0.2 mm thick). Reactions were monitored by TLC and spectrophotometry. ^{1}H NMR spectra were performed using 200, 250 or 400 MHz Brüker apparatus; chemical shifts are expressed in ppm relative to deuterochloroform (7.27 ppm) and/or deuteromethanol (3.31 ppm). NMR data are presented in the following order: chemical shift, coupling constant, peak multiplicity, integration and assignment. ^{13}C NMR spectra were recorded at 50.3, 62.5 or 100.6 MHz and referenced to internal deuterochloroform (77.0 ppm) and/or deuteromethanol (49.0 ppm). Infrared spectra were obtained using a FT-IR Brüker IFS-66 spectrometer. Low-resolution mass spectrometry and high-resolution mass spectrometry analysis were performed by electrospray on Finnigan Mat 95 with positive ionization mode (resp. (ES-MS) and (HR-MS (ES)) or with negative ionization mode (resp. (ES-NEG-MS) and (HR-MS (ES-NEG)). The mass spectra of the final products were obtained by matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry, using R30-10 Nermag apparatus, at the University of Paris VI. Electronic absorption spectra were recorded on a Safas Des 190 spectrophotometer. The elemental analysis were performed by the microanalytical laboratory at the ICSN, CNRS, Gif-sur Yvette.

4.1.1. α,α-5,10-Bis-(*o*-aminophenyl)-15,20-diphenylporphyrin ($BADPPH_2$ (1)). Benzaldehyde (7.4 mL, 73.2 mmol, 1.3 equiv.) and *o*-nitrobenzaldehyde (8.45 g, 55.9 mmol, 1 equiv.) were dissolved in 310 mL propionic acid, and the resulting solution was brought to reflux. A solution of freshly distilled pyrrole (9 mL, 129.0 mmol, 2.3 equiv.) in 40 mL of propionic acid was then slowly added to the boiling solution and the mixture was refluxed for 30 min. The resulting dark solution was then allowed to cool down and stand for 20 h at 4 °C. A dark purple solid was collected by filtration, washed with water and dried; yield 6.78 g. The free nitro-porphyrin of interest was not isolated and the resulting crude product was used as obtained in further reactions.

Half of the crude product (3.35 g) was dissolved in CH_2Cl_2 and 100 mL of concentrated HCl were subsequently added. The dark solution was treated with an excess of $SnCl_2 \cdot 2H_2O$ (16.08 g, 71.3 mmol) and stirred at room temperature for 48 h. The reaction mixture was then placed in an ice bath before neutralization by addition of KOH pellets, taking care to maintain the temperature under 10 °C throughout the exothermic reaction. CH_2Cl_2 was added to the solution and the organic layer was separated. The aqueous layer was extracted several times with CH_2Cl_2 and all the organic extracts were combined and washed twice with water before drying over anhydrous sodium sulfate. After filtration, the solvent was removed by evaporation under reduced pressure and the diamino-porphyrin (**1**) was purified by successive column chromatographies using first a CH_2Cl_2/cyclohexane mixture (5:5 v/v), and then a CH_2Cl_2/AcOEt mixture (99:1 and 95:5 v/v) as the mobile phase; yield 40 mg. R_f (CH_2Cl_2/Et_2O, 9:1): 0.60. UV/Vis (dichloromethane, λ_{max}, nm (ε, L mmol^{-1} cm^{-1})(: 419 (386), 515 (22), 549 (8), 590 (7), 646 (4). FT-IR (NaCl): 3447 (NH_2), 1612–1559 and 1490 (Ar) cm^{-1}. RMN ^{1}H ($CDCl_3$, 250 MHz) δ: −2.63 (br s, NH), 3.49 (br s, NH_2), 7.07 (d, J=8.03 Hz, 2H, H-3), 7.21 (t, J=7.38 Hz, 2H, H-5), 7.62 (td, J=7.38, 0.67 Hz, 2H, H-4), 7.75–7.86 (m, 6H, H-3′, H-4′ and H-5′), 7.93 (d, J=7.38 Hz, 2H, H-6), 8.22–8.33 (m, 4H, H-2′ and H-6′), 8.94 (d, J=2.68 Hz, 4H, H-β pyrr.), 8.95 (d, J=2.69 Hz, 4H, H-β pyrr.) (for the numbering of protons see Fig. 2). RMN ^{13}C ($CDCl_3$, 62.5 MHz) δ: 115.19, 115.44, 117.48, 120.48, 126.69, 127.00, 127.77, 129.58, 131.14 (br.), 131.58 (br.), 134.50, 134.78, 141.98, 146.81. ES-MS (3 kV) *m/z* 645.1 (M+1, 100%). Anal. calcd for $C_{44}H_{32}N_4 \cdot 3/2H_2O$: C, 78.67; H, 5.25; N, 12.51, found C, 78.71; H, 5.06; N, 12.41).

4.1.2. α,α-5,10-Bis-((*o*-(2-carboxyethyl)carboxamido (phenyl(-15,20-diphenyl-porphyrin ($TPPH_2diSucc(COOH)_2$ (2)). $BADPPH_2$ (**1**) (130 mg, 0.2 mmol, 1 equiv.) was stirred in 40 mL of CH_2Cl_2 at room temperature until complete dissolution of the porphyrin and subsequently 500 μL of pyridine and excess succinic anhydride (320 mg,

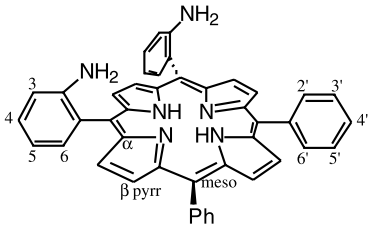


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Figure 2. Numbering of protons in α,α-5,10-bis-(*o*-aminophenyl)-15,20-diphenylporphyrin.

3.17 mmol, 15.85 equiv.) were added. The resulting mixture was maintained at room temperature under stirring for 48 h.

The organic layer was washed with a solution of HCl pH 5 and the solvent was evaporated under reduced pressure. The resulting dark purple solid was washed with a solution of HCl pH 5 and dried. The crude product was then purified by column chromatography using a CH_2Cl_2/MeOH/AcOH mixture (94:6:1 v/v for the elution of the porphyrin of interest). Fractions containing the desired product were combined and evaporated to dryness to produce (**2**) as a purple solide; yield 119 mg (70%). R_f (CH_2Cl_2/MeOH/AcOH, 96:4:1): 0.26. UV/Vis (dichloromethane, λ_{max}, nm (ε, L mmol^{-1} cm^{-1})(: 419 (394), 515 (18), 549 (6), 589 (6), 645 (3). FT-IR (KBr): 3410 (large, OH_{acid} and NH_{amide}), 2928 (C–H_{alkyl}), 1664 (large, C=O), 1579–1517 and 1467 (Ar), 1442, 1348, 1155. RMN ^{1}H ($CDCl_3$, 250 MHz) δ: 1.88 (br., 8H, CH_2), 7.51 (t, J=6.83 Hz, 2H, H-5), 7.69 (s, NH amide), 7.70–7.88 (m, 8H, H-4, H-3′, H-4′ and H-5′), 7.96 (d, J=6.83 Hz, 2H, H-6), 8.21 (d, J=6.83 Hz, 4H, H-2′ and H-6′), 8.45 (d, J=6.84 Hz, 2H, H-3), 8.79 (d, J=4, 89 Hz, 4H, H-β pyrr.), 8.88 (d, J=5.86 Hz, 2H, H-β pyrr.), 8.90 (s, 2H, H-β pyrr.). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 28.39 (*C*H_2CONH), 31.05 (*C*H_2COOH), 114.25, 121.40, 122.61, 123.40, 126.82, 128.03, 129.48, 130.91 (br.), 132.35, 134.48, 134.86, 138.34, 141.48, 146.28 (br.), 147.48 (br.), 170.43 (CONH), 175.59 (COOH). ES-MS (3 kV) *m*/*z* 845.1 (M+1, 100%). HR-MS calcd for [$C_{52}H_{41}N_6O_6$] 845.30872, found 845.308758. Anal. calcd for $C_{52}H_{40}N_6O_6\cdot 2H_2O$: C, 70.90; H, 5.03; N, 9.54, found C, 70.96; H, 5.05; N, 9.51.

4.1.3. Testo-3-carboxymethyloxime (T-3-CMO (3)). A solution of carboxymethoxylamine hemihydrochloride (1.75 g, 8 mmol, 1.6 equiv.) in 300 mL of ethanol was treated with testosterone (1.44 g, 5 mmol, 1 equiv.) and stirred for 36 h at room temperature. The volume of the resulting mixture was reduced to 50 mL under reduced pressure. The solution was then acidified with 25% HCl to precipitate the product. The resulting solid was washed successively with 25% HCl and water, filtered and dried. The crude product was then purified by column chromatography using a CH_2Cl_2/MeOH mixture (95:5 v/v) to afford 1.497 g (83% yield) of the oxime (**3**) as a white powder. This product proved to be a mixture of the two *Z* and *E* diastereoisomers of the oxime, with a ratio of 40:60 respectively. R_f (CH_2Cl_2/MeOH, 90:10): 0.30. Melting point, IR, ^{1}H NMR and UV/Vis data are in agreement with the literature.[28,36] ^{13}C NMR (CD_3OD, 100.6 MHz) (for the numbering of carbons see Fig. 3) δ: 11.59 (C-18), 18.21 and 18.44 (C-19 resp. *E* and *Z*), 20.49, 21.90, 22.09, 24.27, 25.34, 30.61, 33.05, 33.46, 33.50, 33.97, 35.89, 37.09, 37.15, 37.43, 37.81, 37.87, 39.19, 40.12, 43.92, 51.92, 51.98, 55.46, 55.75, 70.86, 71.03, 82.32, 111.99 (C-4(*Z*)), 117.59(C-4(*E*)), 156.00, 158.31, 159.13, 161.85, 173.91 (COOH). ES-NEG-MS (3 kV) *m*/*z* 360.2 (M−1, 100%). HR-MS (ES-NEG) calcd: 360.2175 for [$C_{21}H_{30}NO_4$], found 360.2173. Anal. calcd for $C_{21}H_{31}NO_4\cdot 1/3H_2O$: C, 68.64; H, 8.69; N, 3.81, found C, 68.58; H, 8.92; N, 3.83.

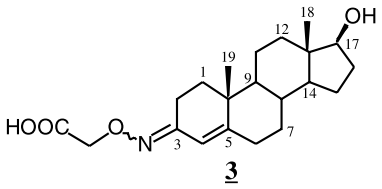

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Figure 3. Numbering of carbons in testo-3-carboxymethyloxime.

4.1.4. Mono-(2-N-Boc-aminoethyl)-mono-(2-aminoethyl)disulfide (Cyst monoBoc (4)). A suspension of cystamine dihydrochloride (3.37 g, 15 mmol, 3 equiv.) in 100 mL of $CHCl_3$ was treated with Et_3N (21 mL, 30 mmol, 6 equiv.) and stirred for 15 min at room temperature. A solution of $(Boc)_2O$ (1.09 g, 5 mmol, 1 equiv.) in 50 mL of $CHCl_3$ was then added dropwise over 3 h at 0 °C. The reaction mixture was warmed at room temperature for 12 h, poured into 20 mL of water and washed a second time with 20 mL of H_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford a yellow solid. Purification by flash chromatography on silica gel (elution with 90% CH_2Cl_2/MeOH and 1% NH_4OH) gave 432 mg (34% yield) of Boc-cystamine as a yellow oil. R_f (CH_2Cl_2/MeOH/NH_4OH, 90:10:1): 0.22. FT-IR (NaCl): 3363 (NH_2), 2977 (C–H_{alkyl}), 1699 (C=O), 1506, 1391 and 1366 (δ_s CH_{3Boc}), 1253, 1164, 1044 (C–S) cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.45 (s, 9H, CH_3), 1.55 (s, NH_2), 2.77 (t, J=5.86 Hz, 2H, CH_2S), 2.79 (t, J=5.86 Hz, 2H, CH_2S), 3.02 (t, J=5.86 Hz, 2H, CH_2NH_2),), 3.44 and 3.46 (2t, J=5.86 Hz, 2H, C*HH*'NHBoc), 4.95 (br. s, NH). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 28.0 (CH_3), 37.9 (C-NH_2), 39.0 (CH_2S), 40.1 (CH_2S), 41.9 (C-NHBoc), 78.9 ($OC(Me)_3$), 155.5 (OCONH). ES-MS (3 kV) *m*/*z* 253.1 (M+1, 100%). HR-MS (ES) calcd: 253.10443 for [$C_9H_{21}N_2O_2S_2$], found 253.10375.

4.1.5. Mono-(2-N-Boc-aminoethyl)-mono-(2-(testo-3-carboxamidomethyloxime)ethyl)disulfide (TcystBoc (5)). Isobutylchloroformate (0.23 mL, 1.78 mmol, 2 equiv.) and 4-methylmorpholin (0.19 mL, 1.78 mmol, 2 equiv.) were added to a solution of T-3-CMO (322 mg, 0.89 mmol, 1equiv.) in 5 mL of a mixture of anhydrous CH_2Cl_2/dioxane (4:1, v:v) at −5 °C under argon atmosphere. The reaction mixture was stirred for 1 h and was treated with Boc-cystamine (300 mg, 0.89 mmol, 1 equiv.) diluted in 1.4 mL of anhydrous CH_2Cl_2. The resulting mixture was warmed at room temperature for 18 h, filtered and concentrated to give a white solid. Purification by flash chromatography on silica gel (elution 95% CH_2Cl_2/MeOH and 1% NH_4OH) afforded 267 mg (yield 50%) of adduct **5** as a white solid. R_f (CH_2Cl_2/MeOH/NH_4OH, 90:1:1): 0.60. FT-IR (NaCl): 3435 (O–H, N–H), 3013 (=C–H), 2937 (C–H_{alkyl}), 1700 (C=O, C=N), 1507, 1367 (δ_s CH_{3Boc}), 1216, 1167, 1076 (C–S) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.80–2.45 (overlapping m, 19H), 0.78 (s, 3H, H-18), 1.09 and 1.13

(s, 3H, H-19 resp *E* and *Z*), 1.45 (s, 9H, CH_{3Boc}), 2.79 (t, J= 6.35 Hz, 2H, CH_2S), 2.83 (t, J=6.35 Hz, 2H, CH_2S), 3.02 (ddd, J=2.45, 4.40, 17.09 Hz, H-2α(*E*)), 3.43 and 3.45 (2t, J=6.35 Hz, 2H, C*HH'*NHBoc), 3.64 (t, J=6.35 Hz, 2H, CH_2NH), 3.67 (t, 1H, H-17), 4.52 and 4.51 (2s, 2H, CHH'_{CMO}), 5.00 (s, 1H, NH), 5.76 (s, 1H, H-4(*E*)), 6.42 (s, 1H, H-4(*Z*)), 6.73 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 10.91 (C-18), 17.58 and 17.83 (C-19 resp. *E* and *Z*), 19.47, 20.56, 20.76, 23.17, 24.29, 28.20 (CH_{3Boc}), 30.15, 31.51, 31.87, 32.30, 32.85, 34.36, 35.59, 35.87, 36.38, 37.47, 38.28, 38.88, 39.23, 42.59, 42.63, 50.40, 53.61, 53.86, 72.32, 72.52, 79.29, 81.28, 110.25(C-4(*Z*)), 116.29 (C-4(*E*)), 155.40, 155.64, 157.18, 158.23, 161.45, 170.18 and 170.37 (CONH). ES-MS (2.9 kV) *m/z* 618.3 (M+1+Na), 695 (M+1+K). Anal. calcd for $C_{30}H_{49}N_3O_5S_2$: C, 60.47; H, 8.29; N, 7.05, found C, 60.38; H, 8.38; N, 7.05.

4.1.6. Mono-(2-aminoethyl)-mono-(2-(testo-3-carboxamidomethyloxime)ethyl)disulfide (Tcyst (6)). TcystBoc (**5**) (119 mg, 0.2 mmol, 1 equiv.) was dissolved in 1 mL of water. The solution was cooled to 0 °C and 3 mL of trifluoroacetic acid (0.04 mmol, 0.2 equiv.) were added dropwise. The temperature of the reaction mixture was then raised to room temperature and the reaction mixture stirred during 40 min. The resulting solution was evaporated under reduced pressure to remove the trifluoroacetic acid and the aqueous layer was neutralized with a solution of NH_4OH 3% (v:v). After saturation of the aqueous layer with NaCl, the crude product was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and concentrated. The resulting crude product was then purified on silica gel using a CH_2Cl_2/MeOH/NH_4OH mixture (94:6:0.4 v/v) to afford 58 mg (yield 59%) of a white solid corresponding to the expected compound. Because of its instability, this amino intermediate was used immediatly after the purification. R_f (CH_2Cl_2/MeOH/NH_4OH, 90:1:1): 0.50. FT-IR (NaCl): 3425 (O–H, N–H), 3018 (=C–H), 2941 (C–H_{alkyl}), 1717 (C=O), 1669 (C=N), 1533, 1436, 1215, 1077 (C–S) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.80–2.45 (overlapping m, 19H and NH_2), 0.78 (s, 3H, H-18), 1.09 and 1.13 (s, 3H, H-19 resp. *E* and *Z*), 2.77 (t, J=6.35 Hz, 2H, CH_2S), 2.83 (t, J=6.35 Hz, 2H, CH_2S), 3.01 (t, J=6.35 Hz, 3H, CH_2NH_2 and H-2α(*E*)), 3.55–3.70 (m, 3H, H-17 and CH_2NH), 4.50 and 4.52 (2s, 2H, CHH'_{CMO}), 5.76 (s, 1H, H-4(*E*)), 6.42 (s, 1H, H-4(*Z*)), 6.70 (s br., NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 11.05 (C-18), 17.81, 18.06, 19.69, 20.78, 20.97, 23.38, 24.54, 30.49, 31.71, 32.09, 32.51, 33.08, 34.61, 35.84, 36.12, 36.59, 37.56, 37.84, 38.06, 40.62, 42.58, 42.82, 50.64, 53.83, 54.09, 72.62, 72.83, 81.71, 110.44 (C-4(*Z*)), 116.57 (C-4(*E*)), 155.61, 157.31, 158.42, 161.59, 170.24 and 170.46 (CONH). ES-MS (3 kV) *m/z* 496.3 (M+1, 100%).

4.1.7. Free-base porphyrin-testosterone conjugate: $TPPH_2$diSucc-mono(Tcyst) (7). In a Schlenk, $TPPH_2$ diSucc$(COOH)_2$ (**2**) (20 mg, 23.7 μmol, 1 equiv.), freshly distilled dicyclohexylcarbodiimide (5.86 mg, 28.4 μmol, 1.2 equiv.) and *N*-hydroxysuccinimide (2.72 mg, 23.7 μmol, 1 equiv.) were dissolved under argon atmosphere at 0 °C in 5 mL of anhydrous CH_2Cl_2. The reaction mixture was stirred between 0 and 4 °C for 3 days. A solution of compound **6** (14.6 mg, 29.6 μmol, 1.25 equiv.) in 5 mL of anhydrous CH_2Cl_2 was then transfered into the solution of activated ester. The resulting mixture was allowed to stir at 4 °C for 5 days. The solvent was then evaporated and replaced with ethyl acetate in order to precipitate the dicyclohexylurea formed during the reaction. The organic layer was filtered and concentrated. The crude product (**7**) was purified by chromatography on silica gel with a mixture of CH_2Cl_2/MeOH (93:7 v/v) and 0.4% NH_4OH to afford 13 mg (41%) of a violet solid. R_f (CH_2Cl_2/MeOH/NH_4OH 90:10:1): 0.33. FT-IR (KBr): 3425 (large), 3010 (Ar-H), 2924 and 2854 (C–H_{alkyl}), 1654 (large), 1523, 1444, 1384, 1087. UV/Vis (dichloromethane, λ_{max}, nm (ε, L $mmol^{-1}$ cm^{-1})(: 419 (393), 515 (18), 549 (6), 588 (6), 645 (3). ^1H NMR ($CDCl_3$, 250 MHz) (see numbering of the molecule Scheme 3) δ −2.80 (s, 2H, NH pyrr.), 0.60–2.50 (overlapping m, $H_{steroid}$, CH_{2Succ}, CH_2S), 0.68 (s, 3H, H-18), 0.89 and 1.08 (2s, 3H, H-19 (*E*) and (*Z*) resp.), 3.20–3.85 (m, 5H, H-17, CH_2NH), 4.26 and 4.28 (2s; 2H, CH_{2CMO}), 5.60 (s, 1H, H-4 (*E*)), 6.18 (br. s, 1H, NH), 6.32 (s, 1H, H-4 (*Z*)), 6.52 (br. s, 1H, NH), 7.50 (t; J=7.33 Hz; 1H, H-24), 7.54 (t, J=7.81 Hz, 1H, H-30), 7.70–7.84 (m, 10H, H-34, H-35, H-36, H-23, H-29 and 2NH), 7.95 (d, J= 7.32 Hz, 1H, H-25), 8, 03 (d, J=7.81 Hz, 1H, H-31), 8.12–8.30 (m, 4H, H-32 and H-37), 8.44 (d, J=7.82 Hz, 1H, H-22), 8.59 (d, J=7.33 Hz, 1H, H-28), 8.72–8.94 (m, 8H, H-β pyrr.). MS (MALDI-TOF) *m/z* 1322.95 (M+1, 100%).

4.1.8. Testosterone-(tetraphenylporphyrinato)manganese(III) acetate conjugate: (OAc)Mn^{III}($TPPH_2$diSucc-mono(Tcyst)) (8). $TPPH_2$diSucc-mono(Tcyst) (4.5 mg, 3.40 μmol, 1 equiv.) was dissolved in a mixture of $CHCl_3$/MeOH (70/30, v:v) at room temperature and treated with a large excess of manganese acetate tetrahydrate (41.5 mg, 163 μmol, 47.9 equiv.). The resulting mixture was stirred at room temperature for 8 days. The solvent was then evaporated and replaced by CH_2Cl_2. The organic layer was washed with water for the removal of excess of $Mn(OAc)_2 \cdot 4H_2O$. The solution was then dried over Na_2SO_4, filtered and concentrated to afford a brown solid. The reaction was quantitative. UV/Vis (CH_2Cl_2, λ_{max}, nm (ε, L $mmol^{-1}$ cm^{-1}))(: 376 (10.5), 401 (10), 474 (24), 578 (2), 609 (1.6). MS (MALDI-TOF) *m/z* 1375.36 (M+1, 100%).

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Sequenced elimination–reduction and elimination–cyclopropanation reactions of 2,3-epoxyamides promoted by samarium diiodide. Synthesis of 2,3-dideuterioamides and cyclopropanamides

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Abstract—An easy and general sequenced elimination/reduction or elimination/cyclopropanation process promoted by samarium diiodide or/and CH_2I_2/Sm provide an efficient method for synthesising 2,3-dideuterioamides **3** or cyclopropanamides **8**, respectively. The transformations take place in high yields and with total or high selectivity from the easily available 2,3-epoxyamides.

1. Introduction

Samarium diiodide is a polyvalent reducing agent and constitutes an effective reagent for sequential reactions,[1] which present a high potential because less time, effort, and material are required. Epoxides are useful intermediates in organic synthesis and have been widely used because of their chemical reactivity.[2] However, the reduction of epoxides to hydrocarbons has been scarcely reported,[3] and to the best of our knowledge, transformation of 2,3-epoxyamides into saturated or 2,3-dideuterioamides has not been published. Other possible alternative to reduce 2,3-epoxyacid derivatives can be performed by its transformation into α,β-unsaturated acid derivatives and subsequent reduction to corresponding saturated compounds. In this sense, selective conjugated reduction of α,β-unsaturated carboxylic acid derivatives has been achieved by using several methodologies.[4] However, the conjugated reduction of α,β-unsaturated amides with deuterium instead of hydrogen has been scarcely reported.[5] To the best of our knowledge, only two examples have hitherto been described,[6] both of wich involved catalytic addition of D_2. Taking into account the utility of isotopically labelled compounds to establish the mechanisms of organic reactions and the biosynthesis of many natural products,[7] the development of an effective general method for the synthesis of 2,3-dideuterioamides would seem to be a valuable goal.

Moreover, the use of cyclopropanes in mechanistic studies,[8] their utility as synthetic intermediates,[9] and their presence in a great number of natural products[10] warrants interest in these carbocycles from various fields in organic chemistry. The majority of the methodologies developed for the synthesis of cyclopropanes[11] rely on variants of the following reactions: Simmons–Smith cyclopropanation,[12] transition-metal catalyzed cyclopropanation of alkenes with diazomethane[13] or diazoesters,[14] and cyclopropanation of Michael acceptors.[15] However, these methods have some disadvantages: total control of diastereoselectivity in the synthesis of polysubstituted cyclopropanes is beyond reach, some methodologies call for toxic reagents, and in other cases, synthesis of cyclopropanes from unsaturated compounds in which the C=C bond is tri- or tetrasubstituted cannot be carried out.[16] Consequently, new methods for the diastereoselective construction of cyclopropanamides, in which the cyclopropane ring is polysubstituted, are of significant interest.[17]

Previously, we reported the transformation of 2,3-epoxyesters into saturated esters by using SmI_2[18] and 2-chloro-3-hydroxyamides into cyclopropanamides promoted by CH_2I_2/Sm.[19] More recently, we have also reported a β-elimination reaction of aromatic[20] and aliphatic[21] α,β-epoxyamides, obtaining (*Z*)- or (*E*)-α,β-unsaturated amides with total or very high diastereoselectivity.

Keywords: Samarium diiodide; Sequenced reactions; Deuterium; Saturated amides; Cyclopropanamides.
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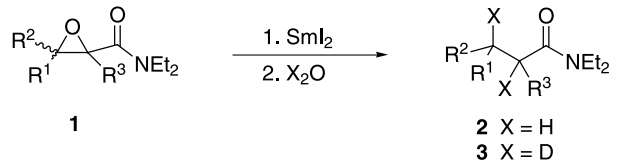
Now, we describe a method to obtain saturated amides and cyclopropanamides from 2,3-epoxyamides by an efficient SmI_2-promoted elimination–reduction or elimination–cyclopropanation sequential reaction, respectively. We have also performed sequenced elimination–reduction reactions to obtain 2,3-dideuterioamides by using D_2O instead of H_2O.



1

2 X = H
3 X = D

Scheme 1.

2. Results and discussion

The starting compounds **1** were easily obtained by reaction of aldehydes or ketones with lithium or potassium enolates derived from chloroacetamides, by using standard methods.[20,21] Thus, epoxyamides **1** were obtained as a mixture *cis*/*trans* and with the yields showed in Table 1.

2.1. Synthesis of saturated 2 or 2,3-dideuterioamides 3

The reaction of different di- or tetrasubstituted 2,3-epoxyamides **1a–c** with SmI_2 (5 equiv.) afforded the corresponding α,β-unsaturated amides. After treatment with H_2O or D_2O gave the corresponding saturated amides **2** or 2,3-dideuterioamides **3**, respectively (Scheme 1, Table 2).

Starting from trisubstituted 2,3-epoxyamides **1**, (Table 2, entries 2, 3 and 7,8) a complex mixture of products was obtained. We have overcome this problem by adding samarium diiodide in two times. Thus, the succesive treatment of trisubstituted 2,3-epoxyamides **1** with a solution of SmI_2 in THF and HMPA (exclusively in the case of aliphatic α,β-epoxyamides) and further treatment with additional SmI_2 and H_2O or D_2O, afforded the corresponding saturated amides **2** or 2,3-dideuterioamides **3** respectively, in good yield (Scheme 1, Table 2).

This proposed methodology to obtain saturated amides **2** or 2,3-dideuterioamides **3** is general. Thus, R^1 and R^3 can be aliphatic or aromatic, and can be performed from 2,3-epoxyamides in which the oxirane ring is di-, tri- or tetrasubstituted. No significant differences were observed in the reaction when D_2O was used instead of H_2O.

The position of deuteration was established by ^1H and ^{13}C NMR spectrometry of compounds **3**, while complete deuterium incorporation (>99%) was determined by mass spectroscopy.[22] The obtained 2,3-dideuterioamides **3** were isolated as mixture of diastereoisomers (ranging between 1:1 and 2:1) due to the fact that incorporation of deuterium generates two new stereogenic centres. It is noteworthy that D_2O is the most widely available deuteration reagent for obtaining organic compounds isotopically labelled with deuterium.

A postulated mechanism is illustrated in Scheme 2. In the first step, the metalation of **1** by SmI_2 generates an enolate intermediate **4**, which suffers a β-elimination reaction affording α,β-unsaturated amides **5**.[20,21] In the second step, the 1,4-reduction of **5**, is initiated by a single electron transfer from SmI_2 to generate the enolate radical **6**[23] which, upon reaction with a second equivalent of SmI_2 produces the dianion **7**. Subsequent protonation of **7** by D_2O or H_2O, affords the corresponding compound **3** or **2**, respectively.

Table 1. Synthesis of epoxyamides **1**

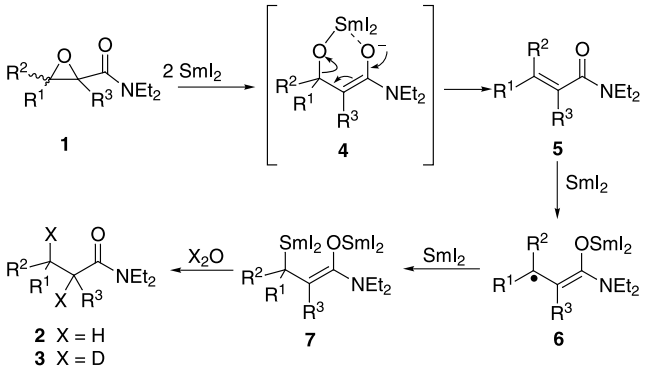
Entry	1[a]	R^1	R^2	R^3	Yield (%)[b]	*trans* /*cis*[c]
1	**1a**	Ph	H	H	62	2/1
2	**1b**	*p*MeO–C_6H_4	H	H	69	1.4/1
3	**1c**	Bu	H	Ph	74	1.6/1
4	**1d**	Cyclohexyl	H	Me	85	1.7/1
5	**1e**	C_7H_{15}	H	Me	92	2.7/1
6	**1f**	H	Ph	Me	83	1.3/1
7	**1g**	H	*p*MeO–C_6H_4	Me	79	3/1
8	**1h**	Ph	Et	Me	95	1.5/1

[a] General procedure to obtain compounds **1** is described in references 20 and 21.
[b] Isolated yield after column chromatography.
[c] Diastereoisomers ratio determined by ^{13}C NMR analysis.

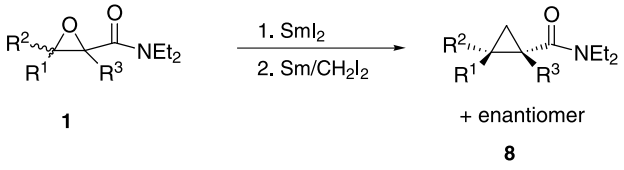
Table 2. Synthesis of saturated amides **2** and 2,3-dideuterioamides **3**

Entry	Compound[a]	R^1	R^2	R^3	X	Yield (%)[b]
1	**2a**	Ph	H	H	H	95
2	**2c**	Bu	H	Ph	H	69
3	**2d**	Cyclohexyl	H	Me	H	82
4	**2h**	Ph	Et	Me	H	66
5	**3a**	Ph	H	H	D	94
6	**3b**	*p*MeO–C_6H_4	H	H	D	71
7	**3c**	Bu	H	Ph	D	67
8	**3f**	H	Ph	Me	D	61

[a] All products were fully characterized by spectroscopic methods [IR, NMR, and MS].
[b] Isolated yield after column chromatography based on compound **1**.



Scheme 2.

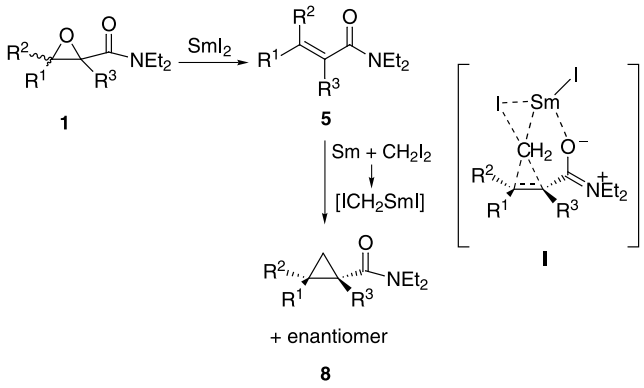


Scheme 3.

2.2. Preparation of cyclopropanamides 8

The reaction of 2,3-epoxyamides with SmI_2 at room temperature and further treatment with a mixture of Sm/CH_2I_2 afforded the corresponding cyclopropanamide **8** in high yield and with total or very high distereoselectivity (Scheme 3 and Table 3). Starting from trisubstituted aliphatic 2,3-epoxyamides, the elimination reaction was carried out by using HMPA as cosolvent to enhance the diastereoselectivity of the process (Table 3, entries 2 and 3). In the case of trisubstituted aromatic epoxyamides, the use of MeOH as cosolvent in the first step increases the diastereoselectivity of the β-elimination reaction and avoids side reactions (Table 3, entries 4 and 5). In this case, the solvents were eliminated previously to carry out the second step due to no cyclopropanation reaction takes place in the presence of MeOH. Consequently, in these two cases the process is one-pot instead of a sequential reaction. Results in Table 3 show that this elimination–cyclopropanation reaction is general: the starting compounds can be aliphatic or aromatic and the oxirane ring can be di-, tri- or tetrasubstituted.

The stereochemistry of the cyclopropane ring was dependent on the structure starting epoxyamide. Thus, from aliphatic (Table 3, entries 2 and 3) and di- or tetrasubstituted aromatic epoxyamides (entries 1 and 6), *trans*-cyclopropanamides were obtained, while from trisubstituted aromatic epoxyamides *cis*-cyclopropanamides were prepared (Table 3, entries 4 and 5). Taking into account that the cyclopropanation reaction is stereospecific, the stereochemistry of the cyclopropane ring is directly related with the stereochemistry of the double bond C=C formed in the first step.



Scheme 4.

The diastereoisomeric purity of compounds **8** was determined on the crude reaction products by ^1H NMR spectroscopy (300 MHz) and GC-MS. The relative *trans* or *cis* configuration of substituents on the cyclopropane ring was established by analysis of ^1H NMR coupling constant between the cyclopropane protons of compound **8a**, by NOE experiments (**8h**) and by comparison of their ^1H and ^{13}C NMR spectra with authentic samples, as has been previously described.[19]

The course of the synthesis of **8** can be thought to occur as shown in Scheme 4, through a sequential elimination-cyclopropanation reaction. Initially, **1** suffers an elimination reaction promoted by SmI_2, affording *cis*- (from trisubstituted aromatic epoxyamides) or *trans*-α,β-unsaturated amides **5** (from the rest), with high diastereoselectivity. In the second step, carbenoids of Sm (II) (e.g., $ISmCH_2I$)[24] produce a stereospecific cyclopropanation of **5**.[25] Tentatively, we propose a transition state model **I**,[26] in which the coordination of the divalent samarium atom with the oxygen atom of the amide group provides cyclopropylamide **8**, whilst maintaining the geometry about the C=C bond. The abundance of the zwitterionic specie of the amide seems to be the responsible of the reaction of samarium carbenes with the olefin, in a similar way as this described for allylic alcohols.[27]

Table 3. Synthesis of cyclopropanamides **8**

Entry	8[a]	R^1	R^2	R^3	d.e.[b]	Yield (%)[c]
1	**8a**	Ph	H	H	>98	73
2	**8d**	Cyclohexyl	H	Me	>98	60
3	**8e**	C_7H_{15}	H	Me	97	62
4	**8f**	H	Ph	Me	>98	88
5	**8g**	H	*P*meO–C_6H_4	Me	>98	84
6	**8h**	Ph	Et	Me	>98	87

[a] All products were fully characterized by spectroscopic methods [IR, NMR, and MS].
[b] Diastereoisomeric excess determined by GC/MS and 300 MHz ^1H NMR analysis of the crude products.
[c] Isolated yield after column chromatography based on compound **1**.

3. Conclusion

In conclusion, two efficient sequential methodologies have been described. In the first, the SmI_2-promoted elimination–reduction sequence (in the presence of D_2O or H_2O) provides an efficient method for synthesising 2,3-dideuterioamides or non-deuterated saturated amides. In the second, elimination–cyclopropanation affords *cis*- or *trans*-cyclopropanamides with total or very high diastereoselectivity.

4. Experimental

4.1. General remarks

Reactions which required an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried (120 °C). THF was distilled from sodium/benzophenone ketyl immediately prior to use. All reagents were purchased from Aldrich or Merck and were used without further purification. Samarium diiodide was prepared by reaction of CH_2I_2 with samarium powder by ultrasonic irradiation.[28] Silica gel for flash chromatography was purchased from Merck (230–400 mesh), and compounds were visualized on anlytical thin layer chromatograms (TLC) by UV light (254 nm). ^{1}H NMR spectra were recorded at 200 or 300 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 50 or 75 MHz. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), which is used as an internal standard, and coupling constants J are reported in Hz. The diastereoisomeric excesses were obtained from ^{1}H NMR analysis and GC-MS of crude products. GC-MS and HRMS were measured at 70 eV. Only the most important IR absorptions (cm^{-1}) and the molecular ions and/or base peaks in MS are given.

4.2. General procedure for the synthesis of compounds 2 and 3 from di- or tetrasubstituted 2,3-epoxyamides 1

A solution of SmI_2 (2.3 mmol) in THF (24 mL) was added, under nitrogen atmosphere, to a stirred solution of the corresponding 2,3-epoxyamide **1** (0.4 mmol) in THF (4 mL) at room temperature. After stirring for 30 min, H_2O or D_2O (1 mL) was added to the reaction. The mixture was stirred for 30 min at room temperature. Then, the reaction was quenched with aqueous HCl (0.1 M, 10 mL). Usual workup afforded crude saturated amides **2** or 2,3-dideuterioesters **3**, which were purified by column flash chromatography over silica gel (hexane/ethyl acetate).

4.3. General procedure for the synthesis of compounds 2 and 3 from trisubstituted 2,3-epoxyamides

A solution of SmI_2 (1.6 mmol) in THF (19 mL) and HMPA (2 mmol), in the case of aliphatic α,β-epoxyamides, was added, under nitrogen atmosphere, to a stirred solution of the corresponding epoxyamide **1** (0.4 mmol) in THF (4 mL) at room temperature. After stirring for 30 min at room temperature, a solution of SmI_2 (1.1 mmol) in THF (12 mL) and H_2O or D_2O (1 mL) was added to the solution and the mixture was stirred for 3 h at room temperature. Then, the reaction was quenched with aqueous HCl (0.1 M, 10 mL). Usual workup afforded crude saturated amides **2** or 2,3-dideuterioamides **3**, which were purified by column flash chromatography over silica gel (hexane/ethyl acetate).

4.3.1. *N,N*-Diethyl-3-phenylpropionamide (2a). ^{1}H RMN (300 MHz, $CDCl_3$): δ=7.32–7.15 (m, 5H), 3.38 (q, J=7.18 Hz, 2H), 3.21 (q, J=7.18 Hz, 2H), 3.17–2.94 (m, 2H), 2.65–2.54 (m, 2H), 1.11 (t, J=7.18 Hz, 3H), 1.09 (t, J=7.18 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.0 (C), 141.4 (C), 128.2 (CH), 125.8 (CH), 41.7 (CH_2), 40.0 (CH_2), 34.9 (CH_2), 31.5 (CH_2), 14.1 (CH_3), 12.9 (CH_3); MS (70 eV): *m/z* (%): 205 (100) $[M]^+$, 176 (12), 133 (4), 105 (28), 91 (44), 77 (16); IR 3083, 3059, 3028, 2975, 1640 cm^{-1}; HRMS Calcd for $C_{12}H_{19}NO$ 205.1466; found 205.1468; R_f 0.2 (hexane/AcOEt 5/1).

4.3.2. *N,N*-Diethyl-2-phenylheptanamide (2c). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.41–7.17 (m, 5H), 3.52–3.01 (m, 4H), 2.67–2.56 (m, 1H), 2.22–1.53 (m, 2H), 1.49–1.11 (m, 6H), 1.08–0.65 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.0 (C), 140.8 (C), 128.3 (CH), 127.5 (CH), 126.4 (CH), 48.7 (CH), 41.4 (CH_2), 40.1 (CH_2), 35.2 (CH_2), 31.6 (CH_2), 27.4 (CH_2), 22.3 (CH_2), 14.2 (CH_3), 13.8 (CH_3), 12.6 (CH_3); IR 2939, 1636, 1456, 1380 cm^{-1}. Anal. Calcd for $C_{17}H_{22}NO$: C, 78.11; H, 10.41; N, 5.36; found: C, 78.06; H, 10.39; N, 5.44; R_f 0.3 (hexane/AcOEt 3/1).

4.3.3. 3-Cyclohexyl-*N,N*-diethyl-2-methylpropanamide (2d). ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.63–3.29 (m, 4H), 1.88–0.72 (m, 14H), 2.19 (t, J=7.2 Hz, 6H), 1.09 (d, J=7.4 Hz, 3H); ^{13}C RMN (75 MHz, $CDCl_3$): δ=176.2 (C), 41.9 (CH_2), 41.7 (CH_2), 40.2 (CH_2), 35.3 (CH), 33.9 (CH_2), 33.1 (CH_2), 32.5 (CH), 26.5 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 18.1 (CH_3), 14.8 (CH_3), 13.0 (CH_3); IR 2924, 1624, 1448, 1380 cm^{-1}. Anal. Calcd for $C_{14}H_{27}NO$: C, 74.61; H, 12.08; N, 6.21; found: C, 74.58; H, 12.07; N, 5.38; R_f 0.3 (hexane/AcOEt 3/1).

4.3.4. *N,N*-Diethyl-3-phenyl-2-methylpentanamide (2h). (Diastereoisomeric mixture); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.35–7.09 (m, 10H), 3.54–2.63 (m, 16H), 1.27 (t, J=7.1 Hz, 6H), 1.15 (t, J=7.1 Hz, 6H), 1.04 (t, J=7.1 Hz, 6H), 0.83 (d, J=5.9 Hz, 6H), 0.74–0.61 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=175.3 (C), 174.8 (C), 143.2 (C), 142.8 (C), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 126.0 (CH), 125.8 (CH), 51.4 (CH), 50.4 (CH), 42.0 (CH), 41.9 (CH), 41.5 (CH_2), 41.4 (CH_2), 40.5 (CH_2), 39.8 (CH_2), 27.1 (CH_2), 23.9 (CH_2), 17.2 (CH_3), 16.2 (CH_3), 14.8 (CH_3), 14.3 (CH_3), 12.9 (CH_3), 12.3 (CH_3), 12.1 (CH_3), 11.9 (CH_3); IR 2968, 1635, 1456, 1380 cm^{-1}. Anal. Calcd for $C_{16}H_{25}N$: C, 77.68; H, 10.19; N, 5.66; found: C, 77.75; H, 10.09; N, 5.67; R_f 0.4, 0.3 (hexane/AcOEt 3/1).

4.3.5. 2,3-Dideuterio-*N,N*-diethyl-3-phenylpropanamide (3a). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.34–7.19 (m, 5H), 3.38 (q, J=7.18 Hz, 2H), 3.23 (q, J=7.18 Hz, 2H), 3.00–2.94 (m, 1H), 2.61–2.55 (m, 1H), 1.12 (t, J=7.18 Hz, 3H), 1.11 (t, J=7.18 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.0 (C), 141.2 (CH), 128.2 (CH), 125.8 (CH), 41.6 (CH_2), 39.9 (CH_2), 34.4 (t, J=19.7 Hz, CHD), 31.0 (t, J=19.7 Hz, CHD), 14.0 (CH_3), 12.8 (CH_3); MS (70 eV): *m/z* (%): 207 (42) $[M]^+$, 178 (7), 149 (10), 135 (4), 107 (18), 92 (53), 77 (50); IR 3083, 3060, 3025, 2973, 2932, 1638 cm^{-1}; HRMS

Calcd for $C_{13}H_{17}D_2NO$ 207.1466; found 207.1589; R_f 0.2 (hexane/AcOEt 5/1).

4.3.6. 2,3-Dideuterio-*N*,*N*-diethyl-3-[4-(methoxy)phenyl]propanamide (3b). ^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.14 (d, J=8.7 Hz, 2H), 6.83 (d, J=8.7 Hz, 2H), 3.78 (s, 3H), 3.37 (q, J=7.2 Hz, 2H), 3.21 (q, J=7.2 Hz, 2H), 2.98–2.78 (m, 1H), 2.62–2.44 (m, 1H), 1.11 (t, J=7.2 Hz, 3H), 1.10 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 171.2 (C), 157.8 (C), 133.4 (C), 129.2 (CH), 113.7 (CH), 55.1 (CH_3), 41.7 (CH_2), 40.0 (CH_2), 34.8 (CHD, t, J= 19.2 Hz), 30.2 (CHD, t, J=19.2 Hz), 14.1 (CH_3), 12.9 (CH_3); MS (70 eV): m/z (%): 227 (2) $[M]^+$, 222 (2), 147 (35), 72 (100); IR 3060, 1636, 1514, 1458 cm^{-1}; R_f 0.3 (hexane/AcOEt 3/1).

4.3.7. 2,3-Dideuterio-*N*,*N*-diethyl-2-phenylheptanamide (3c). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.39–7.19 (m, 5H), 3.56–3.06 (m, 4H), 2.18–1.53 (m, 2H), 1.49–1.10 (m, 5H), 1.17–0.78 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=172.1 (C), 140.8 (C), 128.5 (CH), 127.7 (CH), 126.5 (CH), 48.3 (CD, t, J=19.4 Hz), 41.5 (CH_2), 40.3 (CH_2), 34.9 (CHD, t, J=19.4 Hz), 31.7 (CH_2), 27.4 (CH_2), 22.4 (CH_2), 14.4 (CH_3), 13.9 (CH_3), 12.8 (CH_3); IR 2939, 1636, 1456, 1380 cm^{-1}. Anal. Calcd for $C_{17}H_{25}D_2NO$: C, 74.61; H, 11.10; N, 5.32; found: C, 74.60; H, 10.09; N, 5.39; R_f 0.3 (hexane/AcOEt 3/1).

4.3.8. 2,3-Dideuterio-*N*,*N*-diethyl-3-phenyl-2-methylpropanamide (3f). (Diastereoisomeric mixture); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.30–7.15 (m, 10H), 3.48–3.36 (m, 2H), 3.25–3.13 (m, 2H), 3.05 (q, J=7.18 Hz, 4H), 2.62 (s, 2H), 1.26 (s, 3H), 1.16 (s, 3H), 1.02 (t, J=7.18 Hz, 6H), 0.93 (t, J=7.18 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 175.0 (C), 140.6 (C), 140.1 (C), 129.0 (CH), 128.9 (CH), 128.1 (CH), 126.0 (CH), 125.7 (CH), 41.6 (CH_2), 40.3 (CH_2), 40.3 (t, J=19.8 Hz, CHD), 37.6 (t, J=19.8 Hz, CD), 18.0 (CH_3), 14.5 (CH_3), 12.9 (CH_3); MS (70 eV): m/z (%): 221 (36) $[M]^+$, 206 (22), 121 (19), 92 (100); IR 3062, 3026, 2971, 1636, 1379 cm^{-1}; HRMS Calcd for $C_{14}H_{19}D_2NO$ 221.1735; found 221.1749; R_f 0.3 (hexane/AcOEt 3/1).

4.4. General procedure for the synthesis of compounds 8

Over a solution of SmI_2 (1.1 mmol for di- or tetrasubstituted aromatic 2,3-epoxyamides **1** and 1.7 mmol for the rest) in THF (12 and 20 mL, respectively), a solution of the corresponding 2,3-epoxyamide **1** (0.4 mmol) in THF (4 mL) was added, under nitrogen atmosphere, at room temperature. After stirring for 30 min, the complete formation of **5** was checked by TLC. Then, when samarium diiodide remained, iodine pearls were added till colour changed from blue to yellow. The reaction mixture was cooled to −30 °C and 16 mL of dry THF, 2.4 mmol of samarium powder and 2.4 mmol of CH_2I_2 were added. After stirring at −30 °C during 10 h, the excess samarium diiodide was destroyed by oxidation with air, and the reaction was quenched with aqueous HCl (0.1 M, 10 mL). Usual workup afforded crude cyclopropanamides **8**, which were purified by short column flash chromatography over silica gel (hexane/ethyl acetate 3:1).

In the case of synthesis of **8b**,**c** or **8d**,**e**, HMPA (0.5 mL) or MeOH (0.4 mL) were used, respectively, as cosolvent to carry out the first step.[9,10] In the last case, previously to the addition of CH_2I_2 and Sm, solvents were eliminated to dryness.

In the obtention of **8a**, cyclopropanation took place at 0 °C, during 2 h and just with 1.4 mmol of samarium powder and 1.4 mmol of CH_2I_2.

4.4.1. (1*S,2*S**)-*N*,*N*-Diethyl-2-phenylcyclopropanocarboxamide (8a).** ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.31–7.10 (m, 5H), 3.44 (q, J=7.18 Hz, 2H), 3.43 (q, J=7.18 Hz, 2H), 2.49 (ddd, J=9.11, 5.98, 4.27 Hz, 1H), 1.93 (ddd, J= 8.25, 5.41, 4.27 Hz, 1H), 1.65 (ddd, J=9.11, 5.41, 3.99 Hz, 1H), 1.25 (ddd, J=8.25, 5.98, 3.99 Hz, 1H), 1.19 (t, J= 7.18 Hz, 3H), 1.14 (t, J=7.18 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.9 (C), 141.0 (C), 128.3 (CH), 126.0 (CH), 42.0 (CH_2), 40.8 (CH_2), 25.3 (CH), 23.1 (CH), 16.1 (CH_2), 14.8 (CH_3), 13.2 (CH_3); MS (70 eV): m/z (%): 217 (37) $[M]^+$, 145 (25), 117 (39), 72 (91), 42 (100); IR 3019, 2971, 1627, 1452, 1377 cm^{-1}; HRMS Calcd for $C_{14}H_{19}NO$ 217.1467; found 217.1495; R_f 0.3 (hexane/AcOEt 3/1).

4.4.2. (1*S,2*R**)-2-Cyclohexyl-*N*,*N*-diethyl-1-methylcyclopropanocarboxamide (8d).** ^{1}H NMR (400 MHz, [D_6]DMSO): δ=3.48 (q, J=7.05 Hz, 4H), 1.95–1.69 (m, 5H), 1.45–0.98 (m, 6H), 1.33 (s, 3H), 1.17 (t, J=7.05 Hz, 6H), 1.06 (dd, J=8.97, 4.20 Hz, 1H), 0.90 (dd, J=8.97, 4.77 Hz, 1H), 0.27 (dd, J=4.77, 4.20 Hz, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ=172.7 (C), 39.1 (CH_2), 36.9 (CH), 32.2 (CH_2), 27.8 (CH), 25.5 (CH_2), 25.3 (CH_2), 25.1 (CH_2), 24.5 (C), 16.9 (CH_2), 15.7 (CH_3), 12.6 (CH_3); MS (70 eV): m/z (%): 237 (10) $[M]^+$, 222 (5), 100 (25), 55 (52), 41 (100); IR 2981, 2924, 1627, 1429, 1379 cm^{-1}; HRMS Cald. for $C_{15}H_{27}NO$ 237.2093 found 237.2101; R_f 0.4 (hexane/AcOEt 3/1).

4.4.3. (1*S,2*S**)-*N*,*N*-Diethyl-2-heptyl-1-methylcyclopropanocarboxamide (8e).** ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.59–3.19 (m, 4H), 1.60–0.95 (m, 17H), 1.20 (s, 3H), 1.09 (t, J=7.12 Hz, 3H), 0.83 (t, J=6.55 Hz, 3H), 0.13 (dd, J=5.41, 4. 84 Hz, 1H); ^{13}C RMN (50 MHz, $CDCl_3$): δ= 174.5 (C), 40.8 (CH_2), 40.1 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 24.4 (C), 22.6 (CH_2), 22.3 (CH), 18.5 (CH_2), 16.4 (CH_3), 14.3 (CH_3), 14.0 (CH_3), 13.6 (CH_3); MS (70 eV): m/z (%): 253 (18) $[M]^+$, 238 (10), 154 (18), 100 (81), 41 (100); IR 2929, 1626, 1425, 1377 cm^{-1}; HRMS Calcd for $C_{16}H_{31}NO$ 253.2406; found 253.2406; R_f 0.4 (hexane/AcOEt 3/1).

4.4.4. (1*R,2*S**)-*N*,*N*-Diethyl-1-methyl-2-phenylcyclopropanocarboxamide (8f).** ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.28–7.03 (m, 5H), 3.48–3.33 (m, 2H), 2.96–2.87 (m, 1H), 2.74–2.87 (m, 1H), 2.16 (dd, J=5.6, 8.8 Hz, 1H), 2.10 (dd, J=6.5, 8.8 Hz, 1H), 1.73 (aparent t, J=6.0 Hz, 1H), 1.45 (s, 3H), 0.76 (t, J=7.1 Hz, 6H); ^{13}C RMN (75 MHz, $CDCl_3$): δ=170.5 (C), 138.6 (C), 127.9 (CH), 126.3 (CH), 125.8 (CH), 40.4 (CH_2), 38.2 (CH_2), 31.7 (CH), 31.5 (C), 23.3 (CH_3), 19.5 (CH_2), 13.2 (CH_3), 11.8 (CH_3); MS (70 eV): m/z (%): 231 (64) $[M]^+$, 216 (12), 202 (5), 158 (32), 144 (11), 140 (26), 131 (46), 115 (38), 100 (72), 91 (100), 72 (82); IR 3062, 2975, 2931, 2878, 1632, 1461,

1427, 1382, 1253, 1129, 1066 cm^{-1}; R_f (0.2 hexane/AcOEt 3/1).

4.4.5. (1*R,2*S**)-*N*,*N*-Diethyl-1-methyl-2-(4-methoxyphenyl)cyclopropanocarboxamide (8g).** ^1H NMR (300 MHz, $CDCl_3$): $\delta=6.97$–6.72 (m, 4H), 3.50 (s, 3H), 3.48–3.29 (m, 2H), 3.07–2.89 (m, 1H), 2.79–2.67 (m, 1H), 2.06–2.01 (m, 1H), 1.65 (aparent t, $J=6.0$ Hz, 1H), 1.42 (s, 3H), 1.01 (dd, $J=5.5$, 8.8 Hz, 1H), 0.86–0.76 (m, 6H); ^{13}C RMN (100 MHz, $CDCl_3$): $\delta=170.6$ (C), 157.7 (C), 130.6 (C), 127.2 (CH), 113.2 (CH), 55.0 (CH_3), 40.4 (CH_2), 38.1 (CH_2), 31.0 (C), 30.9 (CH), 23.2 (CH_3), 19.1 (CH_2), 13.2 (CH_3), 11.8 (CH_3); MS (70 eV): *m/z* (%): 261 (32) $[M]^+$, 192 (28), 188 (100), 174 (19), 161 (49), 145 (31), 134 (20), 121 (43), 115 (29), 100 (26), 91 (47), 72 (56); IR 3035, 2947, 2878, 2837, 1628, 1516, 1442, 1381, 1300, 1249, 1129, 1034 cm^{-1}; R_f (0. 28 hexane/AcOEt 1/1).

4.4.6. (1*S,2*R**)-*N*,*N*-Diethyl-2-ethyl-2-phenyl-1-methylcyclopropanocarboxamide (8h).** ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.45$–7.01 (m, 5H), 3.54–3.27 (m, 4H), 2.75–2.49 (m, 2H), 2.21 (d, $J=5.41$ Hz, 1H), 1.46 (s, 3H), 1.03 (t, $J=7.12$ Hz, 3H), 0.82 (t, $J=7.12$ Hz, 3H), 0.53 (d, $J=5.41$ Hz, 1H), 0.32 (t, $J=7.12$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=171.4$ (C), 138.8 (C), 127.6 (CH), 127.5 (CH), 125.7 (CH), 40.8 (CH_2), 37.9 (CH_2), 35.6 (C), 34.3 (C), 25.7 (CH_2), 22.9 (CH_2), 18.8 (CH_3), 13.5 (CH_3), 11.0 (CH_3), 10.8 (CH_3); MS (70 eV): *m/z* (%): 259 (25) $[M]^+$, 244 (12), 91 (91), 42 (100); IR 3058, 2968, 1628, 1450, 1381 cm^{-1}; HRMS Calcd for $C_{17}H_{25}NO$ 259.1936; found 259.1933; R_f 0.3 (hexane/AcOEt 3/1).

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Synthesis of chiral *ortho*-(*p*-tolylsulfinyl) benzyl ketones

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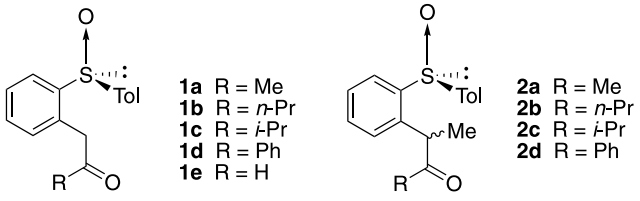
Dedicated to the late Dr. Martina Vicente for her valuable contribution to asymmetric organic synthesis

Abstract—(*S*)-*ortho*-(*p*-Tolylsulfinyl)benzyl alkyl (and aryl) ketones **1a–e** were prepared in good yields by reaction of esters or nitriles with the lithium benzyl carbanion derived from 2-(*p*-tolylsulfinyl) methylbenzene. α-Methylbenzyl ketones **2** were prepared as ca. 1:1 diastereoisomeric mixtures by methylation of the unsubstituted ketones **1** with NaH/MeI. The use of the ethylbenzene derivative as the starting material afforded complex mixtures. The obtention of pure (*S*,(S)*S*)-**2** diastereoisomers could be attained in good yields by oxidation with PCC of the alcohols (epimeric mixtures at the hydroxylic carbon) obtained from reactions of aldehydes with the lithium carbanion derived from 2-(*p*-tolylsulfinyl)ethylbenzene.

1. Introduction

The use of the sulfinyl group as a diastereo- and enantiocontrolling element in asymmetric synthesis has been profusely developed since 1980.[1] For reactions taking place on electrophilic or nucleophilic centers close to the chiral sulfur (1,2[2]- or 1,3-related[3–6]), numerous highly stereoselective methods have been reported. Much smaller is the number of reports concerning induction processes promoted by the sulfinyl group at remote positions (1,*n*-stereocontrol, with $n>3$). 1,4-Asymmetric induction on electrophilic centers are involved in the reductions[7] and other nucleophilic additions[8] to γ-ketosulfoxides. Recently we have demonstrated that the sulfinyl groups are also able to control the stereoselectivity of the additions of *ortho*-sulfinyl benzyllithium carbanions to different electrophiles.[9] These good results prompted us to evaluate the ability of the sulfinyl group to control 1,5-asymmetric induction processes, that, to our knowledge, lack of precedents in the literature. In this paper we describe different approaches to the synthesis of the optically pure *ortho*-(*p*-tolylsulfinyl)-benzyl alkyl (and aryl) ketones **1a–1d**, the *ortho*-(*p*-tolylsulfinyl)phenylacetaldehyde (**1e**), and their corresponding α-methyl derivatives (**2**) (Scheme 1). The use of these compounds as chiral electrophiles will be reported in due course.



Scheme 1.

2. Results and discussion

The synthesis of ketones **1a–d** was performed from (*S*)-2-methyl-1-(*p*-tolylsulfinyl)benzene (**3**)[9c,10] by deprotonation at −78 °C with lithium diisopropylamide (LDA) followed by reaction with different electrophiles. The use of 10 equiv of nitriles (method A, Table 1), allowed us to obtain good yields of ketones **1a** and **1d**. However the results obtained with *n*-Pr-CN and *i*-Pr-CN were unsuccessful (starting material was recovered). We tried to improve these results by using 1:1 mixtures of R-CN:$BF_3\cdot OEt_2$ as the electrophiles (method B, Table 1). Compounds **1b** (41%) and **1c** (31%) could be so obtained with 1.5 equiv of R-CN:$BF_3\cdot OEt_2$. A higher number of equivalents scarcely improved the yields.

Surprisingly, the reactions performed with esters as the electrophiles were more successful (method C, Table 1).

Keywords: Stereoselective ketone synthesis; Chiral benzyl ketones; Chiral benzyllithium.
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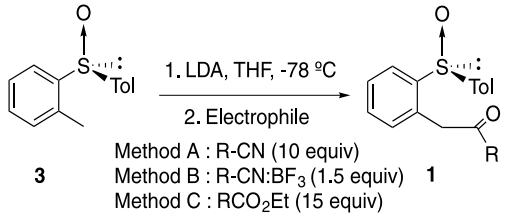
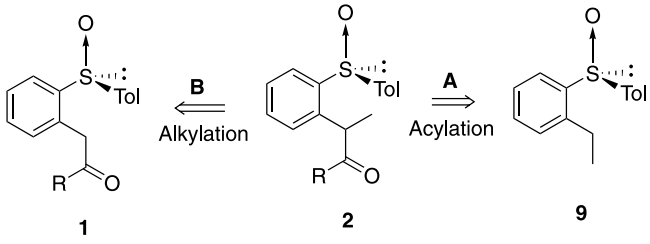
Table 1. Synthesis of *ortho*-(*p*-Tolylsulfinyl)benzyl ketones **1**



R	Compound	Isolated yield (%)		
		A	**B**	**C**
Me	**1a**	75	—	81
n-Pr	**1b**	0	41	81
i-Pr	**1c**	0	31	80
Ph	**1d**	87	—	—
H	**1e**	—	—	14

However, good yields could be obtained in all cases only by using a large excess of ester (15 equiv).

The synthesis of the aldehyde **1e** from ethyl formate (method C) was troublesome, mainly due to its unstability as well as its reactivity (it reacted with a second equivalent of the benzyl carbanion yielding a secondary alcohol). When the reaction was performed by addition of a highly diluted solution of the benzylic anion on a large excess of the ethyl formiate (40 equiv), the ^{1}H NMR spectrum of the reaction crude showed the formation of **1e** as the main product, but only a 14% yield could be isolated after chromatographic purification. By using DMF as the electrophile[11] the isolated yield of **1e** slightly increased (25%). Other formylation agents such as *N*-formylpiperidine,[12] or paraformaldehyde followed by oxidation,[13] were not successful. We prepared enantiomerically pure compound **1e** from *o*-bromobenzaldehyde **4**, following a Wittig based strategy (Scheme 2). The reaction of **4** with (methoxy)triphenylphosphoranylidenemethane yields **5** which evolves into the corresponding 2-*o*-bromophenylacetaldehyde dimethylacetal (**6**)[14] by reaction with methanol and *p*-toluenesulfonic acid. This compound could be easily transformed into the sulfinyl acetal **7** upon treatment with butyllithium and further

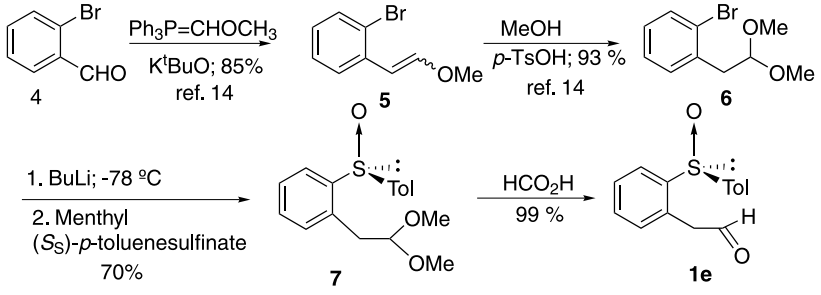


Scheme 3.

reaction with menthyl [(S)*S*]-*p*-toluenesulfinate. Hydrolysis of **7** with formic acid afforded the aldehyde **1e** in quantitative yield. Enantiomeric purity of **1e** (ee≥99%) was determined by chiral HPLC with a Chiralcel AD column.[†]

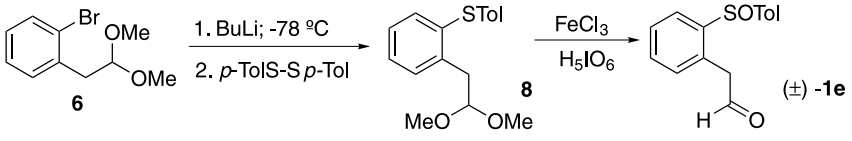
The synthesis of the sulfinylketones **2**, bearing a methyl group at the benzylic position, was tried by the two routes shown in Scheme 3, involving the acylation of 2-(*p*-tolylsulfinyl)ethylbenzene **9** (route A) and the alkylation of the ketones **1** previously obtained (route B), respectively.

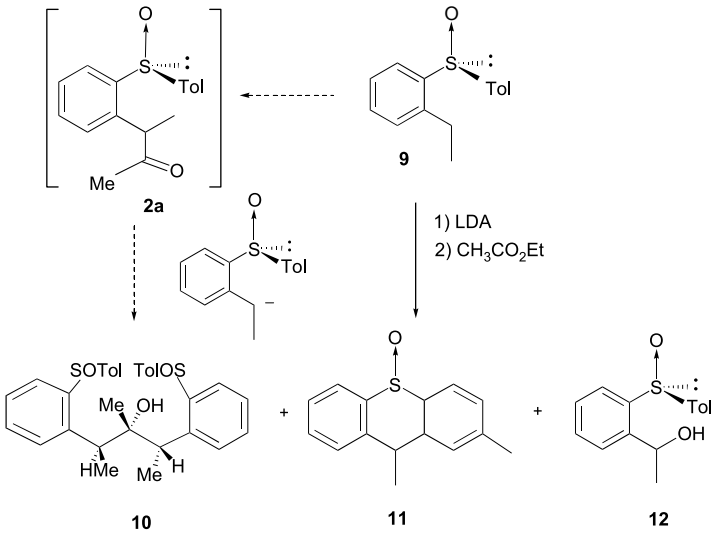
The reaction of compound **9** with LDA and subsequent addition of R-CO_2Et (R=Me, *n*-Pr, *i*-Pr, Ph) or R-CN (R=Me, COMe, Ph) did not afford the expected ketones **2** in good yields. A detailed study of the reaction with ethyl acetate was performed. Initially, we observed the formation of not easily reproducible complex mixtures, compounds **10**, **11** and **12** being their three main components (Scheme 4), in a ratio which was strongly dependent upon the experimental conditions. Significant amounts of the starting material **9**, and the desired ketone **2a** in a very low proportion, were also obtained in most of cases. After exhaustive experimental research we found out that compound **10**, resulting from a double addition of the anion to the ester, could be obtained in 68% yield, when neat ethyl acetate was quickly added into the preformed anion at −78 °C. It indicates that the difference of reactivity between **2a** and ethyl acetate is so large that it cannot be compensated with the excess of the latter. Remarkably, only one diastereoisomer was formed in these reactions, which



Scheme 2.

[†] Racemic **1e** was prepared by sulfenylation of lithium derivative obtained from **6**.





Scheme 4.

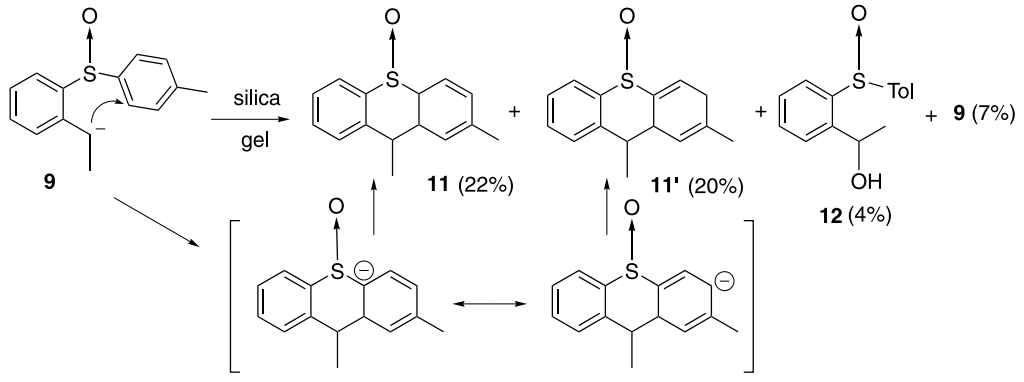
suggests that the anion derived from **9** reacts with both ethyl acetate and **2a** in a completely diastereoselective manner.[‡] On the other hand, the slow addition of the electrophile (solved in THF) into the lithium derivative gave mainly the unaltered starting material. It is worth mentioning the surprising change produced by the inverse addition of the reagents. In fact, when the anion derived from **9** was added into a solution containing ethyl acetate, compound **12** was the major component of the mixture (tertiary alcohol **10** was not detected), traces of compound **11**[¶] being also observed. However, the proportion of both compounds was not coincident in the different experiences which were performed and the reactions were not reproducible in our hands. It is worth mentioning that the alcohol **12** was always obtained as a sole diastereoisomer, and in some cases with a 62% isolated yield.

Then we tried to obtain the ketones **2** by alkylation of **1** (method B, Scheme 3). NaH was chosen as the base[§] because it had been reported to give the best results in the α-alkylation of β-ketosulfoxides.[3c] Deprotonation of ketosulfoxides **1** with NaH followed by reaction with MeI afforded ketosulfoxides **2** as an almost equimolecular mixture of epimers at the benzylic carbon (**A** and **B**, Table 2). In those experiences yielding a significant amount of dimethylderivative (entry 3) the A/B ratio became 1:3, thus suggesting that the second alkylation was easier for isomer **A** than for isomer **B**. The best conditions, optimized from ketosulfoxide **1a**, were achieved by using 1.7 equiv of base and 3.6 equiv of the electrophile at −40 °C (entry 2). Smaller amounts of the hydride (<1.4 equiv) gave low conversions (≤55%, entry 1), whereas more than 2 equiv of both reagents yielded a significant proportion of the bismethylated ketone (entry 3, Table 2).

Chromatographic separation of diastereoisomers **A** and **B**, obtained from the methylation with methyl iodide, is not an easy task. It was unsuccessful in our hands except for the

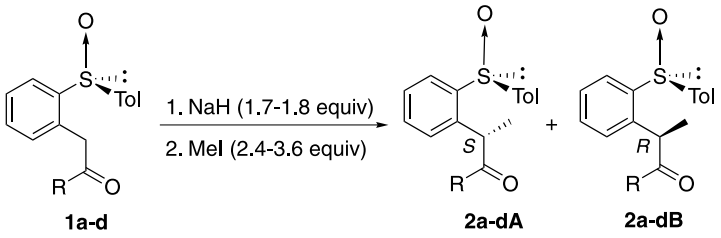
[‡] The fact that reactions from compound **3**, under similar conditions, only evolved into ketones **1** instead of producing alcohols such as **10**, could be due to the immediate enolization of **1**, once formed from **3**. The lower stability of the enolates derived from **2**, containing a tetrasubstituted double bond, could account for their more difficult enolization.

[¶] The formation of compound **11** can be explained by the intramolecular attack of the benzylic carbanion to the sulfinylated ring and subsequent protonation of the resulting anion. The electronic transfer from the carbanion to produce an anion-radical on the tolyl ring cannot be discarded. With the aim of verifying that the formation of compound **11** does not require the electrophile participation, we directly dropped the lithium derivative of **9** (formed, as usually, with LDA at –78 °C during 1 h) over a preparative TLC of silica gel, and left to dry overnight. Under these conditions a mixture of compounds **11** and **11′** were obtained as the major products.



[§] The use of LDA did not improve the results.

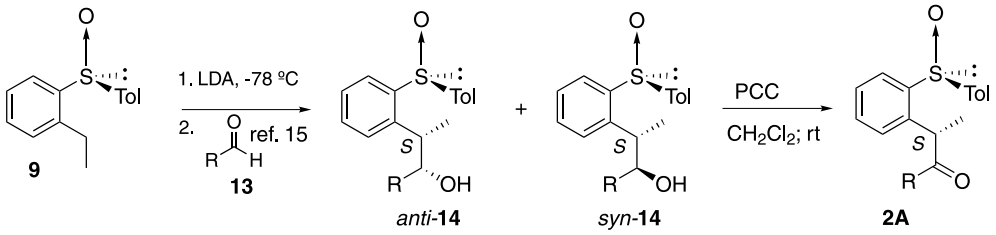
Table 2. Synthesis of γ-methyl δ-ketosulfoxide **2a–d** by alkylation of **1**



Entry	NaH (equiv)/CH_3I (equiv)	Ketone (R)	A:B ratio[a]	Conversion (yield %)
1	1.4/2.4	**2a** (CH_3)	46:54	55
2	1.7/3.6	**2a** (CH_3)	47:53	100 (78)
3	2.2/2.4	**2a** (CH_3)	29:71	100 (37)[b]
4	1.8/2.4	**2b** (*n*-Pr)	47:53	100 (67)
5	1.8/3.6	**2c** (*i*-Pr)	44:56	100 (87)
6	1.8/3.6	**2d** (Ph)	59:41	100 (77)

[a] Established from the ^1H NMR spectra of the reaction crudes.
[b] α,α′-Dimethyl ketone was obtained as the major product (53%).

Table 3. Synthesis of γ-methyl δ-ketosulfoxide **2A** by PCC oxidation of *syn*+*anti* mixtures of γ-methyl δ-hydroxysulfoxides **14**



Entry	Aldehyde (R)	*anti*-**14**: *syn*-**14**[a]	PCC (equiv)	Time (h)	Ketone (yield %)
1	**13d** (Ph)	85:15	1.5	5	**2dA** (65)
2	**13f** (*n*-Bu)	37:63	2.0	21	**2fA** (74)
3	**13g** (*t*-Bu)	24:76	2.0	21	**2gA** (73)
4	**13h** (*p*-$OMeC_6H_4$)	84:16	1.5	6	**2hA** (74)
5	**13i** (2,6-diMeC_6H_3)	67:33	1.5	7	**2iA** (71)

[a] Data taken from Ref. 15.

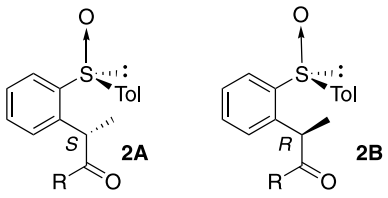
epimers **2aA** and **2aB** (R=Me), that were obtained diastereomerically pure by using a hexane:ethyl acetate 2:1 mixture as the eluent, **2aA** being the isomer with higher R_f. Configurational assignment of the epimers **A** and **B** based on of their NMR parameters proved to be difficult.

Taking into account the above-mentioned difficulties to obtain diastereomerically pure compounds **2b–d**, we decided to exploit the reported high stereoselectivity at the benzylic position of the reactions of the lithium carbanion derived from **9** with aldehydes.[15] As these reactions afforded alcohols **14** as epimeric mixtures at the hydroxylic carbon, both with the same *S* configuration at the benzylic carbon, the oxidation of their hydroxylic groups would yield enantiomerically pure ketones **2** of known configuration. As expected, the use of pyridinium chlorochromate (PCC) at room temperature in dichloromethane afforded the desired diastereomerically pure ketones **2** in excellent yields (Table 3).

The resulting ketones exhibit the *S* configuration at the benzylic carbon.[15]In the case of **2d**, its spectroscopic ^1H NMR parameters are those corresponding to the diastereoisomers denoted as **A** in the mixture obtained by methylation of **1d**, which differ significantly from those of the epimer **B** only in the chemical shift of the methyl group (see Table 4). On this base, the configurational assignments

Table 4. Significant ^1H NMR parameters for the configurational assignment of γ-methyl δ-ketosulfoxides **2**

Compound	R	δ (H_2)	δ (CH_3)
2aA	CH_3	4.25	1.11
2aB	CH_3	4.14	0.94
2bA	*n*-Pr	4.13	1.13
2bB	*n*-Pr	4.13	0.94
2cA	*i*-Pr	4.37	1.10
2cB	*i*-Pr	4.29	0.90
2dA	Ph	5.14	1.41
2dB	Ph	5.05	1.07
2fA	*n*-Bu	4.21	1.21
2gA	*t*-Bu	4.84	1.22
2hA	(*p*-OMe)C_6H_4	5.08	1.37
2iA	(2,6-diMe)C_6H_3	5.16	1.64



Scheme 5.

of the compounds **2aA**, **2aB**; **2bA**, **2bB** and **2cA**, **2cB** (as a mixture) could be made unambiguously (Scheme 5).

In summary we have described the synthesis of the δ-ketosulfoxides **1** and **2** in optically pure form, as well as the problems related to some of the involved reactions. The use of these compounds as chiral electrophiles and nucleophiles under different conditions will be reported at a later date.

3. Experimental

3.1. General

NMR spectra were obtained in a Bruker spectrometer (300 and 75 MHz for ^{1}H and ^{13}C, respectively) in $CDCl_3$ solutions. Melting points were measured using a Gallemkamp apparatus in open capillary tubes. Mass spectra (MS) were determined by FAB$^+$, APCI or EI (70 eV). Specific rotations were measured in a Perkin–Elmer 241 MC polarimeter. De's were evaluated by integration of well-separated signals of the NMR spectra. All reactions were carried out in anhydrous solvents under argon atmosfere. THF and diethyl ether were distilled from sodium-benzofenone under argon. CH_2Cl_2 was distilled from P_2O_5. Flash column chromatography was perfomed using silica gel Merck-60 (230–400 mesh).

3.2. Synthesis of δ-ketosulfoxides

Method A. By reaction of (S)-1-methyl-2-(p-tolylsulfinyl)-benzene with RCN. A solution of *n*-BuLi (5.19 mmol, 2.5 M in hexanes) was added into a solution of *i*-Pr_2NH (7.70 mmol) in THF (26.0 mL) at 0 °C. After stirring for 30 min, the mixture was cooled at −78 °C and a solution of the sulfoxide **3** (4.34 mmol) in THF (17.3 mL) was then added. The mixture was stirred at the same temperature for 1 h, before adding the corresponding nitrile (43.40 mmol) at −78 °C. The reaction mixture was stirred for 30 min, quenched (5% aqueous HCl solution, 30 mL) and stirred for 12 h. The crude product was extracted with CH_2Cl_2 (3× 40 mL), dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by flash chromatography (the eluent was indicated in each case).

Method B. By reaction of (S)-1-methyl-2-(p-tolylsulfinyl)-benzene with RCN-BF_3. A solution of *n*-BuLi (5.19 mmol, 2.5 M in hexanes) was added into a solution of *i*-Pr_2NH (7.70 mmol) in THF (26.0 mL) at 0 °C. After stirring for 30 min, the mixture was cooled at −78 °C and a solution of the sulfoxide **3** (4.34 mmol) in THF (17.3 mL) was then added. The reaction mixture was stirred at the same temperature for 1 h, before adding a mixture, previously stirred (1 h) at −78 °C, of the corresponding nitrile (12.90 mmol) and boron trifluoride etherate (13.00 mmol) in CH_2Cl_2 over the carbanion. The reaction mixture was stirred for 30 min. The work up to extract the crude was performed as in method A.

Method C. By reaction of (S)-1-methyl-2-(p-tolylsulfinyl)-benzene with RCO_2Et. A solution of *n*-BuLi (5.19 mmol, 2.5 M in hexane) was added into a solution of *i*-Pr_2NH (7.70 mmol) in THF (26.0 mL) at 0 °C. After stirring for 30 min, the mixture was cooled at −78 °C. A solution of the sulfoxide **3** (4.34 mmol) in THF (17.3 mL) was then added. The reaction flask was stirred at the same temperature for 1 h, before adding the corresponding carbanion over the ester (65.1 mmol) at −78 °C. The reaction flask was maintained 30 min under stirring before quenching with saturated aqueous NH_4Cl. The crude ketone was extracted with CH_2Cl_2 (3×40 mL), the extracts dried ($MgSO_4$), and the solvent evaporated. The residue was purified by flash chromatography (the eluent was indicated in each case).

3.2.1. (*S*)-1-[2-(*p*-Tolylsulfinyl)phenyl)propan-2-one (1a). It was prepared following method C. Eluent: hexane–ethyl acetate 1:1. Yield: 81%; white solid; mp: 77–79 °C (diethyl ether); $[\alpha]_D^{20}=-9.6$ (*c* 1.1, $CHCl_3$); IR (NaCl): 2922, 1722, 1473, 1034 cm^{-1}; ^{1}H NMR: δ 7.77 (m, 1H), 7.55–7.40 (m, 5H), 7.24 (d, $J=8.0$ Hz, 1H), 7.15 (m, 1H), 4.04 and 3.89 (AB system, $J=17.3$ Hz, 2H), 2.34 (s, 3H), 2.11 (s, 3H); ^{13}C NMR: δ 204.5, 143.8, 141.5, 140.9, 133.2, 131.7, 131.5, 130.0, 128.5, 126.7, 125.7, 46.5, 29.6, 21.3; MS (EI$^+$) *m/z*: 273 (M$^+$); HRMS [M$^+$]: calcd for $C_{16}H_{16}O_2S$: 273.0871; found, 273.0949.

3.2.2. (*S*)-1-[2-(*p*-Tolylsulfinyl)phenyl]pentan-2-one (1b). It was prepared following method C. Eluent: hexane–ethyl acetate 2:1. Yield: 81%; white solid; mp: 40–41 °C; $[\alpha]_D^{20}=-97.6$ (*c* 0.5, $CHCl_3$); IR (KBr): 2969, 1703, 1409, 1034 cm^{-1}; ^{1}H NMR: δ 7.78–7.69 (m, 1H), 7.47–7.33 (m, 4H), 7.25–7.10 (m, 3H), 3.97 and 3.84 (AB system, $J=17.2$ Hz, 1H), 2.35–2.26 (m, 2H), 2.31 (s, 3H), 1.52 (s, $J=7.5$ Hz, 2H), 0.82 (t, $J=7.5$ Hz, 3H); ^{13}C NMR: δ 206.4, 143.6, 141.3, 140.8, 133.1, 131.4, 131.2, 129.7, 128.2, 126.3, 125.5, 45.5, 44.1, 21.1, 16.8, 13.4; MS (FAB) *m/z*: 301 [M+1]$^+$; HRMS [M+1]$^+$: calcd for $C_{18}H_{21}O_2S$: 301.1184; found, 301.1255. Anal. calcd for $C_{18}H_{20}O_2S$: C, 71.96; H, 6.71; S, 10.67. Found: C, 71.73; H, 6.69; S, 10.51.

3.2.3. (*S*)-3-Methyl-1-[2-(*p*-tolylsulfinyl)phenyl]butan-2-one (1c). It was prepared following method C. Eluent: hexane–ethyl acetate 2:1. Yield: 80%; white solid; mp: 46–47 °C; $[\alpha]_D^{20}=-98.3$ (*c* 1.0, $CHCl_3$); IR (NaCl): 2962, 1715, 1083, 1035 cm^{-1}; ^{1}H NMR: δ 7.70–7.67 (m, 1H), 7.48–7.37 (m, 4H), 7.24–7.21 (m, 2H), 7.40–7.11 (m, 1H), 4.11 and 3.94 (AB system, $J=17.3$ Hz, 1H), 2.66 (sp, $J=$ 6.8 Hz, 1H), 2.33 (s, 3H), 1.09 (d, 6H); ^{13}C NMR: δ 210.2, 143.8, 141.2, 140.8, 133.5, 131.4, 131.3, 129.7, 128.3, 126.5, 125.5, 43.4, 40.6, 21.2, 18.2, 18.1; MS (FAB) *m/z*: 301 (M+1)$^+$; HRMS (M+1)$^+$: calcd for $C_{18}H_{21}O_2S$: 301.1184; found, 301.1274. Anal. calcd for $C_{18}H_{20}O_2S$: C, 71.96; H, 6.71; S, 10.67. Found: C, 71.82; H, 6.68; S, 10.65.

3.2.4. (*S*)-1-Phenyl-2-[2-(*p*-tolylsulfinyl)phenyl]ethan-1-one (1d). It was prepared following method A. Eluent: hexane–ethyl acetate 2:1. Yield: 87%; white solid; mp:

106–108 °C; $[\alpha]_D^{20}=-120.2$ (*c* 1.0, $CHCl_3$); IR (KBr): 3424, 1686, 1323, 1077 cm^{-1}; ^1H NMR: δ 7.91–7.88 (m, 2H), 7.82–7.29 (m, 1H), 7.57–7.53 (m, 1H), 7.45–7.38 (m, 6H), 7.20–7.11 (m, 3H), 4.58 and 4.48 (AB system, $J=16.9$ Hz, 2H), 2.29 (s, 3H); ^{13}C NMR: δ 195.7, 143.6, 141.1, 140.6, 135.9, 133.5, 133.2, 131.6, 131.2, 129.7, 128.4, 128.2, 128.0, 126.5, 125.5, 41.3, 21.1; MS (FAB) *m/z*: 335 $[M+1]^+$; HRMS $[M+1]^+$: calcd for $C_{21}H_{19}O_2S$: 335.1027; found, 335.1103. Anal. calcd for $C_{21}H_{18}O_2S$: C, 75.42; H, 5.42; S, 9.59. Found: C, 75.29; H, 5.49; S, 9.47.

3.3. Synthesis of sulfinyl aldehyde 1e

3.3.1. (*S*)-1-(2,2-Dimethoxyethyl)-2-(*p*-tolylsulfinyl)benzene (7). A solution of bromide **6** (0.40 mmol) in THF (0.4 mL) at −78 °C was added into a solution of *n*-BuLi (0.40 mmol, 2.5 M in hexane), and the reaction flask was stirred for 45 min at the same temperature before the addition over a solution of (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (0.34 mmol) in THF (0.2 mL) at −78 °C. The reaction mixture was stirred for 6 h at −78 °C until completion, and then it was hydrolyzed with a saturated aqueous NH_4Cl solution (0.5 mL), extracted with CH_2Cl_2 (3×0.5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by flash chromatography with hexane–ethyl acetate 1:1 as the eluent. Yield: 70%; yellow oil; $[\alpha]_D^{20}=-31.8$ (*c* 3.2, $CHCl_3$); IR (NaCl): 2956, 2934, 1439, 1118 cm^{-1}; ^1H NMR: δ 7.82–7.79 (m, 1H), 7.44–7.15 (m, 7H), 4.34–4.30 (m, 1H), 3.24 (s, 3H), 3.20 (s, 3H), 3.08–2.95 (m, 2H), 2.27 (s, 3H); ^{13}C NMR: δ 143.6, 141.5, 141.2, 134.9, 130.8, 130.7, 129.6, 127.6, 125.6, 125.0, 104.1, 53.7, 53.3, 35.3, 21.0; MS (FAB) *m/z*: 273 $[(M+1)-MeOH]^+$.

3.3.2. (*S*)-2-[2-(*p*-Tolylsulfinyl)phenyl]acetaldehyde (1e). A solution of the acetal **7** (0.83 mmol) in formic acid (41.57 mmol) was stirred for 1 h at room temperature. Then, the mixture was diluted with dichloromethane, washed ($NaHCO_3$ saturated aqueous solution) and the solvents evaporated under reduced pressure. The residue was purified by flash chromatography using as the eluent hexane–ethyl acetate 2:1. Enantiomeric purity (ee≥99%) was determined by HPLC (Chiralcel AD column) with 70:30 hexane–isopropanol as the eluent (1 mL min^{-1}, 35 °C; (*S*): $t_R=6.1$; (*R*): $t_R=6.8$(. Yield: 99%; yellow oil; $[\alpha]_D^{20}=-21.0$ (*c* 0.5, $CHCl_3$); IR (NaCl): 3331, 2924, 1723 cm^{-1}; ^1H NMR: δ 9.46 (t, $J=1.6$ Hz, 1H), 7.88–7.83 (m, 1H), 7.47–7.39 (m, 4H), 7.22–7.13 (m, 3H), 3.91 (dd, $J=17.3$ Hz, 1.6 Hz, 1H) 3.82 (dd, 1H). 2.30 (s, 3H); ^{13}C NMR: δ 197.2, 143.6, 141.6, 140.4, 131.7, 131.4, 130.9, 129.9, 128.5, 126.3, 125.5, 46.0, 21.1; MS (FAB) *m/z*: 259 $(M+1)^+$; HRMS $(M+1)^+$: calcd for $C_{15}H_{15}O_2S$: 259.0715; found, 259.0802.

3.4. Protocol for obtaining dimeric sulfoxide 10

3.4.1. ((S)*S*,2*S*,4*S*)-2,4-Bis-[2-(*p*-tolylsufinyl)phenyl]-3-methylpentan-3-ol (10). To a solution of *n*-BuLi (5.19 mmol, 2.5 M in hexane) was added *i*-Pr_2NH (7.70 mmol) in THF (5.0 mL) at 0 °C. After stirring for 30 min, the mixture was cooled at −78 °C. A solution of the sulfoxide **9** (4.34 mmol) in THF (5.0 mL) was then added, and the mixture was stirred for 1 h. Ethyl acetate (65.1 mmol) was added quickly at −78 °C over the purple lithium derivative of compound **9**. The reaction flask was stirred for 30 min. The reaction was quenched (saturated NH_4Cl), extracted with diethyl ether (3×20 mL), dried ($MgSO_4$), and the solvent was evaporated to yield a crude mixture of compounds **10** and **2aA** (^1H NMR). The residue was purified by flash chromatography (hexane–ethyl acetate 1:3) to afford pure compound **10**. Yield: 68%; colorless oil; $[\alpha]_D^{20}=+31.9$ (*c* 0.2, CH_3COCH_3); IR (NaCl): 3329, 1592, 1492, 810 cm^{-1}; ^1H NMR: δ 8.02 (dd, $J=7.9$, 1.4 Hz, 1H), 7.73 (dd, $J=7.6$, 1.4 Hz, 2H), 7.51 (m, 13H), 5.18 (bs, 1H), 3.72 (q, $J=7.1$ Hz, 1H), 3.52 (q, $J=7.1$ Hz, 1H), 2.40 (s, 6H), 1.19 (d, $J=7.1$ Hz, 3H), 0.77 (d, $J=7.1$ Hz, 3H), 0.47 (s, 3H); ^{13}C NMR: δ 145.7, 145.5, 142.4, 142.1, 141.6, 141.3, 141.2, 140.5, 132.2, 132.1, 131.4, 130.8, 130.4, 129.8, 126.9, 126.4, 126.3, 126.2, 125.4, 124.3, 75.9, 40.1, 39.7, 21.4, 21.2, 19.9, 16.5, 15.9. Anal. calcd for $C_{32}H_{34}O_3S_2$: C, 72.42; H, 6.46; S, 12.08. Found: C, 72.48; H, 6.50; S, 12.10.

3.5. Protocols for the synthesis of ketones 2

Method A. General procedure for methylation of ketones **1**. A solution (0.26 M in THF) of δ-ketosulfoxides **1a–d** was added into a stirred suspension of NaH (1.7 or 1.8 equiv, free of paraffin) in THF (2 mL) at room temperature. After stirring for 1 h, the mixture was cooled at −40 °C and methyl iodide (3.6 or 2.4 equiv) was injected under stirring at the same temperature (see Table 2 in the text for proportions). Then, an aqueous saturated solution of NH_4Cl was added, and the mixture was left under stirring to reach room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried ($MgSO_4$) and the solvent evaporated. The residue was purified by flash chromatography (the eluent was indicated in each case).

Method B. General procedure for oxidation of alcohols **14**. The epimeric mixture of alcohols **14**, obtained following the previously described procedure,[15] was solved in dry CH_2Cl_2 and PCC was added (1.5 or 2.0 equiv for aromatic or aliphatic derivatives, respectively). The mixture was stirred at room temperature (see reaction times in Table 3) and then the solvent was partially evaporated and the residue was chromatographied.

3.5.1. [3*S*,(S)*S*] and [3*R*,(S)*S*]-3-[2-(*p*-Tolylsulfinyl)-phenyl]butan-2-one (2aA) and (2aB). They were obtained as a 47:53 epimeric mixture by methylation of ketone **1a** and separated by flash chromatography (hexane–ethyl acetate 3:1).

Compound [3*S*,(S)*S*]-(**2aA**). It was obtained as a white solid. Yield: 26%; mp: 87–90 °C; $[\alpha]_D^{20}=+103$ (*c* 0.8, $CHCl_3$); ^1H NMR: δ 7.90 (m, 1H), 7.45–7.37 (AA'BB' system, 4H), 7.19 (m, 2H), 7.05 (m, 1H), 4.25 (q, 1H, $J=6.9$ Hz, CH_3CH), 2.31 (s, 3H, CH_3Ar), 1.63 (s, 3H, CH_3CO), 1.12 (d, $J=6.9$ Hz, 3H, CH_3CH); ^{13}C NMR: δ 207.5, 142.7, 142.1, 141.3, 139.6, 131.9, 130.1, 128.5, 128.1, 126.9, 126.1, 47.6, 28.4, 21.3, 17.5; MS (APCI$^+$) *m/z*: 287.1 $[M+1]^+$; HRMS: calcd for $C_{17}H_{19}O_2S$: 287.1100. Found: 287.1114.

Compound [3*R*,(S)*S*]-(**2aB**). It was obtained as a colorless oil. Yield: 53%; $[\alpha]_D^{20}=-248$ (*c* 3.9, $CHCl_3$); ^1H NMR: δ 7.95 (dd, $J=7.7$, 1.6 Hz, 1H), 7.45–7.35 (m, 4H), 7.19 (d, $J=7.7$ Hz, 2H), 7.06–7.02 (m, 1H), 4.14 (q, 1H, $J=6.7$ Hz, CH_3CH), 2.30 (s, 3H, CH_3Ar), 1.92 (s, 3H, CH_3CO), 0.94 (d, 3H, $J=6.7$ Hz, CH_3CH); ^{13}C NMR: δ 206.7, 142.6, 141.9, 141.2, 138.7, 131.6, 130.0, 128.2, 127.8, 126.0, 125.6, 47.4, 28.3, 21.2, 16.5; MS ($APCI^+$) *m/z*: 287.1 $[M+1]^+$. Anal. calcd for $C_{17}H_{18}O_2S$: C, 71.30; H, 6.34; S, 11.20. Found: C, 71.38; H, 6.35; S, 10.70.

3.5.2. [2*S*,(S)*S*] and [2*R*,(S)*S*]-2-[2-(*p*-Tolylsulfinyl)-phenyl]hexan-3-one (2bA) and (2bB). They were obtained as a 47:53 epimeric mixture by methylation from ketone **1b**. Chromatographic purification (hexane–ethyl acetate 3:1) afforded the mixture of **2bA** and **2bB** as a yellow oil. Overall yield: 67%; ^1H NMR: δ 7.97–7.92 (m, 2H), 7.43–7.33 (m, 8H), 7.21–7.18 (m, 4H),7.06–7.03 (m, 2H), 4.13 (q, $J=6.8$ Hz, 2H, CH_3CH), 2.29 (s, 6H, CH_3Ar), 2.19–2.16 (m, 2H, CH_2–CO), 1.73–1.67 (m, 2H, CH_2CO), 1.47–1.33 (m, 2H, CH_2CH_2CO), 1.29–1.18 (m, 2H, CH_2CH_2CO), 1.13 (d, $J=6.9$ Hz, 3H, CH_3CHCO, **A**), 0.94 (d, $J=6.7$ Hz, 3H, CH_3CHCO, **B**), 0.69 (t, $J=7.5$ Hz, 3H, CH_3CH_2, **B**), 0.55 (t, $J=7.3$ Hz, 3H, CH_3CH_2, **A**); ^{13}C NMR: δ 209.5, 209.0, 142.2, 142.0, 141.9, 141.5, 141.4, 139.5, 138.9, 131.7, 131.6, 130.1, 130.0, 128.3, 128.2, 128.0, 127.9, 126.4, 126.3, 126.0, 125.6, 46.8, 43.3, 42.9, 21.3, 17.7, 17.1, 16.9, 16.8, 13.4, 13.3; MS ($APCI^+$) *m/z*: 315.1 $[M+1]^+$. Anal. calcd for $C_{19}H_{22}O_2S$: C, 72.57; H, 7.05; S, 10.20. Found: C, 72.07; H, 7.03; S, 10.04.

3.5.3. [4*S*,(S)*S*] and [4*R*,(S)*S*]-2-Methyl-4-[2-(*p*-tolylsulfinyl)phenyl]pentan-3-one (2cA) and (2cB). They were obtained as a 44:56 epimeric mixture by methylation of ketone **1c**. Chromatographic purification (hexane–ethyl acetate 2:1) afforded a mixture of **2cA** and **2cB** as a yellow oil. Overall yield: 87%; ^1H NMR: δ 7.97–7.86 (m, 2H), 7.44–7.34 (m, 8H), 7.22–7.19 (m, 4H), 7.08–7.03 (m, 2H), 4.37 (q, 1H, $J=6.7$ Hz, CH_3CH, **A**), 4.29 (q, $J=6.9$ Hz, 1H, CH_3CH, **B**), 2.51 (s, $J=7.1$ Hz, 1H, $CH(CH_3)_2$, **B**), 2.31 (s, 3H, CH_3Ar, A), 2.30 (s, 3H, CH_3Ar, B), 2.07 (s, $J=7.1$ Hz, 1H, $CH(CH_3)_2$, A), 1.10 (d, $J=6.7$ Hz, 3H, CH_3CH, **A**), 1.03 (d, $J=7.1$ Hz, 3H, $(CH_3)_2CH$, **A**), 0.90 (d, $J=6.9$ Hz, 3H, CH_3CH, **B**), 0.81 (d, $J=7.1$ Hz, 3H, $(CH_3)_2CH$, **A**), 0.76 (d, $J=7.1$ Hz, 3H, $(CH_3)_2CH$, **B**), 0.69 (d, $J=7.1$ Hz, 3H, $(CH_3)_2CH$, **B**); ^{13}C NMR: δ 209.6, 209.1, 142.3, 142.1, 141.9, 141.5, 139.6, 138.9, 131.8, 131.6, 130.1, 128.4, 128.2, 128.1, 127.9, 125.7, 46.9, 43.4, 42.9, 21.4, 21.3, 17.8, 17.2, 16.9, 16.8, 13.5, 13.4; MS ($APCI^+$) *m/z*: 315.1 $[M+1]^+$; HRMS $[M+1]^+$: calcd for $C_{19}H_{23}O_2S$: 315.1413. Found: 315.1419.

3.5.4. [2*S*,(S)*S*] and [2*R*,(S)*S*]-1-Phenyl-2-[2-(*p*-tolylsulfinyl)phenyl]propan-1-one (2dA) and (2dB). They were obtained as a 59:41 epimeric mixture by methylation of ketone **1d**. Chromatographic purification (hexane–ethyl acetate 1:1) afforded a mixture of **2dA** and **2dB** as a colorless oil. Overall yield: 77%.

Compound [2*S*,(S)*S*]-(**2dA**). Obtained by oxidation from a 85:15 mixture of *anti*- and *syn*-**14d**. Reaction time: 5 h. Eluent for chromatography: hexane–ethyl acetate 1:1. Yield: 65%. $[\alpha]_D^{20}$: +236.1 (*c* 1, $CHCl_3$); IR: 3058, 2979, 1683, 1499, 1180, 1083, 1032 cm^{-1}; ^1H NMR: δ 7.94 (m, 1H), 7.58 (m, 2H), 7.46–7.34 (m, 5H), 7.21–7.16 (m, 5H), 5.14 (q, $J=6.9$ Hz, 1H, CH_3CH), 2.35 (s, 3H, CH_3Ar), 1.41 (d, $J=6.9$ Hz, 3H, CH_3CH); ^{13}C NMR: δ 199.6, 141.8, 141.5, 140.8, 140.1, 135.8, 132.8, 131.8, 130.0, 128.7, 128.5, 128.3, 127.9, 126.5, 126.4, 42.6, 21.3, 18.9. MS (EI^+) *m/z*: 348 (M^+, 16), 243 (43), 225 (76), 135 (39), 105 (100), 91 (36), 77 (93); HRMS: calcd for $C_{22}H_{20}O_2S$: 348.1184. Found: 348.1184.

Compound [2*R*,(S)*S*]-(**2dB**) *from a mixture of* **A**+**B**, *obtained following method A*; ^1H NMR: δ 8.03 (dd, $J=7.7$, 1.6 Hz, 1H), 7.60–7.33 (m, 8H), 7.27–7.17 (m, 5H), 5.05, (q, $J=6.6$ Hz, 1H, CH_3CH), 2.34 (s, 3H, CH_3Ar), 1.07 (d, $J=6.6$ Hz, 3H, CH_3CH); ^{13}C NMR: δ 189.9, 142.3, 141.9, 141.2, 139.4, 135.7, 133.1, 131.6, 130.9, 130.2, 128.2, 128.1, 126.6, 126.2, 125.6, 42.4, 21.4, 18.4; MS ($APCI^+$) *m/z*: 349.0 $[M+1]^+$. Anal. calcd for $C_{22}H_{20}O_2S$: C, 75.83; H, 5.79; S, 9.20. Found: C, 75.54; H, 5.96; S, 8.95.

3.5.5. [2*S*,(S)*S*]-2-[2-(*p*-Tolylsulfinyl)phenyl]heptan-3-one (2fA). Obtained by oxidation of a 37:63 mixture of *anti*- and *syn*-**14f**. Reaction time: 21 h. Eluent for chromatography: hexane–ethyl acetate 3:2. Yield: 74%. $[\alpha]_D^{20}$: +152.5 (*c* 1, $CHCl_3$); IR: 2930, 1714, 1468, 1083, 1033 cm^{-1}; ^1H NMR: δ 8.00 (m, 1H), 7.51–7.42 (m, 2H), 7.47 and 7.27 (AA'BB' system, 4H), 7.12 (m, 1H), 4.21 (q, $J=6.9$ Hz, 1H, CH_3CH), 2.37 (s, 3H, CH_3Ar), 1.80 (m, 2H, $COCH_2$), 1.33–1.18 (m, 2H, $CH_2CH_2CH_2$), 1.21 (d, $J=6.9$ Hz, 3H, CH_3CH), 1.06–0.93 (m, 2H, CH_2CH_3), 0.72 (t, $J=7.3$ Hz, 3H, CH_3CH_2); ^{13}C NMR: δ 209.6, 142.2, 142.0, 141.5, 139.5, 131.7, 130.1, 128.3, 127.9, 126.4, 126.3, 46.9, 40.7, 25.5, 21.9, 21.3, 17.8, 13.6; MS (EI^+) *m/z*: 328 (M^+, 15), 243 (33), 225 (100), 211 (52), 151 (44), 135 (94), 91 (54), 77 (27); HRMS: calcd for $C_{20}H_{24}O_2S$: 328.1496. Found: 328.1497.

3.5.6. [4*S*,(S)*S*]-2,2′-Dimethyl-4-[2-(*p*-tolylsulfinyl)-phenyl]pentan-3-one (2gA). Obtained by oxidation from a 24:76 mixture of *anti*- and *syn*-**14g**. Reaction time: 21 h. Eluent for chromatography: hexane–ethyl acetate 3:2. Yield: 73%. $[\alpha]_D^{20}$: +75.1 (*c* 1, $CHCl_3$); IR: 2970, 1703, 1470, 1084, 1054 cm^{-1}; ^1H NMR: δ 7.83 (m, 1H), 7.52 (m, 2H), 7.45–7.30 (m, 5H), 4.84 (q, $J=6.9$ Hz, 1H, CH_3CH), 2.41 (s, 3H, CH_3Ar), 1.22 (d, $J=6.9$ Hz, 3H, CH_3CH), 0.93 (s, 9H, $(CH_3)_3$); ^{13}C NMR: δ 215.8, 141.8, 141.3, 140.7, 140.6, 131.8, 130.0, 128.0, 127.7, 127.3, 126.1, 45.0, 40.6, 26.2, 21.3, 20.5; MS (EI^+) *m/z*: 328 (M^+, 10), 243 (31), 225 (100), 211 (31), 151 (23), 135 (69), 91 (44), 77 (22); HRMS: calcd for $C_{20}H_{24}O_2S$: 328.1500. Found: 328.1497.

3.5.7. [1*S*,(S)*S*]-1-(*p*-Methoxyphenyl)-2-[2-(*p*-tolylsulfinyl)phenyl)]propanone (2hA). It was obtained by oxidation of a 84:16 mixture of *anti*- and *syn*-**14h**. Reaction time: 6 h. Eluent for chromatography: hexane–ethyl acetate 1:1. Yield: 74%; mp: 139–140 °C (diethyl ether–hexane). $[\alpha]_D^{20}$: +183.2 (*c* 1, $CHCl_3$); IR: 1674, 1600, 1510, 1263, 1084, 1030 cm^{-1}; ^1H NMR: δ 7.94 (m, 1H), 7.57 and 7.45 (AA'BB' system, 4H), 7.38 (m, 2H), 7.22 and 6.57 (part of AA'BB' system, 4H), 7.19 (m, 1H), 5.08 (q, $J=6.9$ Hz, 1H, CH_3CH), 3.77 (s, 3H, OCH_3), 2.37 (s, 3H, CH_3Ar), 1.37 (d, 3H, CH_3CH); ^{13}C NMR: δ 198.1, 163.2, 141.8, 141.3, 140.8, 140.5, 131.8, 130.9, 130.1, 128.7, 127.8, 126.5,

126.4, 113.5, 53.3, 42.3, 21.3, 19.0. Anal. calcd for $C_{23}H_{22}O_3S$: C, 72.99; H, 5.86; S, 8.47. Found: C, 73.05; H, 5.37; S, 8.00; MS (EI^+) *m/z*: 378 (M^+, 2), 243 (22), 225 (21), 135 (100), 91 (9), 77 (17); HRMS: calcd for $C_{23}H_{22}O_3S$: 378.1290. Found: 378.1295.

3.5.8. (2*S*,(S)*S*)-1-(2,6-Dimethylphenyl)-2-[2-(*p*-tolysulfinyl)phenyl)]propanone (2iA).[15] It was obtained by oxidation of a 67:33 mixture of *anti*- and *syn*-**14i**. Reaction time: 7 h. Eluent for chromatography: hexane–ethyl acetate 1:1. Yield: 71%; mp: 106–107 °C (diethyl ether–hexane). $[\alpha]_D^{20}$: −48.2 (*c* 0.75, $CHCl_3$); IR: 1698, 1466, 1085, 1033 cm^{-1}; ^1H NMR: δ 7.57–7.51 (m, 2H), 7.47 (dt, J= 1.6, 8.1 Hz, 1H), 7.35 (dt, J=1.6, 8.1 Hz, 1H), 7.15 (t, J= 7.7 Hz, 1H), 7.03 and 6.92 (AA'BB' system, 4H), 6.84 (d, J=8.1 Hz, 2H), 5.16 (q, J=6.9 Hz, 1H, CH_3CH–), 2.32 (s, 3H, CH_3Ar), 2.00 (s, 6H, 2 CH_3Ar), 1.64 (d, J=6.9 Hz, 3H, CH_3–CH–); ^{13}C NMR: δ 208.2, 144.7, 141.4, 140.9, 140.6, 138.1, 133.4, 131.6, 129.7, 128.9, 128.6, 128.0, 127.3, 124.7, 48.1, 21.3, 19.5, 18.5. Anal. calcd for $C_{24}H_{24}O_2S$: C, 76.56; H, 6.42; S, 8.52. Found: C, 76.73; H, 6.27; S, 8.06; MS (EI^+) *m/z*: 376 (M^+, 5), 243 (10), 225 (24), 133 (100), 105 (36), 91 (10), 77 (13); HRMS: calcd for $C_{24}H_{24}O_2S$: 376.1497. Found: 376.1491.

3.6. Protocol for obtaining compounds 11 and 11′

To a solution of *n*-BuLi (0.86 mmol, 2.5 M in hexane) was added *i*-Pr_2NH (1.28 mmol) in THF (5.1 mL) at 0 °C. After stirring for 30 min, the mixture was cooled at −78 °C and a solution of the sulfoxide **9** (0.71 mmol) in THF (2.5 mL) was added. After stirring for 40 min the purple carbanion **9** was added slowly with a syringe to a preparative TLC plate of silica gel. After 12 h the mixture was extracted with ethyl acetate, and filtered. The solvent was evaporated and the residue was separated by flash chromatography (ethyl acetate–hexane 2:1) to afford pure compounds **11** and **11′**.

3.6.1. Compound 11. It was obtained as a colorless oil. Yield: 22%; ^1H NMR: δ 7.70 (dd, J=7.6, 1.6 Hz, 1H), 7.40–7.20 (m, 3H), 6.01 (dd, J=9.6, 4.7 Hz, 1H, CH=CH–C–CH_3), 5.84 (d, J=9.6 Hz, 1H, CH=CH–C–CH_3), 5.09 (m, 1H, CH=C–CH_3), 3.83 (ddd, J=12.3, 4.7, 1.7 Hz, 1H, CHSO), 3.47 (dq, J=7.2, 2.9 Hz, 1H, $CHCH_3$), 3.26 (m, 1H, CH–CH–CH_3), 1.61 (m, 3H, CH=C–CH_3), 1.29 (d, J= 7.2 Hz, 3H, $CHCH_3$); ^{13}C NMR: δ 141.8, 141.7, 130.9, 130.4, 126.9, 126.8, 126.6, 120.6, 120.5, 64.9, 38.4, 36.7, 21.3, 16.9.

3.6.2. Compound 11′. It was obtained as a white solid. Yield: 20%; $[\alpha]_D^{20}$ = −129 (*c* 0.54, $CHCl_3$); ^1H NMR: δ 7.77 (dd, J=7.3, 1.5 Hz, 1H), 7.55–7.25 (m, 3H), 6.91 (t, J= 9.6 Hz, 1H, CH=C–S), 5.46 (m, 1H, CH=C–CH_3), 3.91 (m, 1H, CH_3–CH–CH), 3.10 (dq, J=7.1, 4.1 Hz, 1H, CH–CH_3), 2.85 (m, 2H, CH_2–CH–CH_3), 1.78 (s, 3H, CH= C–CH_3), 0.96 (d, J=7.1 Hz, 3H, CH–CH_3); ^{13}C NMR: δ 142.2, 137.8, 131.7, 131.4, 131.2, 130.1, 129.9, 127.8, 120.7, 40.0, 32.7, 32.3, 22.7, 18.7; MS ($APCI^+$) *m/z*: 245.1 $[M+1]^+$. Anal. calcd for $C_{15}H_{16}OS$ C, 73.73; H, 6.60; S, 13.12. Found: C, 72.92; H, 6.60; S, 12.64; HRMS: calcd for $C_{15}H_{16}OS$: 244.0922. Found: 244.0917.

3.7. Protocol for the synthesis of alcohol 12

3.7.1. Compound [1*S*,(S)*S*]-1-[2-(*p*-tolylsulfinyl)phenyl]-ethanol (12).[7f] To a solution of *n*-BuLi (0.33 mmol, 2.5 M in hexanes) was added *i*-Pr_2NH (0.49 mmol) in THF (1.7 mL) at 0 °C. After stirring for 30 min, the mixture was cooled at −78 °C and a solution of the sulfoxide **9** (0.27 mmol) in THF (1.1 mL) was added. After stirring for 1 h the purple carbanion **9** was slowly added, into a solution of ethyl acetate (10.9 mmol) in THF (1.1 mL) at −78 °C. The reaction was stirred for 30 min and quenched with saturated NH_4Cl, extracted with CH_2Cl_2 (3×20 mL), dried ($MgSO_4$) and the solvent evaporated. The residue was purified by flash chromatography (ethyl acetate–hexane 6:4) to afford alcohol **12** as a colorless oil. Yield: 62%. $[\alpha]_D^{20}$= −37 (*c* 9.1, $CHCl_3$); ^1H NMR: δ 7.86 (d, J=7.7 Hz, 1H), 7.59–7.23 (m, 7H), 5.26 (dq, J=6.5, 3.6 Hz, 1H, CH–CH_3), 2.99 (d, J=3.6 Hz, 1H, OH), 2.36 (s, 6H, CH_3Ar), 1.46 (d, J=6.5 Hz, 3H, $CHCH_3$); ^{13}C NMR: δ 144.1, 142.0, 141.3, 131.9, 129.9, 128.4, 126.5, 126.4, 126.3, 125.3, 65.1, 23.2, 21.3; MS (FAB^+) *m/z*: 261 $[M+1]^+$, 260 (4), 243 (100), 242 (88). Anal. calcd for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19; S, 12.32. Found: C, 69.22; H, 6.47; S, 11.75.

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Synthesis and stereochemical resolution of functional [5]pericyclynes

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Abstract—Three different kinds of ring *carbo*-mers of [5]cyclitol ethers were targeted as challenging examples of functional [5]pericyclynes. Three *tertiary* pentaaryl-*carbo*-[5]cyclitol methyl ethers were synthesized through a [11+4] ring-closing double addition of triphenyl- and tri-*p*-anisyl-undecatetrayn-diides to dibenzoylacetylene. These compounds, obtained as oily mixtures of stereoisomers, are stable and can behave as acetylenic ligands of one or two $Co_2(CO)_6$ units. NMR analysis reveals that the broad diasteroisomeric dispersity of a triether, is consistently reduced in the symmetrized pentaether. Three bis-*secondary* triaryl-*carbo*-[5]cyclitol methyl ethers with adjacent CH(OR) vertices were synthesized through a similar [11+4] ring-closing process, where the same tetrayn-diides add to both the carbaldehyde ends of the (η^2–OCH–C≡C–CHO)$Co_2(CO)_6$ complex. Despite the possibility of tautomeric isomerization, the occurrence of two adjacent bis-propargylic carbinol vertices does not diminish the stability of the [5]pericyclyne framework. Finally, two bis-*secondary carbo*-[5]cyclitol methyl ethers with non-adjacent CH(OH) vertices were synthesized through an alternative [10+5] ring-closing process. The bis-*secondary carbo*-[5]cyclitols are regarded as isohypsic equivalents of the challenging $[C,C]_5$*carbo*-cyclopentadienyl cation. A diphenyl-hexaoxy-[5]pericyclyne with two non-adjacent secondary carbinol vertices was also prepared through a [10+5] ring-closing strategy: this molecule is an isohypsic equivalent of the previously calculated zwitterionic *carbo*-cyclopentadienone, which could be observed as a DCI/NH_3-MS fragment after treatment with $SnCl_2$/HCl. Analytical HPLC showed that the C_{11} triphenyl-undecatetrayne precursor of the [11+4] strategy was obtained as a statistical 1:2:1 mixture of the three possible diastereoisomers. Semi-preparative HPLC allowed for the resolution of this mixture. The pure major diastereoisomer was employed to prepare a partly resolved sample of pentamethoxy-pentaphenyl-[5]pericyclyne. Analytical HPLC showed that the latter corresponds to the statistical distribution of the expected three residual diastereoisomers. Semi-preparative HPLC finally afforded samples of diastereoisomerically pure pentamethoxy-[5]pericyclyne as crystalline solids.

1. Introduction

In the general field of carbon-rich molecules,[1] we have been interested for some time in a carbon 'enrichment' process which could preserve some memory of its poorer parent molecule. Meeting the field of polyacetylenic chemistry,[2] it consists in the linear insertion of two sp carbon atoms into each bond of the parent Lewis skeleton. It is readily checked from basic VSEPR and mesomerism that the resulting '*carbo*-mer' structure preserves essential features of the parent model (connectivity, shape, symmetry, π-resonance, CIP configurations of stereogenic centers), while it has experienced a three-fold size expansion.[3] Focusing on cyclic hydrocarbons, *carbo*-mers of unsaturated rings such as annulenes[4] and radialenes,[5] were theoretically compared in terms of aromaticity. In a more subtle manner, ring *carbo*-mers of saturated cycloalkanes were theoretically compared in terms of *homo*-aromaticity.[6] These '*carbo*-cycloalkanes' are actually [N]pericyclynes, a generic term coined by Scott et al. in 1983 as they reported the synthesis of the first representative, decamethyl[5]pericyclyne (Scheme 1).[7] An octamethyl analogue was later reported.[8] The fascinating structure and stability of these rigid π-electron-rich 15-membered rings then attracted a considerable theoretical interest.[9,2,4,6] Nevertheless, an open question is whether the stability of [5]pericyclynes is compatible with functionalities at the sp^3 vertices. Hexaoxy-[6]pericyclynes,[10a] and expanded peroxy-pericyclynes (made with butadiyne edges and ketal vertices) have been described.[10b] To the best of our knowledge however, beside mentions of few peralkyl-monohydroxy-[5]periclynes,[11] no functional simple [5]pericyclyne was hitherto described in the literature. We focus here on the synthesis of pentaoxy-[5]pericyclynes, which can be alternatively regarded as '*carbo*-[5]cyclitol' derivatives (Scheme 1). Beyond the

Keywords: *Carbo*-mers; Pericyclynes; Cyclization reactions; Acetylenedicarbaldehyde; Diastereoisomeric resolution.

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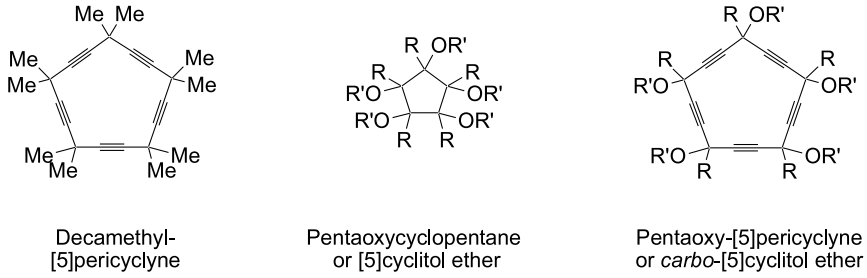
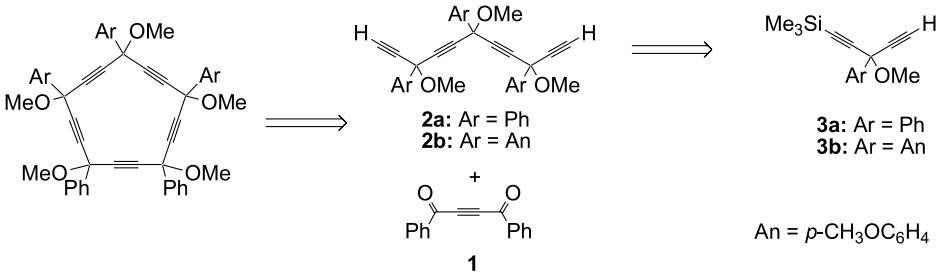


Scheme 1. Scott's [5]pericyclyne,[7] [5]cyclitol ethers and ring *carbo*-mer thereof.



Scheme 2. Targeted functional [5]pericyclynes (R≠H).

academic aestetical concern, one may figure out applications such as, for example, rigid crown ether-like properties or possible aromatization to the challenging ring *carbo*-mers of cyclopentadienyl cations.[4]

The envisioned pathways to *tertiary* and bis-*secondary* *carbo*-[5]cyclitol ethers (Scheme 2) are based on sequential alkynyl-propargyl coupling reactions.[12] The results are described in Sections 1 and 2. Since the stereogenic carbons of the *carbo*-[5]cyclitols stand in remote (γ) positions, their relative configuration is likely poorly controlled. A third section is therefore devoted to the diastereomeric resolution of *carbo*-[5]cyclitol ethers using HPLC techniques.

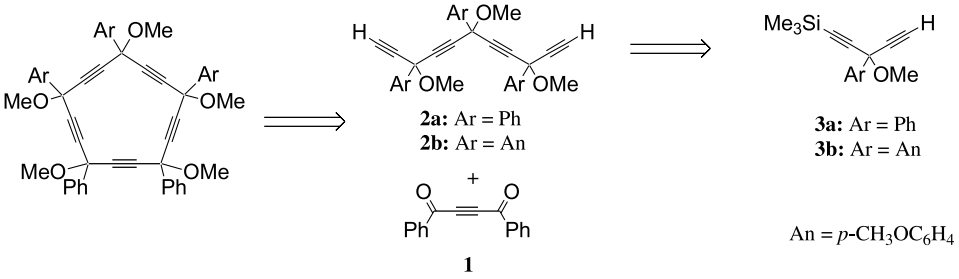
2. Results and discussion

2.1. *Tertiary carbo*-[5]cyclitol ethers

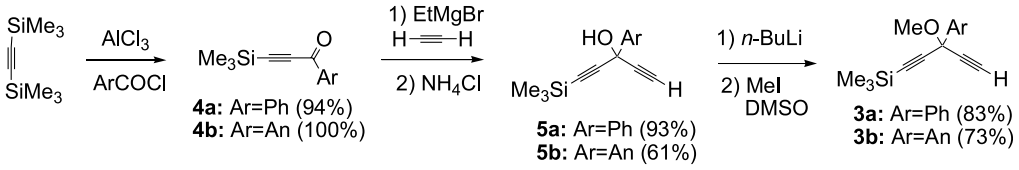
The selected strategy is straightforwardly inspired from the previously attempted [11+4] ring-closing double substitution of 1,4-ditosyloxy-but-2-yne ($TsOCH_2C{\equiv}CCH_2$-OTs). This strategy actually afforded a cyclic isomer and a cyclic dimer of the desired [5]pericyclyne through [11+4] and [11+4+11+4] processes, respectively.[13] Just changing the C_4 dielectrophile, the present strategy is based on a ring-closing double addition to the dibenzoylacetylene **1** (Scheme 3).

Some procedures will be inspired from those utilized by Ueda, Kuwatani et al. for the synthesis of homologous '*carbo*-[6]cyclitol' derivatives.[10a] The synthesis of the known triphenylundecatetrayne **2a** was extended to the trianisyl analogue **2b**.[13] In analogy with **3a**, the starting diyne **3b** was thus prepared through the three-step sequence depicted in Scheme 4. Acylation of bistrimethylsilylacetylene with *p*-anisoyl chloride afforded the anisylethynylketone **4b**. Reaction of **4b** with magnesium acetylide lead to the diethynyl-anisyl carbinol **5b**, the X-ray crystal structure of which was determined (see Section 2.2.2 and Fig. 3). The ether **3b** was finally obtained by methylation of the monolithium salt of **5b**.

Two equivalents of the lithium salt of **3b** reacted with anisoyl chloride to give **6b** in 52% yield (instead of 77% in the phenyl series **6a** from **3a**).[13] Methylation of the lithium alkoxide of **6b** with MeI/DMSO,[10a] followed by desilylation with K_2CO_3/MeOH,[14] afforded the undecatetrayne **2b**. The



Scheme 3. Retrosynthetic analysis to tertiary *carbo*-[5]cyclitol ethers.



Scheme 4. Synthesis of the 1,4-pentadiynes precursors of the C_{11} tetraynes **2a** and **2b**.

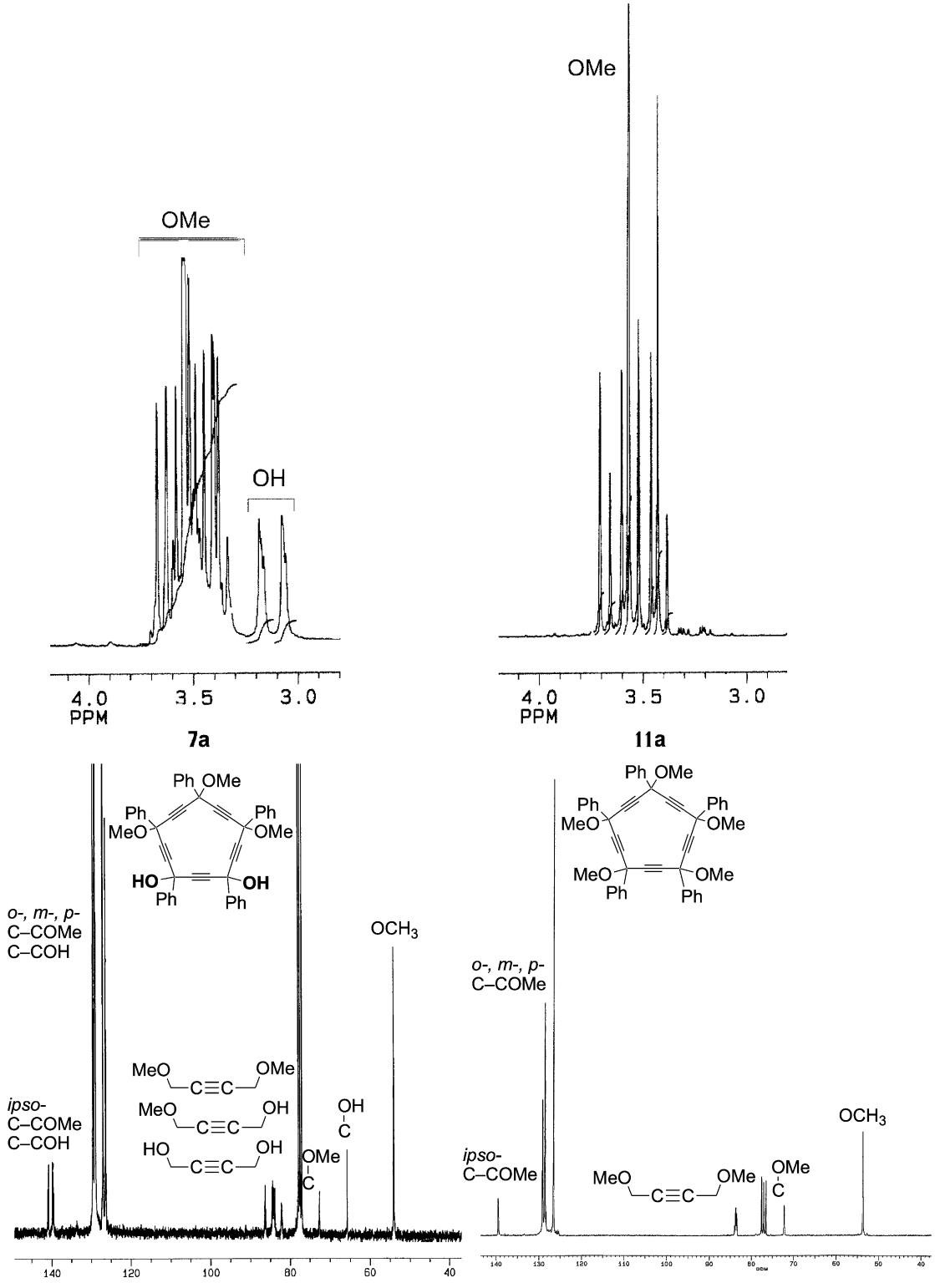
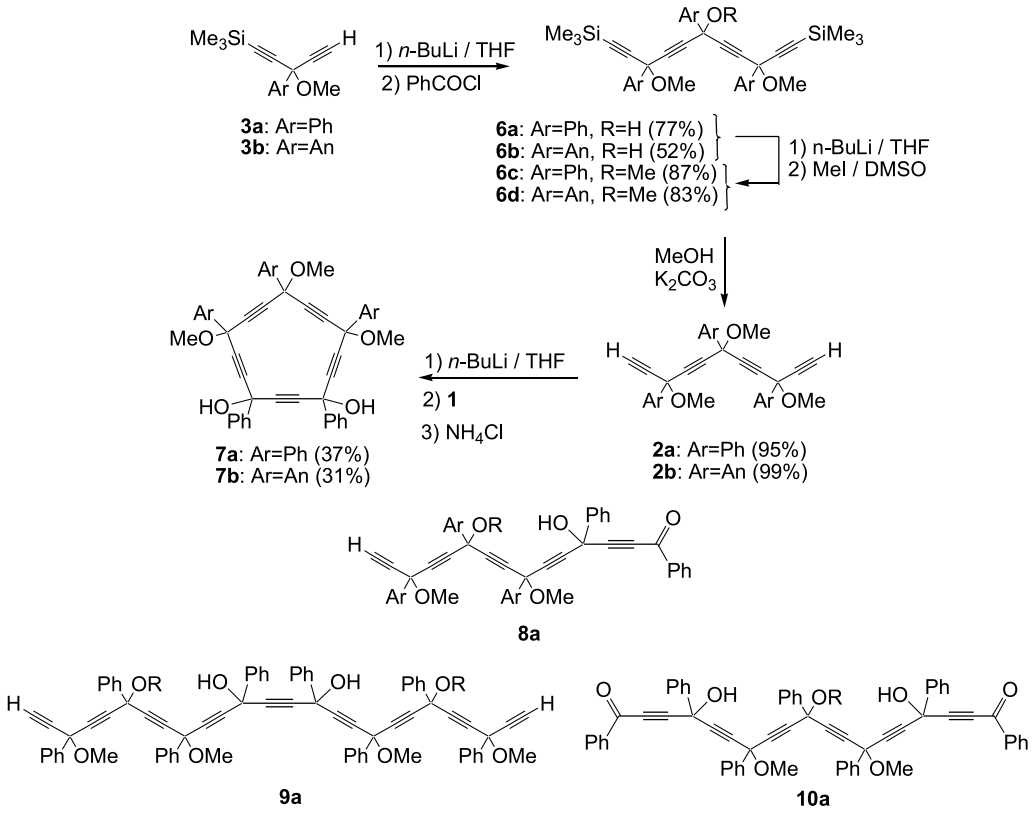


Figure 1. ^{1}H (250 MHz) and ^{13}C NMR (100 MHz, 62 MHz) spectra in $CDCl_3$ of the less symmetric triether **7a** as compared with those of the more symmetric pentaether **11a**.



Scheme 5. Synthesis of tertiary *carbo*-[5]cyclitol derivatives (**7**) and isolated side-products (**8**–**10**).

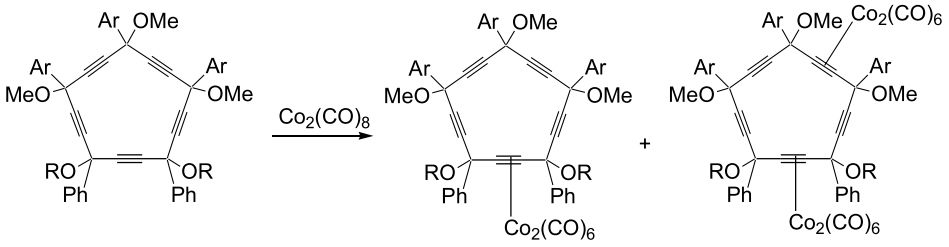
tetraynes **2a** and **2b** were obtained as statistical mixtures of stereoisomers (see Section 2.3 for the HPLC analysis of **2a**). The stereoisomers of these open-chain polyynes are nearly degenerate in their ^{1}H and ^{13}C NMR spectra (see Section 2.3, Fig. 6). This is due partly to the remote γ positions of the stereogenic centers, but mainly to an averaging free rotation process. Indeed the NMR degeneracy clears up in the next locked cyclic derivatives **7** (see discussion below, and Fig. 1). The latters were indeed obtained upon double-attack of the dilithium salts of **2a** and **2b** to dibenzoyl-acetylene **1**, prepared from the *trans*-1,2-dibenzoylethylene according to the Schuster's procedure.[15] Beside some unreacted tetraynes **2** and several acyclic products **8**, **9**, **10** (isolated in the phenyl series **a**), pentaphenyl[5]pericyclyne **7a** and diphenyl-trianisyl-[5]pericyclyne **7b** were formed rather selectively, in 37 and 31% yield, respectively. These novel functional pentaoxy-[5]perictyclynes are stable and could be characterized by MS, IR, ^{1}H and ^{13}C NMR spectroscopy (Scheme 5).

Starting from a mixture of the three stereoisomers of undecatetraynes **2a**–**2b**, the obtained [5]pericyclynes with two adjacent CPh(OH) vertices and three CAr(OMe) vertices are theoretically obtained as mixtures of 10 diastereoisomers (six of them being chiral). Considering the possible symmetry-equivalence of pairs of MeO groups, 26 different OCH_3 signals are a priori expected in the NMR spectrum of **7a** (resp. **7b**). Consistently, a large number of signals (ca. 16) are indeed observed in the range 3.3–3.7 ppm. The possibility of overlap precludes an exact count of the stereoisomers of **7a** (Fig. 1). Nevertheless, two well-separated broad D_2O-exchangeable OH signals of equal intensities occur at 3.05 and 3.15 ppm. Assuming that the primary factor determining the chemical shifts of these hydroxyls is their relative *cis* or *trans* orientation with respect to the mean ring plane, this observation suggests that the ring closing process is definitely non-stereoselective.[16] It must be stressed that the ^{13}C chemical shifts are much less sensitive to diastereotopicity than are the ^{1}H chemical shifts: the formers solely undergo the influence of the proximate (topological) chemical environement (Fig. 1).

For the pentaphenyl derivative **7a**, methylation of the two hydroxyl groups results in an increased symmetry (all the five vertices become identical in nature: CPh(OMe), and would allow to reduce the theoretical number of diastereoisomers from ten to four (Scheme 6).

Scheme 6. Symmetrization of a *carbo*-[5]cyclitol triether to the corresponding pentaether.

The NMR spectra of the pentamethoxy-pentaphenyl-[5]pericyclyne **11a** are indeed significantly simplified (Fig. 1). Only eight well-resolved ^{1}H NMR signals are now observed in the OCH_3 region, out of 10 expected in the



Scheme 7. Cobalt complexes of pentaoxy[5]pericyclynes. The depicted regiochemistry of the complexation may not be unique, but it corresponds to experimental data on decamethyl-[5]pericyclyne.[8] For **12** and **12′**, the preferred complexation on the 'butyndiol edge' is suggested by DFT calculations on a model butyndiol complex revealing chelating hydrogen bonds involving the carbonyl ligands of the $Co_2(CO)_6$ moiety.[17]

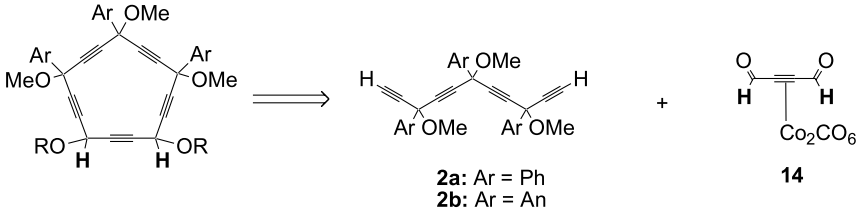
statistical distribution. All the possible diastereoisomers are thus significantly present in the product (two signals are likely degenerate with other(s) under the most intense signal(s): Fig. 1). As stressed above, the ^{13}C chemical shifts are much less sensitive to diastereotopicity and all carbons of given chemical type resonate as single frequencies in all the stereoisomers (only sp-carbon atoms, at the midpoint between two stereogenic vertices, remain very slightly non-degenerate: Fig. 1). No stereochemical correlation was thus possible. A first attempt at separation of the diastereoisomers by HPLC remained unsuccessful, thus requiring a stepwise resolution method (see Section 2.3).

Scott et al. showed that peralkylpericyclynes act as ligands for one or two $Co_2(CO)_6$ units, and that use of a large excess $Co_2(CO)_8$ does not lead to further complexation.[8] This behaviour was tested for functional versions. Reaction of the *carbo*-[5]cyclitol ethers **7a**, **7b** or **11a** with a single equivalent of $Co_2(CO)_8$ lead to two red complexes which could be separated by chromatography (Scheme 7). According IR, MS (APCI>0/CH_3CN, MALDI) and elemental analyses, the less polar products **12a**, **12b**, **13a** (isolated in 50–60% yield) contain a single $Co_2(CO)_6$ unit. The most polar products **12a′**, **13a′** (20–30% yield) contain two $Co_2(CO)_6$ units. The proposed structures in Scheme 7 are based on Scott's results on decamethyl-[5]pericyclyne, showing that the two $Co_2(CO)_6$ units of the bis-complex are bound to non-adjacent triple bonds. For **12a**, **12a′** and **12b**, the proposed hapticity of the triple bonds lying between the CPh(OH) vertices is supported by standard steric arguments, and by DFT calculations (B3PW91/6-31G**/LANL2DZ(Co)) on a model $Co_2(CO)_6$ complex of 2*R*,5*R*-diphenyl-hexa-3-yn-2,5-diol displaying two stabilizing O–H···(CO) hydrogen bond-like distances (2.34 Å).[17]

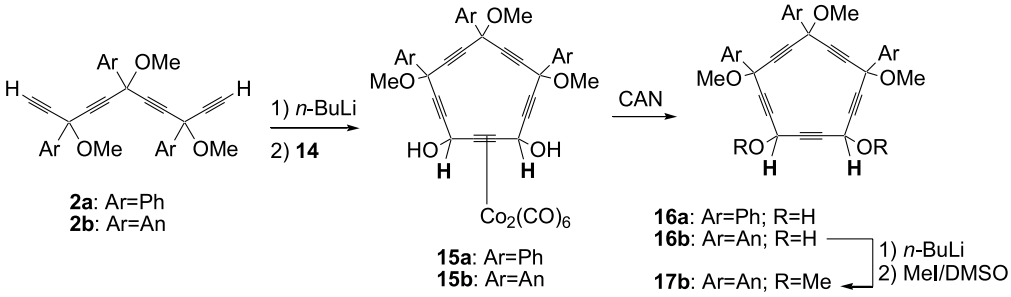
2.2. Bis-*secondary carbo*-[5]cyclitol ethers

[5]Pericyclynes with several secondary carbinol vertices are specifically interesting for several reasons: (i) they are not exemplified in the literature,[18] and possibly tautomerically instable;[19] (ii) if stable, they are more versatile than their all-tertiary counterparts for further functionalization (by full reduction to CH_2 or full oxidation to C=O); and (iii) they are redox (isohypsic) equivalents of the challenging *carbo*-cyclopentadienyl ring cation.[4a,b,6] The synthesis of [5]pericyclynes with two secondary carbinol vertices at either adjacent or non-adjacent positions (Scheme 2) has been envisioned through two cyclization strategies, [11+4] and [10+5].

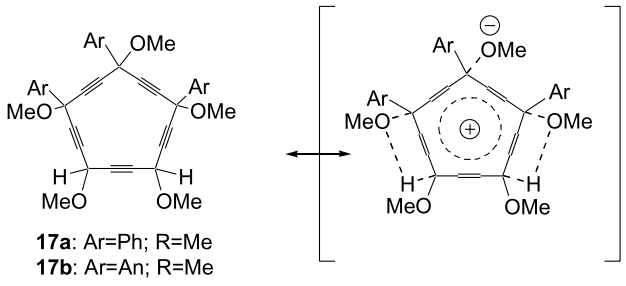
2.2.1. Bis-*secondary carbo*-[5]cyclitol ethers with adjacent CH(OH) vertices: a [11+4] strategy. The preceeding route to pentaaryl-*carbo*-[5]cyclitol ethers (Section 2.1) suggests the replacement of dibenzoylacethylene **1** for acetylenedicarbaldehyde (CHO–C≡C–CHO). Extensive studies by Gorgues et al. have shown that this highly functional C_4 molecule is however quite instable,[20] and cannot be used as such for synthetic purpose. Nonetheless, it can be stabilized as a ligand in the cobalt(0) complex **14**. X-ray diffraction analyses of single crystals of **14** showed that the propargylic aldehyde functions do not interact with the cobalt centers.[21] This structural feature is consistent with our recent studies showing that the dialdehyde ligand preserves its theoretical 1,4-electrophilicity, not only towards neutral nucleophiles (silylenol ethers and trimethoxybenzene in Nicholas-type reactions),[22] but also towards anionic nucleophiles.[23] Despite the presence of six 'electrophilic' carbonyl ligands, alkyl, aryl, ethynyl lithium and Grignard reactants add to both aldehydic functions in a



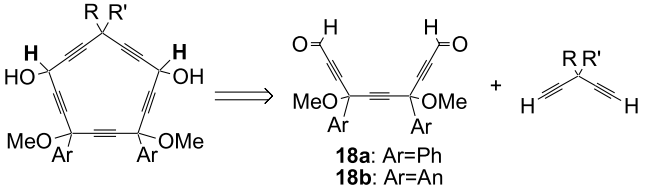
Scheme 8. [11+4] retrosynthesis of bis-secondary pentaoxy[5]pericyclynes based on the use of Gorgue's complex **14**.



Scheme 9. Synthesis of bis-*secondary* pentaoxy[5]pericyclynes *via* cobaltcarbonyl complexes.



Scheme 10. Formal isohypsic equivalence of bis-secondary pentaoxy[5]-pericyclynes with *carbo*-cyclopentadienyl cations.

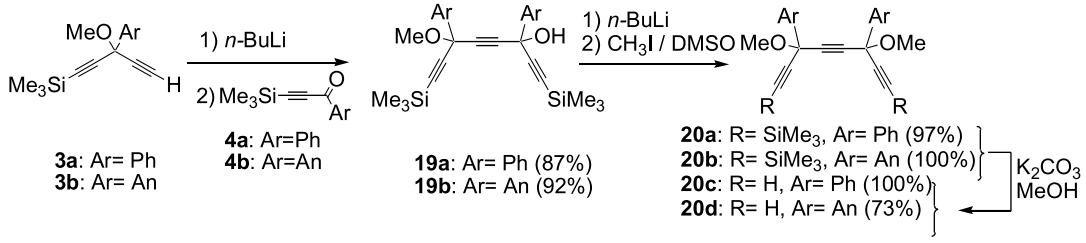


Scheme 11. [10+5] retrosynthesis of bis-*secondary* pentaoxy-[5]pericyclynes.

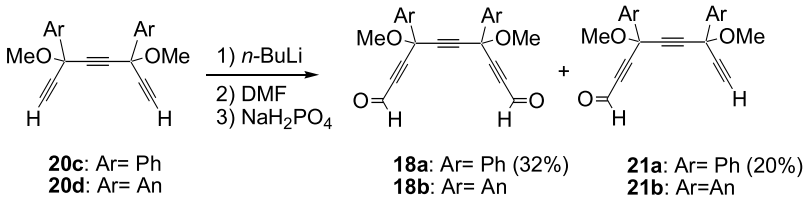
chemo- and regio-selective manner. Moreover, the double additions take place with some stereoselectivity (*meso*:*dl* ratio up to 80:20). We therefore envisioned to apply the reaction in a ring-closing version from tetraynes **2a** and **2b** (Scheme 8).

Double deprotonation of the triphenyl-tetrayne **2a** with *n*-BuLi in THF followed by addition of the acetylene-dicarbaldehyde complex **14** and protonation, afforded a mixture of compounds. Chromatography allowed to isolate a single-spot red complex, whose ^{1}H, ^{13}C NMR and IR analyses are consistent with the expected structure **15a** (25% yield, Scheme 9). The same sequence from the trianisyl-tetrayne **2b** afforded the analogous complex **15b** (6% yield. Scheme 9). Rather surprisingly, whereas 2 equiv. of various monoacetylides (RC≡C–Li) were shown to afford the corresponding acyclic triyndiol complexes in rather low yields (9–16%) as compared with alkyl and aryl nucleophiles,[23] the yield in the cyclic product **15a** is here relatively high. The tandem cyclic feature of the process is therefore highly beneficial. Nevertheless, none of the classical MS methods, including atmospheric pressure chemical ionization (APCI), gave relevant fragmentation peaks. Their structure was confirmed in the next step. Indeed, oxidative decomplexation of the corresponding samples of **15a–b** afforded the bis-*secondary carbo*-[5]cyclitols **16a** ($[MNH_4]^+=558$) and **16b** ($[M]^+=630$; $[MH-MeOH]^+=599$: stabilized α-*p*-anisyl carbocationic fragment). The procedure previously employed for O-methylation of *tertiary* diethynyl-aryl carbinols (deprotonation with *n*-BuLi, then MeI/DMSO) turned out to be unsuccessful for *secondary* diethynyl carbinols (from diol **16a**) in the phenyl series. In one attempt in the anisyl series (from diol **16b**), however, it afforded a crude compound whose NMR and MS spectra were consistent with the bis-*secondary* pentamethoxy-[5]pericyclyne structure **17b** ($[MH-MeOH]^+=627$).

These stable molecules constitute the first examples of redox (isohypsic) equivalents of *carbo*-cyclopentadienyl cations (Scheme 10).[4a,b,6] The corresponding fragments could however not be detected in their mass spectrum. In an attempt at triggering aromatization through double 1,4-elimination of methanol, a yellow solution of **17b** ($CDCl_3$, −60 °C) treated with triflic acid turned immediately to violet with concomitant formation of a black precipitate. No signal could be detected by ^{1}H NMR analysis of the highly diluted supernatent, but the water-sensitive violet color remained persistent over 12 h at room-temperature. Despite the expected stabilizing effect of three anisyl substituents,



Scheme 12. Preparation of the octatriyne precursors of the C_{10} dialdehydes envisioned in the [10+5] strategy (Scheme 11).



Scheme 13. Double formylations of triynes **20**,[25] affording the key C_{10} dialdehydes for the envisioned [10+5] strategy (Scheme 11).

compound **17b** is definitely more prone to polymerization than to dissociative aromatization. Speculatively, 1,4-elimination from **17** is indeed not regio-directed: if it first took place on the bis-secondary edge, the resulting trisubstituted butatriene edge (≡C–(H)C=C=C=C(OMe)–C≡) in a not-yet-aromatic pentagonal ring would be likely quite instable. The design of an optimized precursor structure was therefore suggested as a prerequisite for any further attempt at quantitative formation of the *carbo*-cyclopentadienyl ring cation.

2.2.2. Bis-*secondary carbo*-[5]cyclitol ethers with non-adjacent CH(OH) vertices: a [10+5] strategy. The second kind of bis-*secondary carbo*-[5]cyclitols (Scheme 2) was targeted through the alternative [10+5] strategy disclosed in Scheme 11.

The C_{10} trisacetylenic dialdehyde precursors **18a**, **18b** were prepared in three steps from the 1,4-diynes **3a**, **3b** (Schemes 12 and 13). Addition of the corresponding lithium acetylides to trimethylsilylpropynal afforded the corresponding triynes **19a** and **19b** as mixtures of *meso* and *dl* isomers in an undetermined ratio (the ^{1}H NMR signals are not split significantly). After methylation of the hydroxyl group, both the terminal alkynes were readily deprotected with K_2CO_3/MeOH, affording **20c** and **20d** in 84 and 67% yield, respectively.

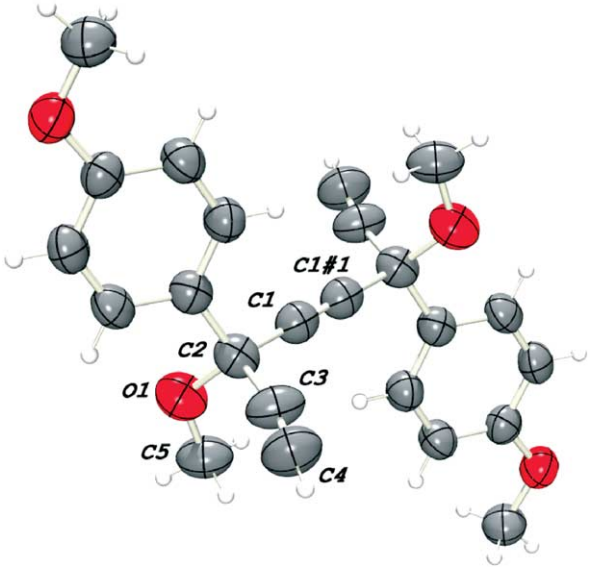


Figure 2. ORTEP view of **20d** with 50% probability displacement ellipsoids for non-hydrogen atoms. Bond distances (Å): C(2)–C(3)=1.473(6); C(3)–C(4)=1.139(6); C(1)–C(2)=1.494(6); C(2)–O(1)=1.450(5); C(1)–C(1)#1=1.187(8). Bond angles (°): C(1)#1–C(1)–C(2)=177.6(5); C(3)–C(2)–C(1)=107.6(4); C(4)–C(3)–C(2)=166.5(6).

While **20c** was isolated as an orange oil, its anisyl couterpart **20d** is an orange powder. A single crystal of **20d** was obtained as an orange powder, revealing a *meso* configuration in a perfect C_2 conformation (Fig. 2). The crystal structure can be compared with the structure of the 1,4-diyne precursor **5b**. In *meso*-**20d**, the measured bond angle at the C3 sp carbon atom and the corresponding triple bond distance are C2–C3–C4(H)=166.5(6)° and C3–C4=1,139(6) Å, respectively. These values appear as rather 'abnormal' with respect to the classical structural features of alkynes and to the 'normal' values measured from the X-ray crystal structure of the dialkynylcarbinol **5b** (true racemate, Fig. 3: C1–C2–C3(H)=177.66(14)°; C2–C3=1,184(2) Å). Beyond possible experimental error, the apparent bond shortening can be due to an artifact of the X-ray measurement, as previously discussed for tetraethynylmethane on the basis of a 'π electron compression' effect.[24]

The carbaldehyde groups were then introduced by double formylation according to the Journet and Cai's procedure.[25] The hydrolysis step is crucial for a successful production of

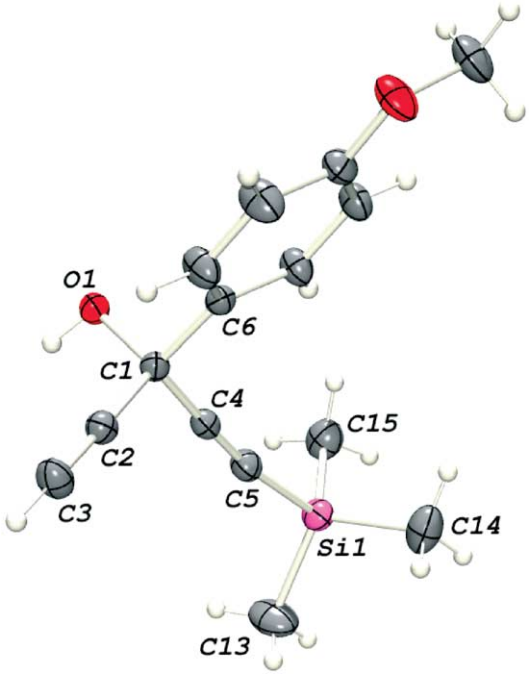
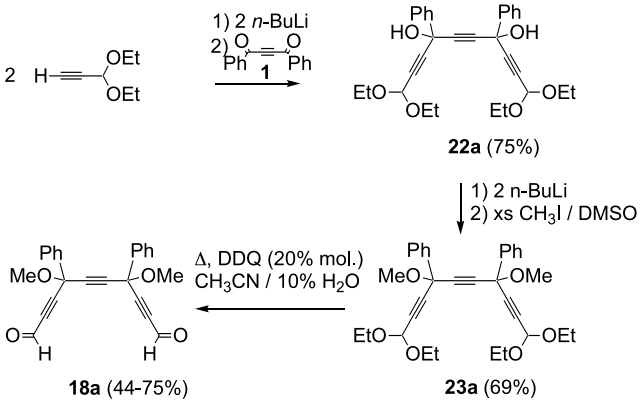


Figure 3. ORTEP view of **5b** with 50% probability displacement ellipsoids for non-hydrogen atoms. Bond distances (Å): C(1)–C(2)=1.475(2); C(1)–C(4)=1.4832(19); O(1)–C(1)=1.4437(15); C(2)–C(3)=1.184(2); Si(1)–C(5)=1.8499(17). Bond angles (°): C(3)–C(2)–C(1)=177.66(14); C(5)–C(4)–C(1)=177.02(15); C(2)–C(1)–C(4)=108.78(11); C(4)–C(5)–Si(1)=172.16(12).



Scheme 14. Alternative synthesis of the key C_{10} dialdehyde **18a** for the envisioned [10+5] strategy (Scheme 11).

18a–18b: it consists in the addition of the alkaline solution into a 1:1 mixture of diethylether and KH_2PO_4 aqueous buffer (alternatively, $NaHPO_4$+KCl, can be used. The use of other acids triggered back reaction and untransformed triyne **20** was recovered). Monoaldehydes **21a**, **21b** were formed as side-products in ca. 20% yield according to NMR analysis of the crude materials.

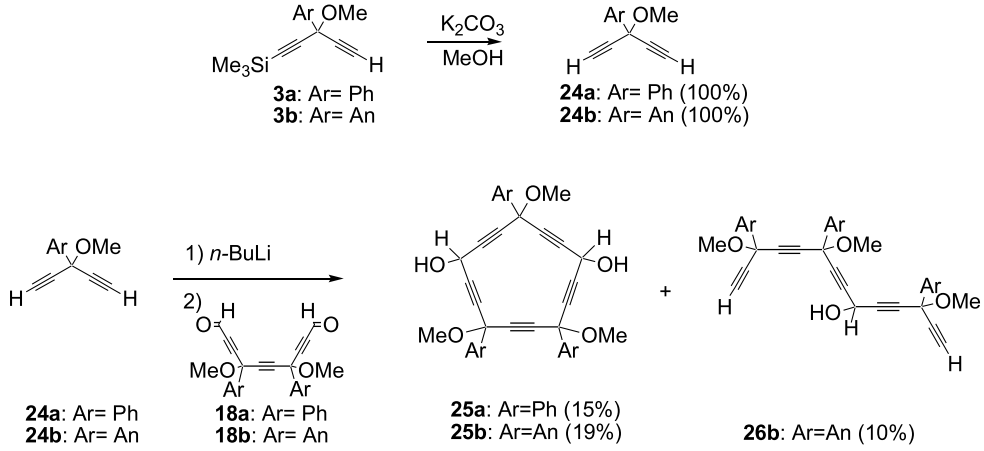
Attempts at purification by chromatography resulted in partial decomposition, affording pure **18a** in 32% yield only. The anisyl derivative **18b** could not be successfully purified. To make up this problem, an alternative route was addressed from commercially available propiolaldehyde diethylacetal and dibenzoylacetylene **1** (Scheme 14).

Addition of two equivalents of lithium 3,3-diethoxypropynide to diketone **1** in THF and subsequent hydrolysis afforded diol **22a**. After methylation of the hydroxyl groups, hydrolysis of the acetal functions by conventional acidic treatments (formic acid or PTSA) remained unsuccessful. Compound **23a** could, however, be deprotected in an 'oxidizing' neutral medium using DDQ in the dark.[26] Dialdehyde **18a** was finally obtained in three steps and 61% yield. At this stage, the lack of a rapid procedure for the preparation of the dianisyl analogue of diketone **1**, prevented the use of this strategy (Scheme 14) to obtain the anisyl analogue **18b**. The crude dialdehyde **18b** obtained by the first method (Scheme 13) was thus used as such in the cyclization step (see below).

The C_5 1,4-diyne moieties **24a**, **24b** were obtained by quantitative desilylation of the diynes **3a**, **3b** in basic medium (Scheme 15). The [10+5] ring closing step is based on a double nucleophilic attack of the dilithium salts of **24a**, **24b** to the C_{10} dialdehyde moieties **18a**, **18b**. In the phenyl series, the *carbo*-[5]cyclitol ether **25a** was isolated in 15% yield. Attempt at templating the triyne electrophiles with $AgBF_4$ did not increase the yield. In the anisyl series, two major products were obtained from the crude mixture **18b**+**21b** (Scheme 13). The *carbo*-[5]cyclitol ether **25b** and the acyclic product **26b** could finally be separated in 19 and 10% yield, respectively.

The DCI/NH_3 mass spectrum of the *carbo*-[5]cyclitol ether **25a** exhibits a base peak at $m/e=558$ ($[MNH_4]^+$) and a major peak at $m/e=509$ ($[MH–MeOH]^+$) (Fig. 4). Two secondary peaks at $m/e=526$ and 494 correspond to the '*carbo*-cyclopentene' ($[M+NH_4–MeOH]^+$) and '*carbo*-cyclopentadiene' ($[M-2MeOH+NH_4]^+$) parent ions respectively. The corresponding *carbo*-cyclopentadienyl fragments (($[MH-3MeOH]^+$or ($[M+NH_4-3MeOH]^+$) were not observed. The DCI/NH_3 mass spectrum of the anisyl *carbo*-[5]cyclitol ether **25b** exhibits similar features, with a main base peak at $m/e=599$, corresponding to $[MH-MeOH]^+$(stabilized α-*p*-anisyl carbocation, as in the case of **7b** discussed in Section 2.1).

As an alternative C_5 1,4-diyne fragment, the pentadiyn-3-one ketal **27** possesses a non-asymmetric bis-propargylic carbon center. It was used by Bunz et al. for the synthesis of functional expanded pericyclynes.[10b] Within the framework of the present [10+5] strategy, the resulting [5]pericyclyne should be topologically more symmetrical, with a reduced number of diastereoisomers (five instead of eight in the previous case). The known C_5 precursor **27** was prepared by addition of 2 equiv. of trimethylsilylacetylide to ethyl formate, followed by oxidation of alcohol **28**, and ketalization of ketone **29** with 2,2-dimethyl-1,3-propandiol under specific conditions of dilution in toluene (instead of benzene in the previously described procedure).[10b] Quantitative



Scheme 15. Ultimate steps of the [10+5] strategy, affording pentaoxy-[5]pericyclynes with non adajacent CH(OH) vertices.

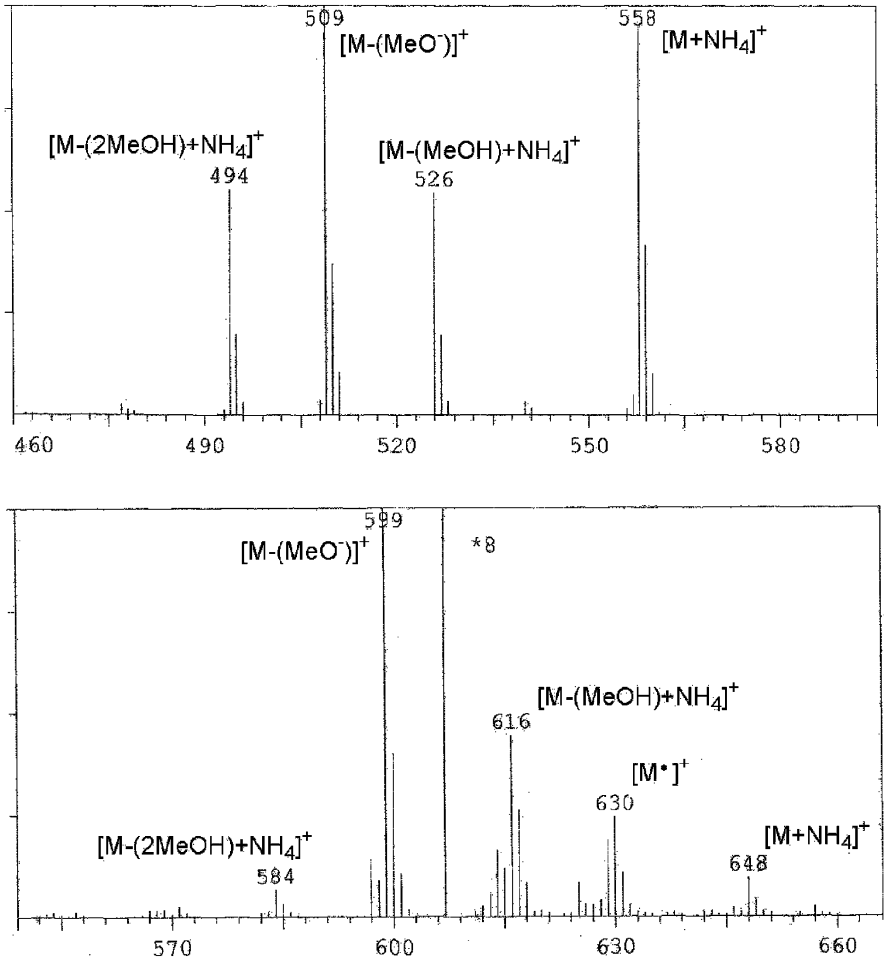
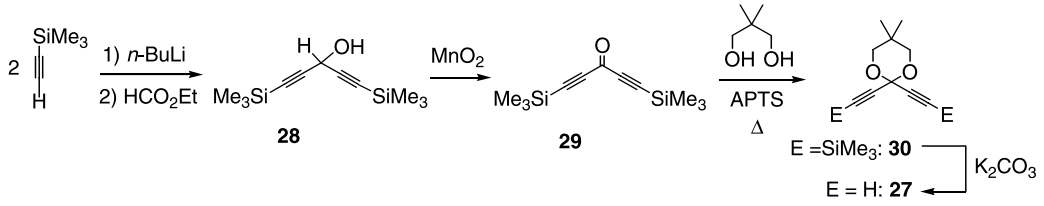
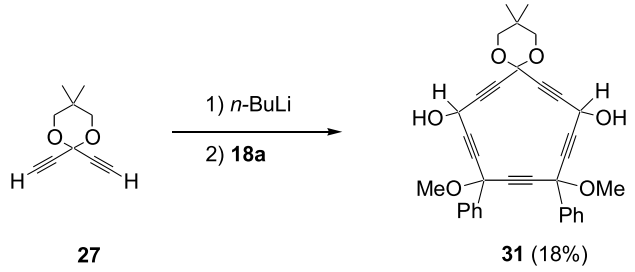


Figure 4. MS (DCI/NH_3) spectra of bis-*secondary* pentaoxy-[5]pericyclynes **25a** and **25b** showing the preferred fragmentations through one or two methanol eliminations from the protonated or ammoniated species. The third methanol elimination which could produce the corresponding dihydroxy-triphenyl-*carbo*-cyclopentadienyl cations was not observed.



Scheme 16. Four-step synthesis of the 2,2-dimethyl-1,3-propanediol ketal of diethynyl ketone,[10b] an alternative C_5 moiety for the [10+5] strategy.

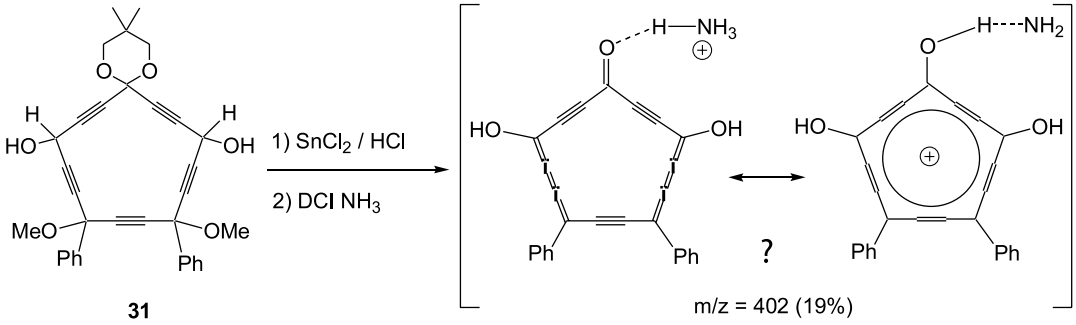


27 **31** (18%)

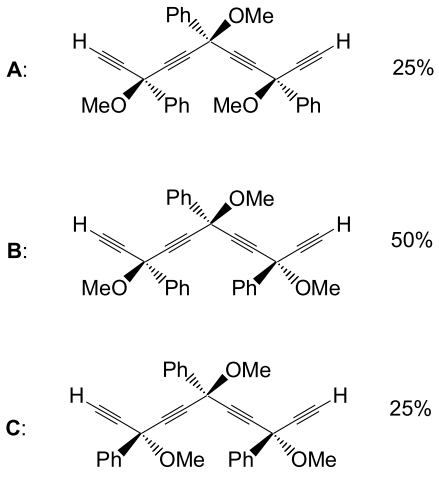
Scheme 17. [10+5] ring closing process affording a bis-*secondary* hexaoxy[5]pericyclyne.

desilylation of **30** afforded **27** in 27% overall yield (Scheme 16).

The dilithium salt of **27** was then allowed to react with dialdehyde **18a**, affording the novel [5]pericyclyne **31** as a pale yellow powder in 18% yield (Scheme 17). All attempts at deprotection of the ketal vertex of **31** remained unsuccessful. Inspection of the literature reveals that no effective deprotection of such hindered ketals of dialkynyl-ketones has been hitherto reported. In particular, deprotection of Bunz decaoxy-expanded [5]pericyclyne was not reported.[10b] Moreover, it seems that **30** is the sole known ketal derivative of the ketone **29**, and consistently, our



Scheme 18. Possible aromaticity-stabilized structure of the observed fragment at $m/z=402$ in the DCI/NH_3 mass spectrum of the hexaoxy-[5]pericyclyne after acidic treatment.



Scheme 19. Stereoisomers **A**, **B**, **C** of the tetrayne **2a** and their statistical ratio.

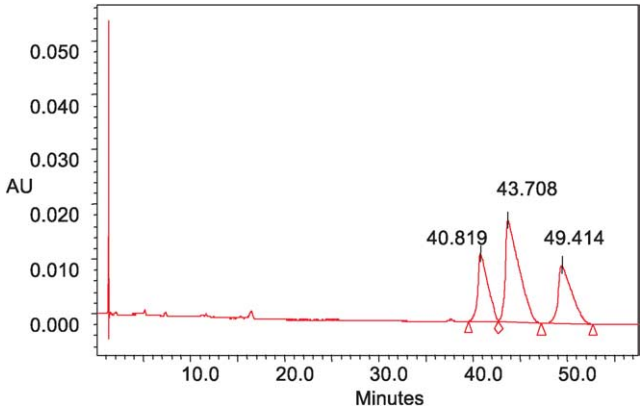


Figure 5. HPLC separation of the stereoisomers **A**, **B**, **C** (Scheme 19).

personal attempts at preparing the less hindered 1,3-propylene ketal or the acyclic diethylketal of **29** failed.

Aromatisation of the *carbo*-[5]cyclitol derivative **31** with the classical reactant $SnCl_2/HCl$[10a] afforded a complex mixture of products. However, DCI-MS analysis of the mixture exhibited a secondary peak at $m/z=402$ (19%). This value is consistent with the parent *carbo*-cyclopentadienone-ammonium structure or with its zwitterionic oxyl-*carbo*-cyclopentadienyl resonance form (Scheme 18). The geometry of the *carbo*-cyclopentadienone model molecule ($C_{15}H_4O$) was optimized at the B3PW91:6-31G** level,[27] and it was shown that this model is aromatic in both the structural sense (planarity, C···O distance of 1.44 Å corresponding to $a^{+}C–O^{-}$ single bond description) and the magnetic sense (NICS = −8.1 ppm,).[28] This aromaticity might account for the observed MS fragmentation of ketal **31**.

2.3. Diastereoisomeric resolution of *carbo*-[5]cyclitol pentaether 11a

As previously stressed (Section 2.1), all the compounds containing more than two dialkynylcarbinol units were obtained as mixtures of diastereoisomers. All attempts at separating them by TLC and column chromatography failed. Focusing on the most symmetric pentaoxy-[5]pericyclyne target **11a** (with four diastereoisomers only: Scheme 6), we therefore turned to HPLC techniques. Since **11a** is obtained from tetrayne **2a** and dibenzoylacetylene **1**, and since the three stereogenic sp^3 carbon atoms of **2a** are retained in **11a**, a preliminary diastereoselective separation of **2a** was attempted. In theory, **2a** possesses three diastereisomers **A**, **B** and **C**, anticipated to form in the statistical distribution **A**:**B**:**C** = 1:2:1 (Scheme 19).

Their separation was achieved by HPLC, with a direct phase column of Prontosil type. After several trials, a 70:30 pentane:dichloromethane mixture was determined as an optimal eluting system. The analytical HPLC chromatogram displays three peaks with baseline separation for retention times of 40.8, 43.7 and 49.4 min, integrating for 25, 50 and 25%, respectively (Fig. 5). The three peaks correspond to identical UV spectra, as expected for closely related diastereoisomers **A**, **B**, **C**. This confirmed the statistical ratio, and allowed for the assignment of the major intermediate signal (at $R_t=43.7$ min) to the structure **B** (Scheme 19).

The three diastereoisomers were then sequentially separated twice by semi-preparative HPLC. The three stereochemically pure products are oils, the NMR spectra of which were recorded separately (Fig. 6). It is predicted that the isomer **B** should exhibit three non-equivalent methoxy NMR signals, while both **A** and **C** should exhibit two different signals only. These features were confirmed, in accordance with the

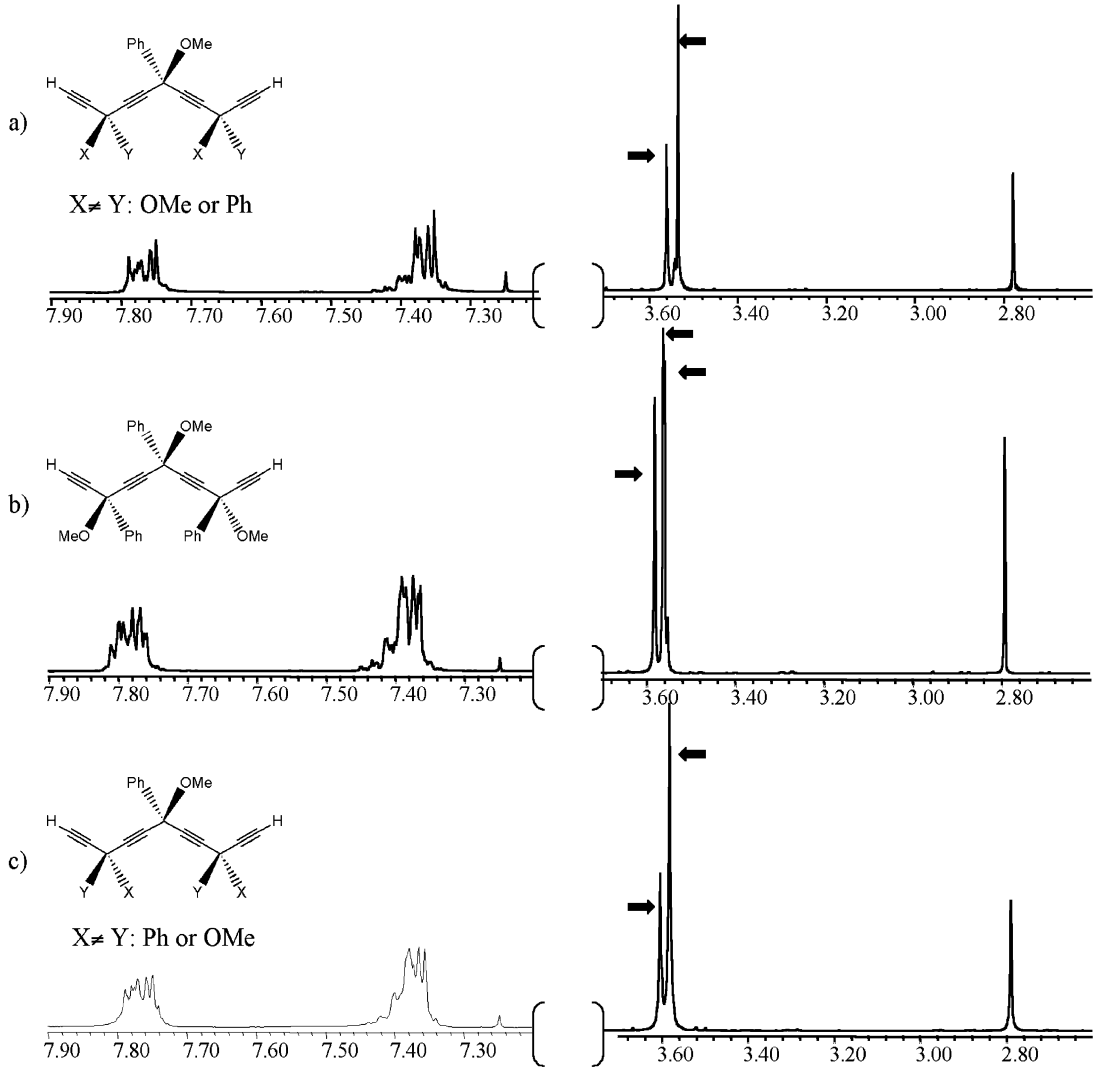
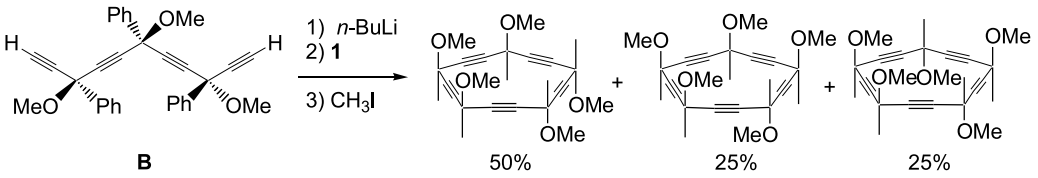


Figure 6. NMR spectra ($CDCl_3$, 250 MHz) of separated diastereoisomers of tetrayne **2a**. a) Stereoisomer **A** or **C**. b) Stereoisomer **B**. c) Stereoisomer **C** or **A**, different from the stereoisomer corresponding to spectrum a).



Scheme 20. Statistical stereoisomeric distribution of the pentamethoxy-[5]pericyclyne **11a** resulting from a [11+4] ring closing process involving the pure isomer **B** of tetrayne **2a**. For clarity, the phenyl substituents are not depicted.

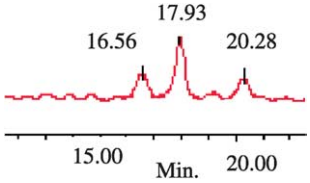


Figure 7. HPLC separation of the three isomers of pericyclyne **11a** in statistical distribution (Scheme 19).

HPLC assignment. In particular, only the compound of the major HPLC peak displays three OCH_3 NMR signals of equal intensities, thus confirming structure **B** (Fig. 6(b)). Nonetheless, neither the HPLC integration nor the multiplicities of the NMR signals allow for an assignment of structures **A** and **B** to their respective HPLC retention time and ^{1}H NMR spectrum.

Having pure diastereoisomers of **2a** in hand, the double addition to dibenzoylacetylene **1** was carried out from the

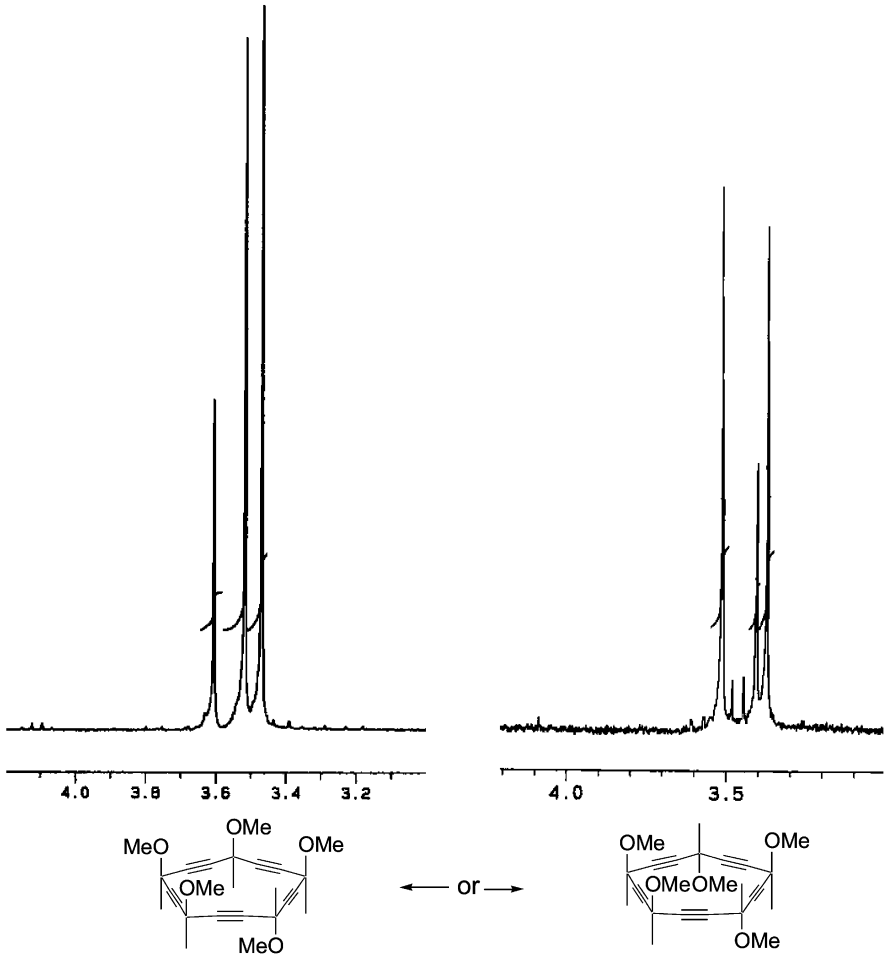


Figure 8. ^{1}H NMR spectra ($CDCl_3$, 250 MHz) of two minor isomers of pentamethoxy-pentaphenyl -[5]pericyclynes (R_t=16.56 and 20.26 min in Fig. 7). R=Me. The exact assignment.

dilithium salt of the major diastereoisomer **B** (Scheme 20); the cyclization process creates two additional stereogenic carbon atoms. After methylation in situ of the intermediate OLi groups of the partly resolved salt of **7a**, the expected number of stereoisomers of the product **11a** is reduced to three. Their corresponding statistical ratio would be 1:2:1 (Scheme 20).

Analytical HPLC resolution was successfully attempted: three peaks were obtained with baseline separation, and their relative UV-integration confirmed the statistical distribution (Fig. 7).

Semi-preparative HPLC separation of the mixture was carried out under optimized conditions (see Section 4). Two out of three diastereoisomers were finally isolated as pure white crystalline compounds. Their respective NMR spectra confirmed their stereochemical purity, and were consistent

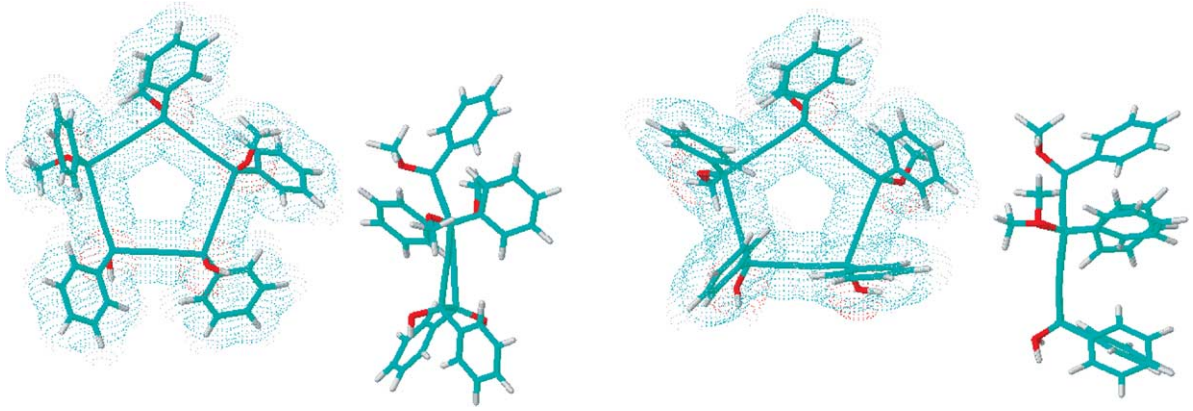


Figure 9. MM2-optimized geometries of two stereoisomer of **11a**.[4].

with the theoretical number (3) and relative intensities (1:2:2) of non-equivalent OCH_3 signals for the proposed structures (Fig. 8). These compounds are the first examples of disymmetrically and stereoselectively substituted functional [5]pericyclynes.

3. Conclusion

Functional [5]pericyclynes with either tertiary or secondary carbinol vertices are definitely stable compounds. The stereochemical complexity arising from the stereogenicity of the sp^3 vertices (with respect to the symmetrical decamethyl- and pentacyclopropylidene-derivatives)[29] has been studied by NMR and resolved by HPLC techniques. Monocrystals of stereochemically pure samples were not suitable for an X-ray structure determination, but insights may be gained on the basis of MM modeling (Fig. 9). The phenyl and methoxy substituents do not alter the features calculated at higher (DFT) level for unsubstituted models (slight ring distortion from planarity, absence of homo-aromaticity as revealed by the lengths of 'fixed' single and triple bonds).[6] Although effective dissociation of isohypsic equivalents of the *carbo*-cyclopentadienyl cation remains to be achieved, preliminary MS data on **31** are encouraging. Much work however has still to be done, especially in terms of scale-up of the stereoisomeric resolution. Alternatively, direct stereoselective synthesis under the influence of chiral auxiliaries or catalysts deserves to be envisioned.

4. Experimental

4.1. General

All reagents were used as commercially available from Acros Organics, Avocado, Aldrich, Lancaster, Strem. THF and diethylether were dried and distilled on sodium/benzophenone, pentane and dichloromethane on P_2O_5. Commercial solutions of EtMgBr are 3 M in diethylether. Commercial solutions of *n*-BuLi are 1.6 or 2.5 M in hexane, and their effective concentration were checked by titration with 2,2,2′-trimethylpropionanilide.[30] Previously described procedures were used for the preparation of **1**,[15] **4a**, **5a** and **3a**,[10a] **6a**, **6c** and **2a**,[13] **14**,[21,23], **28**, **29**, **30** and **27**.[10b] All reactions were carried out under nitrogen or argon atmosphere, using Schlenk and vacuum line techniques. Column chromatographies were carried out with SDS silicagel (60 Å C.C 70–200 μm). Thin Layer Chromatography plates were purchased from SDS (60F254, 0.25 mm) and revealed by treatment with an ethanolic solution of phosphomolybdic acid (20%). The following analytical instruments were used. IR: 0.1 mm CaF_2 cell, Perkin-Elmer GX FT-IR. ^1H and ^{13}C NMR: Brucker AC 200, WM 250, DPX 300 or AMX 400. X-Ray diffraction: IPds STOE. Mass spectrometry: Quadrupolar Nermag R10-10H. Elemental analyses: Perkin-Elmer 2400 CHN (flash combustion and detection by catharometry). Analytical and semi-preparative HPLC chains: Waters quaternary chains (600 Controller), coupled with UV detectors and driven with a Millenium software (version 4.00). HPLC columns: analytical Prontosil 120-3-SI column 150 mm×4.0 mm i.d., particle size: 3 μm, Bischoff); semi-preparative Prontosil 120-5-SI column (250 mm×8 mm i.d., particle size: 5 μm, Bischoff). All IR and NMR spectra were recorded in $CDCl_3$ solutions. IR absorption frequencies ν are in cm^{-1}. NMR chemical shifts δ are in ppm, with positive values to high frequency relative to the tetramethylsilane reference; coupling constants J are in Hz. Since most compounds are isolated as oily mixtures of diastereoisomers, characteristic assignments are given to trace the analytical consistency within the quite homogeneous series of compounds studied (diethynyl carbinol series and phenyl- and *p*-anisyl-derivatives thereof).

4.1.1. 3-Trimethylsilyl-1-(4-methoxyphenyl) prop-2-yn-1-one (4b). Aluminum chloride (9.00 g, 67 mmol) was added to a solution of bistrimethylsilylacetylene (13.1 mL, 67 mmol) and anisoyl chloride (11.50 g, 67 mmol) in DCM (160 mL) at 0 °C. After stirring for 3 h at r.t., the mixture was cooled to 0 °C, hydrolyzed with ice (50 g) and extracted in dichloromethane. The organic layer was washed with saturated aqueous $NaHCO_3$ and water, then dried over $MgSO_4$. The solvent was removed under reduced pressure to give crude ketone **4b** as an orange oil (15.66 g, 100%), displaying satisfactory analytical data. $R_f \approx 0.45$ (heptane/EtOAc 9:1). ^1H NMR: $\delta=0.24$ (s, 9H; $Si(CH_3)_3$), 3.79 (s, 3H; OCH_3), 6.87 (d, 2H; *m*-C*H*), 8.03 (d, 2H; *o*-C*H*). ^{13}C NMR: $\delta=-0.69$ (q, $^1J_{CH}=120$ Hz; $Si(CH_3)_3$), 55.51 (q, $^1J_{CH}=145$ Hz; OCH_3), 99.38 (s; *C*≡CSi), 100.96 (s; ≡*C*–Si), 113.79 (d, $^1J_{CH}=158$ Hz; *m*-*C*H), 129.66 (s; *ipso*-*C*–C═O), 131.92 (d, $^1J_{CH}=159$ Hz; *o*-*C*H), 164.48 (s; *p*-*C*–OMe), 176.22 (s; *C*═O). IR: $\nu=2978$, 2875 (C–H), 2155 (C≡CSi), 1634 (C═O), 1598, 1509 (aromatic C–C), 1257 (C–Si), 1166, 1110, 1040–1026 (C–O).

4.1.2. 1-Trimethylsilyl-3-(4-methoxyphenyl)penta-1,4-diyn-3-ol (5b). A saturated solution of acetylene in THF (350 mL) at 0 °C was treated with EtMgBr (81.0 mL, 243 mmol) for 1 h at 0 °C. Anisylketone **4b** (15.66 g, 67 mmol) was added, and the stirring was continued overnight (17 h) at r.t. The reaction mixture was hydrolyzed with a saturated aqueous NH_4Cl, and extracted with diethylether. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Purification through column chromatography on silicagel (heptane/EtOAc 8:2) afforded diyne **5b** as a brown oil (10.72 g, 61%). $R_f \approx 0.20$ (heptane/EtOAc 85:15). MS (DCI/NH_3): $m/z=258$ ($[M]^+$), 241 ($[M-OH]^+$), 161 ($[M-C{\equiv}CSiMe_3)]^+$). ^1H NMR: $\delta=0.20$ (s, 9H; $Si(CH_3)_3$), 2.74 (s, 1H; ≡C–*H*), 3.24 (s, 1H; O*H*), 3.78 (s, 3H; OCH_3), 6.91 (d, 2H; *m*-C*H*), 8.09 (d, 2H; *o*-C*H*). ^{13}C NMR: $\delta=-0.48$ (q, $^1J_{CH}=121$ Hz; $Si(CH_3)_3$), 55.26 (q, $^1J_{CH}=144$ Hz; OCH_3), 64.51 (s, >*C*(OH)An), 73.03 (d, $^1J_{CH}=154$ Hz; ≡*C*–H), 83.75 (d, $^2J_{CH}=49$ Hz; *C*≡CH), 89.92 (s; *C*≡CSiMe$_3$), 104.01 (s; ≡*C*–SiMe$_3$), 113.61 (d, $^1J_{CH}=170$ Hz; *m*-*C*H), 127.62 (d, $^1J_{CH}=153$ Hz; *o*-*C*H), 133.32 (s; *ipso*-*C*–C), 159.66 (s; *p*-*C*–OMe). IR: $\nu=3576$ (O–H), 3305 (≡CH), 2963 (C–H), 2840 (OC–H), 2176 (C≡CSi), 2101 (≡CH), 1608, 1510 (aromatic C–C), 1252 (C–Si), 1173, 1091, 1035 (C–O).

4.1.3. 1-Trimethylsilyl-3-(4-methoxyphenyl)-3-methoxypenta-1,4-diyne (3b). A solution of alcohol **5b** (10.72 g, 42 mmol) in THF (180 mL) was treated with *n*-butyllithium (18.80 mL, 42 mmol) at −78 °C. After stirring for 0.5 h,

methyl iodide (20.4 mL, 328 mmol) was added dropwise. The temperature was allowed to warm up to −25 °C, and DMSO (2.9 mL, 42 mmol) was added. After stirring for 1 h at −25 °C, then 2 h at r.t., the reaction mixture was treated with saturated aqueous NH_4Cl and extracted with diethylether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give ether **3b** as an orange powder (8.16 g, 73%). $R_f \approx 0.34$ (heptane/EtOAc 85:15). MS (DCI/NH_3): $m/z = 272$ ($[M]^+$) = 241 ($[M-OCH_3]^+$). ^1H NMR: $\delta = 0.22$ (s, 9H; $Si(CH_3)_3$), 2.73 (s, 1H; ≡C–*H*), 3.46 (s, 3H; Csp^3–OCH_3), 3.81 (s, 3H; CH_3O–C_6H_4), 6.87 (d, 2H; *m*-C*H*), 7.68 (d, 2H; *o*-C*H*). ^{13}C NMR: $\delta = -0.43$ (q, $^1J_{CH} = 121$ Hz; $Si(CH_3)_3$), 55.15 (q, $^1J_{CH} = 144$ Hz; OCH_3), 55.66 (q, $^1J_{CH} = 143$ Hz; OCH_3), 71.81 (s, >*C*(OMe)An), 73.03 (d, $^1J_{CH} = 254$ Hz; ≡*C*–H), 81.27 (d, $^2J_{CH} = 49$ Hz; *C*≡CH), 91.71 (s; –*C*≡$CSiMe_3$), 101.37 (s; ≡*C*–$SiMe_3$), 113.41 (d, $^1J_{CH} = 154$ Hz; *m*-*C*H), 127.81 (d, $^1J_{CH} = 160$ Hz; *o*-*C*H), 131.79 (s; *ipso*-*C*–C–OMe), 159.75 (s; *p*-*C*–OMe). IR: $\nu = 3305$ (≡CH), 2961 (C–H), 2839 (OC–H), 2170 (C≡CSi), 2117 (≡CH), 1609, 1509 (aromatic C–C), 1252 (C–Si), 1174, 1089, 1060 (C–O).

4.1.4. 1,11-Bis(trimethylsilyl)-3,9-dimethoxy-3,6,9-tris(4-methoxyphenyl)undeca-1,4,7,10-tetrayn-6-ol (6b). A solution of diyne **3b** (12.64 g, 46 mmol) in THF (100 mL) was treated with *n*-butyllithium (19.73 mL, 46 mmol) at −78 °C. After stirring for 10 min, anisoyl chloride (3.96 g, 23 mmol) was added and the reaction mixture was stirred for 3 h at r.t. The mixture was hydrolyzed with saturated NH_4Cl and extracted with diethylether. The organic layer was washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification through column chromatography (heptane/EtOAc 9:1) afforded tetrayne **6b** as a brown oil (8.18 g, 52%). $R_f \approx 0.21$ (heptane/EtOAc 85:15). MS (DCI/NH_3): $m/z = 679$ ($[MH]^+$), 661 ($[M-OH]^+$), 647 ($[M-OCH_3]^+$). ^1H NMR: $\delta = 0.19$–0.21 (m, 18H; $Si(CH_3)_3$), 3.12 (s, 1H; O*H*), 3.41–3.46 (m, 6H; Csp^3OCH_3), 3.71–3.81 (m, 9H; $C_6H_4OCH_3$), 6.83–6.91 (m, 6H; *m*-C*H*), 7.62–7.73 (m, 6H; *o*-C*H*). ^{13}C NMR: $\delta = -0.02$ (q, $^1J_{CH} = 120$ Hz; $Si(CH_3)_3$), 52.92 (q, $^1J_{CH} = 144$ Hz; Csp^3–OCH_3), 55.29 (q, $^1J_{CH} = 144$ Hz; C_6H_4–OCH_3), 67.94 (s; >*C*(OH)An), 74.48 (s; >*C*(OMe)An), 83.02 and 86.18 (s; *C*≡C), 92.08 (s; *C*≡$CSiMe_3$), 101.50 (s; ≡*C*–$SiMe_3$), 113.65 (d, $^1J_{CH} = 155$ Hz, *m*-*C*H), 127.20 (d, $^1J_{CH} = 154$ Hz, *o*-*C*H), 132.00 (broad s; *ipso*-*C*–O), 159.96 (s; *p*-*C*–OMe). IR: $\nu = 3570$ (O–H), 2961 (C–H), 2840 (OC–H), 2171 (C≡CSi), 1609, 1510 (aromatic C–C), 1252 (C–Si), 1174, 1061, 1035 (C–O).

4.1.5. 1,11-Bis(trimethylsilyl)-3,6,9-dimethoxy-3,6,9-tris(4-methoxyphenyl)undeca-1,4,7,10-tetrayne (6d). A solution of alcohol **6b** (8.18 g, 12 mmol) in THF (200 mL) was treated with *n*-butyllithium (7.6 mL, 12 mmol) at −78 °C for 10 min. Iodomethane (6.0 mL, 96 mmol) was added and the temperature was allowed to warm up to −25 °C. DMSO (0.86 mL, 12 mmol) was added, and stirring was continued for 1 h at −20 °C, then for 3 h at r.t. After treatment with saturated aqueous NH_4Cl and extraction with ether, the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give ether **6d** as a brown oil (7.22 g, 83%). The crude product displays satisfactory analyses and was used as such in the next step. $R_f \approx 0.23$ (heptane/EtOAc 9:1). MS (DCI/NH_3): $m/z = 693$ ($[MH]^+$), 661 ($[M-OCH_3]^+$). ^1H NMR: $\delta = 0.21$–0.22 (s, 18H; $Si(CH_3)_3$), 3.45–3.54 (s, 9H; Csp^3OCH_3), 3.79–3.80 (m, 9H; $C_6H_4OCH_3$), 6.83–6.88 (m; 6H; *m*-C*H*), 7.63–7.69 (m, 6H; *o*-C*H*). $^{13}C\{^1H\}$NMR: $\delta = -0.43$ ($Si(CH_3)_3$), 53.06 (Csp^3–OCH_3), 55.13 (C_6H_4–OCH_3), 71.47 (>*C*(OMe)An), 83.82 and 84.53 (*C*≡C), 91.86 (*C*≡$CSiMe_3$), 101.45 (≡*C*–$SiMe_3$), 113.08 (*m*-*C*H), 127.70 (*o*-*C*H), 131.81 (*ipso*-*C*–C), 159.83 (*p*-*C*–OMe). IR: $\nu = 2960$, 2935 (C–H), 2840 (OC–H), 2170 (C≡CSi), 1609, 1509 (aromatic C–C), 1252 (C–Si), 1174, 1061 (C–O).

4.1.6. 3,6,9-Trimethoxy-3,6,9-tris(4-methoxyphenyl)-undeca-1,4,7,10-tetrayne (2b). Tetrayne **6d** (7.22 g, 10 mmol) and K_2CO_3 (7.20 g, 52 mmol) were dissolved in methanol (25 mL) at 0 °C. After stirring for 1 h at r.t., the reaction mixture was filtered, concentrated and diluted with diethylether (100 mL). The organic layer was washed with water (2×50 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated to dryness under reduced pressure to give crude tetrayne **2b** as a brown oil (5.45 g, 99%). $R_f \approx 0.18$ (heptane/EtOAc 8:2). MS (DCI/NH_3): $m/z = 566$ ($[M+NH_4]^+$), 548 ($[MH]^+$), 517 ($[M-OCH_3)]^+$). ^1H NMR: $\delta = 2.76$ (s, 2H; ≡C–*H*), 3.49–3.53 (m, 9H; Csp^3–OCH_3), 3.79–3.81 (m, 9H; $C_6H_4OCH_3$), 6.84–6.92 (m, 6H; *m*-C*H*), 7.65–7.70 (m, 6H; *o*-C*H*). ^{13}C NMR: $\delta = 53.75$ (q, $^1J_{CH} = 152$ Hz; Csp^3–OCH_3), 54.53 (q, $^1J_{CH} = 144$ Hz; C_6H_4–OCH_3), 71.65 (s; ≡*C*–H), 72.41 (s; >*C*(OMe)An), 74.95 (s, *C*≡CH), 84.01 and 84.33 (s; *C*≡C), 113.57 (d, $^1J_{CH} = 155$ Hz; *m*-*C*H), 127.82 (d, $^1J_{CH} = 154$ Hz; *o*-*C*H), 131.62 (s; *ipso*-*C*–C), 159.93 (s; *p*-*C*–OMe). IR: $\nu = 3305$ (≡CH), 3003, 2957, 2936 (C–H), 2839, 2826 (OC–H), 2117 (≡CH), 1609, 1508 (aromatic C–C), 1258, 1177, 1060 (C–O).

4.1.7. 1,4,13-Trimethoxy-1,4,7,10,13-pentaphenylcyclopentadeca-2,5,8,11,14-pentayn-7,10-diol (7a) and side-products. A solution of tetrayne **2a** (300 mg, 0.65 mmol) in THF (10 mL) was treated with *n*-butyllithium (0.59 mL, 1.31 mmol) for 10 min between −78 °C and −15 °C while the color turned to deep green. After cooling back to −78 °C, a solution of dibenzoylacetylene **1** (153 mg, 65 mmol) in THF (12 mL) was added dropwise. The temperature was allowed to warm up to r.t. over a 45 min period, and stirring was continued for a further 1.5 h. The mixture was diluted with diethylether (50 mL), treated with saturated aqueous NH_4Cl (30 mL). The organic layer was separated, washed with aqueous NH_4Cl (30 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The dark brown crude oil (370 mg) was chromatographed over silicagel (heptane/acetone 8:2) to afford [5]pericyclyne **7a** as an orange oil (166 mg, 37%). $R_f = 0.20$ (heptane/acetone 8:2). MS (DCI/NH_3): $m/z = 710$ ($[M+NH_4]^+$), 661 ($[M-CH_3O]^+$). ^1H NMR: $\delta = 3.09$ and 3.18 (2s, 2H; O*H*), 3.40–3.69 (m, 9H; OCH_3), 7.32–7.47 (m, 15H; *m*-, *p*-C*H*), 7.68–7.90 (m, 10H; *o*-C*H*). $^{13}C\{^1H\}$ NMR: $\delta = 53.96$–54.10 (OCH_3), 65.68 (>*C*(OH)Ph), 72.58 (>*C*(OMe)Ph), 81.80–82.30 and 83.77–84.48 and 86.05–86.31 (*C*≡C), 126.26–127.00 (*m*-, *p*-C*H*), 128.87–129.67 (*o*-C*H*), 139.50–139.78 (*ipso*-*C*–C–OMe), 140.82–140.95 (*ipso*-*C*–C–OH). IR: $\nu = 3683$, 3558, 3291 (O–H), 3062–2896

(C–H), 2822 (OC–H), 1604, 1490 (aromatic C–C), 1451 (C–H), 1224, 1178, 1069 (C–O). The main characteristics of three side-products (**8a**–**10a**, 10–25%) are listed below.

4.1.8. 4-Hydroxy-7,10,17-trimethoxy-1,4,7,10,13-pentaphenylpentadeca-2,5,8,11,14-pentayn-1-one (8a). $R_f \approx 0.26$ (heptane/acetone 8:2). MS (DCI/NH_3): $m/z = 710$ ($[M+NH_4]^+$). ^{1}H NMR: $\delta = 2.76$ (s, 1H; ≡C–*H*), 3.50–3.55 (m, 9H; OCH_3), 7.32–7.46 (m, 12H; Csp^3-phenyl *m*-, *p*-C*H*), 7.52–7.58 (m, 3H; benzoyl *m*-, *p*-C*H*), 7.72–7.82 (m, 8H; Csp^3-phenyl *o*-C*H*), 8.05–8.10 (m, 2H; benzoyl *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 53.62$ (O*C*H$_3$), 65.56 (>*C*(OH)Ph), 71.97 (>*C*(OMe)Ph), 75.52 (≡*C*–H), 80.64 (*C*≡CH), 81.21–91.87 (*C*≡C), 125.78–136.33 (aromatic *C*H), 139.36 (*ipso-C*–C–OCH$_3$), 139.89 (*ipso-C*–C–OH), 177.37 (*C*=O). IR: $\nu = 3571$ (O–H), 3305 (≡C–H), 1649 (C=O).

4.1.9. 3,6,9,18,21,24-Hexamethoxy-3,6,9,12,15,18,21,24-octaphenylhexacosa-1,4,7,10,13,16,19,22,25, 28-nonayn-12,15-diol (9a). $R_f \approx 0.15$ (heptane/acetone 8:3). MS (DCI/NH_3): $m/z = 1168$ ($[M+NH_4]^+$). ^{1}H NMR: $\delta = 2.75$ (s, 2H; ≡C–*H*), 3.09 (m, 2H; O*H*) 3.46–3.51 (m, 18H; OCH_3), 7.31–7.34 (m, 18H; *m*-, *p*-C*H*), 7.71–7.73 (m, 12H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 53.33$ and 53.48 (O*C*H$_3$), 65.17 (>*C*(OH)Ph), 71.92 (>*C*(OMe)Ph), 75.45 (≡*C*–H), 80.52 (*C*≡CH), 82.55–86.34 (*C*≡*C*), 125.84–129.01 (aromatic *C*H), 139.44 (*ipso-C*–C–OMe), 140.76 (*ipso-C*–C–OH). IR: $\nu = 3571$ (O–H), 3305 (≡C–H).

4.1.10. 4,16-Dihydroxy-7,10,13-trimethoxy-1,4,7,10,13,16,19-heptaphenylnonadeca-2,5,8,11,14,17-hexayn-1,19-dione (10a). $R_f \approx 0.15$ (heptane/acetone 8:2). MS (DCI/NH_3): $m/z = 944$ ($[M+NH_4]^+$). ^{1}H NMR: $\delta = 3.49$–3.52 (m, 9H; OCH_3), 3.90 (m, 2H; O*H*), 7.25–7.44 (m, 15H; Csp^3-phenyl *m*-, *p*-C*H*), 7.54–7.60 (m, 6H; benzoyl *m*-, *p*-C*H*), 7.70–7.80 (m, 10H; Csp^3–phenyl *o*-C$_6H_5$), 8.04–8.10 (m, 4H; benzoyl *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 53.62$ (O*C*H$_3$), 64.94 (>*C*(OH)Ph), 72.02 (>*C*(OMe)Ph), 81.64–85.79 and 92.02 (*C*≡C), 125.89–136.33 (aromatic *C*H), 139.12 (*ipso-C*–C–OMe), 139.78 (*ipso-C*–C–OH), 177.52 (*C*=O).

4.1.11. 1,4,13-Trimethoxy-1,4,13-tris(4-methoxyphenyl)-7,10-diphenyl-cyclopentadeca-2,5,8,11, 14-pentayn-7,10-diol (7b). The above Section 4.1.9 for the preparation of **7a** was applied to tetrayne **2b** (412 mg, 0.75 mmol) and dibenzoylacetylene **1** (176 mg, 0.75 mmol) to afford trianisyl-[5]pericyclyne **7b** as an orange oil (180 mg, 31%). $R_f \approx 0.20$ (heptane/EtOAc 7:3). MS (DCI/NH_3): $m/z = 800$ ($[M+NH_4]^+$), 768 ($[M-MeOH+NH_4]^+$), 751 ($[M-MeO]^+$). ^{1}H NMR: $\delta = 3.30$–3.62 (m, 9H; OCH_3), 3.69–3.86 (m, 9H; C$_6$H$_4$OCH_3), 6.78–6.92 (m, 6H; *p*-anisyl *m*-C*H*), 7.30–7.40 (m, 6H; phenyl *m*-, *p*-C*H*), 7.51–7.84 (m, 10H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 53.44$ (Csp^3–O*C*H$_3$), 55.45 (C$_6$H$_4$O*C*H$_3$), 65.22 (>*C*(OH)Ph), 71.76 (>*C*(OMe)An), 81.63–85.85 (*C*≡C), 113.87 (*p*-anisyl *m*-*C*H), 125.94–129.07 (phenyl *C*H), 128.63 (*p*-anisyl *o*-*C*H), 131.45 (anisyl *ipso-C*–C–OMe), 140.67 (phenyl *ipso-C*–C–OH), 160.15 (*p*-anisyl *p*-*C*–OMe).

4.1.12. 1,4,7,10,13-Pentamethoxy-1,4,7,10,13-pentaphenylcyclopentadeca-2,5,8,11,14-pentayne (11a). *n*-Butyllithium (105 μL, 0.23 mmol) was syringed into a solution of [5]pericyclyndiol **7a** (80 mg, 0.12 mmol) in THF (3 mL) at −78 °C. After stirring for 15 min, methyl iodide was added (115 μL, 1.85 mmol), and the temperature was allowed to warm up to −25 °C. DMSO (20 μL; 0.23 mmol) was added and stirring was continued at −25 °C for 1 h, then at r.t. for a further 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and extracted with diethylether. The organic layer was washed with aqueous NH_4Cl and brine, dried with magnesium sulfate and the solvent was removed under reduced pressure. Purification by column chromatography (heptane/acetone 7:3) gave **11a** as a yellow oil (80 mg, 92%). $R_f \approx 0.26$ (heptane/acetone 7:3). MS (DCI/NH_3): $m/z = 738$ ($[M+NH_4]^+$), 689 ($[M-CH_3O]^+$). MS (APCI/CH_3CN): $m/z = 730$ ($[M-CH_3O+CH_3CN]^+$). ^{1}H NMR: $\delta = 3.37$–3.69 (8s, 15H; OCH_3), 7.33–7.45 (m, 15H; *m*-, *p*-C*H*), 7.74–7.90 (m, 10H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 53.73$ (O*C*H$_3$), 72.35 (>*C*(OMe)Ph), 83.42–83.86 (*C*≡C), 126.57 (*m*-, *p*-*C*H), 128.32–129.16 (*o*-*C*H), 139.53 (*ipso-C*–C–OMe). IR: $\nu =$ 3067–2902 (C–H), 2827 (OC–H), 1601, 1490, 1451 (aromatic C–C), 1230, 1178, 1154, 1071 (C–O). Notice: the cylization step (4.8) and methylation steps can also be performed subsequently in one pot.

4.1.13. Dicobalthexacarbonyl-1,4,13-trimethoxy-1,4,7,10,13-pentaphenylcyclopentadeca-2,5,8, 11,14-pentayn-7,10-diol (12a), and side-product. Dicobaltoctacarbonyle (126 mg, 0.37 mmol) was added into a solution of [5]pericyclyndiol **7a** (256 mg, 0.37 mmol) in diethylether (25 mL) at 0 °C. The color turned red, and the reaction was monitored by TLC. After stirring for 30 min, the solution was concentrated and the oily residue was chromatographed over silicagel (heptane/acetone 8:2). The dinuclear complex **12a** was obtained as a red-orange oil (231 mg, 64%). $R_f \approx 0.33$ (heptane/acetone 7:3). MS (APCI>0/CH_3CN): $m/z = 716$ ($[M-Co_2(CO)_6-OH+CH_3CN]^+$), 702 ($[M-Co_2(CO)_6-CH_3O+CH_3CN]^+$). MS (MALDI/dithranol–NaI): $m/z = 1001$ ($[M+Na]^+$), 715 ($[M+Na-Co_2(CO)_6]^+$). Elemental analysis % (calcd): C = 65.96 (66.27), H = 4.22 (3.71), Co = 10.07 (12.04). ^{1}H NMR: $\delta = 3.27$–3.72 (m, 9H; OCH_3), 7.19–7.42 (m, 15H; *m*-, *p*-C*H*), 7.52–7.80 (m, 10H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta =$ 52.11–52.92 (O*C*H$_3$), 72.02 (>*C*(OMe)Ph), 85.26–86.03 (*C*≡*C*), 100.72–101.55 ((*C*≡*C*)(Co$_2$(CO)$_6$)), 125.56–129.16 (aromatic *C*H), 139.54 (*ipso-C*–C–OMe), 141.78 (*ipso-C*–C–OH), 198.75 (Co$_2$(*C*≡O)$_6$). IR: $\nu = 3689$, 3536 (O–H), 2097, 2063 and 2037 (CoC≡O).

The less polar tetranuclear complex **12a′** was also isolated as a red oil from the chromatography column (79 mg, 17%): bis(dicobalthexacarbonyl)-1,4,13-trimethoxy-1,4,7,10,13-penta-phenylcyclo-pentadeca-2,5,8,11,14-pentayn-7,10-diol (**12a′**) $R_f \approx 0.48$ (heptane/acetone 7:3). MS (MALDI/dithranol–NaI): $m/z = 715$ ($[M+Na-2Co_2(CO)_6]^+$). Elemental analysis % (calcd): C = 57.79 (56.98), H = 3.00 (2.87). ^{1}H NMR: $\delta = 3.29$–3.57 (m, 9H; OCH_3), 7.21–7.44 (m, 15H; *m*-, *p*-C*H*), 7.59–7.80 (m, 10H; *o*-C*H*). IR: $\nu =$ 3689, 3409 (O–H), 2095, 2064, 2035 (Co$_2$(C≡O)$_6$).

4.1.14. Dicobalthexacarbonyl-1,4,13-trimethoxy-1,4,13-tris(4-methoxyphenyl)-7,10-diphenyl-cyclopentadeca-2,5,8,11,14-pentayn-7,10-diol (12b). The above Section 4.1.13 for the preparation of **12a** was applied to

pericyclyndiol **7b** (180 mg, 0.23 mmol) and dicobalt–octacarbonyle (80 mg, 0.23 mmol) to afford the dinuclear complex **12b** as a red oil (180 mg, 57%). $R_f \approx 0.24$ (heptane/EtOAc 7:3). ^{1}H NMR: $\delta = 3.21$–3.57 (m, 9H; OCH_3), 3.61–3.86 (m, 9H; C_6H_4–OCH_3), 6.64–6.97 (m, 6H; *m*-C*H*), 7.31–7.50 (m, 6H; phenyl *m*-, *p*-C*H*), 7.53–7.81 (m, 10H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 53.43$ (Csp^3–OCH_3), 55.44 (C_6H_4–OCH_3), 64.55 (>*C*(OH)Ph), 71.83 (>*C*(OMe)An), 84.32–89.35 (*C*≡*C*), 103.06 (*C*≡C(Co_2 $(CO)_6$)), 113.87 (*p*-anisyl *m*-*C*H), 125.53–129.45 (aromatic *C*H), 128.17 (*p*-anisyl *o*-*C*H), 133.67 (i*pso*-*C*–C–OMe), 143.83 (*ipso*-*C*–C–OH), 160.12 (*p*-*C*–OMe), 198.29 (*C*≡O). IR: $\nu =$ 3536 (O–H), 2097, 2062, 2036 (Co_2(C≡O)$_6$).

4.1.15. Dicobalthexacarbonyle-1,4,7,10,13-pentamethoxy-1,4,7,10,13-pentaphenylcyclopenta-deca-2,5,8,11,14-pentayne (13a). The above Section 4.1.13 for the preparation of **12a** was applied to pericyclyne **11a** (80 mg; 0.11 mmol) and dicobaltoctacarbonyle (38 mg; 0.11 mmol) to afford the dinuclear complex **13a** as a reddish oil (56 mg, 54%). $R_f \approx 0.38$ (heptane/acetone 7:3). MS (APCI/CH_3CN): $m/z = 730$ ([M−$Co_2(CO)_6$–CH_3O+CH_3CN]$^+$), 689 ([M−$Co_2(CO)_6$–CH_3O]$^+$). ^{1}H NMR: $\delta = 3.11$–3.81 (m, 15H; OCH_3), 6.89–7.20, 7.35–7.45 and 7.54–7.94 (m, 25H; aromatic C*H*). ^{13}C{^{1}H} NMR: $\delta = 52.51$–53.94 (OCH_3), 85.23–87.05 (*C*≡*C*), 100.77–101.57 (*C*≡C($Co_2CO)_6$)), 125.63–129.15 (aromatic *C*H), 139.57 (*ipso*-*C*–C–OMe), 141.75 (*ipso*-*C*–C–OMe in β position from Co), 198.73–199.33 (*C*≡O). IR: $\nu = 3065$–2900 (C–H), 2827 (OC–H), 2094, 2060, 2034 (Co_2(C≡O)$_6$). 1600, 1490 (aromatic C–C), 1450 (C–H), 1230, 1177, 1151, 1068 (C–O).

The less polar tetranuclear complex **13a′** was also isolated as a red oil from the chromatography column (38 mg, 27%): bis(dicobalthexacarbonyl)-1,4,7,10,13-pentamethoxy-1,4,7,10,13-penta-phenylcyclopentadeca-2,5,8,11,14-pentayne (**13a′**) $R_f \approx 0.50$ (heptane/acetone 7:3). ^{1}H NMR: $\delta = 3.29$–3.57 (m, 9H; OCH_3), 7.21–7.44 (m, 15H; *m*-, *p*-C*H*), 7.59–7.80 (m, 10H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 52.52$–53.95 (OCH_3), 85.26–87.04 (*C*≡C), 100.72–101.55 (*C*≡*C*($Co_2(CO)_6$)), 125.64–129.14 (aromatic *C*H), 139.54 (*ipso*-*C*–C–OMe), 141.73 (*ipso*-*C*–C–OMe in β position from Co), 198.75–199.32 (*C*≡O). IR: $\nu = 2095$, 2064, 2035 (Co_2(C≡O)$_6$).

4.1.16. Dicobalthexacarbonyle-1,4,13-trimethoxy-1,4,13-triphenylcyclopentadeca-2,5,8,11,14-pentayn-7,10-diol (15a). *n*-Butyllithium (1.00 mL, 2.18 mmol) was added dropwise into a solution of tetrayne **2a** (500 mg, 1.09 mmol) in THF (30 mL) at −78 °C. The temperature was allowed to warm up to −15 °C while the color turned to green. After cooling back to −78 °C, a solution of complex **14** (401 mg, 1.09 mmol) in THF (25 mL) was added dropwise. The temperature was allowed to warm up to −30 °C and then quenched with saturated aqueous NH_4Cl (30 mL), and diluted with diethylether (50 mL). The organic layer was separated, then washed with saturated aqueous NH_4Cl (2× 20 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The deep red residue (580 mg) was purified by column chromatography over silicagel (heptane/acetone 7:3). Complex **15a** was isolated as a deep red oil (226 mg, 25%). $R_f \approx 0.36$ (heptane/acetone 7:3). ^{1}H NMR: $\delta = 3.21$–3.27 (m, 2H; O*H*), 3.32–3.69 (m, 9H; OCH_3), 5.76–5.79 (m, 2H; >C*H*(OH)), 7.36–7,44 (m, 9H; *m*-, *p*-C*H*), 7.69–7.77 (m, 6H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 53.35$–53.51 (OCH_3), 63.50 and 63.94 (>*C*H(OH)), (>*C*(OMe)Ph), 83.34–85.68 (*C*≡*C*), 92.21–93.13 ((*C*≡*C*)($Co_2(CO)_6$)), 126.50–129.09 (aromatic *C*H), 138.93 (*ipso*-*C*–C–OMe), 198.39–198.63 (*C*≡O). IR: $\nu =$ 3583 (O–H), 3066–2900 (C–H), 2827 (OC–H), 2100, 2066, 2038 (Co_2(C≡O)$_6$), 1600–1577, 1490 (aromatic C–C), 1450 (C–H), 1228, 1178, 1069 (C–O).

4.1.17. Dicobalthexacarbonyle-1,4,13-trimethoxy-1,4,13-tris(4′-methoxyphenyl)cyclopentadeca- 2,5,8,11,14-pentayn-7,10-diol (15b). The above Section 4.1.16 for the preparation of **15a** was applied to tetrayne **2b** (197 mg, 0,36 mmol), *n*-butyllithium (0.29 mL, 0.72 mmol) and complex **14** (130 mg, 0.36 mmol) to afford complex **15b** as a red-orange oil (22 mg, 6%). $R_f \approx 0.25$ (heptane/EtOAc 7:3). ^{1}H NMR: $\delta = 3.29$–3.50 (m, 9H; OCH_3), 3.80–3.81 (m, 9H; C_6H_4–OCH_3), 5.74 and 5.78 (2s, 2H; C*H*(OH)), 6.80–6.92 (m, 6H; anisyl *m*-C*H*), 7.57–7.70 (m, 6H; anisyl *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 53.32$ (Csp^3–OCH_3), 55.34 (C_6H_4–OCH_3), 63.96 (*C*H(OH)), 71.67 (>*C*(OMe)An), 84.02 and 84.34 (*C*≡*C*), 92.65 ((*C*≡*C*)$Co_2(CO)_6$), 113.63 (anisyl *m*-*C*H), 127.85 (anisyl *o*-*C*H), 131.66 (*ipso*-*C*–C–OMe), 160.13 (anisyl *p*-*C*–OMe), 198.52 (Co_2(*C*≡O)$_6$). IR: $\nu =$ 3689, 3587, 3537 (O–H), 2097, 2062, 2036 (Co_2(C≡O)$_6$).

4.1.18. 1,4,13-Trimethoxy-1,4,13-triphenylcyclopentadeca-2,5,8,11,14-pentayn-7,10-diol (16a). Cerium ammonium nitrate (146 mg, 0.27 mmol) was added to a solution of complex **15a** (110 mg, 0.14 mmol) in acetone (6 mL) at 0 °C. After 15 min, the reaction mixture was warmed to r.t. and stirring was continued for 1.5 h. The IR spectrum reveals the complete disappearance of carbonyl stretching vibrations. The reaction mixture was treated with water and diluted with diethylether. The organic layer was separated, washed with water (2×10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed over silicagel (heptane/acetone 8:2) to give free [5]pericyclyndiol **16a** as a brown oil (50 mg, 70%). $R_f \approx 0.22$ (heptane/acetone 7:3). MS (DCI/NH_3): $m/z = 558$ ([M+NH_4]$^+$), 526 ([M−MeOH+NH_4]$^+$), 509 ([MH−MeOH]$^+$), 494 ([M−2MeOH+NH_4]$^+$). ^{1}H NMR: $\delta = 3.35$–3.62 (m, 9H; OCH_3), 5.14–5.21 (m, 2H; >C*H*(OH)), 7.21–7.39 (m, 9H; *m*-, *p*-C*H*), 7.60–7.79 (m, 6H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 52.89$ and 53.04 (OCH_3), 63.22 and 63.36 (>*C*H(OH)), 71.97 (>*C*(OMe)Ph), 83.32–85.75 (*C*≡*C*), 126.53–129.15 (aromatic *C*H), 138.97 (*ipso*-*C*–C–OMe).

4.1.19. 1,4,13-Trimethoxy-1,4,13-tri(4-methoxyphenyl)-cyclopentadeca-2,5,8,11,14-pentayn-7,10-diol (16b). The above Section 4.1.18 for the preparation of **16a** was applied to complex **15b** (22 mg; 0,03 mmol), ceric ammonium nitrate (33 mg, 0,06 mmol) to afford free [5]pericyclyndiol **16b** as an orange oil (16 mg, 100%). $R_f \approx 0.31$ (heptane/EtOAc 5:5). MS (DCI/NH_3): $m/z = 630$ ([M]$^+$), 599 ([M−CH_3O]$^+$). ^{1}H NMR: $\delta = 2.82$ (m, 2H; O*H*), 3.37–3.60 (s, 9H; OCH_3), 3.80–3.82 (s, 9H, C_6H_4–CH_3O), 5.15–5.21 (m, 2H; C*H*(OH)), 6.87–6.90 (m, 6H; *m*-C*H*), 7.59–7.68 (m, 6H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 53.32$ (OCH_3), 55.44 (C_6H_4–OCH_3), 65.76 (*C*H(OH)), 71.55 (>*C*(OMe)An), 83.03 and 83.56 (*C*≡*C*), 113.82 (*m*-*C*H), 128.45 (*o*-*C*H), 131.12

(*ipso-C*–C–OMe), 160.15 (*p-C*–OMe). IR: $\nu = 3686$ (O–H), 2923 (C–H), 2843 (OC–H), 1605, 1509 (aromatic C–C), 1457 (C–H), 1250, 1170, 1060, 1034 (C–O).

4.1.20. 1,4,7,10,13-Pentamethoxy-1,4,13-tri(4-methoxyphenyl)cyclopentadeca-2,5,8,11,14-pentayne (17b). *n*-Butyllithium (20 μL, 0.05 mmol) was syringed dropwise into a solution of [5]pericyclyndiol **16b** (16 mg, 0.03 mmol) in THF (3 mL) at −78 °C. After stirring for 10 min, methyl iodide (27 μL; 0.40 mmol) was added, and the temperature was allowed to warm up to −25 °C. DMSO (4 μL; 0.05 mmol) was introduced and the reaction mixture was stirred for 1 h at −25 °C, and then for a further 2 h at r.t. The reaction mixture was diluted with diethylether (20 mL) and treated with saturated aqueous NH_4Cl (20 mL). The organic layer was separated, washed with saturated aqueous NH_4Cl (2×10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Crude pentamethoxy[5]pericyclyne **17b** (13 mg, 67%) exhibited consistent spectroscopic data. $R_f \approx 0.40$ (heptane/EtOAc 5:5). MS (DCI/NH_3): $m/z = 627$ ($[M-CH_3O]^+$). ^{1}H NMR: $\delta =$ 3.32–3.66 (s, 9H; Csp^3–OCH_3), 3.81–3.83 (s, 9H; C_6H_4–OCH_3), 5.19 (m, 2H; C*H*(OMe)), 6.83–6.98 (m, 6H; *m*-C*H*), 7.51–7.73 (m, 6H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = 53.3$–55.4 (O*C*H_3), 71.7 (>*C*–OMe), 113.8 (*m-C*H), 128.5 (*o-C*H), 131.1 (*ipso-C*–C–OMe), 160.2 (*p-C*−OMe).

4.1.21. 1,8-Bis(trimethylsilyl)-6-methoxy-3,6-diphenylocta-1,4,7-triyn-3-ol (19a). EtMgBr (0.33 mL, 0.99 mmol) was added dropwise into a solution of diyne **3a** (239 mg, 0.99 mmol) in THF (4 mL) at 0 °C. After stirring for 1 h at 0 °C, benzoylethynylketone **4a** (200 mg, 0.99 mmol) was introduced and the reaction mixture was stirred for 2 h at r.t. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and diluted with dietehylether (20 mL). The organic layer was separated, washed with saturated aqueous NH_4Cl (2×5 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated under reduced pressure. Purification by column chromatography (heptane/acetone 8:2) gave **19a** as a brown oil (415 mg, 87%). $R_f \approx 0.30$ (heptane/acetone 8:2). ^{1}H NMR: $\delta = 0.22$ and 0.24 (2s, 18H; Si(CH_3)$_3$), 3.02 (s, 1H; O*H*), 3.50–3.51 (m, 3H; OCH_3), 7.36–7.40 (m, 6H; *m*-, *p*-C*H*), 7.77–7.83 (m, 4H; *o*-C*H*). ^{13}C NMR: $\delta = -0.21$ (q, $^1J_{CH} =$ 120 Hz; Si(*C*H_3)$_3$), 53.14 (q, $^1J_{CH} = 143$ Hz; O*C*H_3), 65.33 (s; >*C*(OH)Ph), 72.07 (s, >*C*(OMe)Ph), 82.7 and 86.77 (2 s; C–*C*≡*C*–C), 90.54 (s, (HO)C–*C*≡C–SiMe$_3$), 92.32 (s, (MeO)C–*C*≡C–SiMe$_3$), 101.39 (s; (MeO)C–C≡*C*–SiMe$_3$), 104.05 (s; (HO)C–C≡*C*–SiMe$_3$), 126.03–129.67 (m; aromatic *C*H), 139.75 (s; *ipso*-*C*–C–OMe), 141.18 (s; *ipso*-*C*–C–OH).

4.1.22. 1,8-Bis(trimethylsilyl)-6-methoxy-3,6-di(4-methoxyphenyl)octa-1,4,7-triyn-3-ol (19b). The above Section 4.1.21 for the preparation of **19a** was applied to diyne **3b** (5.00 g, 183 mmol), EtMgBr (6.70 mL, 183 mmol) and anisoylethynylketone **4b** (4.28 g; 183 mmol) to afford triyne **19b** as an orange oil (8.8 mg, 92%). ^{1}H NMR: $\delta = 0.20$ (s, 18H; Si(CH_3)$_3$), 3.56 (m, 2H; O*H*), 3.78 (s, 6H; C_6H_4–OCH_3), 6.89 (d, $^3J_{HH} = 9$ Hz, 4H; *m*-C*H*), 7.70 (d, $^3J_{HH} =$ 9 Hz, 4H; *o*-C*H*). ^{13}C NMR: $\delta = -0.37$ (q, $^1J_{CH} = 12$ Hz; Si(*C*H_3)$_3$), 55.19 (q, $^1J_{CH} = 144$ Hz; C_6H_4–O*C*H_3), 64.66 (s; *C*–OH), 84.74 (s, *C*≡*C*), 89.73 (s; *C*≡CSiMe$_3$), 104.35 (s; C≡*C*–SiMe$_3$), 113.55 (dd, $^1J_{CH} = 160$ Hz, $^2J_{CH} = 5$ Hz; *m-C*H), 127.39 (dd, $^1J_{CH} = 160$ Hz, $^2J_{CH} = 5$ Hz; *o-C*H), 133.66 (s; *ipso-C*–C–OH), 159.39 (s; *p-C*–OMe).

4.1.23. 1,8-Bis(trimethylsilyl)-3,6-dimethoxy-3,6-diphenylocta-1,4,7-triyne (20a). *n*-Butyllithium (2.20 mL, 5.50 mmol) was added dropwise into a solution of alcohol **19a** (1.18 g, 2.75 mmol) in THF (20 mL) at −78 °C. After stirring for 10 min, methyl iodide was added (2.74 mL, 44 mmol), and the temperature was allowed to warm up to −25 °C before addition of DMSO (0.40 mL, 5.50 mmol). Stirring was continued for 1 h at −25 °C, for a further 1 h at r.t. Diethylether (25 mL) was added and the organic layer was washed with saturated aqueous NH_4Cl (2×20 mL) and brine (20 mL), then dried over $MgSO_4$, and concentrated under reduced pressure. Crude diether **20a** was obtained as an orange oil (1.23 g, 97%) displaying satisfactory analytical data. ^{1}H NMR: $\delta = 0.20$–0.24 (s, 18H; Si(CH_3)$_3$), 3.50 and 3.51 (2s, 6H; OCH_3), 7.34–7.38 (m, 6H; *m*-, *p*-C*H*), 7.74–7.78 (m, 4H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta = -0.25$ (Si(*C*H_3)$_3$), 53.25 (O*C*H_3), 72.17 (>*C*(OMe)Ph), 84.55 (C–*C*≡*C*–C), 92.28 (–*C*≡CSiMe$_3$), 101.53 (≡*C*–SiMe$_3$), 126.62–128.89 (m; aromatic *C*H), 139.84 (*ipso*-*C*–C–OMe). IR: $\nu = 3065$–2901 (C–H), 2826 (OC–H), 2171 (C≡CSi), 1600, 1490 (aromatic C–C), 1450 (C–H), 1251 (C–Si), 1062 (C–O).

4.1.24. 1,8-Bis(trimethylsilyl)-3,6-dimethoxy-3,6-di(4-methoxyphenyl)octa-1,4,7-triyne (20b). The above Section 4.1.23 for the preparation of **19a** was applied to alcohol **19b** (0.83 g, 1.68 mmol), *n*-butyllithium (1.69 mL, 3.69 mmol), methyl iodide (1.67 mL, 27 mmol) and DMSO (0.26 mL, 3.69 mmol). Crude diether **20b** was obtained as an orange oil with a single TLC spot and a consistent ^{1}H NMR spectrum (0.87 g, quant.). $R_f \approx 0.25$ (heptane/EtOAc 7:3). ^{1}H NMR: $\delta = 0.21$ (s, 18H; Si(CH_3)$_3$), 3.51 and 3.53 (2s, 6H; OCH_3), 3.76 (s, 6H; C_6H_4–OCH_3), 6.84–6.92 (m, 4H; *m*-C*H*), 7.65–7.70 (m, 4H; *o*-C*H*).

4.1.25. 3,6-Dimethoxy-3,6-diphenylocta-1,4,7-triyne (20c). K_2CO_3 (1.86 g, 13.45 mmol) was added into a solution of **20a** (1.23 g, 2.70 mmol) in methanol (60 mL). TLC monitoring indicates that the reaction was completed after 1.5 h. The reaction mixture was filtered, concentrated to few milliters under reduced pressure, and diethylether (60 mL) was added. The organic layer was washed with saturated aqueous NH_4Cl (2×40 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated to give crude **20c** as a red-orange oil (0.85 g, quant.). MS (DCI/NH_3): $m/z = 332$ ($[M+NH_4]^+$), 315 ($[MH]^+$), 283 ($[M-OCH_3]^+$). ^{1}H NMR: $\delta = 2.77$ (s, 2H; ≡C–*H*), 3.54 (s, 6H; OCH_3), 7.35–7.43 (m, 6H; *m*-, *p*-C*H*), 7.74–7.78 (m, 4H; *o*-C*H*). ^{13}C NMR: $\delta = 53.74$ (q, $^1J_{CH} = 152$ Hz; O*C*H_3), 71.42 (s; >*C*(OMe)Ph), 75.26 (d, $^1J_{CH} = 254$ Hz; ≡*C*–H), 80.52 (d, $^2J_{CH} = 50$ Hz; –*C*≡CH), 84.05 (s; C–*C*≡*C*–C), 126.32–128.96 (m; aromatic *C*H), 139.43 (s; *ipso*-*C*–C–OMe). IR: $\nu = 3306$ (≡C–H), 3065–2901 (C–H), 2827 (OC–H), 2116 (C≡CH), 1600, 1490 (aromatic C–C), 1450 (C–H), 1068 (C–O).

4.1.26. 3,6-Dimethoxy-3,6-di(4-methoxyphenyl)octa-1,4,7-triyne (20d). The above Section 4.1.25 for the preparation of **20c** was applied to triyne **20b** (0.87 g,

1.68 mmol) and K_2CO_3 (2.32 g; 16.80 mmol) to give **20d** as an orange powder. $R_f \approx 0.26$ (heptane/EtOAc). Mp = 103 °C. MS (DCI/NH_3): $m/z = 374$ ($[M]^+$), 343 ($[M-OCH_3]^+$). ^1H NMR: $\delta = 2.79$ (s, 2H; ≡C–*H*), 3.52 (s, 6H; OCH_3), 3.78 (s, 6H; C_6H_4–OCH_3), 6.91 (d, $^3J_{HH} = 9$ Hz, 4H; *m*-C*H*), 7.69 (d, $^3J_{HH} = 9$ Hz, 4H; *o*-C*H*). $^{13}C\{^1H\}$ NMR: $\delta = 53.23$ (OCH_3), 55.34 (C_6H_4–OCH_3), 71.33 (>*C*(OMe)An), 75.18 (≡*C*–H), 80.93 (–*C*≡CH), 84.25 (C–*C*≡*C*–C), 113.75 (*m*-*C*H), 127.95 (*o*-*C*H), 131.90 (*ipso*-*C*–C–OMe), 160.11 (*ipso*-*C*–OMe).

4.1.27. 1,10-Bis(diethoxy)-4,7-diphenyldeca-2,5,8-triyn-4,7-diol (22a). *n*-Butyllithium (15.4 mL, 38.5 mmol) was added into a solution of 3,3-diethoxy-1-propyne (4.94 g, 38.5 mmol) in THF (50 mL) at −78 °C. After 15 min, a solution of diketone **1** (5.67 mL; 19.3 mmol) in THF (50 mL) was added dropwise, and the solution was stirred for a further 30 min at −78 °C. The temperature was allowed to warm up slowly to r.t. After stirrring for another 30 min, the reaction was quenched by saturated aqueous NH_4Cl (30 mL) and diluted with diethylether (50 mL). The organic layer was washed with saturated aqueous NH_4Cl (2×20 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Diol **22a** was obtained as a brown oil (10.97 g, 97%) which was used without further purification in the next step. ^1H NMR: $\delta = 1.19$ (t, $^3J_{HH} = 7$ Hz, 12H; C–C*H*$_3$), 3.62 and 3.63 (2m, 2^d order pattern, 8H; C*H*$_2$Me), 3.83 (s, 2H; O*H*), 5.32 (s; 2H; C*H*(OEt)$_2$), 7.29–7.40 (m, 6H; *m*-, *p*-C*H*), 7.71–7.77 (m, 4H; *o*-C*H*). $^{13}C\{^1H\}$ NMR: $\delta = 15.06$ (q, $^1J_{CH} = 126$ Hz; C–*C*H$_3$), 61.11 (tt-like, $^1J_{CH} = 143$ Hz, $^2J_{CH} \approx 4$ Hz; O–*C*H$_2$Me), 64.68 (s; >*C*(OH)Ph), 80.49, 84.92 and 85.13 (3 s; C–*C*≡*C*–C), 91.23 (d, $^1J_{CH} = 168$ Hz; C*H*(OEt)$_2$), 125.82 (broad d, $^1J_{CH} = 167$ Hz; *m*-or *o*-*C*H), 128.45 (broad d, $^1J_{CH} = 159$ Hz; *o*-or *m*-*C*H), 129.76 (d, $^1J_{CH} = 160$ Hz; *p*-*C*H), 141.18 (t, $^2J_{CH} = 7$ Hz; *ipso*-*C*–C–OH). IR: ν = 3572, 3380 (O–H), 2980, 2932, 2889 (C–H), 1599, 1490 (aromatic C–C), 1450 (C–H), 1328, 1144, 1116, 1051 (C–O).

4.1.28. 1,10-Bis(diethoxy)-4,7-dimethoxy-4,7-diphenyldeca-2,5,8-triyne (23a). *n*-Butyllithium (4.8 mL, 12.05 mmol) was added into a solution of diol **22a** (2.95 g, 6.0 mmol) in THF (15 mL) at −78 °C. After 30 min, methyl iodide (6.0 mL, 96 mmol) was added dropwise, and the temperature was allowed to warm up to −25 °C. DMSO (0.87 mL, 12 mmol) was then added, and the reaction mixture was stirred for 1 h at −25 °C, and then for 10 h at r.t. (TLC monitoring). The reaction mixture was diluted with diethylether (50 mL) and saturated aqueous NH_4Cl (80 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (heptane/acetone 8:2) afforded diether **23a** (2.14 g, 69%) as a brown oil. MS (DCI/NH_3): $m/z = 536$ (100%, $[M+NH_4]^+$) 487 (38%, $[M-CH_3O]^+$). ^1H NMR: $\delta = 1.20$ (t, $^3J_{HH} = 7$ Hz, 12H; C–C*H*$_3$), 3.53 (s, 6H; OCH_3), 3.66 and 3.67 (2qd-like 2^d order pattern $^3J_{HH} \approx 7$ Hz, $^2J_{HH} \approx 18$ Hz, 8H; C*H*$_2$Me), 5.35 (s, 2H; C*H*(OEt)$_2$), 7.29–7.40 (m, 6H; *m*-, *p*-C*H*), 7.71–7.77 (m, 4H; *o*-C*H*). ^{13}C NMR: $\delta = 15.09$ (q, $^1J_{CH} = 128$ Hz; C–*C*H$_3$), 53.44 (q, $^1J_{CH} = 143$ Hz; O*C*H$_3$), 61.05 (tq-like, $^1J_{CH} = 144$ Hz, $^2J_{CH} \approx 4$ Hz; O–*C*H$_2$Me), 71.86 (s; >*C*(OMe)Ph), 82.08, 82.68 et 84.39 (3s; C–*C*≡*C*–C), 91.31 (broad d, $^1J_{CH} = 171$ Hz; C*H*(OEt)$_2$), 126.53 (td-like, $^1J_{CH} = 160$ Hz; *m* or *o*-*C*H), 128.32 (td-like, $^1J_{CH} = 165$ Hz; *o*-or *m*-*C*H), 128.96 (dt-like, $^1J_{CH} = 160$ Hz; *p*-*C*H), 139.67 (broad s; *ipso*-*C*–C–OMe).

4.1.29. 3,6-Dimethoxy-3,6-diphenylocta-1,4,7-triyn-1,8-dial (18a) by formylation of bisterminal triyne (20c). *n*-Butyllithium (1.00 mL, 2.48 mmol) was added dropwise into a solution of triyne **20c** (391 mg, 1.24 mmol) in THF (20 mL) at −78 °C. After warming up to −40 °C, the solution was stirred for 10 min before addition of DMF (1.00 mL, 25 mmol). The reaction mixture was then placed at r.t. and stirring was continued for a further 30 min. The solution was poured into a biphasic mixture of diethylether (7 mL) and 10% aqueous NaH_2PO_4 (7 mL, ca8 equivalents of $H_2PO_4^-$) at 0 °C. The organic layer was separated, washed with water (2x20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue over silicagel (heptane/acetone 8:2) afforded dialdehyde **18a** as an orange oil (146 mg, 32%). $R_f \approx 0.16$ (heptane/acetone 8:2). MS (DCI/NH_3): $m/z = 388$ ($[M+NH_4]^+$), 356 ($[M-MeOH+NH_4]^+$), 339 ($[M-MeO]^+$), 324 ($[M-2MeOH+NH_4]^+$). ^1H NMR: $\delta = 3.56$ (s, 6H; OCH_3), 7.38–7.45 (m, 6H; *m*-, *p*-C*H*), 7.67–7.72 (m, 4H; *o*-C*H*), 9.31 (s, 2H; ≡C–C*H*O). ^{13}C NMR: $\delta = 53.92$ (q, $^1J_{CH} = 144$ Hz; O*C*H$_3$), 71.84 (s; >*C*(OMe)Ph), 83.88, 84.32 and 90.59 (3s; C–*C*≡*C*–C), 126.18–129.52 (m; aromatic *C*H), 137.77 (s; *ipso*-*C*–C–OMe), 175.90 (d, $^1J_{CH} = 190$ Hz; –*C*HO). IR: $\nu = 3088$, 2887 (C–H), 2829 (OC–H), 2740 (aldehydic C–H), 1679 (CH=O), 1599, 1490 (aromatic C–C), 1451 (C–H), 1178–1072 (C–O).

The monoaldehyde 3,6-dimethoxy-3,6-diphenylocta-1,4,7-triynal (**21a**) was also isolated as side-product from the chromatography (85 mg, 20%). $R_f \approx 0.18$ (heptane/acetone 8:2). MS (DCI/NH_3): $m/z = 360$ ($[M+NH_4]^+$), 343 ($[MH]^+$), 328 ($[M-MeOH+NH_4]^+$), 311 ($[M-MeO]^+$), 296 ($[M-2MeOH+NH_4]^+$). ^1H NMR: $\nu = 2.85$ (s, 1H; ≡C–*H*), 3.57–3.60 (m, 6H; O*C*H$_3$), 7.39–7.45 (m, 6H; *m*-, *p*-C*H*), 7.72–7.81 (m, 4H; *o*-C*H*), 9.29 (s, 1H; ≡C–C*H*O). $^{13}C\{^1H\}$ NMR: $\delta = 53.31$ and 53.70 (OCH_3), 71.51 and 71.71 (>*C*(OMe)Ph), 75.76 (≡*C*–H), 80.07 (*C*≡CH), 81.91, 84.07, 86.11 and 90.59 (C–*C*≡*C*–C), 126.27–129.53 (m; aromatic *C*H), 138.05 and 139.11 (*ipso*-*C*–C–OMe), 175.90 (–*C*HO).

4.1.30. 3,6-Dimethoxy-3,6-diphenylocta-1,4,7-triyn-1,8-dial (18a) by deprotection of bisketal (23a). Bisketal **23a** (4.859 g, 9.4 mmol)) and DDQ (2.127 g, 9.4 mmol) were dissolved in a mixture of acetonitrile (243 mL) and water (27 mL). The mixture was refluxed in the dark for 2 h. After cooling to r.t., the mixture was diluted with diethylether and water. The organic layer was separated washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The brown residue was flash-chromatographed over silicagel (heptane/EtOAc 8:2). Dialdehyde **18a** was obtained a light orange oil (2.118 g, 61%). The spectroscopic data are identical to those of samples of **18a** prepared by the formylation method (see Section 4.1.29). Notice: some decomposition occurs on silicagel, and the yield is actually quite erratic (between 40 and 75%).

4.1.31. 3,6-Dimethoxy-3,6-di(4-methoxyphenyl)octa-1,4,7-triyn-1,8-dial (18b). The formylation Section 4.1.29 for the preparation of **18a** was applied to bisketal **20d** (400 mg, 1.07 mmol), *n*-butyllithium (0.94 mL, 2.35 mmol) and DMF (0.50 mL, 6.42 mmol) to give crude dialdehyde **18b** in an orange oil containing 17% of side product assigned to the monoaldehyde structure **21b** (spectroscopic yield of **18b** ≈83%). Attempts at purification by chromatography failed, but the main spectrospcopic characteristics of **18b** could be attributed. $R_f \approx 0.20$ (heptane/EtOAc 8:2).

MS (DCI/NH_3): $m/z=448$ ($[M+NH_4]^+$), 416 ($[M-MeOH+NH_4]^+$), 399 ($[M-MeO]^+$), 384 ($[M-2MeOH+NH_4]^+$). ^{1}H NMR: $\delta=3.53$ (s, 6H; OCH_3), 3.81 (s, 6H; C_6H_4–OCH_3), 6.92 (d, $^3J_{HH}=9$ Hz, 4H; *m*-C*H*), 7.64 (d, $^3J_{HH}=9$ Hz, 4H; *o*-C*H*), 9.31 (s, 2H; ≡C–C*H*O). ^{13}C NMR: $\delta=53.70$ (q, $^1J_{CH}=144$ Hz; OCH_3), 55.39 (q, $^1J_{CH}=139$ Hz; C_6H_4–OCH_3), 71.53 (s; >*C*(OMe)An), 84.00, 84.33 and 91.11 (3s; C–*C*≡*C*–C), 114.01 (d, $^1J_{CH}=161$ Hz; *m*-*C*H), 127.85 (d, $^1J_{CH}=158$ Hz; *o*-*C*H), 129.99 (s; *ipso*-*C*–C–OMe), 160.53 (s; *p*-*C*–OMe), 176.08 (d, $^1J_{CH}=197$ Hz; –*C*HO). IR: $\nu=3006$–2862 (C–H), 2840, 2741 (aldehydic C–H), 2828 (OC–H), 1674 (C=O), 1608, 1463 (aromatic C–C), 1063 (C–O).

4.1.32. 3-Phenyl-3-methoxypenta-1,4-diyne (24a). A solution of diyne **3a** (4.19 g, 16 mmol) in methanol (60 mL) and water (few drops) was treated at 0 °C with K_2CO_3 (11.29 g, 82 mmol). After stirring for 1 h at r.t., the reaction mixture was filtered, concentrated to few milliters under reduced pressure, and diluted with diethylether (100 mL). The organic phase was washed with saturated aqueous NH_4Cl (2×50 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give diyne **24a** as a spectroscopically pure brown oil (2.78 g, quant.). $R_f \approx 0.29$ (heptane/acetone 8:2). ^{1}H NMR: $\delta=2.78$ (s, 2H; ≡C–*H*), 3.54 (s, 3H; OCH_3), 7.37–7.40 (m, 3H; *m*-, *p*-C*H*), 7.75–7.80 (m, 2H; *o*-C*H*).

4.1.33. 3-(4-Methoxyphenyl)-3-methoxypenta-1,4-diyne (24b). The above Section 4.1.32 for the preparation of **24a** was applied to diyne **3b** (3.61 g, 5.22 mmol) and K_2CO_3 (3.60 g, 26 mmol) to give 1,4-pentadiyne **24a** as a spectroscopically pure brown oil (1.05 g, quant.). $R_f \approx 0.29$ (heptane/acetone 8:2). ^{1}H NMR: $\delta=2.77$ (s, 2H; ≡C–*H*), 3.50 (s, 3H; OCH_3), 3.81 (s, 3H; C_6H_4–OCH_3), 6.89 (d, 2H; *m*-C*H*), 7.68 (d, 2H; *o*-C*H*). ^{13}C NMR: $\delta=52.87$ (q, $^1J_{CH}=143$ Hz; C_6H_4–OCH_3), 55.17 (q, $^1J_{CH}=144$ Hz; Csp^3–OCH_3), 71.81 (s; >*C*(OMe)An), 74.89 (d, $^1J_{CH}=263$ Hz, ≡*C*–H), 80.80 (d, $^2J_{CH}=49$ Hz; *C*≡CH), 113.46 (dd, $^1J_{CH}=160$ Hz, $^2J_{CH}=5$ Hz; *m*-*C*H), 127.61 (dd, $^1J_{CH}=160$ Hz, $^2J_{CH}=5$ Hz; *o*-*C*H), 131.89 (s; *ipso*-*C*–C(OMe)–), 159.53 (broad s; *p*-*C*–OMe).

4.1.34. 4,7,13-Trimethoxy-4,7,13-triphenylcyclopentadeca-2,5,8,11,14-pentayn-1,10-diol (25a). *n*-Butyllithium (0.32 mL, 0.80 mmol) was added into a solution of diyne **24a** (150 mg, 0.40 mmol) in THF (8 mL) at −78 °C. After stirring for 10 min, a solution of dialdehyde **18a** (68 mg; 0.40 mmol) in THF (8 mL) was added dropwise. The temperature was allowed to warm up to r.t. and stirring was continued for a further 40 min. The reaction mixture was diluted with diethylether (20 mL) and hydrolyzed with saturated aqueous NH_4Cl (10 mL). The organic layer was separated, washed with and saturated aqueous NH_4Cl (10 mL) and brine (20 mL), dried over magnesium sulfate, and concentrated to dryness under reduced pressure. The brown residue (190 mg) was chromatographed over silicagel (heptane/acetone 8:2) to give [5]pericyclyndiol **25a** as an orange oil (35 mg, 15%). MS (DCI/NH_3): $m/z=558$ ($[M+NH_4]^+$), 526 ($[M-MeOH+NH_4]^+$), 509 ($[M-MeO]^+$), 494 ($[M-2MeOH+NH_4]^+$). MS (APCI/CH_3CN): $m/z=568$ ($[M-MeO+MeCN]^+$), 559 ($[MH]^+$). ^{1}H NMR: $\delta=2.41$ (m, 2H; O*H*), 3.40–3.58 (m, 9H; OCH_3), 5.24–5.34 (m, 2H; >C*H*(OH)), 7.36–7.39 (m, 9H; *m*-, *p*-C*H*), 7.69–7.90 (m, 6H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta=52.23$ and 53.30 (OCH_3), 62.19 (>*C*H(OH)), 71.72 (>*C*(OMe)Ph), 80.79–82.63 (*C*≡*C*), 126.43–128.99 (aromatic *C*H), 138.77 (*ipso*-*C*–C–OMe).

4.1.35. 4,7,13-Trimethoxy-4,7,13-tri(4-methoxyphenyl)-cyclopentadeca-2,5,8,11,14-pentayn-1,10-diol (25b). The above Section 4.1.34 for the preparation of **25a** was applied to pentadiyne **24b** (168 mg, 0.84 mmol), *n*-butyllithium (0.70 mL, 1.68 mmol) and crude dialdehyde **18b** of 83% spectroscopic purity (361 mg, ca0.84 mmol). The pericyclyne **25b** was isolated as an orange oil (100 mg, 19%). $R_f \approx 0.12$ (heptane/acetone 7:3). MS (DCI/NH_3): $m/z=648$ ($[M+NH_4]^+$), 630 ($[M]^+$), 616 ($[M-MeOH+NH_4]^+$), 599 ($[M-MeO]^+$), 584 ($[M-2MeOH+NH_4]^+$). ^{1}H NMR: $\delta=3.35$–3.53 (m, 9H; OCH_3), 3.78–3.87 (s, 9H; C_6H_4–OCH_3), 5.31 (m, 2H; C*H*(OH)), 6.83–6.93 (m, 6H; *m*-C*H*), 7.57–7.72 (m, 6H; *o*-C*H*). ^{13}C{^{1}H} NMR: $\delta=$ 53.15, 52.97 and 52.20 (3s; OCH_3), 55.21 (C_6H_4–OCH_3), 64.85 (*C*H–OH), 71.67 (>*C*(OMe)An), 83.05–84.57 (*C*≡*C*), 113.70 (*m*-*C*H), 128.17 (*o*-*C*H), 138.53 (*ipso*-*C*–C–OMe), 160.07 (*p*-*C*–OMe).

The side-product resulting from the attack of the monoaldehyde impurity (**21b**) was also isolated and partly characterized: 3,9,12-trimethoxy-3,6,9,12-tetra(4-methoxyphenyl)tetradeca-1,4,7, 10,13-pentayn-6-ol (**26b**) $R_f \approx 0.25$ (heptane/acetone 7:3). ^{1}H NMR: $\nu=2.76$ (s, 2H; ≡C–*H*), 3.46–3.48 (m, 9H; –OCH_3), 3.78–3.79 (s, 9H, CH_3O–An–), 5.32 (d, 1H; C*H*(OH)), 6.83–6.90 (m, 6H; *m*-C*H*), 7.62–7.68 (m, 6H; *o*-C*H*).

4.1.36. 12,15-Dimethoxy-12,15-diphenyl-3,3-dimethyl-1,5-dioxaspiro[5.14]icosa-7,10,13,16,19-pentayn-9,18-diol (31). *n*-Butyllithium (2.26 mL, 5.66 mmol) was added to a solution of diyne **27**[10b] (465 mg, 2.83 mmol) in THF (100 mL) at −78 °C. After stirring for 40 min at −50 °C, the solution was cooled back to −78 °C and a solution of dialdehyde **18a** (1.049 g, 2.83 mmol) in THF (100 mL) was added. The reaction mixture was allowed to warm up to r.t. over a 3 h period, and stirring was continued for 1 h at r.t. The reaction was quenched with saturated aqueous NH_4Cl and diluted with diethylether. The organic layer was separated, washed with aqueous NH_4Cl and brine, dried over magnesium sulfate, and the solvents were removed under reduced pressure. Purification through column chromatography (heptane/acetone 8:2) gave [5]pericyclyne **31** as a pale yellow solid (271, mg, 18%). MS (DCI/NH_3) $m/z=552$ (60%; $[MNH_4]^+$), 503 (31%; $[MH-MeOH]^+$), 520 (21%; $[MNH_4-MeOH]^+$), 488 (7%; $[MNH_4-2MeOH]^+$). ^{1}H NMR (250 MHz): $\delta=0.98$ (s, 6H;

C(CH_3)$_2$), 2.44−2.71 (m, 2H; O*H*), 3.33−3.71 (m, 10H; OCH_3+CH_2O−), 5.23−5.33 (m, 2H; C*H*OH); 7.33−7.78 (m, 10H; aromatic C*H*). ^{13}C NMR (62.9 MHz): δ=22.29 (C(CH_3)$_2$), 29.96 (*C*(CH_3)$_2$), 52.15 (>*C*H(OH)), 53.51 (O*C*H$_3$), 71.94 (>*C*(OMe)Ph), 72.88 (CH_2O), 78.67 (≡*C*–CO_2), 80.42, 81.11, 82.15 and 83.26 (other –*C*≡), 87.22 (>CO_2), 126.53 and 128.52 (*o*- and *m*-*C*H), 129.15 (*p*-*C*H), 139.89 (*ipso*-*C*–C–OMe). In another assay, the spectrum exhibited higher resolution, and most signals were split in two or three lines by ca. 0.05 ppm. IR: ν=3585 (O–H), 2961, 2934 and 2872 (C–H), 2827 (OC–H), 1601, 1490, 1450 (aromatic C–C), 1254, 1203, 1178, 1229, 1145, 1116, 1072, 1009 (C–O).

4.2. Semi-preparative HPLC resolution of tetrayne 2a

A diastereoisomeric mixture of tetrayne **2a** (152 mg) was dissolved in dichloromethane (1 mL). Samples (20 μL) were sequentially injected and divided by HPLC (Prontosil column, pentane/dichloromethane 65:35, 4.8 mL/min) in three pools, respectively, enriched in diastereoisomer **A**, **B** and **C**. Each pool was purified further under the same conditions, affording separated diastereoisomers **A** (30 mg), **B** (35 mg) and **C** (21 mg).

4.3. Semi-peparative HPLC resolution of the [5]pericylyne 11a prepared from the isomer B of tetrayne 2a

A diastereoisomeric mixture of the title sample (11 mg) was dissolved in dichloromethane (0.5 mL). Samples (20 μL) were sequentially injected and divided by HPLC (Prontosil column, pentane:EtOAc 97:3, 4.8 mL/min) in three pools, respectively enriched in one of the three diastereoisomers (Scheme 20). Each pool was purified further under the same conditions, affording separated diastereoisomers (ca. 1 mg, 1 mg, 2 mg).

4.4. X-ray crystallographic structure determinations

Data were collected on a Stoe Imaging Plate Diffraction System (IPDS), equipped with an Oxford Cryosystems Cryostream Cooler Device, and using graphite-monochromated Mo K radiation (λ=0.71073 Å). The final unit cell parameters were obtained by means of a least-squares refinement of a set of well-measured reflections, and crystal decay was monitored during data collection; no significant fluctuations in intensity were observed. The structures were solved by Direct Methods using the program SIR92,[31] and refined by least-squares procedures on *F*2 with SHELXL-97.[32] All hydrogen atoms were located on a difference Fourier maps, but introduced and refined by using a riding model, except for OH hydrogen atoms, which were isotropically refined. All non-hydrogens atoms were anisotropically refined.

4.5. Crystallographic and structural parameters for 5b (Fig. 3)

Empirical formula	$C_{15}H_{18}O_2Si$; MW=258.38
Temperature	180(2) K
Crystal system, space group	Monoclinic, *P*21/*n*
Unit cell dimensions	*a*=6.449(5) Å *b*=24.646(5) Å *c*=9.420(5) Å β=99.650(5)°
Volume	1476.0(14) Å^3
Z, Calculated density	4, 1.163 mg/cm^3
Absorption coefficient	0.151 mm^{-1}
F(000)	552
Theta range for data collection	2.34–26.08°
Index ranges	$7\le h\le 7$, $-30\le k\le 30$, $-11\le l\le 11$
Reflections collected/unique	11012/2831 [*R*(int)=0.0328]
Completeness to 2theta=26.08	97.0%
Refinement method	Full-matrix least-squares on *F*2
Data/restraints/parameters	2831/0/171
Goodness-of-fit on *F*2	1.023
Final *R* indices [*I*>2sigma(*I*)]	*R*1=0.0337, *wR*2=0.0867
R indices (all data)	*R*1=0.0427, *wR*2=0.0913
Largest diff. peak and hole	(0.225 and −0.206) e A^{-3}

Bond lengths [A] and angles [deg] for **5b**

Si(1)–C(5)	1.8499(17)	Si(1)–C(15)	1.857(2)	O(2)–C(9)	1.3641(17)
Si(1)–C(13)	1.8513(18)	O(1)–C(1)	1.4437(15)	O(2)–C(12)	1.427(2)
Si(1)–C(14)	1.8521(18)	O(1)–H(1O)	0.86(2)	C(1)–C(2)	1.475(2)
C(1)–C(4)	1.4832(19)	C(2)–C(3)	1.184(2)	C(6)–C(11)	1.380(2)
C(1)–C(6)	1.5321(17)	C(4)–C(5)	1.203(2)	C(6)–C(7)	1.390(2)
C(7)–C(8)	1.380(2)	C(8)–C(9)	1.388(2)	C(9)–C(10)	1.382(2)
C(10)–C(11)	1.3928(19)				
C(5)–Si(1)–C(13)	109.57(8)	O(1)–C(1)–C(2)	109.93(11)	C(4)–C(5)–Si(1)	172.16(12)
C(5)–Si(1)–C(14)	105.93(8)	O(1)–C(1)–C(4)	109.42(11)	C(11)–C(6)–C(7)	118.53(13)
C(13)–Si(1)–C(14)	111.40(10)	C(2)–C(1)–C(4)	108.78(11)	C(11)–C(6)–C(1)	120.86(12)
C(5)–Si(1)–C(15)	107.35(8)	O(1)–C(1)–C(6)	106.00(10)	C(7)–C(6)–C(1)	120.56(12)
C(13)–Si(1)–C(15)	111.53(9)	C(2)–C(1)–C(6)	112.36(11)	C(8)–C(7)–C(6)	120.53(14)
C(14)–Si(1)–C(15)	110.82(9)	C(4)–C(1)–C(6)	110.30(11)	C(7)–C(8)–C(9)	120.45(14)
C(1)–O(1)–H(1O)	107.2(13)	C(3)–C(2)–C(1)	177.66(14)	O(2)–C(9)–C(10)	124.67(13)
C(9)–O(2)–C(12)	117.81(12)	C(5)–C(4)–C(1)	177.02(15)	O(2)–C(9)–C(8)	115.63(13)
C(10)–C(9)–C(8)	119.70(13)	C(9)–C(10)–C(11)	119.31(13)	C(6)–C(11)–C(10)	121.47(13)

4.6. Crystallographic and structural parameters for 20d (Fig. 2)

Empirical formula	$C_{12}H_{11}O_2$; MW = 187.21
Temperature	293(2) K
Crystal system, space group	Triclinic, $P-1$
Unit cell dimensions	a = 6.5680(10) Å, b = 8.382(2) Å, c = 9.674(2) Å α = 105.68(3)°, β = 103.88(3)°, γ = 93.24(3)°
Volume	493.58(17) Å^3
Z, Calculated density	2, 1.260 mg/cm^3
Absorption coefficient	0.085 mm^{-1}
F(000)	198
Crystal size	0.1×0.1×0.1 mm^3
Theta range for data collection	2.27–23.25°
Index ranges	$-7\leq h\leq 7$, $-9\leq k\leq 9$, $-10\leq l\leq 10$
Reflections collected/unique	3643/1347 [R(int) = 0.0469]
Completeness to 2theta = 23.25°	94.4%
Refinement method	Full-matrix least-squares on $F2$
Data/restraints/parameters	1347/0/129
Goodness-of-fit on $F2$	1.080
Final R indices [$I>2$sigma(I)]	$R1$ = 0.0769, $wR2$ = 0.2114
R indices (all data)	$R1$ = 0.1063, $wR2$ = 0.2465
Largest diff. peak and hole	(0.317 and −0.247) e Å^{-3}

Bond lengths [A] and angles [deg] for **20d**

C(1)–C(1)#1	1.187(8)	C(3)–C(4)	1.139(6)	C(8)–C(9)	1.398(6)
C(1)–C(2)	1.494(6)	C(5)–O(1)	1.364(5)	C(9)–O(2)	1.371(5)
C(2)–O(1)	1.450(5)	C(6)–C(7)	1.384(6)	C(9)–C(10)	1.373(6)
C(2)–C(3)	1.473(6)	C(6)–C(11)	1.400(6)	C(10)–C(11)	1.370(6)
C(2)–C(6)	1.521(6)	C(7)–C(8)	1.380(6)	C(12)–O(2)	1.423(5)
C(1)#1–C(1)–C(2)	177.6(5)	C(4)–C(3)–C(2)	166.5(6)	O(2)–C(9)–C(8)	124.3(4)
O(1)–C(2)–C(3)	112.9(3)	C(7)–C(6)–C(11)	118.1(4)	C(10)–C(9)–C(8)	119.6(4)
O(1)–C(2)–C(1)	111.2(3)	C(7)–C(6)–C(2)	122.0(4)	C(11)–C(10)–C(9)	120.7(4)
C(3)–C(2)–C(1)	107.6(4)	C(11)–C(6)–C(2)	119.8(4)	C(10)–C(11)–C(6)	120.7(4)
O(1)–C(2)–C(6)	105.3(3)	C(8)–C(7)–C(6)	121.5(4)	C(5)–O(1)–C(2)	118.5(4)
C(3)–C(2)–C(6)	108.4(3)	C(7)–C(8)–C(9)	119.3(4)	C(9)–O(2)–C(12)	117.3(3)
C(1)–C(2)–C(6)	111.5(3)	O(2)–C(9)–C(10)	116.1(3)		

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Access to ring-fused azepino[3,4-*b*]indole-1,5-dione derivatives by ring-closing olefin metathesis

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Abstract—The new ring-fused azepino[5,6-*b*]indole derivatives **3**, **4** and **5** were prepared from diene precursors **8**, **9**, **13** and **15** in fair yields via a final ring-closing olefin metathesis.

1. Introduction

The azepino framework is encountered in several potent kinase inhibitors such as natural marine hymenialdisine[1] and some close derivatives of **1**.[2] Recently, Meijer et al. have reported that 5-arylhydrazinoazepino[5,6-*b*]indole exhibited good inhibitory activities against cyclin-dependant kinases.[3] In our ongoing research on new azepino[5,6-*b*]indole derivatives,[4] we have recently described the preparation of the pyrrolo[1,2:1′,2′]azepino[5,6-*b*]indole **2**, related to the anthramycin structure, from indole-2-carboxylic acid and a β-aminoester through an intramolecular electrophilic cyclisation (Fig. 1).[5]

Since the discovery of new well-defined catalysts (efficiency, functional-group-tolerance) by Schrock and Grubbs, the ring-closing metathesis (RCM) is considered as one of the most powerful synthetic tools in organic chemistry.[6] RCM provides an efficient and mild route for the synthesis of natural products, medium-ring and macroring carbocyclic or heterocyclic motifs.[7] Based on a RCM approach, we investigated several synthetic pathways to access to the new ring-fused azepino[5,6-*b*]indole derivatives **3**,**4** and **5** from the azepino[5,6-*b*]indoles **1a**[4b] or **1b**.[4b] In this paper, we report in detail the introduction of olefin chains on an azepinic nucleus to generate the dienic precursors and the final RCM.

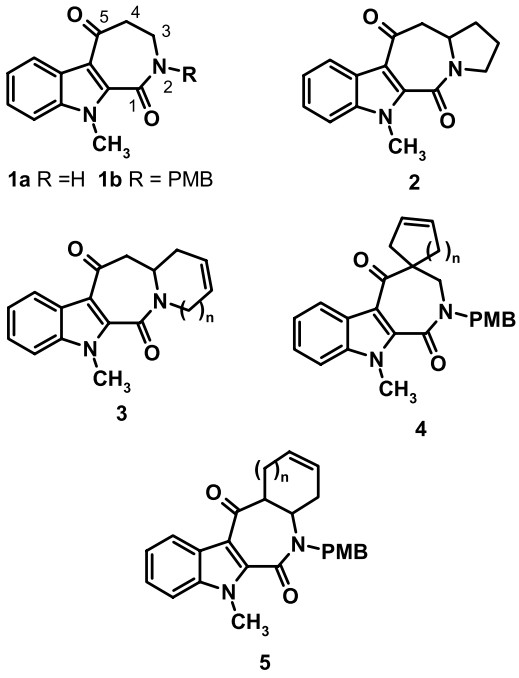

Figure 1. The structures of fused azepino[3,4-*b*]indole-1,5-diones.

2. Results and discussion

Focusing our initial attention on the preparation of the tetracyclic derivatives **3**, a double alkylation of **1a** on positions-2 and 3 was investigated to generate the dienic precursors **8** (Scheme 1). The first olefin chain was introduced on the position-2 by a classical *N*-alkylation. The reaction was carried out in the presence of sodium hydride and bromoalkenes (3-bromopropene, 4-bromobutene,

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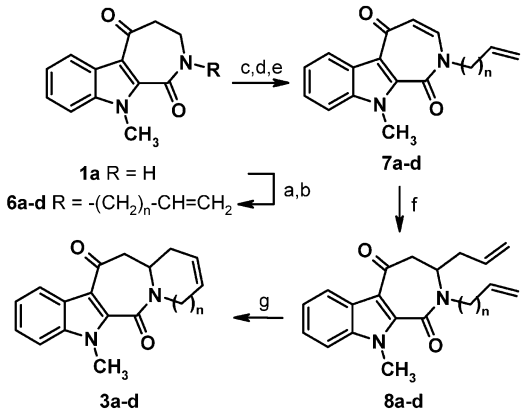


Scheme 1. Reaction conditions (a) NaH (1.1 equiv.), DMF, 0 °C, 1 h; (b) R-Br (1.5 equiv.), DMF, rt, 1 or 12 h, (**6a** $n=1$ 88%, **6b** $n=2$ 54%, **6c** $n=3$ 64%, **6d** $n=4$ 76%); (c) LiHMDS (1.8 equiv.), THF, −78 °C, 2 h; (d) Br_2 (1 equiv.), THF, −78 °C, 15 min; (e) DBU (1.5 equiv.), DMF, rt, 2 h, (**7a–d** 80–83%); (f) $TiCl_4$ (4 equiv.), allylTMS (6 equiv.), CH_2Cl_2, −40 °C to rt, 15 h, (**8a** $n=1$ 69%, **8b** $n=2$ 54%, **8c** $n=3$ 50%, **8d** $n=4$ 48%); (g) Grubb's reagent (10% mol), 0.03 M solution, CH_2Cl_2, rt.

5-bromopentene or 6-bromohexene) in DMF. *N*-Substituted derivatives **6** were obtained in 54–88% yields. The *C*-allylation on the position-3 was more problematic. After many experiments, the Sakurai reaction[8] (1,4-addition) was found to be the best method for the attachment of the allyl chain on the azepinic ring. This route required the preparation of α,β-ethylenic ketones **7**. The α-bromination of ketones **6** was effective using LiHMDS (1.8 equiv.) and bromine (1 equiv.) to lead to unstable bromo intermediates which were directly treated by DBU (1.5 equiv.) to afford ketones **7** in 80–83% overall yields. The formation of α,α-dibromo derivatives was also observed when either the addition of bromine is too slow or with higher reagent concentrations.

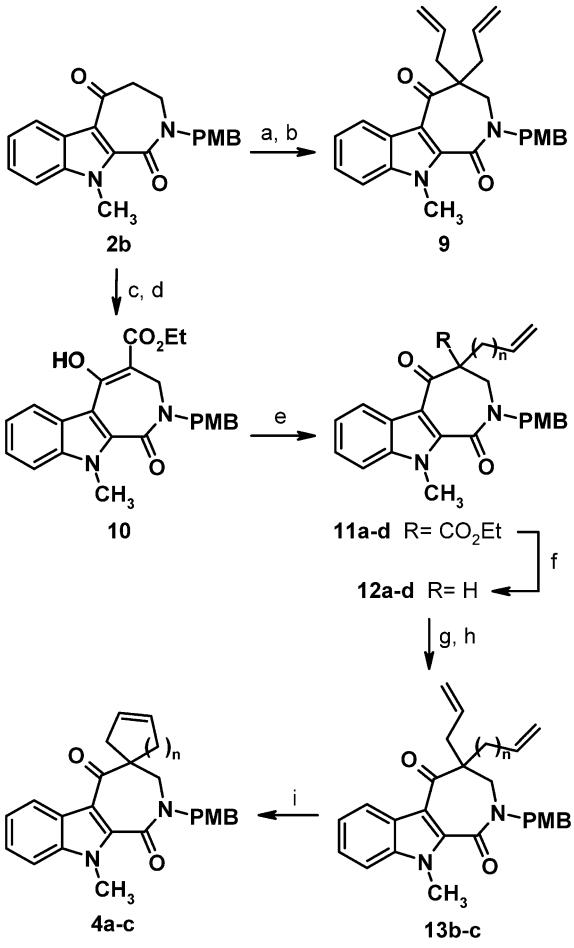
Compounds **7** were, then, subjected to the Sakurai allylation reaction to afford the corresponding 3-allyl derivatives **8**. It should be noted that allyltrimethylsilane and $TiCl_4$ were used in excess to get fair 1,4-addition yield.

We achieved the RCM of **8a** using the Grubb's first generation catalyst (bis-(tricyclo-hexylphosphine)benzylidene ruthenium (IV) dichloride, 10% mol) in CH_2Cl_2 at room temperature (Scheme 1). The tetracyclic compound **3a** was isolated in 84% yield. Similarly, the same reaction conditions applied to **8b–d** afforded the higher ring-sized derivatives **3b–d** in excellent yields (Table 1).

The synthesis of the spiro derivatives **4** required two successive *C*-alkylations on the same position (Scheme 2). Two independent routes were developed to give access to the desired dienes. The simplest way was a diallylation reaction on position-4 of **2b** to give **9** in 77% yield.

Table 1. RCM of dienes **8a–d**

Olefin	Product	*n*	Time (h)	Yield (%)
8a	**3a**	1	1	84
8b	**3b**	2	2	96
8c	**3c**	3	1	98
8d	**3d**	4	48	86



Scheme 2. Reaction conditions: (a) NaH (2 equiv.), THF, 0 °C, 3 h; (b) 3-bromopropene (5 equiv.), THF, rt, 16 h, (77%); (c) LiHMDS (1.8 equiv.), THF, −78 °C, 1 h; (d) $NCCO_2Et$ (1.1 equiv.), THF, −78 °C, 15 min, (92%); (e) K_2CO_3 (5 equiv.), $Br–(CH_2)_n–CH=CH_2$ (5 equiv.), acetone, rflx, 48–72 h, (**11a** $n=1$ 92%, **11b** $n=2$ 47%, **11c** $n=3$ 59%, **11d** $n=4$ 68%); (f) $LiOH.H_2O$ (2 equiv.), $EtOH/H_2O$, rflx, 30 min, (**12a–d** 97–99%); (g) NaH (1.5 equiv.), THF, 0 °C, 1 h; (h) 3-bromopropene (1.2 equiv.), rt, 16 h, (**13b** $n=2$ 93%, **13c** $n=3$ 89%); (i) Grubb's reagent (10% mol), 0.03 M solution, CH_2Cl_2, rt.

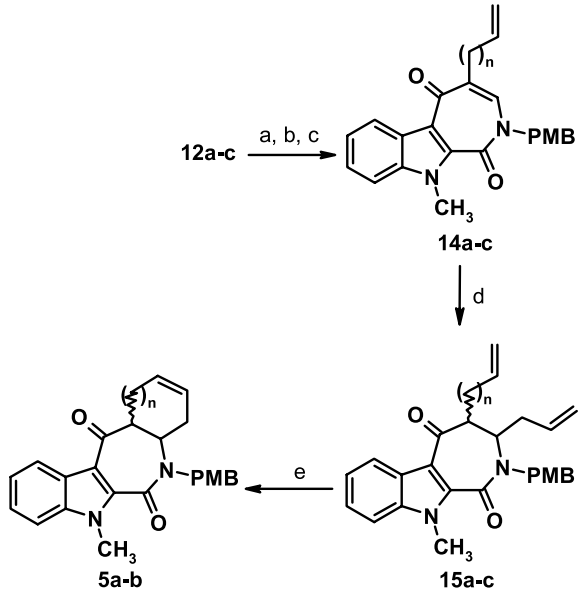
We needed an alternative way to introduce two different olefin side chains since a monoallylation of **2b** or an enolate alkylation with bromoalkenes (4-bromobutene, 5-bromopentene or 6-bromohexene) were unproductive. We then thought to the ketoester derivative **10**, as an interesting intermediate, suitable for a monoalkylation on the position-4 with a low reactive halide, then for decarboxylation prior to perform the second *C*-alkylation with allyl bromide. We easily obtained **10** (92% yield) by treating **2b** with LiHMDS (1.8 equiv.) in THF at −78 °C followed by addition of $NCCO_2Et$ (1.1 equiv.). The enol form of **10** was observed by NMR spectroscopy in $CDCl_3$ solution (see Section 3). The alkylation of **10** in the presence of K_2CO_3 and bromoalkenes (3-bromopropene, 4-bromobutene, 5-bromopentene or 6-bromohexene) in acetone gave *C*-alkylated derivatives **11a–d** in fair yields. The decarboxylation of **11** was carried out with lithium hydroxide hydrate at reflux of EtOH to deliver derivatives **12** in almost quantitative yields.

The final *C*-allylation on **12b** and **12c** was performed to reach the suitable dienes **13b–c**. As reported for the first series, the dienes prepared above were submitted to ring closure (Scheme 2). As can be seen from the results listed in Table 2, the spiro derivatives **4** were again obtained in excellent yields.

Table 2. Preparation of spiro derivatives **4** from dienes **9**, **13**

Olefin	Product	*n*	Time (h)	Yield (%)
9	**4a**	1	8	84
13b	**4b**	2	2	92
13c	**4c**	3	48	90

On the basis of the synthetic results collected from first two families, we reasoned that combining the use of mono-alkylated derivatives **12** as starting material and the Sakurai reaction to introduce the alkenyl chain on position-3 could provide the key diene **15**. As shown in Scheme 3, α,β-ethylenic ketones **14** were obtained following the bromination–elimination sequence and then, the allyl chain was effectively introduced on the position-3 in fair yields by the Sakurai reaction. Except for **15a**, compounds **15** were isolated as a mixture of diastereomers (ratio 4:5). According to the RCM reactions described above, dienes **15** underwent ring closure in very high yields to afford the derivatives **5** (Table 3). The RCM reaction applied on each diastereomer of **15a** gave the corresponding diastereomer of **5a** in the same yield (96% yield).

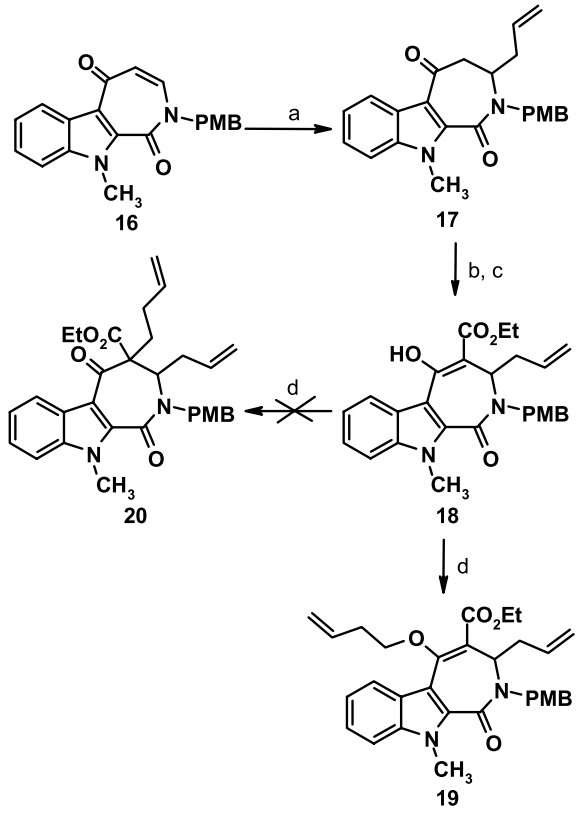


Scheme 3. Reaction conditions (a) LiHMDS (1.5 equiv.), THF, −78 °C, 2 h; (b) Br_2 (1.2 equiv.), rt, 2 h; (c) DBU (1.5 equiv.), 45 min (**14a** $n=1$ 88%, **14b** $n=2$ 84%, **14c** $n=3$ 87%); (d) $TiCl_4$ (4 equiv.), allylTMS (6 equiv.), CH_2Cl_2, −40 °C to rt, 15 h (**15a** $n=1$ 51%, **15b** $n=2$ 56%, **15c** $n=3$ 68%); (e) Grubb's reagent (10% mol), 0.03 M solution, CH_2Cl_2, rt.

Table 3. RCM of dienes **15a–b**

Olefin	Product	*n*	Time (h)	Yield (%)
15a	**5a**	1	8	96
15b	**5b**	2	12	93

An alternative way with the α,β-ethylenic ketone **16**[9] as starting product was also explored (Scheme 4). The Sakurai reaction on **16** gave the 3-allyl derivative **17** in 66% yield. The carboxylation of **17** on position-4 was carried out to afford the ester **18** (91% yield). Unfortunately, the C-4 alkylation using the conditions developed for **10** failed in our hands. In fact, the major product isolated was the *O*-alkylated derivative **19** (56% yield), and not the compound **20**.



Scheme 4. Reaction conditions (a) $TiCl_4$ (4 equiv.), allylTMS (6 equiv.), CH_2Cl_2, −40 °C to rt, 15 h, (66%); (b) LiHMDS (1.8 equiv.), THF, −78 °C, 1 h; (c) $NCCO_2Et$ (1.5 equiv.), THF, −78 °C, 15 min, (91%); (d) K_2CO_3 (5 equiv.), Br-$(CH_2)_2$–CH=CH_2 (5 equiv.), acetone, rflx, 48 h, (56%).

In conclusion, we have developed three new series of ring-fused azepino[5,6-*b*]indole derivatives through a wide preparation of diene precursors which were finally submitted to RCM.

3. Experimental

3.1. General experimental procedures

Melting points were determined using a Büchi capillary instrument and are uncorrected. The infrared spectra of compounds were recorded on a Perkin–Elmer FTIR paragon 1000 spectrometer. NMR spectra were recorded at 300 K in $CDCl_3$ on a Bruker Avance DPX 250. Chemical shifts are

expressed in parts per million relative to tetramethylsilane (TMS). Mass spectra were recorded on Perkin–Elmer SCIEX API 300 using ionspray methodology. Thin-layer chromatographies (TLC) were run on precoated silica gel plates (Merck $60F_{254}$) and the spots were visualised using an UV light at 254 nm. Flash chromatographies were carried out on column using flash silica gel 60 Merck (40–63 μm) using the indicated solvents (petroleum ether (PE): boiling range 40–60 °C). All reactions were performed under a nitrogen atmosphere and those requiring anhydrous conditions were conducted in flame-dried apparatus.

3.2. General procedure for RCM

Grubb's reagent (0.03 mmol) was added to a solution of diene precursor **8**, **9**, **13** or **15** (0.3 mmol) in anhydrous CH_2Cl_2 (10 mL). The final solution was stirred for t h at room temperature. The solvent was evaporated, and the residue obtained was purified by column chromatography to give **3**, **4** or **5**.

3.2.1. 5-Methyl-8,11,11a,12-tetrahydro-5*H*-pyrido[2′,1′:7,1]azepino[3,4-*b*]indole-6,13-dione (3a). Diene precursor: **8a**, $t=1$ h; chromatography eluent: PE/EtOAc 6:4; yield: 84%. Mp 161–162 °C (EtOAc); IR (KBr) ν 1641 (CO), 1614 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.23 (dd, 1H, $J=2.7$, 15.2 Hz, CH_2CHN), 2.60 (dd, 1H, $J=.7$, 15.2 Hz, CH_2CHN), 2.63 (dd, 1H, $J=0.6$, 18.5 Hz, CH_2CO), 3.14 (dd, 1H, $J=11.1$, 18.5 Hz, CH_2CO), 4.06 (s, 3H, NCH_3), 4.13 (dd, 1H, $J=1.5$, 16.1 Hz, NCH_2), 4.23 (dd, 1H, $J=1.5$, 16.1 Hz, NCH_2), 4.65–4.73 (m, 1H, NCH), 6.05–6.07 (m, 2H, 2=CH), 7.31–7.40 (m, 3H, H_{Ar}), 8.34 (d, 1H, $J=$ 7.9 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 29.8 (CH_2), 32.8 (NCH_3), 40.9 (CH_2CO), 49.3 (NCH), 50.6 (NCH_2), 110.3 (CH), 116.2 (C), 123.6 (CH), 123.9 (CH), 124.6 (CH), 125.1 (C), 125.2 (CH), 125.7 (CH), 135.1 (C), 138.7 (C), 162.0 (CO), 196.0 (CO); MS (IS) m/z 281 $(M+1)^+$. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.03; H, 5.94; N, 9.82.

3.2.2. 5-Methyl-9,12,12a,13-tetrahydroazepino[2′,1′:7,1]azepino[3,4-*b*]indole-6,14(5*H*,8*H*)-dione (3b). Diene precursor: **8b**, $t=2$ h; chromatography eluent: PE/EtOAc 1:1; yield: 96%. Mp 187–189 °C (EtOAc); IR (KBr) ν1638 (CO), 1615 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.20–3.08 (m, 6H, CH_2), 3.91–3.99 (m, 1H, NCH_2), 4.06 (s, 3H, NCH_3), 4.10–4.24 (m, 1H, NCH_2), 4.54–4.65 (m, 1H, NCH), 5.63–5.65 (m, 2H, 2=CH), 7.31–7.42 (m, 3H, H_{Ar}), 8.37 (d, 1H, $J=7.9$ Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 30.8 (CH_2), 32.0 (CH_2), 32.9 (NCH_3), 39.0 (CH_2CO), 50.9 (NCH_2), 56.4 (NCH), 110.2 (CH), 116.0 (C), 123.5 (CH), 123.6 (CH), 123.7 (CH), 125.0 (C), 125.5 (CH), 130.7 (CH), 134.7 (C), 138.6 (C), 161.5 (CO), 195.4 (CO); MS (IS) m/z 295 $(M+1)^+$. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.74; H, 6.29; N, 9.34.

3.2.3. 5-Methyl-8,9,10,13,13a,14-hexahydro-5*H*-azocino-[2′,1′:7,1]azepino[3,4-*b*]indole-6,15-dione (3c). Diene precursor: **8c**, $t=1$ h; chromatography eluent: PE/EtOAc 1:1; yield: 98%. Mp 147–149 °C (EtOAc); IR (KBr) ν1638 (CO), 1616 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.72–1.83 (m, 2H, CH_2), 2.03–2.20 (m, 4H, CH_2), 2.65–2.80 (m, 2H, CH_2), 2.90–3.01 (m, 1H, NCH_2), 3.34–3.40 (m, 1H, NCH_2), 4.04 (s, 3H, NCH_3), 4.30–4.37 (m, 1H, NCH), 5.54–5.64 (m, 1H, =CH), 5.85–5.96 (m, 1H, =CH), 7.30–7.41 (m, 3H, H_{Ar}), 8.36 (d, 1H, $J=7.1$ Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 26.3 (CH_2), 29.7 (CH_2), 31.0 (CH_2), 32.7 (NCH_3), 45.4 (CH_2), 49.0 (NCH_2), 57.5 (NCH), 110.2 (CH), 115.6 (C), 123.4 (CH), 123.7 (CH), 125.0 (C), 125.5 (CH), 127.2 (CH), 133.1 (CH), 135.3 (C), 138.5 (C), 162.8 (CO), 195.5 (CO); MS (IS) m/z 309 $(M+1)^+$. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.25; H, 6.72; N, 8.90.

3.2.4. 5-Methyl-9,10,11,14,14a,15-hexahydroazonino-[2′,1′:7,1]azepino[3,4-*b*]indole-6,16(5*H*,8*H*)-dione (3d). Diene precursor: **8d**, $t=48$ h; chromatography eluent: PE/EtOAc 7:3; yield: 86%. Mp 150–152 °C (EtOAc); IR (KBr) ν1631 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.89–2.17 (m, 6H, CH_2), 2.53–2.71 (m, 2H, CH_2), 2.83–2.96 (m, 2H, CH_2), 3.22–3.29 (m, 1H, NCH_2), 3.54–3.63 (m, 1H, NCH_2), 4.07 (s, 3H, NCH_3), 4.82–4.89 (m, 1H, NCH), 5.48–5.55 (m, 1H, =CH), 5.72–5.78 (m, 1H, =CH), 7.32–7.46 (m, 3H, H_{Ar}), 8.49 (d, 1H, $J=7.1$ Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 22.4 (CH_2), 25.5 (CH_2), 27.1 (CH_2), 30.4 (CH_2), 33.3 (NCH_3), 46.7 (CH_2), 49.7 (NCH_2), 56.0 (NCH), 110.3 (CH), 115.4 (C), 123.9 (2CH), 125.0 (C), 125.5 (CH), 127.7 (CH), 132.3 (CH), 137.1 (C), 138.5 (C), 161.7 (CO), 193.0 (CO); MS (IS) m/z 323 $(M+1)^+$. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.22; H, 6.97; N, 8.86.

3.2.5. 4-[Spiro(3-cyclopentenyl)]-2-(4-methoxybenzyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (4a). Diene precursor: **9**, $t=8$ h; chromatography eluent: PE/EtOAc 8:2; yield: 84%. Gum; ^1H NMR (250 MHz, DMSO-d_6, 80 °C) δ 2.28 (d 2H, $J=15.0$ Hz, CH_2), 2.69 (d, 2H, $J=15.0$ Hz, CH_2), 3.60 (s, 2H, NCH_2), 3.74 (s, 3H, OCH_3), 4.04 (s, 3H, NCH_3), 4.75 (s, 2H, NCH_2Ph), 5.65 (s, 2H, 2=CH), 6.91 (d, 2H, $J=8.7$ Hz, H_{Ar}), 7.27–7.32 (m, 3H, H_{Ar}), 7.41 (dd, 1H, $J=7.9$, 8.1 Hz, H_{Ar}), 7.64 (d, 1H, $J=8.1$ Hz, H_{Ar}), 8.23 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.1 (NCH_3), 41.9 ($2CH_2$), 52.0 ($2CH_2$), 55.6 (OCH_3), 59.8 (C), 110.2 (CH), 114.3 (2CH), 116.1 (C), 123.7 (CH), 123.8 (CH), 125.5 (C), 125.7 (CH), 128. (C), 129.7 (2CH), 133.7 (C), 138.6 (C), 159.4 (C), 161.8 (CO), 200.9 (CO); MS (IS) m/z 415 $(M+H)^+$. Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 6.99. Found: C, 74.76; H, 6.17; N, 7.14.

3.2.6. 4-[Spiro(3-cyclohexenyl)]-2-(4-methoxybenzyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (4b). Diene precursor: **13b**. $t=2$ h; chromatography eluent: PE/EtOAc 4:6; yield: 92%. Gum; IR (film) ν 1644 (CO), 1627 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.56–1.66 (m, 2H, CH_2), 2.02–2.30 (m, 3H, 2 CH_2), 2.54 (d, 1H, $J=18.5$ Hz, CH_2), 3.49 (d, 1H, $J=$ 15.5 Hz, NCH_2), 3.61 (d, 1H, $J=15.5$ Hz, NCH_2), 3.81 (s, 3H, OCH_3), 4.11 (s, 3H, NCH_3), 5.15–5.35 (m, 2H, NCH_2Ph), 5.83 (s, 2H, 2=CH), 6.88 (d, 2H, $J=8.8$ Hz, H_{Ar}), 7.27–7.43 (m, 5H, H_{Ar}), 8.34 (d, 1H, $J=7.9$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 22.1 (CH_2), 27.2 (CH_2), 29.4 (CH_2), 32.9 (NCH_3), 48.7 (CH_2), 50.8 (C), 50.9 (CH_2), 55.4 (OCH_3), 110.2 (CH), 114.3 (2CH), 116.1 (C), 123.5 (CH), 123.6 (CH), 124.9 (CH), 125.6 (CH), 125.8 (CH),

129.1 (C), 129.7 (2CH), 130.0 (C), 133.5 (C), 138.7 (C), 159.3 (C), 162.2 (CO), 201.3 (CO); MS (IS) *m/z* 415 $(M+H)^+$. Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.78. Found: C, 74.93; H, 6.49; N, 6.95.

3.2.7. 4-[Spiro(3-cycloheptenyl)]-2-(4-methoxybenzyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5-(2*H*, 10*H*)-dione (4c). Diene precursor: **13c**, $t=48$ h; chromatography eluent: PE/EtOAc 6:4; yield: 90%. Gum; IR (film) ν 1647 (CO), 1622 (CO) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.65–2.30 (m, 7H, 3 CH_2 + CH_2), 2.90–2.96 (m, 1H, CH_2), 3.58 (d, 1H, $J=15.2$ Hz, NCH_2), 3.62 (d, 1H, $J=15.2$ Hz, NCH_2), 3.81 (s, 3H, OCH_3), 4.10 (s, 3H, NCH_3), 4.60–5.10 (m, 2H, NCH_2Ph), 5.62–5.68 (m, 1H, =CH), 6.07–6.12 (m, 1H, =CH), 6.88 (d, 2H, $J=8.8$ Hz, H_{Ar}), 7.27–7.42 (m, 5H, H_{Ar}), 8.27 (d, 1H, $J=7.9$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 18.0 (CH_2), 21.2 (CH_2), 29.1 (CH_2), 32.8 (NCH_3), 44.3 (CH_2), 50.2 (CH_2), 50.7 (CH_2), 54.5 (C), 55.4 (OCH_3), 110.2 (CH), 114.3 (2CH), 115.6 (C), 123.3 (CH), 123.4 (CH), 125.6 (CH), 125.8 (C), 127.1 (CH), 129.6 (C), 129.7 (2CH), 133.2 (C), 134.6 (CH), 138.7 (C), 159.3 (C), 162.6 (CO), 201.2 (CO); MS (IS) *m/z* 429 $(M+H)^+$. Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 76.02; H, 6.72; N, 6.40.

3.2.8. 7-(4-Methoxybenzyl)-5-methyl-7a,8,11,11a-tetrahydroindolo[2,3-*c*][1]benzazepine-6,12(5*H*,7*H*)-dione (5a). Diene precursor: **15a** (Diastereomer 1), $t=8$ h; chromatography eluent: PE/EtOAc 8:2; yield: 96%. Gum; IR (film) ν 1641 (CO), 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.09–2.25 (m, 2H, CH_2), 2.41–2.53 (m, 1H, CH_2), 2.87–2.90 (m, 1H, CH_2), 3.04–3.14 (m, 1H, CHCO), 3.82 (s, 3H, OCH_3), 3.90 (broad s, 1H, NCH), 4.13 (s, 3H, NCH_3), 4.55 (d, 1H, $J=14.2$ Hz, NCH_2), 5.17 (d, 1H, $J=14.2$ Hz, NCH_2), 5.40 (broad s, 1H, =CH), 5.61 (broad s, 1H, =CH), 6.89 (d, 2H, $J=8.5$ Hz, H_{Ar}), 7.32–7.43 (m, 5H, H_{Ar}), 8.50 (d, 1H, $J=7.8$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.1 (CH_2), 29.4 (CH_2), 33.4 (NCH_3), 53.7 (NCH_2), 55.0 (CH), 55.4 (CH_3), 57.3 (NCH), 110.2 (CH), 114.4 (2CH), 115.5 (C), 123.8 (CH), 124.2 (CH), 125.4 (C), 125.6 (CH), 129.5 (C), 130.7 (2CH), 134.4 (CH), 135.5 (C), 136.5 (CH), 138.6 (C), 159.2 (C), 161.2 (CO), 193.7 (CO); MS (IS) *m/z* 401 $(M+H)^+$. Diene precursor: **15a** (Diastereomer 2), $t=8$ h; chromatography eluent: PE/EtOAc 8:2; yield: 96%. Gum; IR (film) ν 1643 (CO), 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.96–2.07 (m, 1H, CH_2), 2.32–2.75 (m, 3H, CH_2), 3.80 (s, 3H, OCH_3), 4.10 (s, 3H, NCH_3), 4.40–4.52 (m, 2H, NCH_2 + NCH), 5.28 (d, 1H, $J=15.6$ Hz, NCH_2), 5.60 (s, 2H, 2=CH), 6.86 (d, 2H, $J=8.5$ Hz, H_{Ar}), 7.19 (d, 2H, $J=8.5$ Hz, H_{Ar}), 7.28–7.44 (m, 3H, H_{Ar}), 8.03 (d, 1H, $J=8.0$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.1 (CH_2), 30.2 (CH_2), 32.3 (NCH_3), 44.6 (NCH_2), 54.3 (CH), 54.8 (CH), 55.4 (OCH_3), 110.2 (CH), 114.4 (2CH), 116.5 (C), 122.3 (CH), 123.2 (CH), 124.2 (CH), 125.2 (C), 125.4 (CH), 125.7 (CH), 128.5 (2CH), 130.7 (C), 134.4 (C), 138.9 (C), 159.0 (C), 163.7 (CO), 199.3 (CO); MS (IS) *m/z* 401 $(M+H)^+$. Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 6.99. Found: C, 74.93; H, 5.92; N, 6.90.

3.2.9. 7-(4-Methoxybenzyl)-5-methyl-7a,8,11,11a-tetrahydroindolo[2,3-*c*][1]benzazepine-6,12(5*H*,7*H*)-dione (5b). Diene precursor: **15b**. $t=12$ h; chromatography eluent: PE/EtOAc 8:2; yield: 93%. Gum; IR (film) ν 1647 (CO); 1625 (CO) cm^{-1}; ^1H NMR and ^{13}C NMR data were not available due to a very bad resolution of the spectra; MS (IS) *m/z* 415 $(M+H)^+$. Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.11; H, 6.49; N, 6.95.

3.3. Typical procedure for the synthesis of 6

Sodium hydride (96 mg, 2.41 mmol, 60% dispersed in oil) was added portionwise to a solution of **2a** (500 mg, 2.19 mmol) in DMF (10 mL) at 0 °C. The mixture was stirred for 1 h at room temperature. Alkenyl bromide (3.29 mmol) was slowly added and the final mixture was stirred for 1 h at room temperature. Water (50 mL) was added and the mixture was extracted with EtOAc (2× 20 mL). The organic layer was washed twice with saturated aqueous NH_4Cl solution then dried over $MgSO_4$. After evaporation, the crude residue was purified by column chromatography to afford **6**.

3.3.1. 2-Allyl-10-methyl-3,4-dihydroazepino[3,4-b]-indole-1,5(2*H*,10*H*)-dione (6a). Alkenyl bromide: 3-bromopropene; chromatography eluent: PE/EtOAc 7:3; yield: 88%. Mp 139–141 °C (EtOAc); IR (KBr) ν 1645 (CO), 1620 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.86–2.90 (m, 2H, CH_2), 3.70–3.74 (m, 2H, CH_2), 4.05 (s, 3H, NCH_3), 4.29 (d, 2H, $J=6.0$ Hz, NCH_2), 5.27–5.34 (m, 2H, $=CH_2$), 5.84–5.99 (m, 1H, =CH), 7.30–7.42 (m, 3H, H_{Ar}), 8.41 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.8 (NCH_3), 43.9 (CH_2), 44.1 (CH_2), 50.1 (NCH_2), 110.2 (CH), 115.6 (C), 118.7 (CH_2), 123.6 (CH), 123.8 (CH), 125.1 (C), 125.6 (CH), 132.8 (CH), 134.5 (C), 138.6 (C), 161.3 (CO), 195.6 (CO); MS (IS) *m/z* 269 $(M+H)^+$. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.92; H, 5.88; N, 10.62.

3.3.2. 2-(3-Butenyl)-10-methyl-3,4-dihydroazepino[3,4-b]indole-1,5(2*H*,10*H*)-dione (6b). Alkenyl bromide: 4-bromobutene; chromatography eluent: PE/EtOAc 8:2; yield: 54%. Mp 113–115 °C (EtOAc/PE); IR (KBr) ν 1635 (CO), 1618 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.43–2.46 (m, 2H, CH_2), 2.86–2.90 (m, 2H, CH_2), 3.70–3.75 (m, 4H, 2 NCH_2), 4.01 (s, 3H, NCH_3), 5.07–5.17 (m, 2H, $=CH_2$), 5.80–5.90 (m, 1H, =CH), 7.23–7.40 (m, 3H, H_{Ar}), 8.39 (d, 1H, $J=8.0$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.8 (NCH_3), 33.0 (CH_2), 43.9 (CH_2), 45.1 (CH_2), 47.7 (CH_2), 110.2 (CH), 115.4 (C), 117.5 (CH_2), 123.5 (CH), 123.7 (CH), 125.0 (C), 125.5 (CH), 133.3 (C), 134.9 (CH), 138.4 (C), 161.4 (CO), 195.5 (CO); MS (IS) *m/z* 283 $(M+H)^+$. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.04; H, 6.53; N, 9.77.

3.3.3. 10-Methyl-2-(4-pentenyl)-3,4-dihydroazepino[3,4-b]indole-1,5(2*H*,10*H*)-dione (6c). Alkenyl bromide: 5-bromopentene; chromatography eluent: PE/EtOAc 8:2; yield: 64%. Mp 104–106 °C (EtOAc/PE); IR (KBr) ν 1647 (CO), 1621 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.74–1.80 (m, 2H, CH_2), 2.11–2.19 (m, 2H, CH_2), 2.84–2.88 (m, 2H, CH_2), 3.60–3.69 (m, 4H, 2 NCH_2), 4.01 (s, 3H, NCH_3), 5.00–5.11 (m, 2H, $=CH_2$), 5.77–5.93 (m, 1H, =CH), 7.31–7.39 (m, 3H, H_{Ar}), 8.38 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 27.9 (CH_2), 31.5 (CH_2), 33.1 (NCH_3), 44.3 (CH_2), 45.3 (CH_2), 48.0 (CH_2),

110.0 (CH), 115.2 (C), 115.4 (CH_2), 123.3 (CH), 123.5 (CH), 124.9 (C), 125.4 (CH), 134.8 (C), 137.4 (CH), 138.3 (C), 161.2 (CO), 195.4 (CO); MS (IS) *m/z* 297 $(M+H)^+$. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.16; N, 9.52. Found: C, 72.83; H, 5.99; N, 9.64.

3.3.4. 2-(5-Hexenyl)-10-methyl-3,4-dihydroazepino[3,4-b]indole-1,5(2*H*,10*H*)-dione (6d). Alkenyl bromide: 6-bromohexene; chromatography eluent: PE/EtOAc 8:2; yield: 76%. Gum; IR (film) ν 1639 (CO), 1622 (CO) cm^{-1};. ^1H NMR (250 MHz, $CDCl_3$) δ 1.42–1.54 (m, 2H, CH_2), 1.64–1.76 (m, 2H, CH_2), 2.03–2.18 (m, 2H, CH_2), 2.86–2.90 (m, 2H, CH_2), 3.62–3.71 (m, 4H, 2 NCH_2), 4.06 (s, 3H, NCH_3), 4.95–5.07 (m, 2H, $=CH_2$), 5.72–5.89 (m, 1H, =CH), 7.27–7.40 (m, 3H, H_{Ar}), 8.42 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 26.2 (CH_2), 27.8 (CH_2), 32.8 (NCH_3), 33.4 (CH_2), 44.0 (CH_2), 44.9 (CH_2), 47.8 (CH_2), 110.1 (CH), 115.0 (C), 115.3 (CH_2), 123.5 (CH), 123.6 (CH), 125.0 (C), 125.5 (CH), 134.9 (C), 138.2 (CH), 138.4 (C), 161.3 (CO), 195.4 (CO); MS (IS) *m/z* 311 $(M+H)^+$. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.02. Found: C, 73.85; H, 6.99; N, 9.21.

3.4. Typical procedure for the synthesis of 7

A solution of LiHMDS 1 M in THF (1.34 mL, 1.34 mmol) was added dropwise to a solution of **6** (0.75 mmol) in anhydrous THF (30 mL) at −78 °C. After 1 h of stirring, a solution of bromine (0.04 mL, 0.75 mmol) in anhydrous THF (1 mL) was quickly added to the mixture at −78 °C. After 10 min of stirring, a saturated aqueous NH_4Cl solution (5 mL) and EtOAc (20 mL) were added. The biphasic solution was decanted and separated. The organic layer was dried over $MgSO_4$. After evaporation in vacuo, the crude monobromide was directly used in the next step. DBU (0.17 mL, 1.12 mmol) was added to a solution of crude monobromide in DMF (5 mL). The mixture was stirred for 2 h at room temperature. 10% HCl solution (5 mL) was added and the mixture was extracted with EtOAc (2× 10 mL); the organic layer was washed with brine (3×5 mL) and dried over $MgSO_4$. After evaporation, the residue was purified by column chromatography to afford **7**.

3.4.1. 2-Allyl-10-methylazepino[3,4-*b*]indole-1,5(2*H*,10*H*)dione (7a). Chromatography eluent: PE/EtOAc 8:2; yield: 83%. Mp 130–132 °C (EtOAc/PE); IR (KBr) ν 1640 (CO), 1628 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.24 (s, 3H, NCH_3), 4.60 (d, 2H, $J=5.5$ Hz, NCH_2), 5.25–5.33 (m, 2H, $=CH_2$), 5.92–6.07 (m, 1H, =CH), 6.01 (d, 1H, $J=$ 10.9 Hz, =CHCO), 6.76 (d, 1H, $J=10.9$ Hz, =CH), 7.36–7.54 (m, 3H, H_{Ar}), 8.88 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 34.0 (NCH_3), 54.7 (NCH_2), 110.0 (CH), 113.6 (CH), 118.2 (CH_2), 120.7 (C), 123.3 (CH), 124.5 (C), 124.8 (CH), 127.0 (CH), 131.7 (C), 132.0 (CH), 134.7 (CH), 139.4 (C), 160.2 (CO), 182.2 (CO); MS (IS) *m/z* 267 $(M+H)^+$. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 71.83; H, 5.45; N, 10.41.

3.4.2. 2-(3-Butenyl)-10-methylazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (7b). Chromatography eluent: PE/EtOAc 7:3; yield: 80%. Mp 114–116 °C (EtOAc/PE); IR (KBr) ν 1638 (CO), 1627 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.03–3.14 (m, 2H, CH_2), 4.06 (t, 2H, $J=7.1$ Hz, NCH_2), 4.26 (s, 3H, NCH_3), 5.09–5.18 (m, 2H, $=CH_2$), 5.79–5.90 (m, 1H, =CH), 6.00 (d, 1H, $J=10.9$ Hz, =CHCO), 6.79 (d, 1H, $J=10.9$ Hz, =CHN), 7.38–7.55 (m, 3H, H_{Ar}), 8.88 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz) δ 33.4 (CH_2), 34.4 (NCH_3), 53.2 (NCH_2), 110.2 (CH), 114.2 (CHCO), 118.3 (CH_2), 121.4 (C), 123.7 (CH), 124.9 (C), 125.4 (CH), 127.4 (CH), 132.2 (C), 133.9 (CH), 135.2 (CH), 139.9 (C), 160.8 (CO), 182.6 (CO); MS (IS) *m/z* 281 $(M+H)^+$. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.12; H, 5.67; N, 10.08.

3.4.3. 10-Methyl-2-(4-pentenyl)azepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (7c). Chromatography eluent: PE/EtOAc 7:3; yield: 81%. Mp 81–83 °C (EtOAc/PE); IR (KBr) ν 1640 (CO), 1625 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.81–1.93 (m, 2H, CH_2), 2.12–2.21 (m, 2H, CH_2), 3.90–3.97 (m, 2H, NCH_2), 4.18 (s, 3H, NCH_3), 5.01–5.12 (m, 2H, $=CH_2$), 5.75–5.89 (m, 1H, =CH), 5.93 (d, 1H, $J=$ 11.0 Hz, =CHCO), 6.76 (d, 1H, $J=11.0$ Hz, =CHN), 7.31–7.49 (m, 3H, H_{Ar}), 8.83 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 27.9 (CH_2), 30.7 (CH_2), 34.3 (NCH_3), 52.2 (NCH_2), 110.1 (CH), 114.0 (CH), 115.7 (CH_2), 121.1 (C), 123.5 (CH), 124.7 (C), 125.1 (CH), 127.2 (CH), 132.1 (C), 135.1 (CH), 137.1 (CH), 139.7 (C), 160.6 (CO), 182.4 (CO); MS (IS) *m/z* 295 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.24; H, 6.32; N, 9.43.

3.4.4. 2-(5-Hexenyl)-10-methylazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (7d). Chromatography eluent: PE/EtOAc 7:3; yield: 83%. Mp 96–98 °C (EtOAc/PE); IR (KBr) ν 1637 (CO), 1623 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.42–1.57 (m, 2H, CH_2), 1.64–1.78 (m, 2H, CH_2), 2.10–2.16 (m, 2H, CH_2), 3.93 (t, 2H, $J=7.5$ Hz, NCH_2), 4.18 (s, 3H, NCH_3), 4.96–5.06 (m, 2H, $=CH_2$), 5.71–5.87 (m, 1H, =CH), 5.95 (d, 1H, $J=11.0$ Hz, =CHCO), 6.75 (d, 1H, $J=11.0$ Hz, =CHN), 7.32–7.52 (m, 3H, H_{Ar}), 8.84 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 26.0 (CH_2), 28.6 (CH_2), 33.4 (CH_2), 34.3 (NCH_3), 53.6 (NCH_2), 110.2 (CH), 114.1 (CH), 115.2 (CH_2), 121.2 (C), 123.6 (CH), 124.8 (C), 125.2 (CH), 127.3 (CH), 132.2 (C), 135.1 (CH), 138.1 (CH), 139.7 (C), 160.7 (CO), 182.5 (CO); MS (IS) *m/z* 309 $(M+H)^+$. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.77; H, 6.40; N, 9.19.

3.5. Typical procedure for Sakurai allylation of 7

Allyltrimethylsilane (0.36 mL, 2.25 mmol) and a solution of $TiCl_4$ 1 M in dichloromethane (1.50 mL, 1.50 mmol) was added to a cooled solution (−40 °C) of **7** (0.37 mmol) in anhydrous dichloromethane (3 mL). The mixture was then stirred for 15 h at room temperature. A saturated aqueous NH_4Cl solution (5 mL) was added and the mixture was extracted with dichloromethane (2×10 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography to afford **8** as a gum.

3.5.1. 2,3-Diallyl-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (8a). Chromatography eluent: PE/EtOAc 7:3; yield: 69%. IR (film) ν 1640 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.38–2.56 (m, 2H, CH_2), 2.96 (dd, 1H, $J=5.9$, 18.2 Hz, CH_2CO), 3.13 (dd, 1H, $J=2.8$,

18.2 Hz, CH_2CO), 3.79–3.83 (m, 1H, NCH), 4.01 (dd, 1H, J=5.8, 14.9 Hz, NCH_2), 4.07 (s, 3H, NCH_3), 4.57 (dd, 1H, J=5.8, 14.9 Hz, NCH_2), 4.90–5.08 (m, 2H, =CH_2), 5.27–5.38 (m, 2H, =CH_2), 5.63–5.74 (m, 1H, =CH), 5.90–6.00 (m, 1H, =CH), 7.36–7.48 (m, 3H, H_{Ar}), 8.49 (d, 1H, J=8.1 Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.2 (NCH_3), 36.1 (CH_2), 47.7 (CH_2), 51.3 (CH_2), 55.2 (NCH), 110.3 (CH), 115.5 (C), 118.8 (CH_2), 118.9 (CH_2), 123.9 (2CH), 125.0 (C), 125.6 (CH), 133.3 (CH), 133.8 (CH), 135.8 (C), 138.5 (C), 161.0 (CO), 193.3 (CO); MS (IS) m/z 309 $(M+H)^+$. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.0; H, 6.54; N, 9.09. Found: C, 73.72; H, 6.38; N, 8.92.

3.5.2. 3-Allyl-2-(3-butenyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (8b). Chromatography eluent: PE/EtOAc 8:2; yield: 54%. IR (film) ν 1645 (CO), 1630 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.40–2.56 (m, 4H, 2 CH_2), 2.98 (dd, 1H, J=5.8, 17.9 Hz, CH_2CO), 3.22 (dd, 1H, J=2.8, 17.9 Hz, CH_2CO), 3.37–3.48 (m, 1H, NCH_2), 3.74–3.80 (m, 1H, NCH), 4.07 (s, 4H, NCH_3+NCH_2), 4.91–5.21 (m, 4H, 2=CH_2), 5.62–5.96 (m, 2H, 2=CH), 7.28–7.38 (m, 3H, H_{Ar}), 8.55 (d, 1H, J=8.1 Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.2 (NCH_3), 33.3 (CH_2), 36.2 (CH_2), 47.8 (CH_2), 49.2 (CH_2), 56.3 (NCH), 110.3 (CH), 115.4 (C), 117.5 (CH_2), 118.9 (CH_2), 123.9 (2CH), 125.0 (C), 125.6 (CH), 133.8 (CH), 135.0 (CH), 136.1 (C), 138.5 (C), 161.0 (CO), 193.1 (CO); MS (IS) m/z 323 $(M+H)^+$. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.78; H, 6.97; N, 8.54.

3.5.3. 3-Allyl-10-methyl-2-(4-pentenyl)-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (8c). Chromatography eluent: PE/EtOAc 7:3; yield: 50%. IR (film) ν 1638 (CO) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.69–1.88 (m, 2H, CH_2), 2.13–2.21 (m, 2H, CH_2), 2.37–2.58 (m, 2H, CH_2), 2.95–3.21 (m, 2H, CH_2), 3.34–3.45 (m, 1H, NCH_2), 3.78–3.96 (m, 2H, $NCH+NCH_2$), 4.06 (s, 3H, NCH_3), 4.90–5.12 (m, 4H, 2=CH_2), 5.64–5.87 (m, 2H, 2=CH), 7.34–7.46 (m, 3H, H_{Ar}), 8.49 (d, 1H, J=8.1 Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 27.9 (CH_2), 31.3 (CH_2), 33.2 (NCH_3), 36.3 (CH_2), 47.9 (CH_2), 49.1 (CH_2), 56.2 (NCH), 110.3 (CH), 115.4 (C), 115.6 (CH_2), 118.9 (CH_2), 123.9 (2CH), 125.0 (C), 125.6 (CH), 133.8 (CH), 136.2 (C), 137.5 (CH), 138.5 (C), 161.0 (CO), 193.1 (CO); MS (IS) m/z 337 $(M+H)^+$. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.25; H, 7.31; N, 8.40.

3.5.4. 3-Allyl-2-(5-hexenyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (8d). Chromatography eluent: PE/EtOAc 8:2; yield: 48%. IR (film) ν 1639 (CO), 1629 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44–1.52 (m, 2H, CH_2), 1.64–1.76 (m, 2H, CH_2), 2.09–2.18 (m, 2H, CH_2), 2.33–2.57 (m, 2H, CH_2), 2.93–3.20 (m, 2H, CH_2), 3.32–3.44 (m, 1H, NCH_2), 3.70–3.81 (m, 1H, NCH), 3.85–3.96 (m, 1H, NCH_2), 4.05 (s, 3H, NCH_3), 4.90–5.08 (m, 4H, 2=CH_2), 5.60–5.89 (m, 2H, 2=CH), 7.31–7.48 (m, 3H, H_{Ar}), 8.48 (d, 1H, J=8.3 Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 26.4 (CH_2), 28.2 (CH_2), 33.2 (NCH_3), 33.5 (CH_2), 36.3 (CH_2), 47.9 (CH_2), 49.2 (CH_2), 56.1 (NCH), 110.3 (CH), 115.1 (CH_2), 115.4 (C), 118.9 (CH_2), 123.90 (CH), 123.92 (CH), 125.0 (C), 125.6 (CH), 133.9 (CH), 136.3 (C), 138.4 (CH), 138.5 (C), 160.9 (CO), 193.2 (CO); MS (IS) m/z 351 $(M+H)^+$. Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.15; H, 7.30; N, 8.15.

3.5.5. 4,4-Diallyl-2-(4-methoxybenzyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (9). At 0 °C, a solution of compound **2b** (200 mg, 0.57 mmol) in anhydrous THF (2 mL) was added dropwise to a suspension of sodium hydride (50 mg, 1.21 mmol, 60% dispersed in oil) in anhydrous THF (2 mL). The mixture was stirred for 3 h at room temperature. 3-Bromopropene (0.25 mL, 2.87 mmol) was added and the final solution was stirred overnight at room temperature. A saturated aqueous NH_4Cl solution (5 mL) and EtOAc (10 mL) were added and the mixture obtained was extracted. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography (eluent PE/EtOAc 8:2) to afford **9** (190 mg, 77%) as a solid. Mp 123–124 °C (EtOAc/PE); IR (KBr) ν 1642 (CO), 1628 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 2.37–2.46 (m, 2H, CH_2), 2.52–2.61 (m, 2H, CH_2), 3.59 (broad s, 2H, NCH_2), 3.81 (s, 3H, OCH_3), 4.10 (s, 3H, NCH_3), 4.76 (broad s, 2H, NCH_2Ph), 5.03–5.12 (m, 4H, 2=CH_2), 5.66–5.82 (m, 2H, 2=CH), 6.90 (d, 2H, J=8.5 Hz, H_{Ar}), 7.27–7.43 (m, 5H, H_{Ar}), 8.35 (d, 1H, J=7.9 Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.9 (NCH_3), 40.2 ($2CH_2$), 51.5 (NCH_2), 51.9 (NCH_2), 55.4 (C), 55.6 (OCH_3), 110.3 (CH), 114.3 (2CH), 116.7 (C), 119.0 ($2CH_2$), 123.5 (CH), 123.6 (CH), 125.3 (C), 125.7 (CH), 128.5 (C), 129.6 (2CH), 133.0 (2CH), 133.3 (C), 138.6 (C), 159.3 (C), 162.0 (CO), 199.2 (CO); MS (IS) m/z 429 $(M+H)^+$. Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 75.68; H, 6.59; N, 6.54. Found: C, 75.90; H, 6.43; N, 6.39.

3.5.6. Ethyl 5-hydroxy-2-(4-methoxybenzyl)-10-methyl-1-oxo-1,2,3,10-tetrahydroazepino[3,4-*b*]indole-4-carboxylate (10). At −78 °C, LiHMDS 1 M in THF (0.78 mL, 0.78 mmol) was slowly added to a solution of **2b** (150 mg, 0.43 mmol) in anhydrous THF (5 mL). After 1 h, ethyl cyanoformate (0.05 mL, 0.47 mmol) was added dropwise and the final solution was stirred at −78 °C for 15 min. 10% Aqueous HCl solution (5 mL) was added and the mixture was extracted with EtOAc (3×10 mL). The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (eluent PE/EtOAc 7:3) to afford **10** (167 mg, 92%) as a solid. Mp 128–130 °C (EtOAc); IR (KBr) ν 1736 (CO), 1628 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (t, 3H, J=7.1 Hz, CH_3), 3.81 (s, 3H, OCH_3), 4.13 (s, 3H, NCH_3), 4.23 (q, 2H, J=7.1 Hz, OCH_2), 4.50 (broad s, 2H, CH_2), 4.97 (broad s, 2H, CH_2Ph), 6.89 (d, 2H, J=8.5 Hz, H_{Ar}), 7.29–7.45 (m, 5H, H_{Ar}), 8.23 (d, 1H, J=8.0 Hz, H_{Ar}), 12.71 (s, 1H, OH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.4 (CH_3), 32.6 (NCH_3), 43.1 (CH_2), 49.4 (CH_2), 55.3 (OCH_3), 60.8 (OCH_2), 97.2 (C), 110.2 (CH), 112.9 (C), 114.0 (2CH), 122.2 (CH), 123.2 (CH), 124.1 (C), 125.4 (CH), 129.5 (C), 129.6 (2CH), 134.6 (C), 138.4 (C), 159.2 (C), 160.7 (CO), 169.4 (C), 170.9 (CO); MS (IS) m/z 421 $(M+H)^+$. Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.27; H, 5.93; N, 6.49.

3.6. Typical procedure for the *C*-alkylation of 10

A mixture of compound **10** (150 mg, 0.357 mmol), potassium carbonate (246 mg, 1.79 mmol) and alkenyl bromide (1.79 mmol) in acetone (5 mL) was heated at

reflux for t h. After cooling, EtOAc (10 mL) and water (5 mL) were added, the final biphasic solution was decanted and separated. The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (eluent PE/EtOAc 8:2) to give **11** as a gum.

3.6.1. Ethyl 4-allyl-2-(4-methoxybenzyl)-10-methyl-1,5-dioxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indole-4-carboxylate (11a). Alkenyl bromide: 3-bromopropene; $t=$ 24 h; chromatography eluent: PE/EtOAc 8:2; yield: 92%. IR (film) ν 1731 (CO), 1643 (CO), 1621 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (t, 3H, $J=7.1$ Hz, CH_3), 2.67–2.76 (m, 1H, CH_2), 3.10–3.17 (m, 1H, CH_2), 3.65 (d, 1H, $J=15.2$ Hz, NCH_2), 3.80 (s, 3H, OCH_3), 3.99 (d, 1H, $J=$ 15.2 Hz, NCH_2), 4.09 (s, 3H, NCH_3), 4.14–4.30 (m, 3H, OCH_2+NCH_2Ph), 4.98 (d, 1H, $J=10.0$ Hz, $=CH_2$), 5.10 (d, 1H, $J=17.0$ Hz, $=CH_2$), 5.42 (d, 1H, $J=14.3$ Hz, NCH_2Ph), 5.59–5.72 (m, 1H, =CH), 6.89 (d, 2H, $J=$ 8.5 Hz, H_{Ar}), 7.27–7.43 (m, 5H, H_{Ar}), 8.43 (d, 1H, $J=$ 7.6 Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2 (CH_3), 32.9 (NCH_3), 39.8 (CH_2), 50.7 (CH_2), 51.4 (CH_2), 55.3 (OCH_3), 62.2 (OCH_2), 62.6 (C), 110.3 (CH), 114.3 (2CH), 115.9 (C), 119.7 (CH_2), 123.6 (CH), 123.8 (CH), 125.3 (C), 125.7 (CH), 128.5 (C), 129.5 (2CH), 132.1 (CH), 133.5 (C), 138.5 (C), 159.3 (C), 161.5 (CO), 171.4 (CO), 193.0 (CO); MS (IS) m/z 461 $(M+H)^+$. Anal. Calcd for $C_{27}H_{28}N_2O_5$: C, 70.42; H, 6.13; N, 6.08. Found: C, 70.71; H, 6.25; N, 5.96.

3.6.2. Ethyl 4-(3-butenyl)-2-(4-methoxybenzyl)-10-methyl-1,5-dioxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indole-4-carboxylate (11b). Alkenyl bromide: 4-bromobutene; $t=72$ h; chromatography eluent: PE/EtOAc 7:3; yield: 47%. IR (film) ν 1729 (CO), 1643 (CO), 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (t, 3H, $J=$ 6.9 Hz, CH_3), 2.01–2.04 (m, 3H, CH_2+CH_2), 2.34–2.45 (m, 1H, CH_2), 3.68 (d, 1H, $J=15.4$ Hz, NCH_2), 3.81 (s, 3H, OCH_3), 4.04 (d, 1H, $J=15.4$ Hz, NCH_2), 4.10 (s, 3H, NCH_3), 4.12–4.30 (m, 3H, OCH_2+NCH_2Ph), 4.89–4.99 (m, 2H, $=CH_2$), 5.43 (d, 1H, $J=14.9$ Hz, NCH_2Ph), 5.65–5.84 (m, 1H, =CH), 6.90 (d, 2H, $J=8.5$ Hz, H_{Ar}), 7.26–7.45 (m, 5H, H_{Ar}), 8.43 (d, 1H, $J=7.8$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2 (CH_3), 28.5 (CH_2), 33.0 (NCH_3), 34.7 (CH_2), 50.7 (CH_2), 51.4 (CH_2), 55.4 (OCH_3), 62.2 (OCH_2), 63.0 (C), 110.3 (CH), 114.3 (2CH), 115.4 (CH_2), 116.1 (C), 123.7 (CH), 123.9 (CH), 125.5 (C), 125.8 (CH), 128.5 (C), 129.6 (2CH), 133.3 (C), 137.5 (CH), 138.6 (C), 159.4 (C), 161.6 (CO), 171.7 (CO), 193.3 (CO); MS (IS) m/z 475 $(M+H)^+$. Anal. Calcd for $C_{28}H_{30}N_2O_5$: C, 70.87; H, 6.37; N, 5.90. Found: C, 70.64; H, 6.44; N, 5.99.

3.6.3. Ethyl 2-(4-methoxybenzyl)-10-methyl-4-(4-pentenyl)-1,5-dioxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]-indole-4-carboxylate (11c). Alkenyl bromide: 5-bromopentene; $t=48$ h; chromatography eluent: PE/EtOAc 8:2; yield: 59%. IR (film) ν 1729 (CO), 1644 (CO), 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.21 (t, 3H, $J=7.1$ Hz, CH_3), 1.28–1.38 (m, 2H, CH_2), 1.95–2.06 (m, 3H, CH_2+CH_2), 2.25–2.38 (m, 1H, CH_2), 3.66 (d, 1H, $J=14.9$ Hz, NCH_2), 3.80 (s, 3H, OCH_3), 4.04 (d, 1H, $J=$ 14.9 Hz, NCH_2), 4.10 (s, 3H, NCH_3), 4.13–4.29 (m, 3H, OCH_2+NCH_2Ph), 4.90–4.99 (m, 2H, $=CH_2$), 5.43 (d, 1H, $J=15.0$ Hz, NCH_2Ph), 5.62–5.79 (m, 1H, =CH), 6.90 (d, 2H, $J=8.5$ Hz, H_{Ar}), 7.26–7.45 (m, 5H, H_{Ar}), 8.43 (d, 1H, $J=7.8$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2 (CH_3), 23.5 (CH_2), 33.0 (NCH_3), 34.2 (CH_2), 35.2 (CH_2), 50.7 (CH_2), 51.4 (CH_2), 55.4 (OCH_3), 62.1 (OCH_2), 63.0 (C), 110.3 (CH), 114.3 (2CH), 115.1 (CH_2), 116.1 (C), 123.7 (CH), 123.9 (CH), 125.4 (C), 125.8 (CH), 128.5 (C), 129.6 (2CH), 133.4 (C), 137.9 (CH), 138.5 (C), 159.4 (C), 161.6 (CO), 171.9 (CO), 193.4 (CO); MS (IS) m/z 489 $(M+H)^+$. Anal. Calcd for $C_{29}H_{32}N_2O_5$: C, 71.29; H, 6.60; N, 5.73. Found: C, 71.02; H, 6.77; N, 5.91.

3.6.4. 4-(5-Hexenyl)-2-(4-methoxybenzyl)-10-methyl-1,5-dioxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indole-4-carboxylate (11d). Alkenyl bromide: 6-bromohexene; $t=48$ h; chromatography eluent: PE/EtOAc 8:2; yield: 68%. IR (film) ν 1732 (CO), 1641 (CO), 1617 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.21 (t, 3H, $J=7.0$ Hz, CH_3), 1.21–1.23 (m, 2H, CH_2), 1.25–1.39 (m, 2H, CH_2), 1.90–2.03 (m, 3H, CH_2+CH_2), 2.25–2.35 (m, 1H, CH_2), 3.65 (d, 1H, $J=$ 15.1 Hz, NCH_2), 3.80 (s, 3H, OCH_3), 4.04 (d, 1H, $J=$ 15.1 Hz, NCH_2), 4.10 (s, 3H, NCH_3), 4.15–4.26 (m, 3H, OCH_2+NCH_2Ph), 4.86–4.96 (m, 2H, $=CH_2$), 5.44 (d, 1H, $J=14.9$ Hz, NCH_2Ph), 5.63–5.79 (m, 1H, =CH), 6.90 (d, 2H, $J=8.8$ Hz, H_{Ar}), 7.27–7.45 (m, 5H, H_{Ar}), 8.43 (d, 1H, $J=7.6$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2 (CH_3), 23.6 (CH_2), 29.4 (CH_2), 33.0 (NCH_3), 33.3 (CH_2), 35.5 (CH_2), 50.6 (CH_2), 51.4 (CH_2), 55.4 (OCH_3), 62.1 (OCH_2), 63.0 (C), 110.3 (CH), 114.3 (2CH), 114.7 (CH_2), 116.1 (C), 123.7 (CH), 123.8 (CH), 125.4 (C), 125.8 (CH), 128.6 (C), 129.6 (2CH), 133.4 (C), 137.9 (CH), 138.5 (C), 159.4 (C), 161.6 (CO), 171.9 (CO), 193.5 (CO); MS (IS) m/z 503 $(M+H)^+$. Anal. Calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 72.03; H, 6.71; N, 5.68.

3.7. Typical procedure for the decarboxylation of 11

A solution of **11** (0.22 mmol) and lithium hydroxide hydrate (18 mg, 0.43 mmol) in ethanol/water (v/v 3:1, 15 mL) was stirred at reflux for 30 min. After cooling, water (5 mL) and EtOAc (10 mL) were added and the mixture was separated. The organic layer was dried over $MgSO_4$ and evaporated to give **12** as a gum.

3.7.1. 4-Allyl-2-(4-methoxybenzyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (12a). Yield: 98%. IR (film) ν 1645 (CO), 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.13–2.23 (m, 1H, CH_2), 2.52–2.59 (m, 1H, CH_2), 2.70–2.79 (m, 1H, CHCO), 3.47 (d, 1H, $J=14.9$ Hz, NCH_2), 3.75 (d, 1H, $J=14.9$ Hz, NCH_2), 3.80 (s, 3H, OCH_3), 4.09 (s, 3H, NCH_3), 4.48 (d, 1H, $J=14.1$ Hz, NCH_2Ph), 5.03–5.10 (m, 3H, $=CH_2+NCH_2Ph$), 5.54–5.70 (m, 1H, =CH), 6.88 (d, 2H, $J=8.5$ Hz, H_{Ar}), 7.26–7.42 (m, 5H, H_{Ar}), 8.38 (d, 1H, $J=7.8$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.9 (NCH_3), 33.8 (CH_2), 47.7 (CH_2), 50.4 (CH_2), 51.8 (CH), 55.4 (OCH_3), 110.2 (CH), 114.3 (2CH), 116.0 (C), 117.8 (CH_2), 123.6 (C), 123.7 (CH), 125.3 (C), 125.6 (CH), 129.0 (C), 130.0 (2CH), 134.1 (C), 137.8 (CH), 138.6 (C), 159.5 (C), 161.6 (CO), 197.0 (CO); MS (IS) m/z 389 $(M+H)^+$. Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21. Found: C, 73.90; H, 6.36; N, 7.34.

3.7.2. 4-(3-Butenyl)-2-(4-methoxybenzyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (12b).

Yield 99%. IR (film) ν 1640 (CO), 1612 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.49–1.60 (m, 1H, CH_2), 1.95–2.13 (m, 3H, 2 CH_2), 2.54–2.60 (m, 1H, CHCO), 3.49 (d, 1H, $J=14.1$ Hz, NCH_2), 3.75 (d, 1H, $J=14.1$ Hz, NCH_2), 3.81 (s, 3H, OCH_3), 4.10 (s, 3H, NCH_3), 4.57 (d, 1H, $J=14.4$ Hz, NCH_2Ph), 4.96–5.06 (m, 3H, $=CH_2+NCH_2Ph$), 5.67–5.83 (m, 1H, =CH), 6.90 (d, 2H, $J=8.5$ Hz, H_{Ar}), 7.28–7.43 (m, 5H, H_{Ar}), 8.39 (d, 1H, $J=7.7$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.5 (CH_2), 31.2 (CH_2), 32.9 (NCH_3), 48.1 (CH_2), 50.6 (CH_2), 51.8 (CH), 55.4 (OCH_3), 110.2 (CH), 114.4 (2CH), 115.6 (CH_2), 116.0 (C), 123.7 (2CH), 125.4 (C), 125.6 (CH), 128.9 (C), 129.8 (2CH), 133.9 (C), 137.7 (CH), 138.6 (C), 159.5 (C), 161.7 (CO), 198.0 (CO); MS (IS) m/z 403 $(M+H)^+$. Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.91; H, 6.45; N, 7.10.

3.7.3. 2-(4-Methoxybenzyl)-10-methyl-4-(4-pentenyl)-3,4-dihydroazépino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (12c). Yield: 97%. IR (film) ν 1641 (CO), 1614 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.22–1.55 (m, 3H, $2CH_2$), 1.82–2.05 (m, 3H, $2CH_2$), 2.45–2.50 (m, 1H, CHCO), 3.48 (d, 1H, $J=14.4$ Hz, NCH_2), 3.77 (d, 1H, $J=14.4$ Hz, NCH_2), 3.80 (s, 3H, OCH_3), 4.10 (s, 3H, NCH_3), 4.48 (d, 1H, $J=14.4$ Hz, NCH_2Ph), 4.94–5.02 (m, 2H, $=CH_2$), 5.11 (d, 1H, $J=14.4$ Hz, NCH_2Ph), 5.68–5.84 (m, 1H, =CH), 6.90 (d, 2H, $J=8.8$ Hz, H_{Ar}), 7.28–7.43 (m, 5H, H_{Ar}), 8.39 (d, 1H, $J=7.7$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 26.4 (CH_2), 28.9 (CH_2), 32.9 (NCH_3), 33.8 (CH_2), 48.2 (CH_2), 50.6 (CH_2), 52.5 (CH), 55.4 (OCH_3), 110.2 (CH), 114.4 (2CH), 115.0 (CH_2), 116.0 (C), 123.6 (CH), 123.7 (CH), 125.4 (C), 125.6 (CH), 128.9 (C), 129.9 (2CH), 133.9 (C), 138.2 (CH), 138.6 (C), 159.5 (C), 161.7 (CO), 198.0 (CO); MS (IS) m/z 417 $(M+H)^+$. Anal. Calcd for $C_{26}H_{28}N_2O_3$: C, 74.98; H, 6.78; N, 6.73. Found: C, 74.67; H, 6.64; N, 6.90.

3.7.4. 4-(5-Hexenyl)-2-(4-methoxybenzyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (12d). Yield: 99%. IR (film) ν 1644 (CO), 1617 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.15–1.52 (m, 5H, $3CH_2$), 1.84–1.98 (m, 1H, CH_2), 2.01–2.06 (m, 2H, CH_2), 2.44–2.52 (m, 1H, CHCO), 3.48 (d, 1H, $J=14.9$ Hz, NCH_2), 3.72–3.79 (d, 1H, $J=14.9$ Hz, NCH_2), 3.80 (s, 3H, OCH_3), 4.10 (s, 3H, NCH_3), 4.49 (d, 1H, $J=14.4$ Hz, NCH_2Ph), 4.93–5.04 (m, 2H, $=CH_2$), 5.11 (d, 1H, $J=14.4$ Hz, NCH_2Ph), 5.70–5.85 (m, 1H, =CH), 6.89 (d, 2H, $J=8.5$ Hz, H_{Ar}), 7.28–7.44 (m, 5H, H_{Ar}), 8.39 (d, 1H, $J=7.8$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 26.6 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 32.9 (NCH_3), 33.6 (CH_2), 48.2 (CH_2), 50.6 (CH_2), 52.6 (CH), 55.4 (OCH_3), 63.0 (C), 110.2 (CH), 114.4 (2CH), 114.7 (CH_2), 116.0 (C), 123.6 (CH), 123.7 (CH), 125.4 (C), 125.6 (CH), 128.9 (C), 129.9 (2CH), 133.9 (C), 138.6 (CH), 159.1 (C), 161.7 (CO), 198.1 (CO); MS (IS) m/z 431 $(M+H)^+$. Anal. Calcd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02; N, 6.51. Found: C, 75.68; H, 6.92; N, 6.37.

3.8. Typical procedure for the allylation of 12b–c

At 0 °C, sodium hydride (16 mg, 0.40 mmol, 60% in dispersed oil) was slowly added to a solution of **12** (0.20 mmol) in anhydrous THF (5 mL). The mixture was stirred for 1 h at 0 °C and 3-bromopropene (0.04 mL, 0.40 mmol) was added. The solution was stirred for 16 h at room temperature. Water (10 mL) was added and the mixture was extracted with EtOAc (2×10 mL). The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography to give **13** as a gum.

3.8.1. 4-Allyl-4-(3-butenyl)-2-(4-methoxybenzyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (13b). Yield: 93%. IR (film) ν 1640 (CO), 1612 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.73–1.78 (m, 2H, CH_2), 2.03–2.10 (m, 2H, CH_2), 2.41–2.60 (m, 2H, CH_2), 3.61 (broad s, 2H, NCH_2), 3.81 (s, 3H, CH_3), 4.10 (s, 3H, OCH_3), 4.84 (broad s, 2H, NCH_2Ph), 4.89–5.13 (m, 4H, 2=CH_2), 5.67–5.79 (m, 2H, 2=CH), 6.90 (d, 2H, $J=8.8$ Hz, H_{Ar}), 7.28–7.43 (m, 5H, H_{Ar}), 8.36 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.3 (CH_2), 33.0 (NCH_3), 39.9 (CH_2), 51.4 (CH_2), 51.5 (CH_2), 52.0 (CH_2), 55.1 (C), 55.4 (OCH_3), 110.3 (CH), 114.4 (2CH), 115.1 (CH_2), 116.6 (C), 119.0 (CH_2), 123.6 (CH), 123.7 (CH), 125.4 (C), 125.7 (CH), 128.8 (C), 129.6 (2CH), 129.9 (C), 133.2 (CH), 138.8 (CH), 138.6 (C), 159.4 (C), 162.0 (CO), 199.4 (CO); MS (IS) m/z 443 $(M+H)^+$. Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 76.33; H, 6.95; N, 6.47.

3.8.2. 4-Allyl-2-(4-methoxybenzyl)-10-methyl-4-(4-pentenyl)-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (13c). Yield: 89%. IR (film) ν 1641 (CO), 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.37–1.40 (m, 2H, CH_2), 1.60–1.75 (m, 2H, CH_2), 1.97–2.04 (m, 2H, CH_2), 2.45–2.59 (m, 2H, CH_2), 3.59 (broad s, 2H, NCH_2), 3.81 (s, 3H, NCH_3), 4.10 (s, 3H, OCH_3), 4.83 (broad s, 2H, NCH_2Ph), 4.90–5.12 (m, 4H, 2=CH_2), 5.64–5.80 (m, 2H, 2=CH), 6.90 (d, 2H, $J=8.8$ Hz, H_{Ar}), 7.27–7.43 (m, 5H, H_{Ar}), 8.36 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 23.3 (CH_2), 33.0 (NCH_3), 34.4 (CH_2), 40.1 ($2CH_2$), 51.5 (CH_2), 52.1 (CH_2), 55.3 (C), 55.4 (OCH_3), 110.2 (CH), 114.3 (2CH), 115.1 (CH_2), 116.7 (C), 118.8 (CH_2), 123.7 (2CH), 125.4 (C), 125.7 (CH), 128.8 (C), 129.6 (2CH), 133.2 (C), 133.4 (CH), 138.2 (CH), 138.6 (C), 159.4 (C), 162.0 (CO), 199.7 (CO); MS (IS): m/z 457 $(M+H)^+$. Anal. Calcd for $C_{29}H_{32}N_2O_3$: C, 76.29; H, 7.06; N, 6.14. Found: C, 75.93; H, 7.17; N, 6.02.

3.8.3. 4-Allyl-2-(4-methoxybenzyl)-10-methylazepino-[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (14a). Following the procedure used for the preparation of **7**, compound **14a** was obtained from **13a** in 88% yield. Chromatography eluent PE/EtOAc 7:3. Mp 89–91 °C (EtOAc/PE); IR (KBr) ν 1630 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.33 (d, 2H, $J=6.3$ Hz, CH_2), 3.80 (s, 3H, OCH_3), 4.26 (s, 3H, NCH_3), 5.06–5.13 (m, 2H, $=CH_2$), 5.14 (s, 2H, NCH_2), 5.84–6.01 (m, 1H, =CH), 6.89 (d, 2H, $J=8.8$ Hz, H_{Ar}), 6.98 (s, 1H, NCH), 7.29 (d, 2H, $J=8.8$ Hz, H_{Ar}), 7.35–7.42 (m, 1H, H_{Ar}), 7.51–7.53 (m, 2H, H_{Ar}), 8.87 (d, 1H, $J=8.6$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 34.2 (CH_3), 36.0 (CH_2), 55.4 (CH_3), 55.7 (CH_2), 110.2 (CH), 114.4 (2CH), 116.7 (CH_2), 121.7 (C), 123.6 (CH), 123.9 (C), 125.3 (C), 125.4 (CH), 127.4 (CH), 128.6 (C), 129.3 (2CH), 131.6 (C), 134.5 (CH), 136.5 (CH), 139.9 (C), 159.5 (C), 160.4 (CO), 182.0 (CO); MS (IS) m/z 387 $(M+H)^+$. Anal.

Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 75.79; H, 5.61; N, 7.33.

3.8.4. 4-(3-Butenyl)-2-(4-methoxybenzyl)-10-methyl-azepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (14b). Following the procedure used for the preparation of **7**, compound **14b** was obtained from **13b** in 84% yield. Chromatography eluent EP/AcOEt 7:3. Gum; IR (film) ν 1631 (CO), 1612 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.60–1.74 (m, 2H, CH_2), 2.59–2.65 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 4.24 (s, 3H, NCH_3), 4.90–5.01 (m, 2H, $=CH_2$), 5.13 (s, 2H, NCH_2), 5.69–5.79 (m, 1H, =CH), 6.88 (d, 2H, $J=8.8$ Hz, H_{Ar}), 6.96 (s, 1H, NCH), 7.26–7.50 (m, 5H, H_{Ar}), 8.87 (d, 1H, $J=8.0$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.2 (CH_2), 29.6 (CH_2), 34.1 (NCH_3), 55.4 (OCH_3), 55.5 (NCH_2), 110.2 (CH), 114.4 (2CH), 115.4 (CH_2), 121.7 (C), 123.5 (CH), 124.9 (C), 125.2 (C), 125.3 (CH), 127.3 (CH), 128.6 (C), 129.2 (2CH), 131.5 (C), 134.2 (CH), 138.0 (CH), 139.8 (C), 159.5 (C), 160.4 (CO), 182.3 (CO); MS (IS) m/z 401 $(M+H)^+$. Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 6.99. Found: C, 75.25; H, 6.19; N, 7.12.

3.8.5. 2-(4-Methoxybenzyl)-10-methyl-4-(4-pentenyl)-azepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (14c). Following the procedure used for the preparation of **7**, compound **14c** was obtained from **13c** in 87% yield. Chromatography eluent EP/AcOEt 7:3. Gum; IR (film) ν 1631 (CO), 1612 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.59–1.68 (m, 2H, CH_2), 2.01–2.10 (m, 2H, CH_2), 2.51–2.57 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 4.24 (s, 3H, NCH_3), 4.91–4.99 (m, 2H, $=CH_2$), 5.13 (s, 2H, NCH_2), 5.71–5.87 (m, 1H, =CH), 6.88 (d, 2H, $J=8.8$ Hz, H_{Ar}), 6.96 (s, 1H, NCH), 7.28 (d, 2H, $J=8.8$ Hz, H_{Ar}), 7.34–7.51 (m, 3H, H_{Ar}), 8.87 (d, 1H, $J=8.3$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.0 (CH_2), 32.6 (CH_2), 33.5 (CH_2), 34.1 (NCH_3), 55.4 (OCH_3), 55.5 (NCH_2), 110.2 (CH), 114.4 (2CH), 114.8 (CH_2), 121.8 (C), 123.6 (CH), 125.3 (C), 125.4 (CH), 125.7 (C), 127.3 (CH), 128.6 (C), 129.2 (2CH), 131.5 (C), 133.8 (CH), 138.7 (CH), 139.8 (C), 159.5 (C), 160.5 (CO), 182.4 (CO); MS (IS) m/z 415 $(M+H)^+$. Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.25; H, 6.19; N, 6.88.

3.8.6. 3,4-Diallyl-2-(4-methoxybenzyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (15a). Following the procedure used for the preparation of **8**, compound **15a** was obtained from **14a** in 51% yield. The two diastereomers were isolated by column chromatography (eluent PE/EtOAc 9:1) as colorless gum (ratio 44:56). Diastereomer 1 (*cis* or *trans*): IR (film) ν 1647 (CO), 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.80–1.94 (m, 1H, CH_2), 2.11–2.17 (m, 1H, CH_2), 2.27–2.40 (m, 1H, CH_2), 2.77–2.82 (m, 1H, CH_2), 2.91–2.97 (m, 1H, CHCO), 3.66–3.70 (m, 1H, NCH), 3.82 (s, 3H, OCH_3), 3.96 (d, 1H, $J=15.9$ Hz, NCH_2Ph), 4.12 (s, 3H, NCH_3), 4.82 (d, 1H, $J=15.9$ Hz, NCH_2Ph), 4.94–5.00 (m, 3H, $=CH_2$), 5.11–5.24 (m, 1H, =CH), 5.54–5.60 (m, 2H, =CH + $=CH_2$), 6.88 (d, 2H $J=8.5$ Hz, H_{Ar}), 7.29–7.45 (m, 5H, H_{Ar}), 8.53 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.6 (CH_2), 32.7 (CH_2), 33.4 (NCH_3), 53.0 (NCH_2), 55.0 (CH), 55.5 (OCH_3), 57.3 (CH), 110.3 (CH), 114.2 (2CH), 115.5 (C), 117.7 (CH_2), 118.2 (CH_2), 123.9 (CH), 124.1 (CH), 125.4 (C), 125.5 (CH), 129.3 (C), 130.7 (2CH), 134.4 (CH), 135.5 (C), 136.5 (CH), 138.5 (C), 159.6 (C), 161.2 (CO), 193.7 (CO); MS (IS) m/z 429 $(M+H)^+$. Diastereomer 2 (*cis* or *trans*): IR (film) ν 1644 (CO), 1614 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.03–2.54 (m, 4H, 2 CH_2), 2.86–2.92 (m, 1H, CHCO), 3.56–3.64 (m, 1H, NCH), 3.82 (s, 3H, OCH_3), 4.15 (s, 3H, NCH_3), 4.46 (d, 1H, $J=13.9$ Hz, NCH_2), 4.67–5.12 (m, 4H, $2=CH_2$), 5.23 (d, 1H, $J=13.9$ Hz, NCH_2), 5.35–5.45 (m, 1H, =CH), 5.68–5.85 (m, 1H, =CH), 6.88 (d, 2H, $J=8.8$ Hz, H_{Ar}), 7.32–7.48 (m, 5H, H_{Ar}), 8.58 (d, 1H, $J=8.1$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.8 (NCH_3), 35.1 (CH_2), 37.3 (CH_2), 55.1 (NCH_2), 55.4 (OCH_3), 55.5 (CH), 58.4 (CH), 110.4 (CH), 114.2 (2CH), 114.5 (C), 117.6 (CH_2), 118.6 (CH_2), 124.0 (CH), 124.3 (CH), 125.5 (C), 127.8 (CH), 129.0 (C), 130.9 (2CH), 133.8 (CH), 135.5 (C), 135.7 (CH), 138.6 (C), 159.6 (C), 161.2 (CO), 195.3 (CO); MS (IS) m/z 429 $(M+H)^+$. Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 75.93; H, 6.44; N, 6.67.

3.8.7. 3-Allyl-4-(3-butenyl)-2-(4-methoxybenzyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (15b). Following the procedure used for the preparation of **8**, compound **15b** was obtained from **14b** in 56% yield as a mixture of non-separable diastereomers (ratio 6:4 determined by ^1H NMR). Chromatography eluent EP/AcOEt 8:2. Gum; IR (film) ν 1635 (CO), 1621 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.11–2.76 (m, 7H, 3 CH_2 + CHCO), 3.52–3.57 (m, 1H, NCH), 3.81 (s, 3H, OCH_3), 4.00 (d, 1H, $J=14.1$ Hz, NCH_2Ph), 4.12 (s, 1.2H, NCH_3), 4.15 (s, 1.8H, NCH_3), 4.68 (d, 1H, $J=14.1$ Hz, NCH_2Ph), 4.81–5.02 (m, 4H, $2=CH_2$), 5.46–5.72 (m, 2H, 2=CH), 6.89 (d, 2H, $J=8.5$ Hz, H_{Ar}), 7.32–7.45 (m, 5H, H_{Ar}), 8.53 (d, 1H, $J=8.1$ Hz, H_{Ar}); No ^{13}C NMR data due a bad resolution of the spectrum; MS (IS) m/z 443 $(M+H)^+$. Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.76; H, 6.97; N, 6.19.

3.8.8. 3-Allyl-2-(4-methoxybenzyl)-10-methyl-4-(4-pentenyl)-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (15c). Following the procedure used for the preparation of **8**, compound **15c** was obtained from **14c** in 68% yield as a mixture of non-separable diastereomers (ratio 6:4 determined by ^1H NMR). Chromatography eluent EP/AcOEt 8:2. Gum; IR (film) ν 1634 (CO), 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88–2.71 (m, 9H, $4CH_2$ + CHCO), 3.52–3.60 (m, 1H, NCH), 3.81 (s, 3H, OCH_3), 3.92 (d, 1H, $J=14.6$ Hz, NCH_2Ph), 4.12 (s, 1.2H, NCH_3), 4.15 (s, 1.8H, NCH_3), 4.60 (d, 1H, $J=14.6$ Hz, NCH_2Ph), 4.79–5.03 (m, 4H, $2=CH_2$), 5.49–5.75 (m, 2H, 2=CH), 6.88 (d, 2H, $J=8.1$ Hz, H_{Ar}), 7.29–7.48 (m, 5H, H_{Ar}), 8.53 (d, 1.2H, $J=8.1$ Hz, H_{Ar}), 8.58 (d, 1.8H, $J=8.3$ Hz, H_{Ar}); No ^{13}C NMR data due a bad resolution of the spectrum; MS (IS) m/z 457 $(M+H)^+$. Anal. Calcd for $C_{29}H_{32}N_2O_3$: C, 76.29; H, 7.06; N, 6.14. Found: C, 75.95; H, 6.97; N, 6.14.

3.8.9. 3-Allyl-2-(4-methoxybenzyl)-10-methyl-3,4-dihydroazepino[3,4-*b*]indole-1,5(2*H*,10*H*)-dione (17). Following the procedure used for the preparation of **8**, compound **17** was obtained from **16**[9] in 66% yield. Chromatography eluent EP/AcOEt 7:3. Gum; IR (film) ν 1648 (CO), 1625 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.36–2.44 (m, 2H, CH_2), 2.72–2.92 (m, 2H, CH_2), 3.80 (s,

4H, CH_3+NCH), 4.11 (s, 3H, NCH_3), 4.40 (d, 1H, J= 14.4 Hz, NCH_2Ph), 4.86 (dd, 1H, J=1.2, 16.9 Hz, =CH_2), 5.01 (dd, 1H, J=1.2, 9.0 Hz, =CH_2), 5.22 (d, 1H, J= 14.4 Hz, NCH_2Ph), 5.50–5.64 (m, 1H, =CH), 6.88 (d, 2H, J=8.5 Hz, H_{Ar}), 7.30–7.44 (m, 5H, H_{Ar}), 8.48 (d, 1H, J= 7.6 Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.1 (NCH_3), 35.9 (CH_2), 47.4 (CH_2), 51.1 (CH_2), 55.0 (NCH), 55.1 (OCH_3), 110.2 (CH), 114.1 (2CH), 115.3 (C), 118.5 (CH_2), 123.6 (CH), 123.7 (CH), 124.8 (C), 125.4 (CH), 129.2 (C), 129.7 (2CH), 133.7 (CH), 135.9 (C), 138.5 (C), 159.3 (C), 161.1 (CO), 193.1 (CO); MS (IS) m/z 389 $(M+H)^+$. Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21. Found: C, 74.65; H, 6.36; N, 7.11.

3.8.10. Ethyl 3-allyl-5-hydroxy-2-(4-methoxybenzyl)-10-methyl-1-oxo-1,2,3,10-tetrahydroazepino[3,4-*b*]indole-4-carboxylate (18). According to the procedure described for for **10**, compound **18** was prepared in 91% yield from **17**. Chromatography eluent EP/AcOEt 7:3. Gum; IR (film) ν 1738 (CO), 1628 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24 (t, 3H, J=7.1 Hz, CH_3), 2.18 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 4.01–4.15 (m, 2H, OCH_2), 4.13 (s, 3H, NCH_3), 4.53 (d, 1H, J=14.4 Hz, NCH_2), 4.65–4.90 (m, 3H, =CH_2+NCH), 5.06 (d, 1H, J=14.4 Hz, NCH_2), 5.34–5.48 (m, 1H, =CH), 6.86 (d, 2H, J=8.6 Hz, H_{Ar}), 7.22–7.47 (m, 5H, H_{Ar}), 8.28 (d, 1H, J=8.0 Hz, H_{Ar}), 13.24 (s, 1H, OH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2 (CH_3), 32.5 (NCH_3), 35.4 (CH_2), 52.3 (NCH_2), 53.4 (NCH), 55.2 (OCH_3), 60.8 (OCH_2), 100.0 (C), 110.2 (CH), 112.1 (C), 113.8 (2CH), 117.6 (CH_2), 122.2 (CH), 123.5 (CH), 124.2 (CH), 125.5 (C), 129.5 (C), 130.0 (2CH), 134.2 (C), 134.6 (CH), 138.3 (C), 159.1 (C), 160.5 (CO), 168.0 (C), 171.1 (CO); MS (IS) m/z 461 $(M+H)^+$. Anal. Calcd for $C_{27}H_{28}N_2O_5$: C, 70.42; H, 6.13; N, 6.08. Found: C, 70.63; H, 5.94; N, 6.20.

3.8.11. Ethyl 3-allyl-5-(3-butenyloxy)-2-(4-methoxybenzyl)-10-methyl-1-oxo-1,2,3,10-tetrahydroazepino-[3,4-*b*]indole-4-carboxylate (19). According to the procedure described for for **11a**, compound **19** was prepared in 56% yield from **18**. Chromatography eluent EP/AcOEt 8:2. Gum; IR (film) ν 1716 (CO), 1628 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.26 (t, 3H, J=7.1 Hz, CH_3), 1.94–2.16 (m, 4H, 2 CH_2), 2.50 (q, 2H, J=6.7 Hz, OCH_2), 3.79 (s, 3H, OCH_3), 4.12 (s, 3H, NCH_3), 4.05–4.18 (m, 2H, OCH_2), 4.53–4.61 (m, 2H, =CH_2), 4.74–4.84 (m, 2H, =CH_2), 4.93–5.11 (m, 3H, NCH_2+NCH), 5.31–5.45 (m, 1H, =CH), 5.71–5.82 (m, 1H, =CH), 6.85 (d, 2H, J= 8.2 Hz, H_{Ar}), 7.23–7.49 (m, 5H, H_{Ar}), 7.98 (d, 1H, J= 7.9 Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.4 (CH_3), 32.2 (NCH_3), 34.4 (CH_2), 34.5 (CH_2), 52.3 (NCH_2), 53.5 (C), 55.3 (CH_3), 56.2 (NCH), 60.7 (OCH_2), 72.1 (OCH_2), 110.4 (CH), 112.4 (C), 113.9 (2CH), 117.2 (CH_2), 117.5 (CH_2), 122.2 (CH), 122.6 (CH), 124.1 (C), 125.2 (CH), 129.8 (C), 130.2 (2CH), 134.3 (CH), 134.6 (CH), 134.7 (C), 137.9 (C), 159.2 (C), 159.9 (C), 160.6 (CO), 166.4 (CO); MS (IS) m/z 515 $(M+H)^+$. Anal. Calcd for $C_{31}H_{34}N_2O_5$: C, 72.35; H, 6.66; N, 5.44. Found: C, 72.72; H, 6.54; N, 5.30.

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Silicon polypodands: a new class of efficient solid–liquid phase-transfer catalysts

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Abstract—Silicon polypodands **1**–**7** were found to be powerful complexing agents of alkali metal salts, even in low polarity media (chlorobenzene) and hence very efficient phase-transfer catalysts. Their catalytic activity was measured in typical anion-promoted reactions under solid–liquid phase-transfer catalysis (SL-PTC) conditions. It is mainly determined by the complexing ability of the ligand, increasing with the number of silicon atoms and binding sites. Comparison with traditional phase-transfer catalysts showed that these polypodands are better catalysts not only than open-chain PEG400Me_2 and TRIDENT, but even than more sophisticated macrocyclic polyethers such as DCH18C6.

1. Introduction

Polypodands are acyclic ligands in which several polyether chains are linked to the same binding centre. These compounds represent a valid alternative not only to the simple podands but also to the cyclic analogues (crown ethers and cryptands) due to their much lower cost combined with comparable complex-forming properties and almost non-toxicity.[1–8] The above reasons explain the growing interest in these open-chain polyethers and their extensive use as anion activators in the past few years.[1–8]

Silicon polypodands **3** and **5**, recently synthesized by our group via reaction of trichloroethyl- ($EtSiCl_3$) and dichlorodimethylsilane (Me_2SiCl_2) with the appropriate polyethyleneglycol monomethylether are of particular interest (Scheme 1).[9] Preliminary data showed in fact that they are remarkable complexing agents of alkali metal salts even in low polarity media (chlorobenzene) with complexation extent values up to 4 mol of salt per mole of ligand. As a consequence, polypodands **3** and **5** were found to be very efficient catalysts in representative anion-promoted reactions (e.g. nucleophilic substitutions, reductions, alkylations) under solid–liquid phase-transfer catalysis (SL-PTC) conditions.[9]

In the light of the promising results obtained, we have extended the study to a new series of silicon polypodands **1**, **2**, **4**, **6**, and **7** with a different number of silicon atoms, polyether chains and binding sites (oxygens).[10] The complexing ability of these ligands has been evaluated together with their catalytic activity in a number of typical reactions under SL-PTC conditions. The results have been compared with those obtained, under the same conditions, by using traditional ligands such as the open-chain podands **9** and **10**, the tris (polyoxaalkyl) amine 'TRIDENT' **8** and the macrocyclic polyether dicyclohexano-18-crown-6 (DCH18 crown 6) (**11**).

2. Results and discussion

2.1. Complexation extent of silicon polypodands 1–7 and ligands 8–11, under SL-PTC conditions

The complexing abilities of **1**–**7**, PEGs **9** and **10**, TRIDENT **8** and crown ether **11** were evaluated for a series of alkali metal salts M^+Y^- (M^+=Na^+, K^+; Y^-=I^-, Br^-, $Ph(CO)_2N^-$, BH_4^-) by stirring a chlorobenzene or acetonitrile solution of ligand with 10–30 molar equiv of salt as a solid phase at 25, 60 and 80 °C (Table 1). The data reported in Table 1 show that the complexation extent, defined as moles of MY complexed per mole of ligand, mainly depends on the topology of the polypodand, increasing with the number of silicon atoms and oxygens. The salt being the same, the highest complexation values (up to 5.6 mol of NaI) were always obtained with the polypodand **7** which has the highest number of donor atoms (54 oxygens).

Keywords: Silicon polypodands; Complexing agents; Phase-transfer catalysts; Solid–liquid phase-transfer catalyzed reactions.
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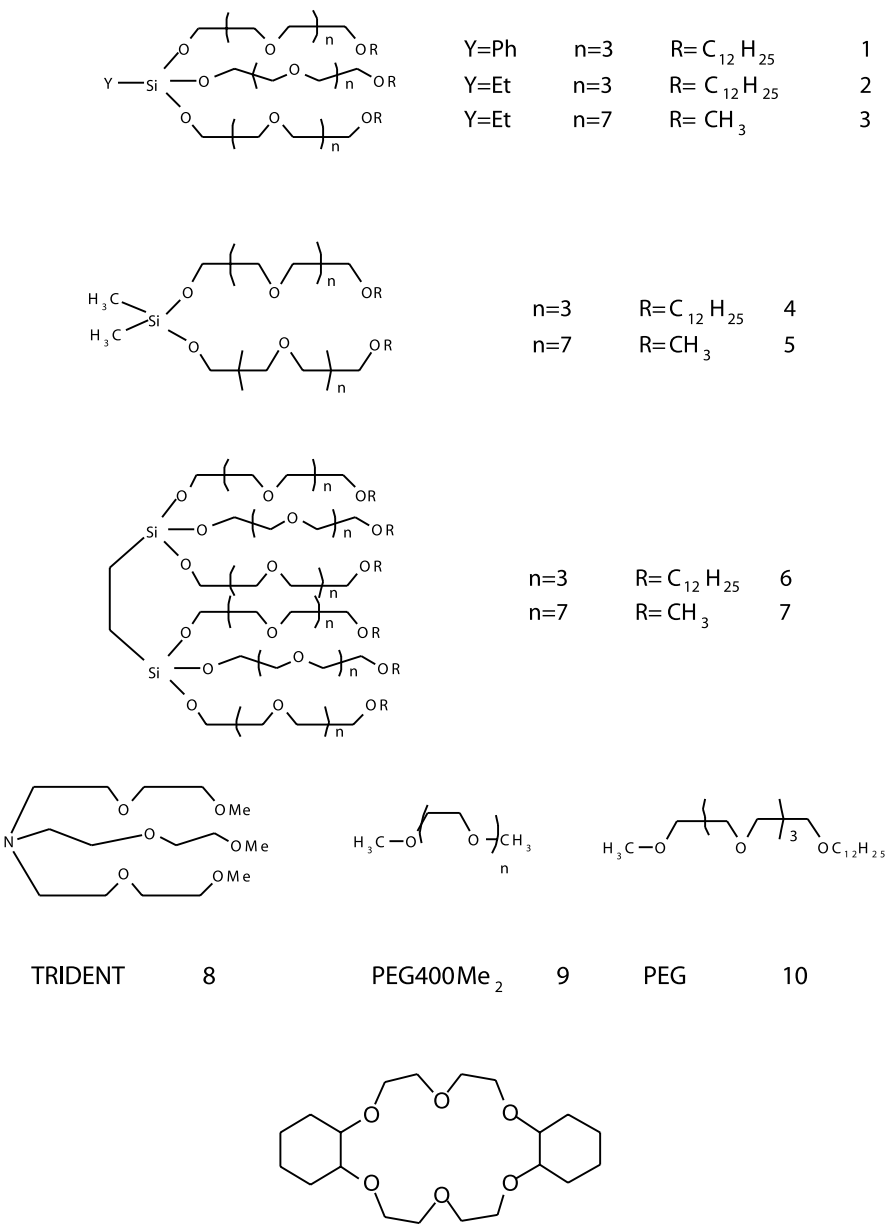

Scheme 1. Silicon polypodands **1**–**7** and polyethers **8**–**11**.

Interestingly, comparison with the corresponding simple podand reveals a 'cooperative effect' of the pendant arms in the complexation process. This is particularly evident for the shortest PEG **10**. As shown in Table 1, the complexation extent of polypodand **6** (with six polyether chains) is about 22 (for NaI) and 60 (for KI) times higher than that of the corresponding podand **10**.

2.2. Catalytic activity of polypodands 1–7 and ligands 8–11 in SL-PTC reactions

As expected on the basis of their high complexation values, polypodands **1**–**7** were shown to be excellent phase-transfer catalysts in a number of typical anion-promoted reactions such as: nucleophilic substitution reactions, reductions, alkylations, oxirane ring opening reactions.

2.2.1. Nucleophilic substitution reactions. The catalytic activity of **1**–**7** was evaluated in typical nucleophilic substitution reactions in organic solvent-solid MY two phase systems (organic solvent=chlorobenzene, acetonitrile; MY=NaI, NaBr, KI) and compared with that exhibited by ligands **8**–**11** under the same conditions (reaction 1).

$$n\text{-}C_8H_{17}X + MY_{solid} \xrightarrow[\text{PhCl (CH}_3\text{CN), 60°C}]{\textbf{1-11}_{cat}} n\text{-}C_8H_{17}Y + MX_{solid} \quad (1)$$

(**12**, **13**)

X = OSO_2Me (**12**), Br (**13**) ; MY = NaI, NaBr, KI

Table 1. Complexation extent[a] of silicon polypodands **1**–**7** and polyethers **8**–**11** under SL-PTC conditions, at 25, 60 and 80 °C

Ligand	NaI	KI	NaBr	$KPh(CO)_2N$	$NaBH_4$
4	1.20	0.48		0.03	
1	1.26		0.26	0.12	
2	1.75	0.80	0.51	0.10	
6	3.45	1.20			
5	2.50	1.30	1.70	0.18	1.00
3	4.00	1.70	1.80	0.18	1.10
7	5.60	3.70	2.40	0.47	1.75
10 (PEG)	0.16	0.02			
9 ($PEG400Me_2$)	0.86	0.47	1.00	0.13	0.20
8 (TRIDENT)	0.95	0.55	1.50	1.10	0.09
11 (DCH18C6)	1.00	1.00	1.10	0.80	0.84

[a] Defined as moles of salt MY complexed per mole of ligand.

The reactions were followed up to conversions ≥90% by GLC analysis of the organic phase evaluating the disappearance of the substrate and/or the appearance of the reaction product with respect to an internal standard (dodecane). The data concerning these reactions are reported in Table 2 and Figure 1. The catalytic activity is mainly related to the complex-forming ability of the podands. The salt MY being the same, the reaction times diminish in the order **4**>**1**>**2**>**6** and **5**>**3**>**7** in agreement with the ligand complexation extent values (Table 1). As expected, the best catalysts (shortest reaction times) are polypodands **6** and **7** with two silicon atoms and six pendant arms, but the catalysts with two and three long polyether chains (**3** and **5**) also have good catalytic activities (Table 2).

The comparison with traditional polyethers **8**–**11** (Table 2) shows that the catalytic activity of silicon polypodands **1**–**7** is always higher than that of simple podands **9** and **10**, in line with their complexation values (Table 1), and comparable with or even better than that of more efficient catalysts such as the crown ether DCH18C6 **11** and TRIDENT **8**, the latter being the catalyst of choice for many solid–liquid phase-transfer reactions.

It is worth noting that in the case of alkali iodides NaI and KI, the catalytic activity remarkably decreases (longer reaction times) on changing from the sodium iodide to the corresponding potassium salt, according with the lower complexation extent found (Tables 1 and 2). We cannot exclude, however, that the metal ion is involved in the transition state of the reaction ('metal ion electrophilic catalysis') as previously found.[11] Indeed, the reaction time for crown ether DCH18C6 **11** is noticeably lower with the sodium salt (0.7 instead of 3 h) even if the complexation extent is the same (1 mol of complexed salt) in both cases (Table 1).

Table 2. Catalytic activity of polypodands **1**–**7** and polyethers **8**–**11** in the reaction (1) where X=OSO_2Me; MY=NaI, KI, NaBr under SL-PTC conditions, at 60 °C

Catalyst	Reaction time (h)[a]		
	NaI	KI	NaBr[b]
—	>70.00	—[c]	113
4	2.50		28
1	1.40		22
2	1.20	6.60	27
6	0.61		
5	0.90	3.00	31
3	0.60	2.20	29
7	0.42	0.95	7
10 (PEG)	12.00	18.00	
9 ($PEG6400Me_2$)	5.00	6.00	57
8 (TRIDENT)	2.30	7.00	47
11 (DCH18C16)	0.70	3.30	57

[a] Conversion ≥90% GLC.
[b] In CH_3CN.
[c] Twenty four percent of reaction after 4 days.

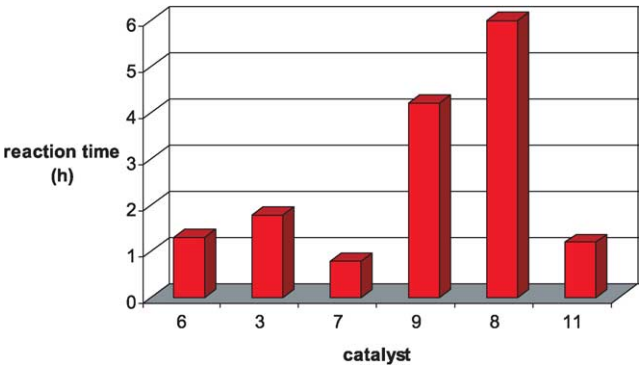

Figure 1. Reaction times (h) for the Br/I nucleophilic substitution reaction (1) catalyzed by **6**, **3**, **7**–**9**, **11**.

2.2.2. Reduction reactions. The reduction of benzaldehyde (**14**) (1 mol) to the corresponding benzylic alcohol (**15**) with $NaBH_4$ (0.3 mol) was carried out at 25 °C in a chlorobenzene-solid $NaBH_4$ two-phase system by using catalytic amounts (0.01 molar equiv) of polypodands **3**, **5** and **7** (reaction 2). The reaction was followed by evaluating (GLC analysis) the disappearance of the benzaldehyde (**14**) in the organic phase with respect to an internal standard (anisole). The results, reported in Figure 2 together with those of ligands **8**, **9** and **11** for sake of comparison, show that the reduction is very fast with all the three polypodands **3**, **5** and **7**. Interestingly, the reaction times are even shorter than those with crown ether **11** (10–30 min instead of about 2 h) in line with their high complexation values reported in Table 1.

$$\underset{\textbf{14}}{C_6H_5CHO} + NaBH_{4\ solid} \xrightarrow[C_6H_5Cl,\ 25°C]{\text{catalyst}} \underset{\textbf{15}}{C_6H_5CH_2OH} \qquad (2)$$

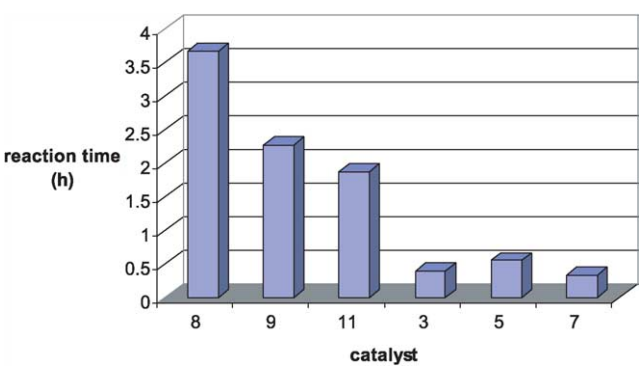

Figure 2. Reaction times (h) for the reduction reaction (2) with catalysts **3**, **5**, **7**–**9**, **11**.

2.2.3. Alkylation reaction. The N-alkylation reaction of potassium phthalimide (**16**) by 1-bromooctane (**13**) was performed at 80 °C in an acetonitrile-solid $C_6H_4(CO)_2NK$ (**16**) two-phase system in the presence of catalytic amounts (0.1 mol/mol of substrate) of ligands **3**, **5**, **7**, **9**, **11** and with a 1/1 molar ratio of potassium phthalimide: alkylbromide (reaction 3). The reactions were followed (up to conversions ≥90%, GLC analysis) by evaluating the disappearance in the organic phase of the alkylbromide **13** with respect to dodecane as an internal standard.

$$\underset{\mathbf{16}}{C_6H_4(CO)_2NK_{solid}} + \underset{\mathbf{13}}{nC_8H_{17}Br} \xrightarrow[CH_3CN,\ 80°C]{\text{catalyst}} \underset{\mathbf{17}}{C_6H_4(CO)_2NC_8H_{17}n} + KBr_{solid} \quad (3)$$

As shown in Table 3, the catalytic activity of silicon polypodands **3**, **5** and **7** is higher than that of $PEG400Me_2$ **9** and comparable with or in the case of **7** even better than that of crown ether DCH18C6 **11**. The comparison with the uncatalyzed reaction provides evidence for the crucial role of the ligand in reducing the reaction times (32 h without any catalyst and only 2 h for polypodand **7**).

Table 3. Catalytic activity of polypodands **3**, **5**, **7** and ligand **9** and **11**, N-alkylation (3) and epoxide opening (4) reactions under SL-PTC conditions

Catalyst	Reaction time (h)[a]	
	N-alkylation (3)	Epoxide opening (4)
—	32.0	56.0
5	4.5	
3	3.8	1.0
7	2.0	0.75
9 ($PEG6400Me_2$)	10.7	6.0
11 (DCH18C6)	3.3	31.5

[a] Conversion ≥90% (by GLC or TLC).

2.2.4. Oxirane ring opening reactions. The ring-opening reaction of 1,2-phenylglycidol (**18**) with LiI to give the corresponding iodohydrine $C_6H_5OCH_2CHOHCH_2I$ (**19**) as the main product (reaction 4) was performed in a chlorobenzene-solid lithium iodide two-phase system in the absence (SL) and in the presence (SL-PTC) of catalytic amounts of polypodands **3** and **7**.

$$\underset{\mathbf{18}}{C_6H_5OCH_2CH(O)CH_2} + LiI_{solid} \xrightarrow[C_6H_5Cl,\ 60°C]{\text{Catalyst}} \underset{\mathbf{19}}{C_6H_5OCH_2CHOHCH_2I} \quad (4)$$

In this reaction the catalytic activity of silicon polypodands was also found to be noticeably higher not only than $PEG400Me_2$ **9** but even than crown ether **11** (31.5 h with DCH18C6 **11** and only 0.75–1 h with polypodands **7** and **3**, respectively). On the other hand, the same reaction performed without any catalyst (solid–liquid SL conditions) is up to 75 times slower than that catalyzed by the polypodand **7** (Table 3).

In addition, it is worth noting that this reaction is faster (about 5 times) with $PEG400Me_2$ **9** than with crown ether **11**. Such behaviour can be explained by assuming a lithium ion participation (metal ion electrophilic catalysis) in the activation process of reaction (4) in analogy with previous results obtained by our group in ring opening reactions of epoxides.[12] The cation being the same, 'electrophilic catalysis' is found to increase, in the order: cyclic<open-chain polyether depending on the ability of the ligand to shield the metal ion charge in the transition state. Whereas good complexing agents, such as cyclic polyethers, activate the ion-paired anion but inhibit metal ion catalysis, less efficient anion activators (PEGs) favor the catalysis. In the latter case, the lower anion activation realized by the ligand is largely compensated for by a higher participation of the cation in the activation process.[12]

3. Conclusion

Silicon polypodands **1**–**7** are powerful complexing agents of alkali metal salts in acetonitrile and in low polarity media such as chlorobenzene. Their complex forming ability increases with the number of silicon atoms and oxaethylenic units. As reported in Table 1, the highest complexation values are always obtained with polypodand **7** which has the highest number of binding sites (54 oxygens).

In line with their complexation values, polypodands **1**–**7** are found to be excellent catalysts in a number of anion-promoted reactions (1–4) in solid–liquid two-phase systems. The catalytic activity reflects their complexing ability, increasing in the same order. The polypodands **6** and **7** in particular are better catalysts not only than open-chain $PEG400Me_2$ **9** and TRIDENT **8**, but even than crown ether DCH18C6 **11**. It is worth noting that the catalytic efficiency of these polypodands is remarkably higher than that of DCH18C6 **11** in ring opening reactions of epoxides (up to 42 times) and in the reduction of benzaldehyde (**14**) to the corresponding benzylic alcohol (**15**) with $NaBH_4$ (more than 10 times) under SL-PTC conditions.

The data as a whole show that this new class of silicon polypodands that combine easy availability and good stability with excellent complexing properties and high catalytic activity represent a valid alternative to the more sophisticated crown ethers as catalysts in solid–liquid phase-transfer reactions, particularly on a large scale.

4. Experimental

4.1. General methods

GLC data were obtained with a Hewlett-Packard 6890 by using a HP-5.5% phenylmethylsiloxane column (30 m×320 μm×0.25 μm).

Potentiometric titrations were carried on with a Metrohm 751 GPD Titrino using a combined silver electrode isolated with a potassium nitrate bridge or a glass electrode isolated with a potassium chloride bridge. Karl Fisher determinations were performed with a Metrohm 684 KF coulometer. ^1H NMR spectra were performed on a Bruker AC 300 spectrometer using TMS as an external reference.

4.2. Materials and solvents

Silicon polypodands **1**–**7** were prepared following a previously reported procedure.[10] Their structures were proved by ^{1}H, ^{13}C and ^{29}Si NMR spectroscopy.[10] Polypodand, yield (%), boiling point (°C)/mm Hg are as follows: **1**, 56, 254–256/1.1; **2**, 51, 258–260/1.1; **3**, 60, 255–258/0.2; **4**, 55, 254–255/1.1; **5**, 75, 113–115/10; **6**, 78, 249–252/1.1; **7**, 79, 243–247/1.1.

Ligands DCH18C6 (mixture of isomers) **11**, PEG **9**, $PEG400Me_2$ **10** and TRIDENT **8** were utilized as purchased. Octylbromide (**13**), benzaldeyde (**14**), *p*-toluenesulfonamide (**20**), dodecane and anisole were commercial products, utilized as purchased. Alkali metal halides (NaI, KI, NaBr, LiI), $NaBH_4$, $NaIO_3$ and $C_6H_4(CO)_2NK$ (**16**), were AnalaR grade commercial products, kept in a dessiccator under vacuum.

Dry (Fluka) chlorobenzene and acetonitrile ($H_2O \leq 20$ ppm) were used. 1,2-Phenylglycidol **18** was a commercial product, purified by distillation and kept over molecular sieves.

Octyl methanesulfonate **12**, bp 92–94 °C at 0.003 mm Hg, n_D^{20} 1.4392, was prepared according to the literature (bp 98 °C at 1.5 mm Hg, n_D^{20} 1.4390).[13]

4.3. Extent of complexation

The extent of complexation of polypodands **1**–**7** and polyethers **8**–**11** under SL-PTC conditions was determined by stirring a standardized chlorobenzene (or acetonitrile) solution (10–20 ml) of ligand (0.02–0.05 M) with 10–50 molar equiv of salt MY, as a solid phase, in a flask thermostatted at 60, 80 °C. The system was stirred for 4–12 h, then kept without stirring for an additional 10 min to allow good separation of the two phases. Aliquots (5–8 ml) of the organic phase were centrifuged, samples (2–3 ml) were withdrawn and titrated with 0.01 M $AgNO_3$ or 0.01 M HCl (potentiometric titration). In the complexation of $NaBH_4$ a chlorobenzene solution of ligand (0.01 M) was stirred for 10–12 h with 30 molar equiv of $NaBH_4$ as a solid phase in a flask thermostatted at 25 °C. Aliquots (3–5 ml) of the organic phase were centrifuged and samples (2–3 ml) were withdrawn and added to an aqueous solution of $NaIO_3$ (1.2 mol/mol of BH_4^-).[14]

After magnetic stirring for about 20 m the iodide formed by the reaction:

$$3BH_4^- + 4IO_3^- \rightarrow 4I^- + 3H_2BO_3^- + 3H_2O$$

was potentiometrically titrated with 0.01 M $AgNO_3$.[14]

4.4. General procedure for the reactions (1–3) under SL-PTC conditions

Solid salt MY (2.5–12.5 mmol) was added to a chlorobenzene or acetonitrile solution (5 ml) of substrate (1–2.5 mmol), catalyst (0.1–0.25 mmol) and an internal standard (0.5–1.25 mmol). The heterogeneous mixture was heated at the appropriate temperature (see Tables 1–3) under vigorous magnetic stirring. The reaction progress was monitored by GLC analysis of the organic phase, with respect to an internal standard. Dodecane was used in all reactions except for the reduction of benzaldehyde, where anisole was employed. In all cases the mass balance was ≥95%.

4.5. General procedure for the epoxide opening reaction (4)

Solid LiI (10 mol/mol of catalyst) was added to a chlorobenzene solution of catalyst (0.003 M) and the heterogeneous mixture stirred for about 2 h. An aliquot (3–5 ml) of the organic phase was withdrawn and the complex titrated with 0.01 M $AgNO_3$. The remaining solution was added with *p*-toluenesulfonamide **20** (0.5 mmol) and 5 ml of a chlorobenzene solution of epoxide (0.06 M). The reaction progress was monitored by TLC (eluant PE/Et_2O 7/3).

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Corrigendum

Corrigendum to "Site-selective formation of *N*-arylmethylimidazoles and *C*-arylimines in the reaction of 4,5-diamino-2,1,3-benzothiadiazole with aromatic aldehydes" [Tetrahedron 60 (2004) 2953]

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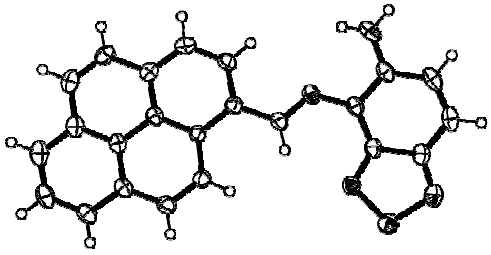
On page 2954, of the above paper, in Figure 2, ORTEP drawing of **4** should be replaced by the following graphic.



On page 2954, of the above paper, on line 54, the sentence should read as, "The single crystal X-ray analysis of **4** shows the close proximity of the imine proton with the nitrogen atom of benzo-2,1,3-thiadiazole ring (0.223 nm) induces the formation of a six-membered ring, that in turn deshields by the nitrogen atom of the 2,1,3-thiadiazole ring with the imine proton".

On page 2956, of the above paper, in Section 4.3.2, on line 22, the sentence should read as, "[Crystal data: for $C_{23}H_{14}N_4S$ **4**], $R_1=0.066$ [$I>2\sigma(I)$] and $wR_2=0.170$ [all reflections]".

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