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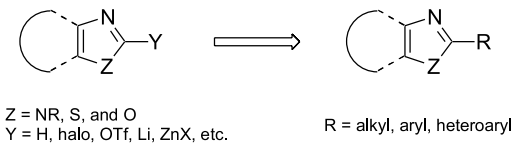
Tetrahedron

Tetrahedron Vol. 60, No. 41, 2004

Contents

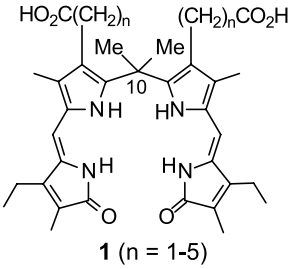
REPORT

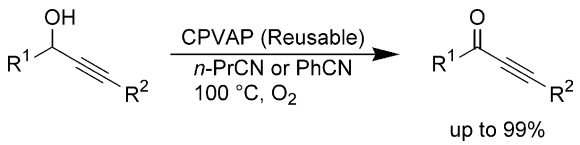


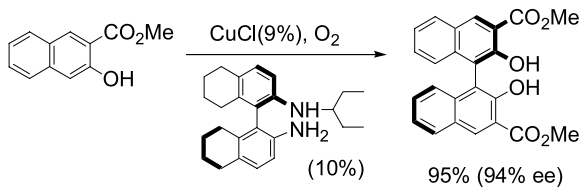
This review surveys the recent literature and focuses on novel methods of substitution and those methods used to construct new carbon–carbon bonds at the azole 2-position. Methods for the construction of azoles from acyclic precursors are not discussed.

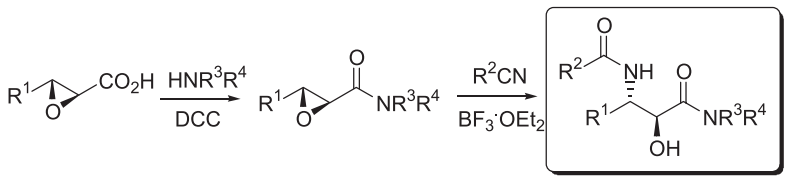
ARTICLES

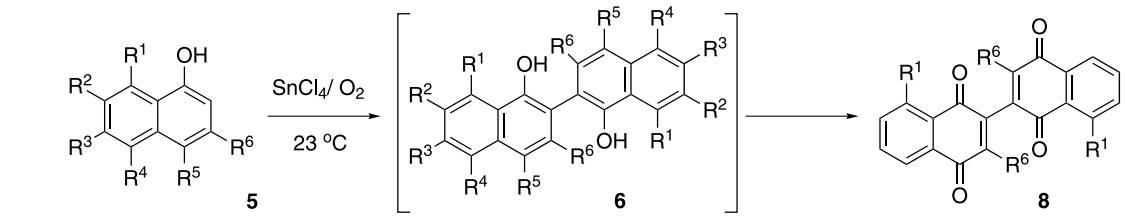
10,10-Dimethylmesobilirubins **1** with carboxylic acid chains ranging from acetic ($n=1$) to hexanoic ($n=5$) acid were synthesized and studied. All tend to fold into intramolecularly hydrogen-bonded ridge-tile-like conformations of varying shape depending on the length of the alkanoic acid. An X-ray crystal structure of **1** ($n=2$) confirmed the conformation.

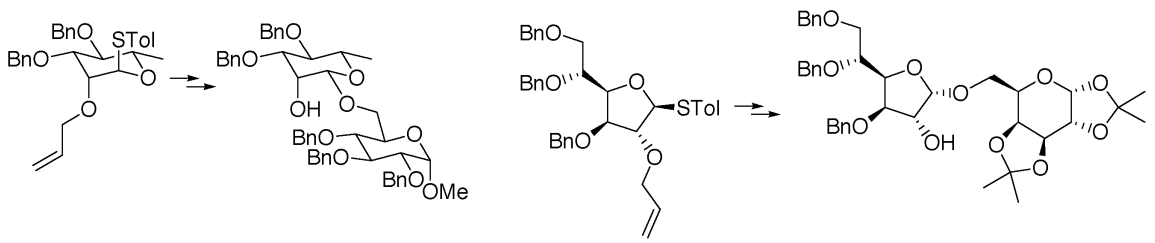


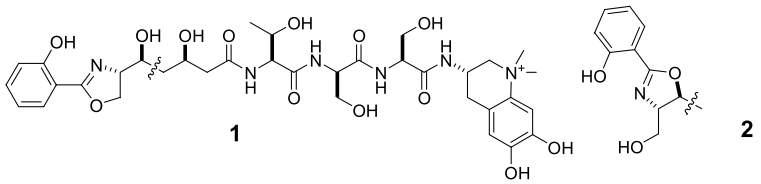




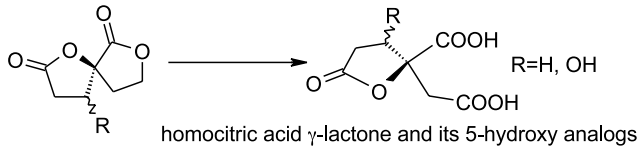


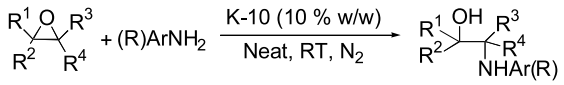


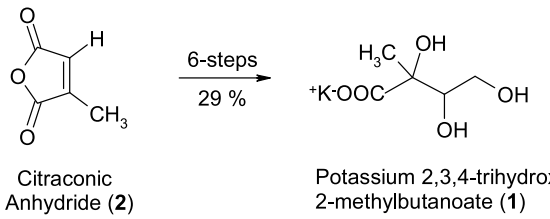


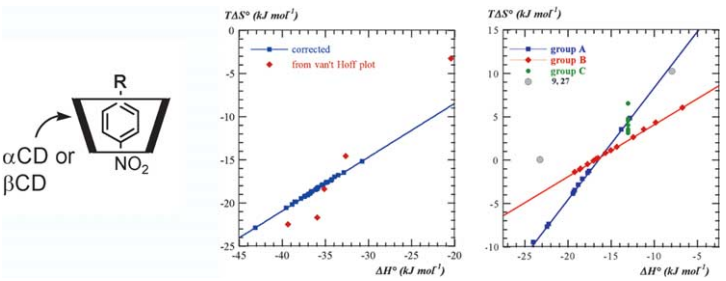


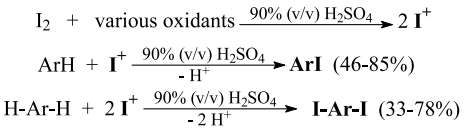
The absolute stereochemistry of anachelins (**1** and **2**) was determined by the application of Boc-phenylglycine and Mosher's method for chemically degraded compounds of **1** and **2**.

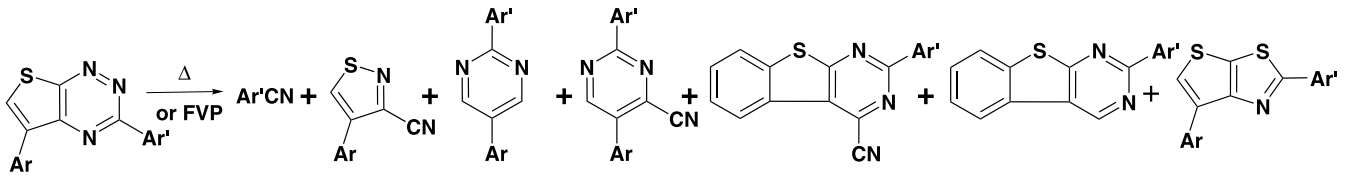


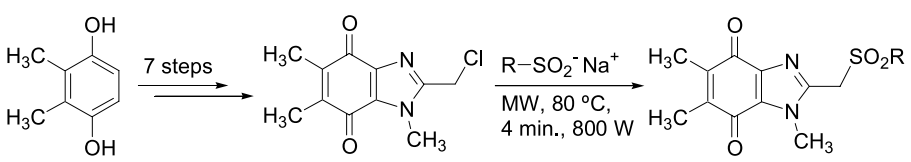


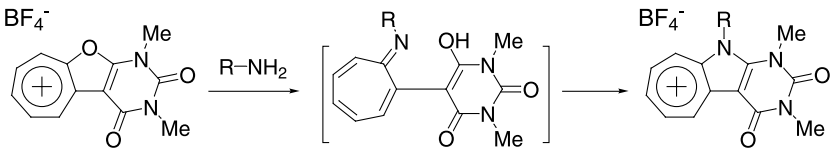


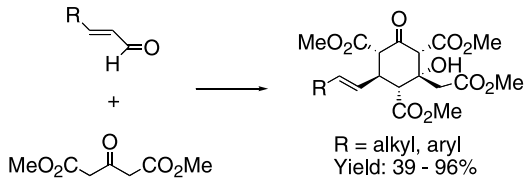


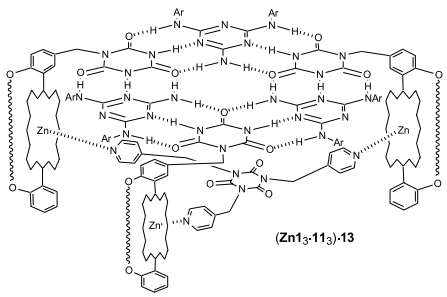


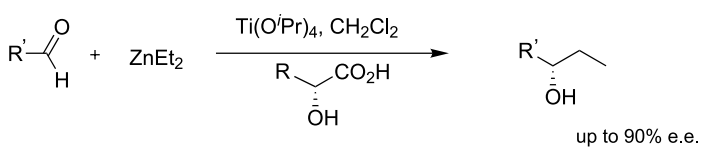


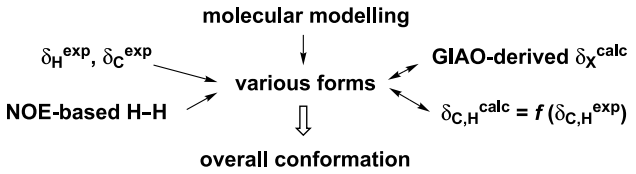


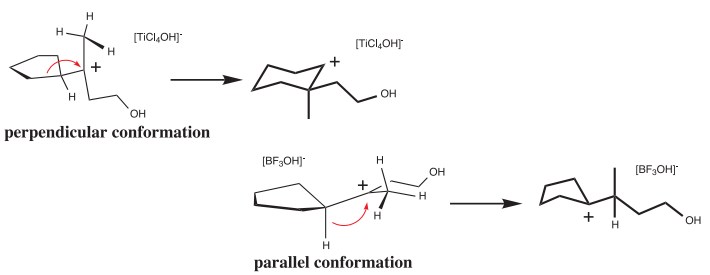


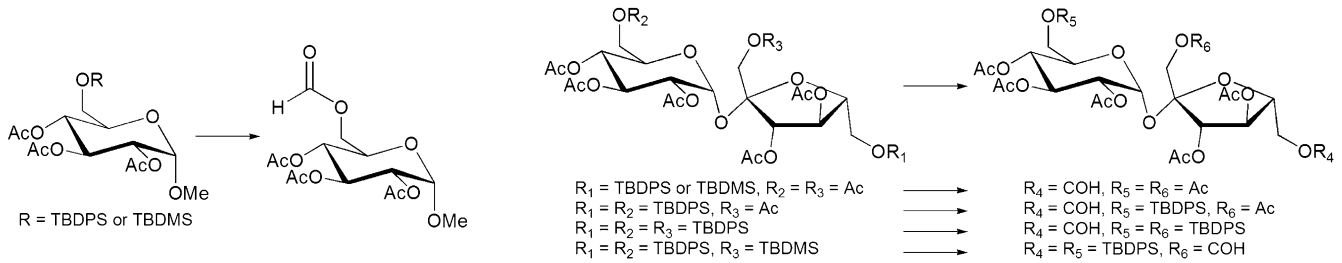


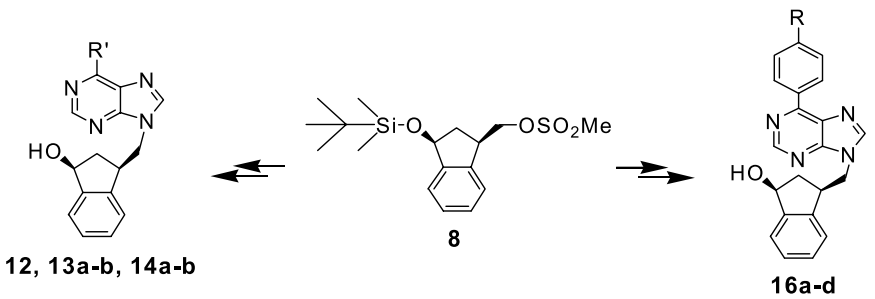


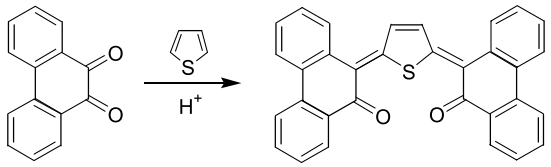


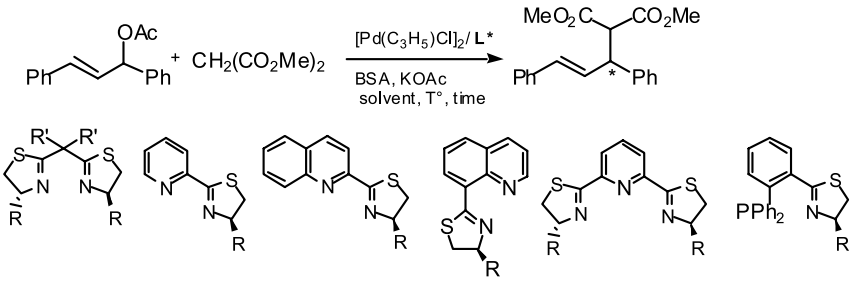


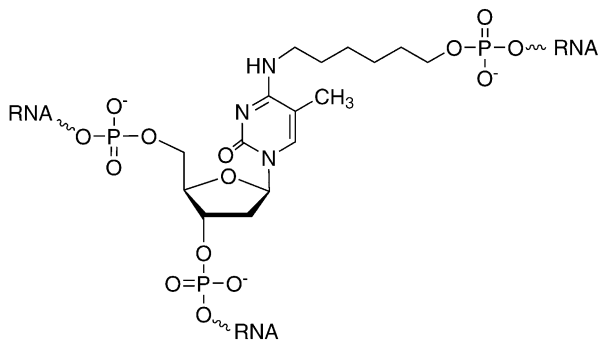


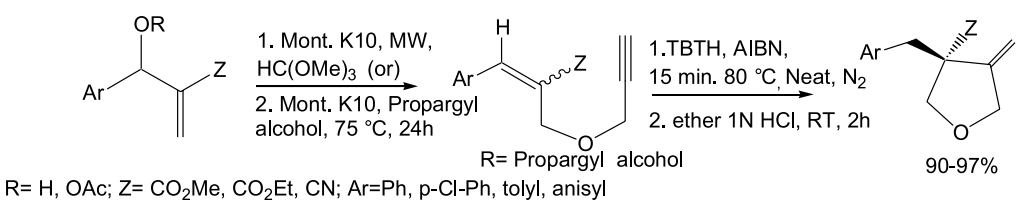


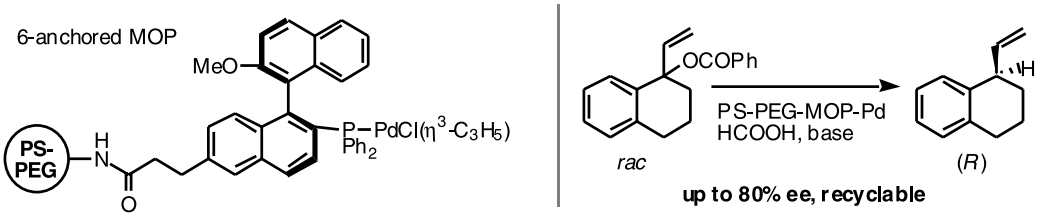


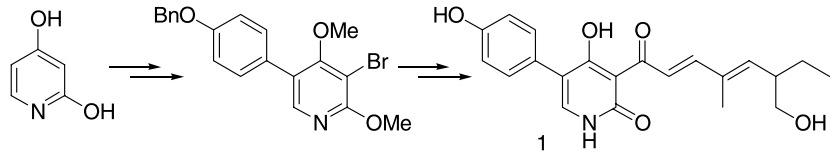












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ELSEVIER

ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8991–9016

Tetrahedron report number 691

Current methods for the synthesis of 2-substituted azoles

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Received 26 March 2004

Available online 18 August 2004

Contents

1. Introduction

1,3 Azoles are important as heterocyclic components of many natural products, drugs, and biologically active molecules.[1,2] Consequently, new, efficient methodologies for the preparation of azole derivatives provide a valuable tool to synthetic organic chemists. Functionalization of 1,3-azoles at the 2-position is readily achieved in both unsubstituted azoles (**1**) and substituted azoles (**2**) that bear an activating group Y, which facilitates the formation of a carbon–carbon bond. This review is intended to survey the recent literature and focus on novel methods of substitution and those methods used to construct new carbon–carbon bonds at the azole 2-position. As such, methods for the construction of azoles from acyclic precursors are not discussed, and heteroatom substitution methods are only briefly described (Fig. 1).

2. Functionalization of 2-H-substituted azoles

2.1. Metal-mediated functionalization

Recently, a number of new methods for the functionalization of heteroaromatic substrates under selective conditions of C–H activation have been developed, particularly through the use of transition metal catalysts. Azoles lacking substitution at the 2-position can react regioselectively under a variety of metal-mediated transformations. Miura has shown the arylation of azoles to occur with oxazole, imidazole and thiazole

Keywords: 2-Substituted azoles; 1,3 Azoles; Imidazole; Thiazole; Oxazole.
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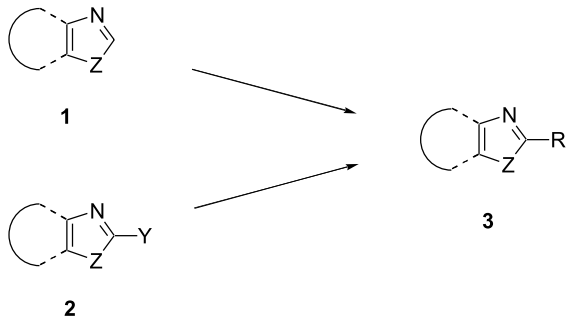
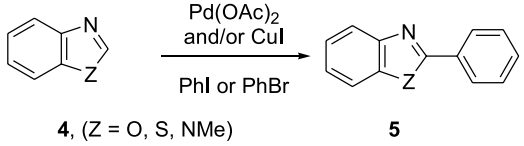
doi:10.1016/j.tet.2004.07.016



Z = NR, S, and O
Y = Cl, Br, I, OTf, N_2^+, SnR'_3, SMe, $SiMe_3$, Li, ZnX, MgX, etc.

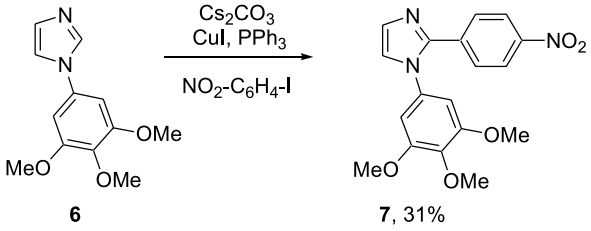
Figure 1.



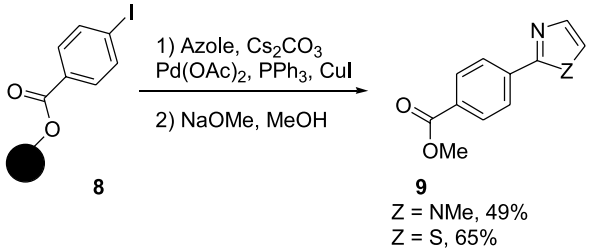
4, (Z = O, S, NMe) **5**

Scheme 1.

derivatives utilizing catalytic palladium (Scheme 1).[3] The addition of copper(I) iodide facilitated the reactions and in specific cases was capable of promoting the reaction without a source of palladium. Non-fused azoles give mixtures of substitution at the 2- and/or 5-position, as demonstrated in a recent study[4] where bulky phosphine ligands gave improved yields of diarylation. This strategy was utilized by Wang and co-workers[5] for the preparation of imidazole **7**, an analog of combrestatin A-4 (Scheme 2). The poor regiospecifity of Miura's coupling reactions was alleviated when Kondo et al. utilized solid-supported aryl iodide **8** (Scheme 3) as a coupling partner.[6] This control was attributed to the solid-phase dilution effect which prohibited a second equivalent of the iodide to interact with already coupled product.

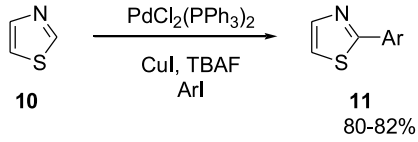


Scheme 2.



Scheme 3.

Mori has introduced improved conditions[7] for the selective arylation of C2 of the thiazole ring utilizing tetrabutylammonium fluoride (Scheme 4) to promote a coupling of thiazole with aryl iodides. The conditions were adapted from initial studies with alkynes and organic electrophiles, and allowed the reaction to progress at 60 °C in DMSO. Alkylidenecyclopropanes are reactive substrates[8] in the palladium catalyzed substitution reaction (Scheme 5) with thiazoles **12** that affords a mixture of alkenes **13** and **14** in moderate yields, as demonstrated by Yamamoto et al.



10 **11** 80-82%

Scheme 4.

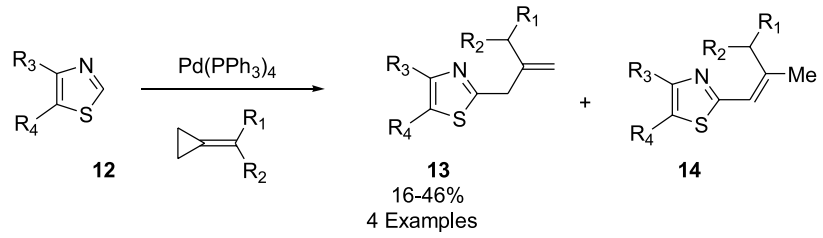
Sames and Sezen have recently reported the metal-mediated arylation of free NH-containing azoles.[9] The addition of copper(I) iodide to the reaction directs arylation to C2; in the absence of copper, the C4 arylated adduct is isolated in 72% yield. In each case, no regioisomeric product is observed. In addition, the authors have also shown highly selective azole couplings mediated by cobalt(II) salts[10] in combination with copper (Scheme 6).

Murai and co-workers have utilized a ruthenium-catalyzed carbonylation[11,12] to substitute 1-methylbenzimidazole in 60% yield whereas thiazole gives a 5:1 mixture of C2- and C4-substitution (Scheme 7). Ellman and co-workers have extended the reaction to other azole derivatives.[13] Murai et al. have also presented an iridium-catalyzed[14] coupling of 1-methylimidazole with a variety of aldehydes to furnish imidazoyl-substituted silyl ethers **20**. The use of dimethylacetylene dicarboxylate as an additive greatly increases the yield, although it does not act as a hydrogen acceptor.

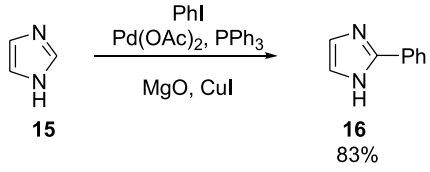
Ellman and co-workers have utilized a rhodium-catalyzed C–H activation[15] method to construct polycyclic imidazoles from azoles possessing a pendant alkenyl functionality (Scheme 8). The *N*-heterocyclic carbene complex **23** has been isolated and shown to be active in the catalytic cycle.[16] Both five- and six-membered carbocycles are prepared by C–H insertion on the terminal end of the pendant alkene. Microwave irradiation accelerates this intramolecular carbocyclization reaction.[17] The use of additives, such as lutidinium chloride,[18] lowered the reaction temperature and permitted the intermolecular coupling of unactivated alkenes displaying a variety of functional groups, and was utilized for the coupling of a large variety of azoles and alkenes.

2.2. Electrophilic substitution

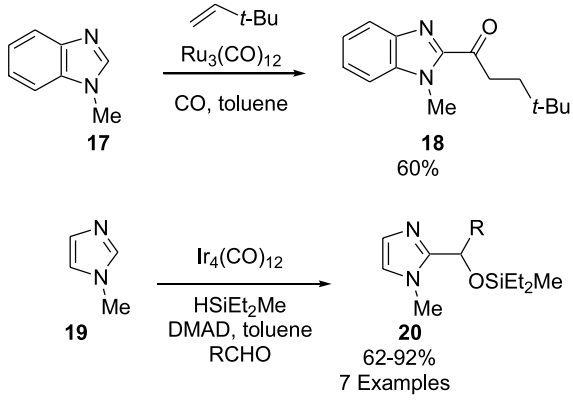
By far the most common method for substitution at the 2-position of unsubstituted 1,3-azoles is electrophilic substitution.[19] 1,3-Azoles readily undergo electrophilic substitution reactions. In fact, halogenation reactions are difficult to control and often result in di- or tri-halogenation. A variety of electrophiles have been investigated, the most common being acid chlorides[20–28] (Scheme 9) and aldehydes[29–33] (Scheme 10). In general, the reactions are run



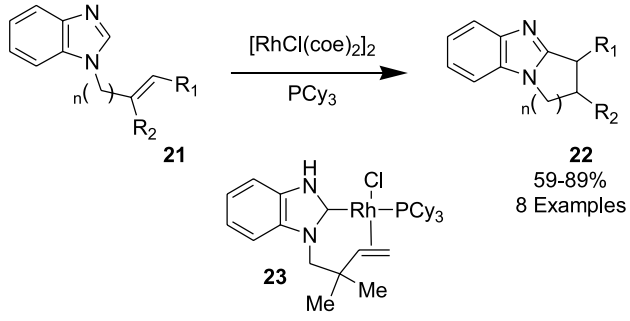
Scheme 5.



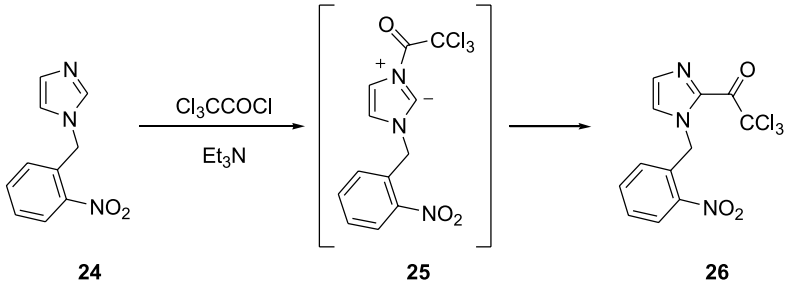
Scheme 6.



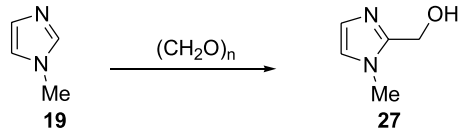
Scheme 7.



Scheme 8.



Scheme 9.

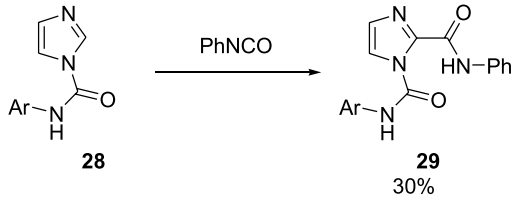


Scheme 10.

with an amine base for acid chlorides and are proposed to proceed via an intermediate carbene/ylide species (**25**).[19]

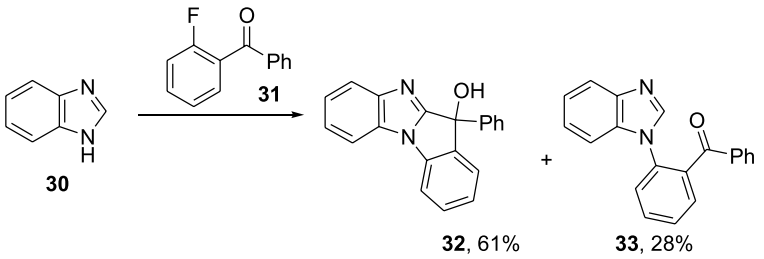
Imidazoles are sufficiently nucleophilic to condense with aldehydes under thermal conditions in the presence of acid to give 2-hydroxymethylimidazoles. The reaction, however, is highly variable and substrate dependent.

Burak demonstrated the addition of imidazole-1-carboxamides **28** to phenyl isocyanate[34] giving the amides **29** in modest yield (Scheme 11). The addition of benzimidazole to fluoro-ketone **30** gave a mixture of carbinol **32** and the product arising from fluoride displacement without addition of the azole C2 to the ketone (Scheme 12).[35] Imidazole, 1,2,4-triazole, and 1,2,3-triazole also form the cyclic carbinol in varying yields.

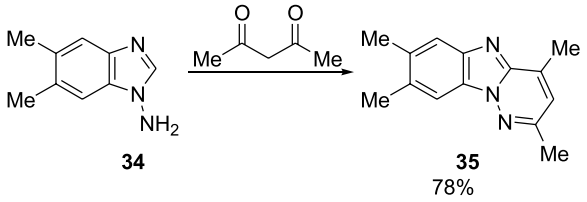


Scheme 11.

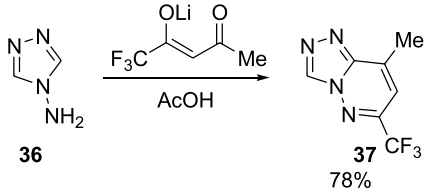
The annulative addition of 1-amino azoles to 1,3-diketones has been demonstrated with 7-aminoadenine, 9-aminoadenine,[36] and 1-aminobenzimidazoles[37] by Kohda (Scheme 13) to give the tricyclic derivatives such as **35**. In a similar



Scheme 12.



Scheme 13.

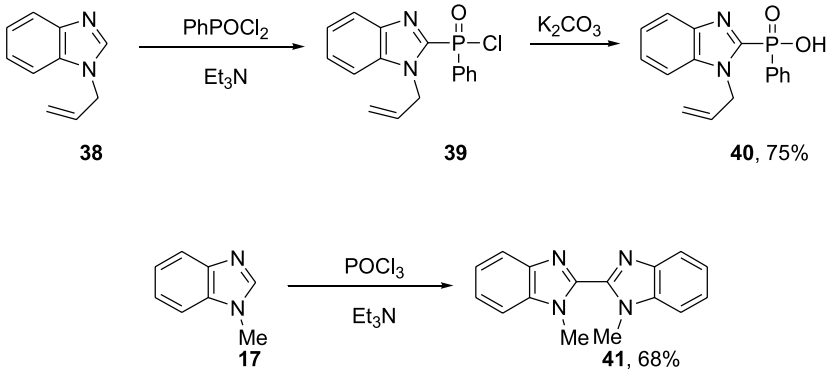


Scheme 14.

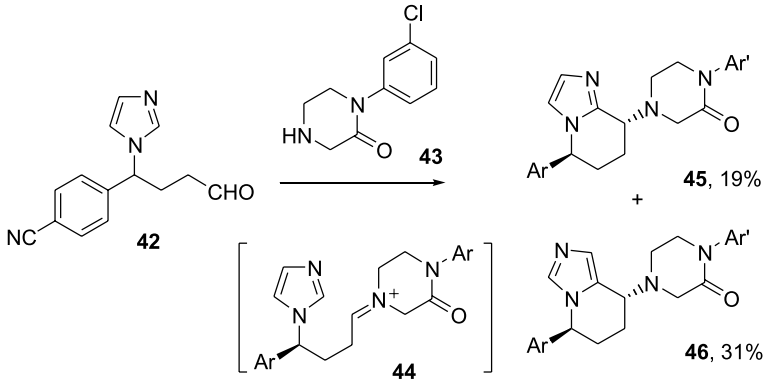
fashion, 4-aminotriazole **36** condenses with 1,1,1-trifluoropentan-2,4-dione in the presence of acetic acid to give the triazolopyridazine **37** (Scheme 14).[38]

Phosphorylation of 1-substituted imidazoles and benzimidazoles (Scheme 15) can be achieved[39] under basic conditions by treatment with phosphorus(V) acid chlorides, and provided good yields of the corresponding phosphinic acid salts after treatment with aqueous base. Additionally, a dimerization reaction was found to occur in good yield when **17** was treated with phosphorus oxychloride.[39] Benzothiazole derivatives were prepared analogously.[40]

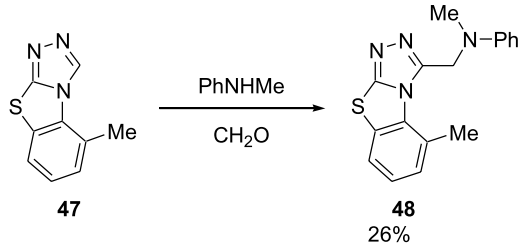
The intramolecular addition of azoles to iminium ions formed from aldehydes and secondary amines afford 2-substitution cleanly only when the 4- or 5-position is blocked. Farnesyltransferase inhibitors containing an imidazo[1,5-*a*]pyridine core were synthesized from the azole-aldehyde **42** and the 1-aryl-piperazinone **43**.[41] The undesired regioisomer resulting from C2-substitution was formed as a byproduct (Scheme 16).



Scheme 15.



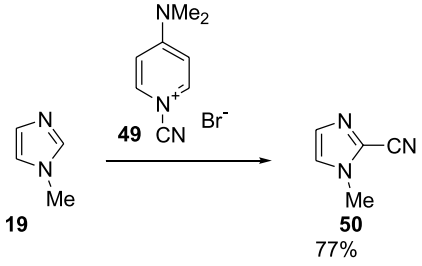
Scheme 16.



Scheme 17.

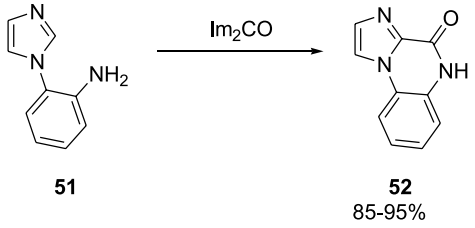
In a similar iminium ion addition, intermolecular addition to the iminium ion resulting from condensation of 1-methylaniline with formaldehyde gives the 2-aminomethyl triazole **48** (Scheme 17) in modest yield.[42]

The preformation of 1-cyano-4-(dimethylamino)pyridinium bromide[43,44] allows for the selective 2-cyanation of 1-methylimidazole (Scheme 18). In the absence of DMAP, cyanogen bromide brominates the 2-position.

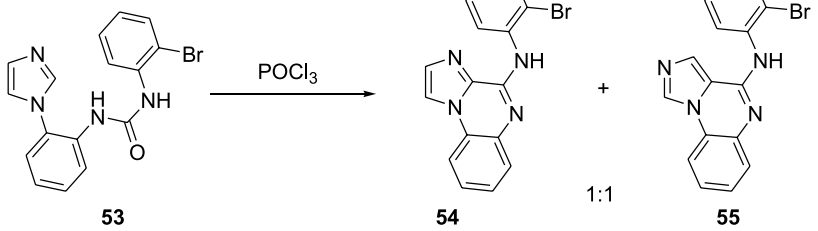


Scheme 18.

The imidazo[1,5-*a*]quinoxaline ring system is a common structure in medicinal chemistry, and is readily constructed by treatment of 1-(2-aminoaryl)imidazoles with 1,1′-carbonyldiimidazole[45] to afford the imidazo[1,5-*a*]quinoxalinone **52** (Scheme 19).[46,47] The reaction of 1-(2-uriedoaryl)imidazoles (Scheme 20) with $POCl_3$ results in a 1:1 mixture of the regioisomeric 4-amino-imidazo[1,2-*a*]quinoxalines **54** and **55**.[48] Similarly, the treatment of 1-(2-amidoaryl)imidazoles with $POCl_3$ results in the formation of an intermediate imino chloride, which on intramolecular condensation gives the 4-substituted-imidazo[1,2-*a*]quinoxalines in 57–72% yield with selective condensation at C2 of the imidazole.[49]



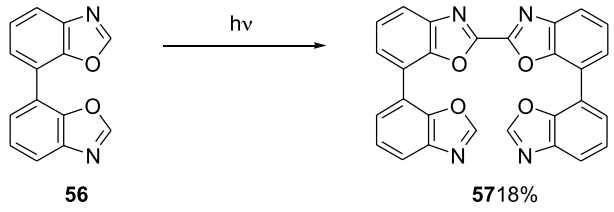
Scheme 19.



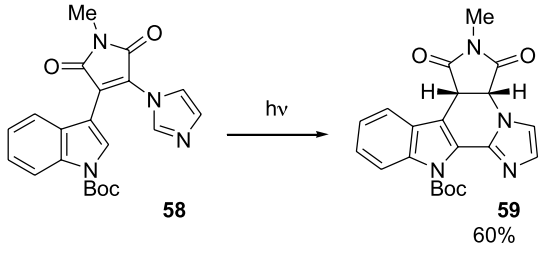
Scheme 20.

2.3. Radical reactions

The reaction of 1,3-azoles with radical intermediates can often be utilized to selectively introduce functionality at C2 of a variety of azoles. The radical counterpart, however, has seen limited expansion beyond simple aliphatic alkyl radicals generated from a variety of precursors. The photochemical activation of azole derivatives allows for the formation of dimeric 2,2′-benzoxazole derivatives[50] such as **57** (Scheme 21); the desired cyclic tetramer, however, was not observed. The irradiation of maleimide derivative **58** gave a mixture of bond formation at C2 and C5 (2:1) in 89% combined yield (Scheme 22)[51] to provide constrained analogs of the alkaloid didemnimide C after dehydrogenation.

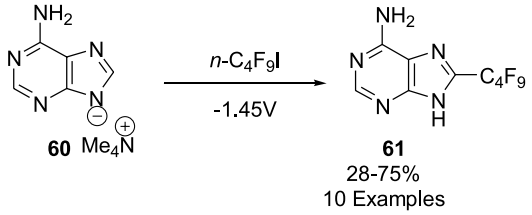


Scheme 21.



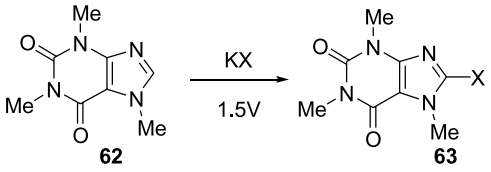
Scheme 22.

The preparation of perfluoroalkyl adenine product **61** by an electrochemical approach has been accomplished by Medébielle and co-workers (Scheme 23) as a method to prepare perfluoroalkylated purine analogs.[52] Other 2-perfluoroalkyl purine derivatives have been synthesized using bis(heptafluorobutyryl) peroxide,[55] and 2-(trifluoromethyl)imidazoles were produced using trifluoromethyl iodide under photochemical conditions.[54] Electrochemical



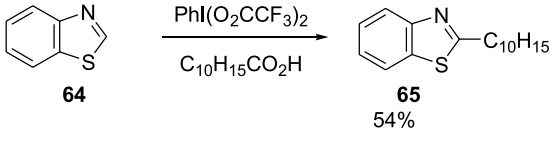
Scheme 23.

oxidation of caffeine[55] and guanosine[56] derivatives in the presence of various electrolytes allowed for the preparation of a variety of derivatives **63** (Scheme 24).

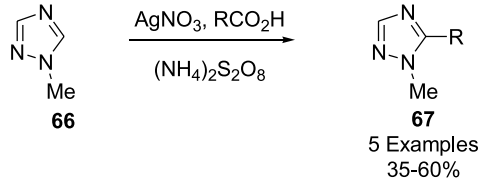


Scheme 24.

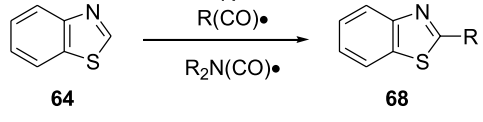
A common method for the alkylation of azoles at C2 is by means of addition of alkyl radicals, which can be generated by a variety of methods. Polyvalent iodine (Scheme 25)[57,58] or silver salts (Scheme 26)[59] may be used to promote radical decarboxylation of acids. Jain and co-workers have utilized the latter to synthesize analogs of histidine and histamine.[60–62] The group of Minisci has developed a number of methods for alkylation,[63–65] acylation,[66] and carbamoylation[67] of heteroaromatic bases, including benzothiazole (Scheme 27) from a variety of sources. Silane reagents[68,69] have been investigated for use in combination with alkyl halides (Scheme 28) under irradiative conditions for radical generation and alkylation of benzothiazole and caffeine.



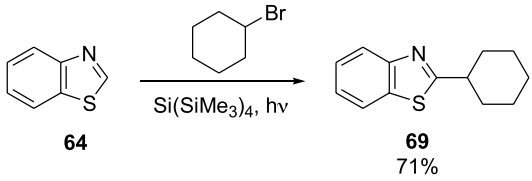
Scheme 25.



Scheme 26.

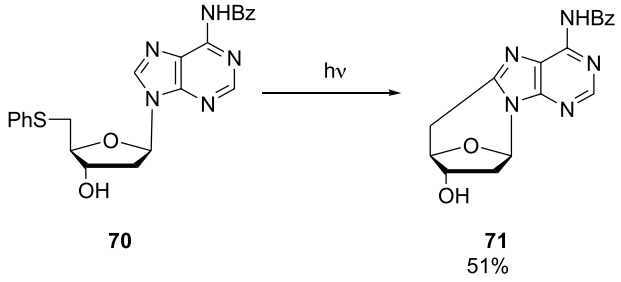


Scheme 27.

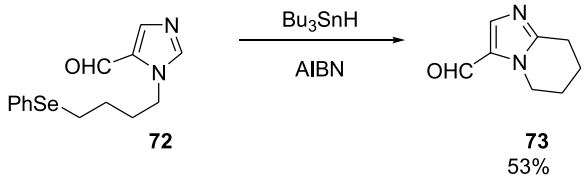


Scheme 28.

Cyclic adenosine derivatives have been prepared under radical conditions, generated from an aryl sulfide (Scheme 29)[70,71] or an anisyl telluride.[72] Aryl-selenide derivatives (Scheme 30) have also been utilized to construct tetrahydroimidazo[1,2-*a*]pyridine[73] product **73**; the imidazo[1,2-*a*] pyrrole analog failed to cyclize.

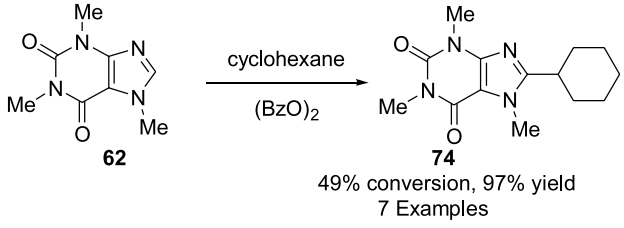


Scheme 29.



Scheme 30.

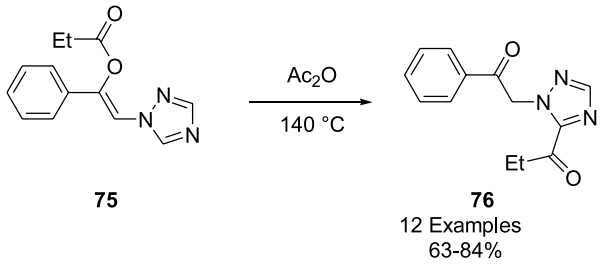
Itahara has utilized benzoyl peroxide as an initiator for the reaction of caffeine with a variety of alkyl groups as solvent (Scheme 31).[74,75] Abstraction of hydrogen from symmetrical solvents leads to single products, whereas compounds possessing multiple abstractable hydrogens generally lead to mixtures.



Scheme 31.

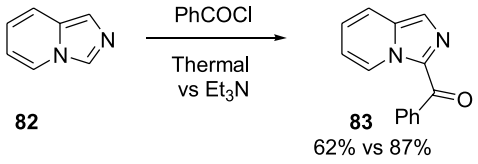
2.4. Activated azoles and other methods

Radul et al. have extensively investigated the rearrangement of enol acylate **75** to furnish triazolyl acetophenone products with acyl transfer (Scheme 32).[76–79] The 1,5-rearrangement is selective, with no crossover occurring with different acyl groups or deuterated acetate in acetic anhydride solvent. The reactivity of acyl imidazoles with an electron-deficient acetylene (Scheme 33)[80] gives a mixture of adducts **78** and **79**

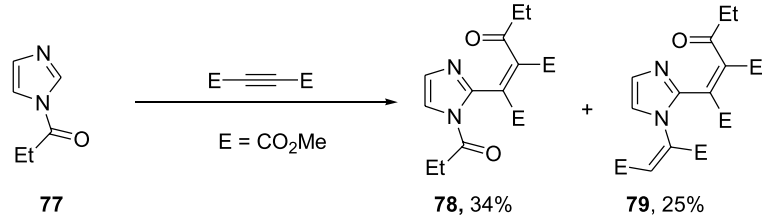


Scheme 32.

wherein the acyl group from the imidazole is transferred to the alkene product arising from reaction at C2. The structure of adduct **78** was assigned by X-ray crystallography.



Scheme 35.



Scheme 33.

An imidazolium ylide intermediate was shown to be the active species in the work of Hlasta and Deng for the reaction of aldehydes with 1,3-azoles (Scheme 34), giving rise to the carbamate products **80**.[81] The scope of azole components in this reaction was later expanded to include substituted imidazoles, thiazoles and triazoles (14 examples, 40–88%)[82a] and was also applied to solid phase synthesis.[82b] More recently the chemistry has been extended to the reaction of imidazoles with sulfonyl imines using di-*tert*-butyldicarbonate as the activating reagent to furnish amine derivates such as **81**.[83] For this reaction, no external base is required as *tert*-butoxide, generated as the byproduct of acylation, serves as the base to deprotonate the C2–hydrogen of imidazole. Similar reactivity had previously been utilized for the regiospecific acylation of imidazo[1,5-*a*]pyridine (Scheme 35).[84] Ylide intermediates were also proposed in the reaction of *N*-alkyl imidazoles with quinoxaline **84** for the formation of tetracyclic derivatives[85] (Scheme 36) wherein the *N*-substitution is lost as an alkyl chloride in order to furnish the aromatic product.

Addition of chloromalonic esters to 5-nitrothiazole at C2 occurs in high yield in 5 min, demonstrating the electrophilicity of **86** (Scheme 37) in a vicarious nucleophilic substitution of hydrogen.[86] The C2-halogenated derivatives resulted in functionalization at C4 under similar conditions.

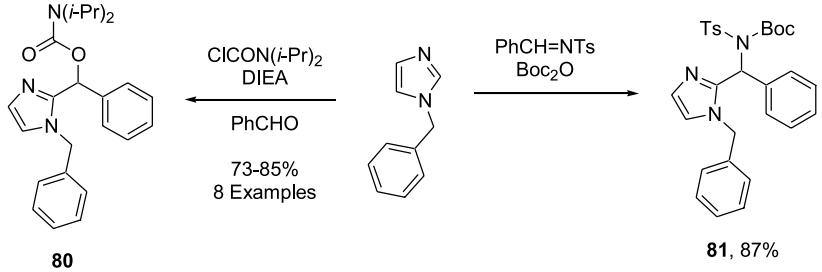
3. Catalytic transition-metal mediated reactions of halogenated azoles

2-Halogenated azoles are the one of the most valuable synthons for further functionalization of 1,3-azoles. They are readily prepared by direct halogenation (Br_2, I_2 or *N*-halosuccinimides) or trapping of C2-metalated (Li, Mg, Zn) azoles. Numerous methods have therefore been developed for their further functionalization. Coupling reactions mediated by transition-metal catalysts allow for bond formation between halogenated azoles and unsubstituted olefins and acetylenes, as well as dimerization reactions.

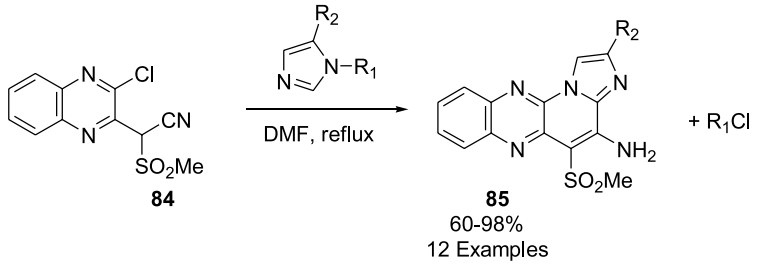
3.1. Heck and Ullmann couplings

2-Bromothiazole has been utilized in an annulation reaction (Scheme 38) that forms 2,5-disubstituted furans from **88**.[87] Classical Heck-type couplings have also been developed for the formation of caffeine derivatives (Scheme 39)[88] as well as epibatidine analogs (Scheme 40) under reductive conditions.[89] The formation of **94** was low yielding and attempts to utilize piperidine as base lead to a major side reaction resulting from displacement of bromine by piperidine.

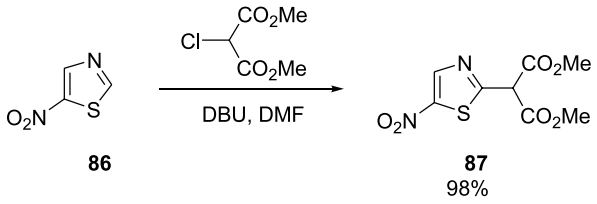
Palladium has also been utilized to catalyze the coupling of halo-azoles with phenylsulfonylacetonitrile anion (Scheme 41).[90] Azole adducts **96** exist as mixtures of the aromatic azole and the conjugated enamine. Dimerization of bromothiazole (Scheme 42),[91] which had previously been described using catalytic nickel,[92] was conducted with



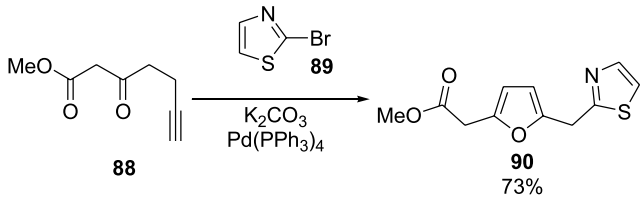
Scheme 34.



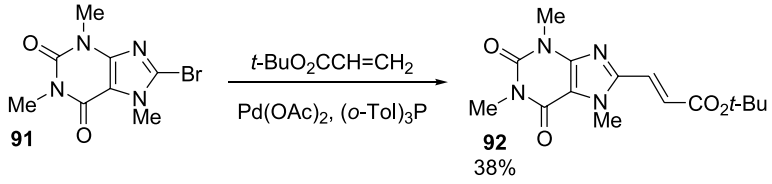
Scheme 36.



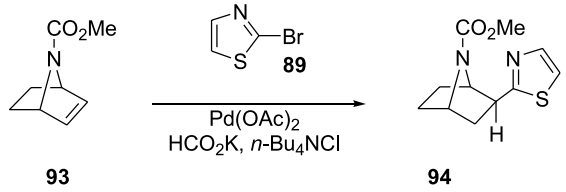
Scheme 37.



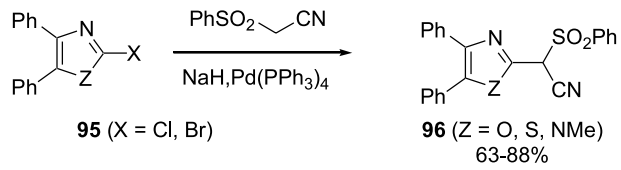
Scheme 38.



Scheme 39.



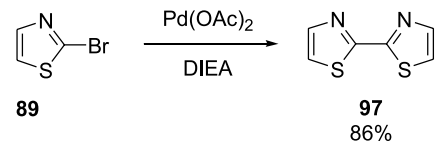
Scheme 40.



Scheme 41.

palladium and formation of **97** was isolated in an improved yield (86% vs. 62%).

One of the more common methods for forming 2,2′-azoles is to utilize copper as a coupling catalyst, as has been described for caffeine (Scheme 43).[93] The symmetric derivative **99** was cyclized in modest yield (Scheme 44) utilizing copper to furnish the tetracyanobiimidazole **100** which was found to be a weak electron acceptor.[94] Selective lithium–bromine exchange on **101** followed by oxidative coupling (Scheme 45) with copper(II) chloride[95] allowed for the formation of dibromobithiazole **102** via a homodimerization at low temperature.

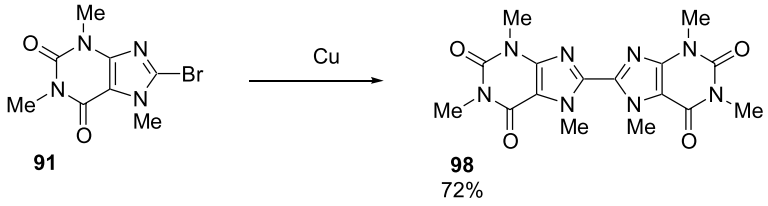


Scheme 42.

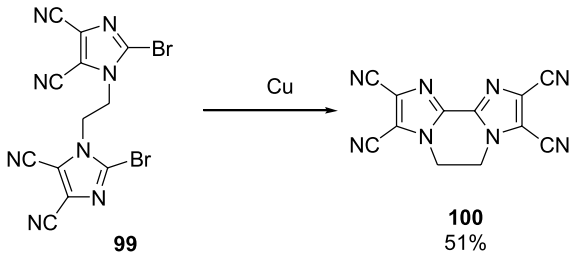
3.2. Sonogashira reaction

Like the Heck coupling, the Sonogashira coupling is one of the most common bond-forming reactions of aromatic halides. Its use in the chemistry of 1,3-azoles is also very common. Adenine and numerous derivatives have been widely utilized to prepare alkynylated azoles (Scheme 46) for use in modeling DNA complexes[96] as well as the preparation of inhibitors and other biological substrates.[97–109] Guanidine derivatives have likewise been prepared (Scheme 47).[110–114]

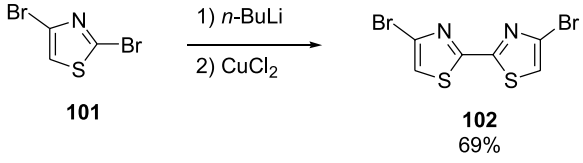
Evans and Bach have utilized a Sonogashira coupling for the preparation of histidine derivatives (Scheme 48) wherein the diiodide **107** undergoes selective coupling as well as dehalogenation in the presence of excess phenylacetylene.[115] Imidazole derivatives (Scheme 49)[116] and thiazole analogs[117–122] have been investigated, and regioselective alkynylation is often feasible (Scheme 50).[117] Oxazolyl and thiazolyl triflates have also been shown to be effective substrates[123] for substitution (Scheme 51) as well.



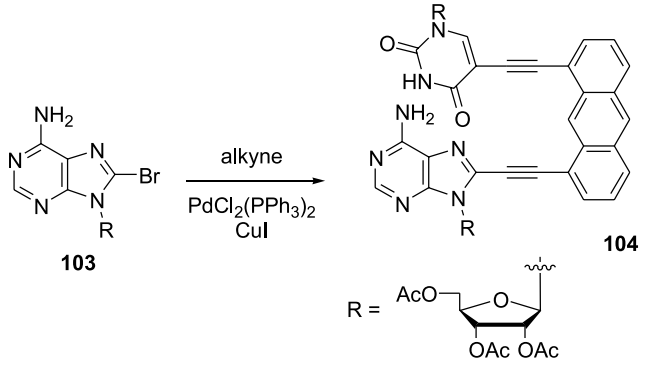
Scheme 43.



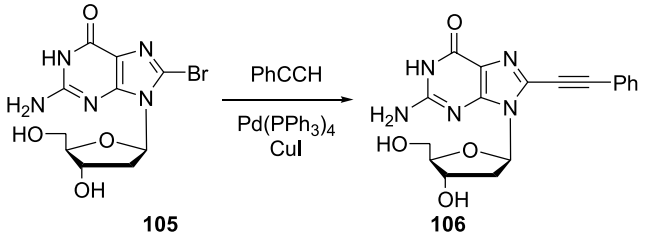
Scheme 44.



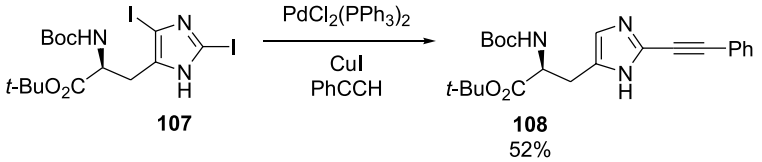
Scheme 45.



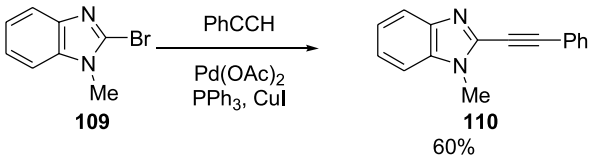
Scheme 46.



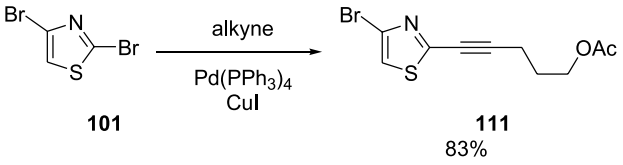
Scheme 47.



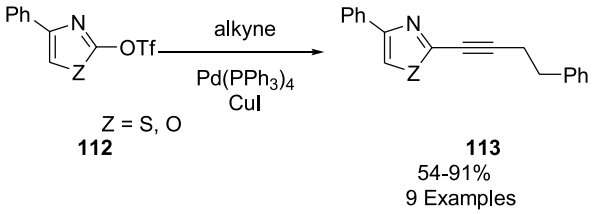
Scheme 48.



Scheme 49.



Scheme 50.



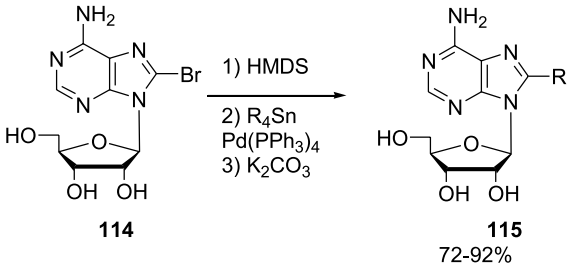
Scheme 51.

4. Stoichiometric organometallic/transition-metal mediated reactions

Whereas the use of 1,3-azoles in coupling reactions with unsubstituted coupling partners (Section 3.1) was somewhat limited, the use of stoichiometric organometallic reagents (as either the 2-substituted 1,3-azole or as the coupling partner) is very broad. The use of organostannanes, boronates and other metal-substituted reagents in transition-metal mediated coupling reactions has been widely examined.

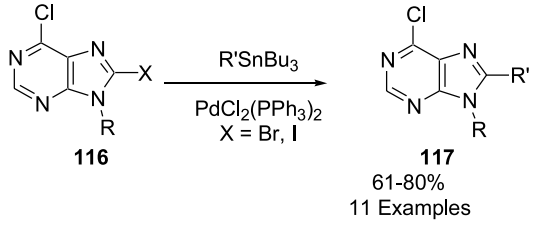
4.1. Stille cross-coupling reactions

The availability of organostannanes and their well-understood cross-coupling reactions with aromatic halides has been extended into the coupling of azole derivatives. The coupling of bromoadenosine (Scheme 52)[124] under Stille



Scheme 52.

conditions has been carried out by first protecting the amine and alcohol functionalities by treatment with HMDS. Regioselective functionalization of 6,8-dihalopurine derivatives has also been investigated (Scheme 53).[125,126] With bromine or iodine substitution at C8, selective coupling could be obtained; however, the use of the dichloride lead to mixtures of coupling at both sites, with C6 being the major product.

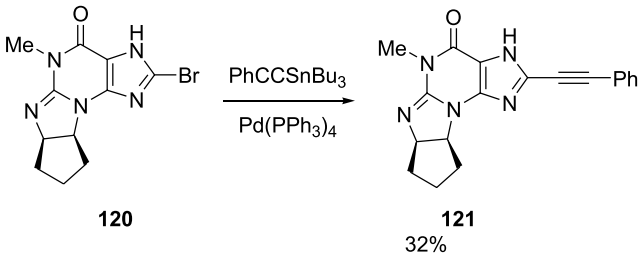


Scheme 53.

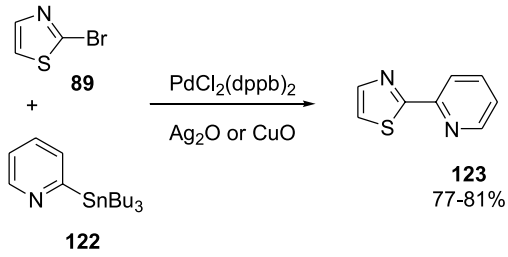
Sessler et al. have utilized a Stille coupling to form aldehyde **119** (Scheme 54),[127] which was used to construct a photosynthesis model via incorporation into a porphyrin ring.[128] The tetracyclic guanosine derivative **121** was synthesized as part of a set of phosphodiesterase (PDE) inhibitors (Scheme 55).[129]

The effects of silver(I) and copper(II) salts on the formation of thiazole-pyridine derivatives was investigated by Gronowitz et al. (Scheme 56).[130,131] The use of copper(II) oxide to facilitate the coupling reaction of silylated diaminopurine derivatives with furyl- and thienylstannanes (Scheme 57) was found to result in improved yields in combination with a bidentate phosphine ligand.[132,133] Triphenylarsine (Scheme 58) has also been utilized as a ligand for palladium in Stille couplings of purine derivatives for the preparation of agents for treatment of sleeping sickness.[134,136]

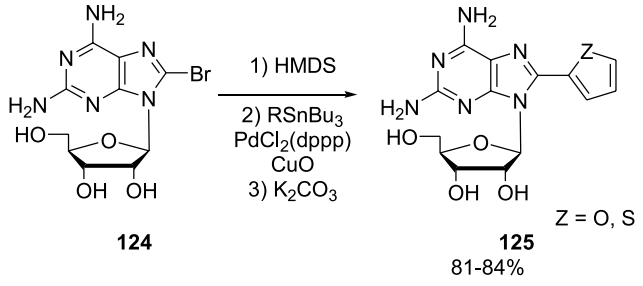
Stannylated thiazole and imidazole derivatives (Scheme 59) have been utilized in a coupling with iodouracil derivatives.[137,138] Standard conditions were effective for incor-



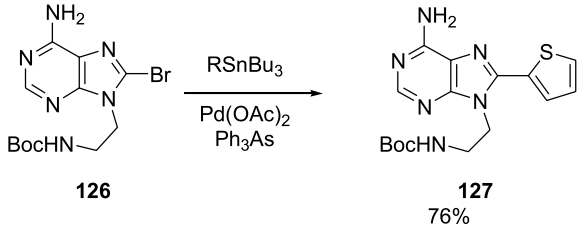
Scheme 55.



Scheme 56.



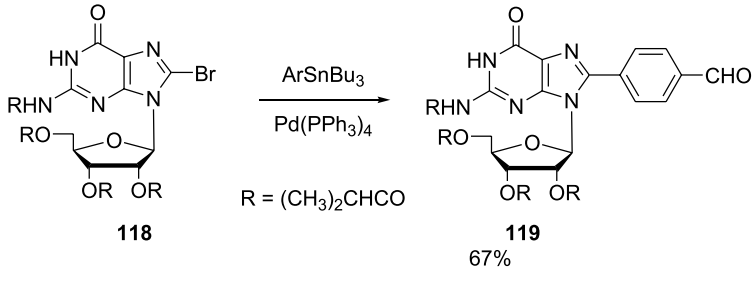
Scheme 57.



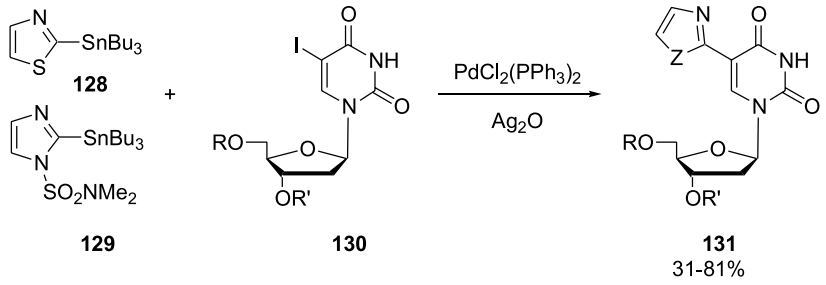
Scheme 58.

poration of the thiazole moiety, however, reaction of **129** necessitated the use of stoichiometric silver(I) oxide.

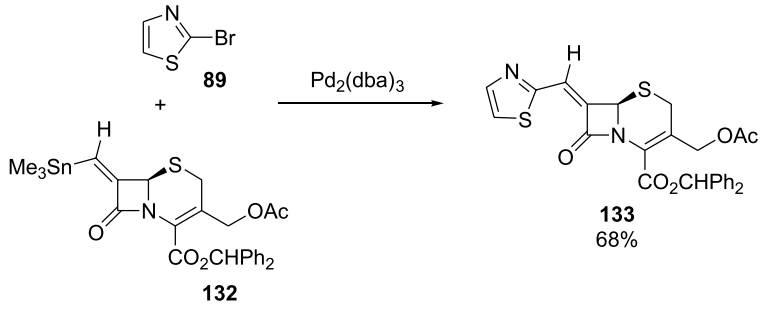
Bromothiazole was utilized to construct alkylidene-cephalosporin derivatives (Scheme 60) as β-lactamase inhibitors



Scheme 54.



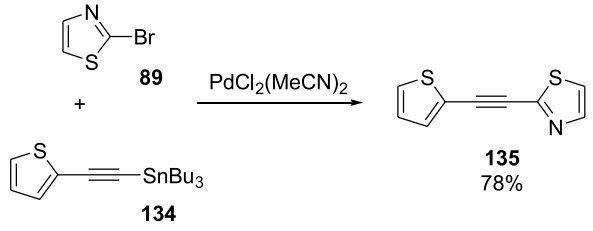
Scheme 59.



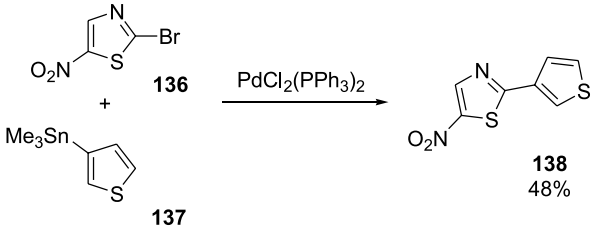
Scheme 60.

via Stille coupling.[139] The isomeric stannane was also coupled, albeit in a reduced yield (48%) and required a longer time (15 h vs. 10 h).

The synthesis of 1,2-heteroarylethynes was carried out with bromothiazole to furnish potential monomers (Scheme 61) for low bandgap conducting polymers.[140] Similarly, oligomeric thiophene/thiazole derivatives (Scheme 62) were prepared due to the interest in biologically active natural products terthiophene and bithiophene, as well as oligomeric thiophenes as repeat units of conducting polymers.[141]

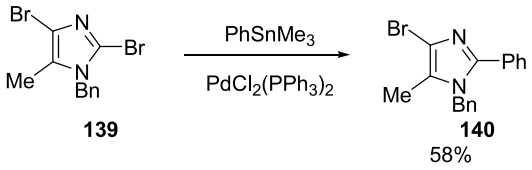


Scheme 61.



Scheme 62.

A good yield of the arylated imidazole derivative **140** was obtained from dibromide **139** (Scheme 63), with good selectivity for C2.[142] Dimethyl sulfomycinamate (**143**) was synthesized via in situ stannane formation (Scheme 64)

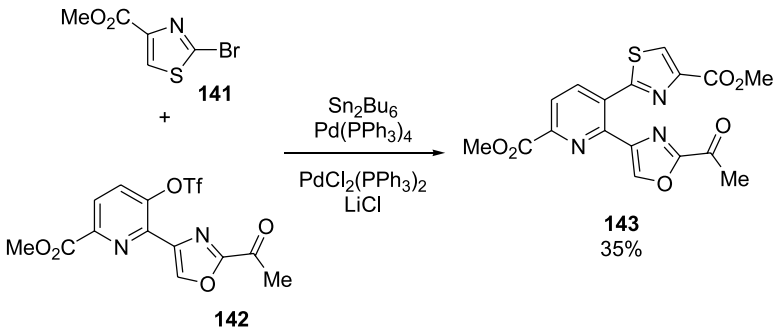


Scheme 63.

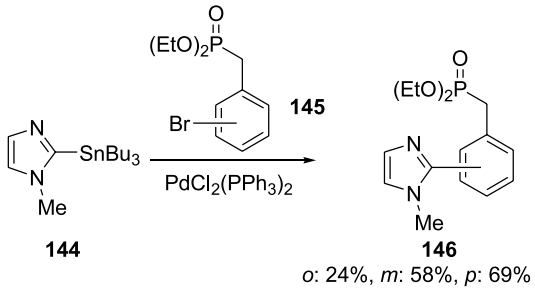
from triflate **142** followed by syringe pump addition of bromide **141** to the reaction.[143] Attempts to generate either coupling partner as a discrete stannane lead to dimeric or decomposition products. A similar strategy[144] was utilized in the synthesis of micrococcinic acid wherein a 2-bromothiazole was coupled to a 2-bromopyridine while attempted isolation of either stannane was impossible due to the formation of dimeric products.

Trialkylstannyl-1,3-azoles have also been utilized as partners in the Stille reaction with aromatic or heteroaromatic halides and triflates. Kennedy has utilized the Stille reaction to prepare all three regioisomeric biaryl phosphonates from the 2-stannyl imidazole **144** (Scheme 65), with yields improving as the bromide moved from the 2- <3- <4-position.[145] 1-Methyl-2-(4-fluoro)phenylimidazole **148** was synthesized to serve as a building block for substituted, quaternary imidazolium salts (Scheme 66).[146] The Stille coupling was used to construct benzothiazole-ninhydrin derivative **151** (Scheme 67) in a series of biaryl ninhydrin adducts targeting improved forensic stains for fingerprint analysis.[147,148]

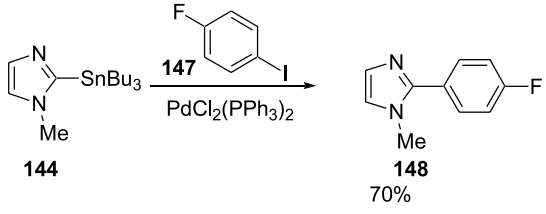
The coupling of stannane **144** with either aryl triflate or iodide **152** gave comparable yields (Scheme 68) for the construction of fluorinated phosphotyrosine mimetics.[149] Silylated cytosine adduct **156** was prepared by Gronowitz and co-workers[150] from stannane **154** (Scheme 69) in good yield. Biaryl triazinone **158** (Scheme 70) was synthesized as



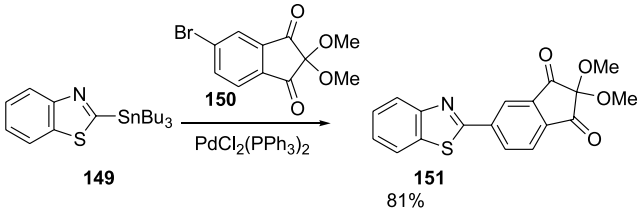
Scheme 64.



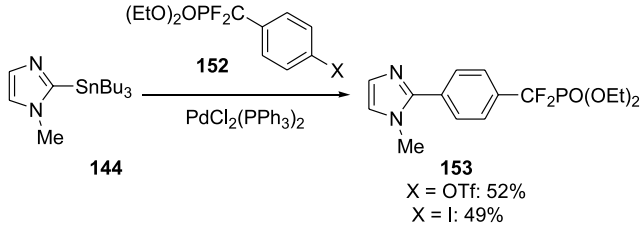
Scheme 65.



Scheme 66.



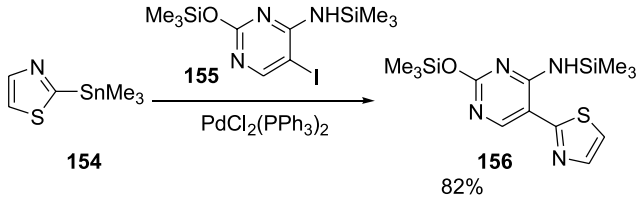
Scheme 67.



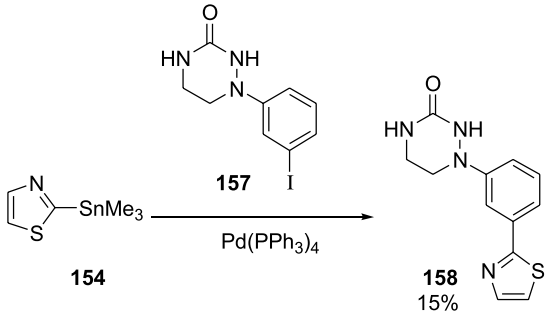
Scheme 68.

part of an SAR program[151] without any need to protect the urea functionality, although the isolated yield was low.

Benzothiazole-fluorene adduct **159** was prepared as a key intermediate (Scheme 71) for the synthesis of photon



Scheme 69.



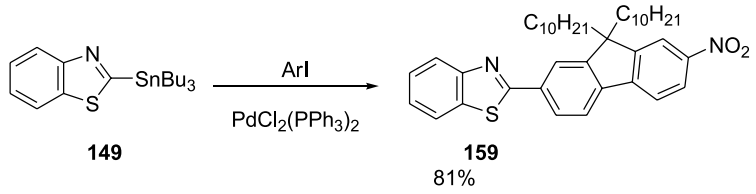
Scheme 70.

absorbers[152] which exhibited high solubility in common organic solvents, including hexanes owing to the two decyl chains on the fluorene system. Benhida et al. prepared indolyl-benzothiazole **161** (Scheme 72) from 6-iodoindole in a high yield.[153] Stille coupling of a bromo-aminoquinoxaline (Scheme 73) also tolerated a free amine one position removed from the reaction center.[154]

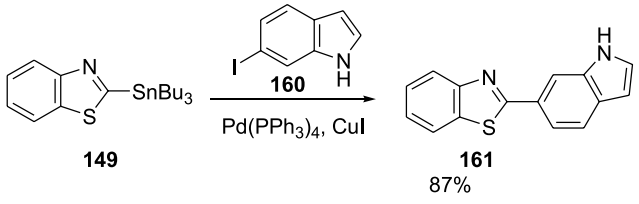
The coupling of oxazole stannane **163** with a triflate (Scheme 74) has been demonstrated by Collins and coworkers to furnish pyridone **164** featuring three separate aryl substitutions.[155] The other aryl moieties arise from a Claisen condensation in the first of seven steps to prepare the triflate. Collins also demonstrated[156] a Stille coupling of stannane **163** with a brominated triazolo[4,2-*b*]pyridazine. Finally, Gaare et al. demonstrated the reaction of stannane **144** with an acid chloride without the presence of any metal catalyst[157] after attempts to utilize a 2-trimethylsilylimidazole gave poor yields (Scheme 75).

4.2. Suzuki–Miyaura cross-coupling reactions

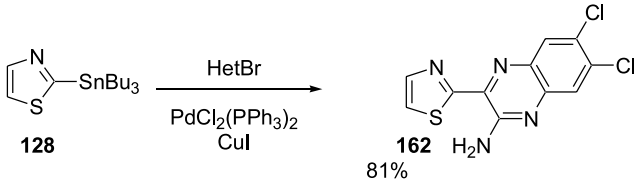
Reactions of azole derivatives which take advantage of a boron-containing partner in the coupling reaction are also very common, but generally utilize a halogenated azole and



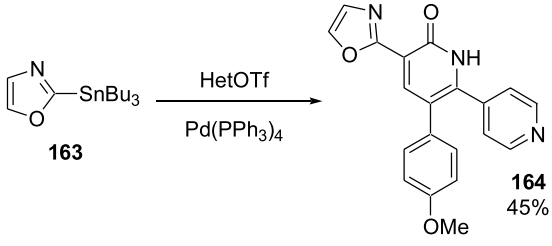
Scheme 71.



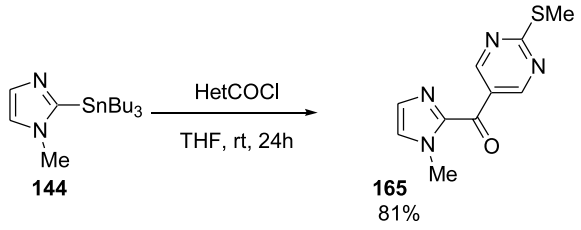
Scheme 72.



Scheme 73.



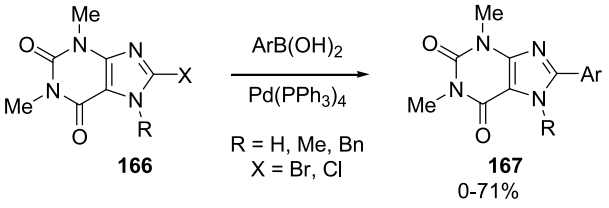
Scheme 74.



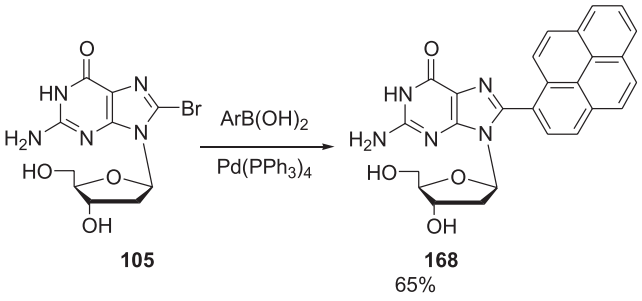
Scheme 75.

an aryl or heteroaryl boronic acid, many of which are now commercially available. The Suzuki reaction is exceptionally tolerant of functional groups which often need protection under other coupling conditions. The reaction of halogenated caffeine and theophylline with various boronic acids (Scheme 76)[158] furnished heterocyclic products **167**; theophylline (R=H) products generally occurred in lower yields but were possible with appropriate halide selection. In order to model charge transfer of DNA bases, the pyrenyl adduct **168** of deoxyguanosine was prepared by Wagenknecht (Scheme 77).[159]

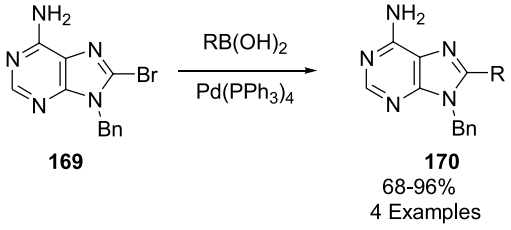
Purine derivatives **169** (Scheme 78) were coupled under



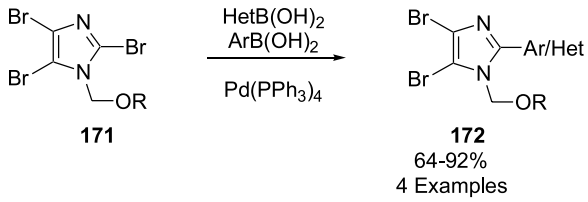
Scheme 76.



Scheme 77.

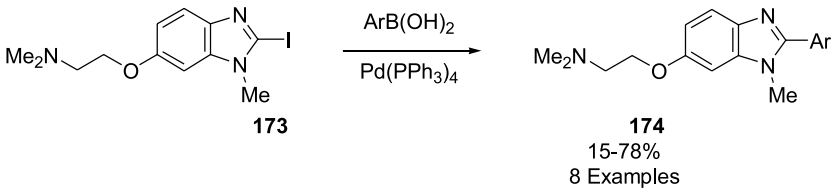


Scheme 78.



Scheme 79.

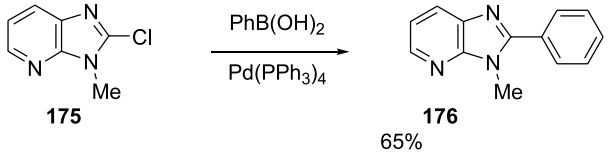
conditions originally optimized for 6-halopurines.[160] Tribromoimidazole **171** (Scheme 79) furnished monarylated products with substituted phenylboronic acids provided 1 equiv. of boronic acid was used;[161] other organometallic species (Zn, Mg) that were generated by metal–halogen exchange, furnished mixtures with lower combined yields. Additionally, more problematic heteroarylboronic acids (2-thienyl or 3-indolyl) could be utilized in this coupling, leading to useful biheteroarene adducts. The regioselectivity of this coupling was exploited for the synthesis of the



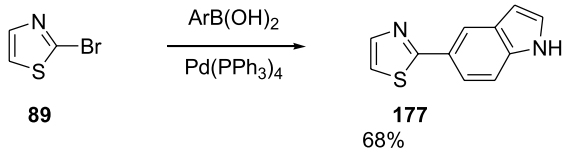
Scheme 80.

marine alkaloids nortopsentins A–D.[162] Iodobenzimidazole **173** (Scheme 80) readily coupled with boronic acids,[163] including 2,6-dimethylaryl boronic acids, in good yield (75%) whereas a 3-nitrophenylboronic acid furnished the biaryl adduct in low (15%) yield.

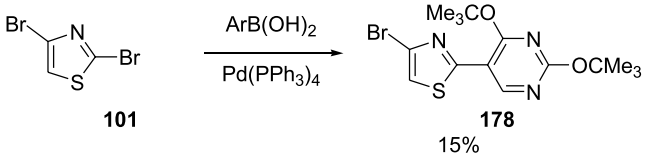
Chlorinated imidazole derivatives[164] also work well to furnish biaryl adducts (Scheme 81) which is advantageous as chlorinated analogs are often easy to prepare or inexpensive.[165] Bromothiazole **89** is a common 2-haloazole for Suzuki coupling reactions (Scheme 82).[166–168] Chemoselective reaction[169] of 2,4-dibromothiazole **101** proceeds selectively at C2 (Scheme 83), as does the 2-bromo-5-chloro derivative **179** (Scheme 84).[170]



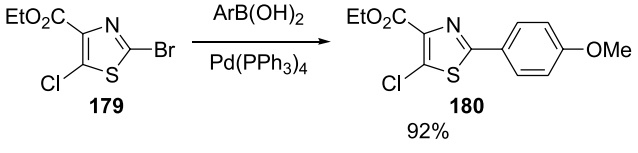
Scheme 81.



Scheme 82.

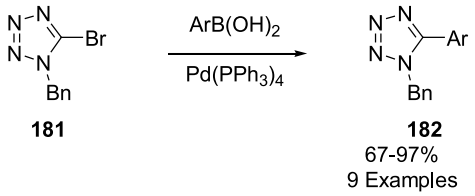


Scheme 83.

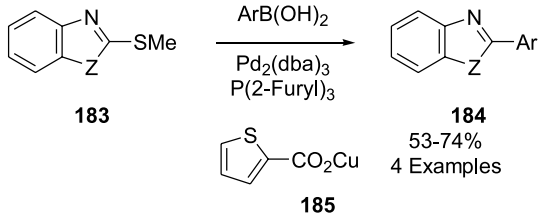


Scheme 84.

The first report of an arylated tetrazole formed via the Suzuki coupling[171] has been reported by Yi (Scheme 85), as well as a novel coupling of thioethers of oxazole, thiazole and tetrazole with boronic acids was reported by Liebeskind.[172] In this coupling, the use of copper(I) thiophene-2-carboxylate **185** was critical (Scheme 86).



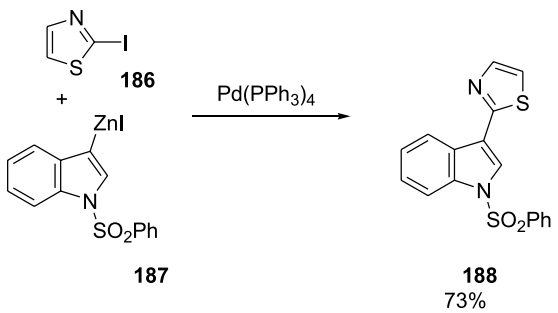
Scheme 85.



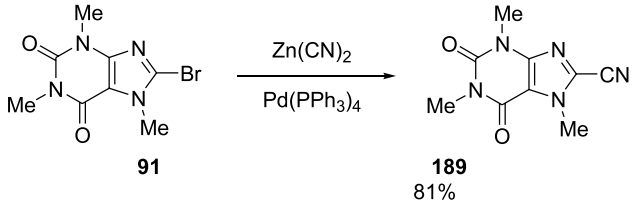
Scheme 86.

4.3. Zinc, magnesium and other couplings

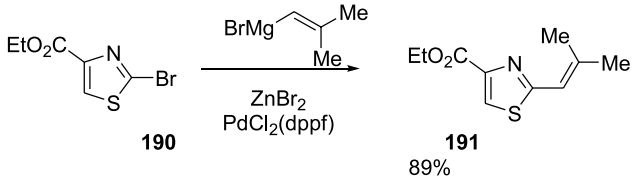
Metal-substituted coupling partners for transition-metal mediated reactions, other than tin and boron, have been of interest for a long time for environmental (tin toxicity) or synthetic (availability of boronates) reasons, among others. Highly active zinc[173,174] was required to generate **187**, which efficiently coupled with 2-iodothiazole to afford indolyl-thiazole adduct **188** (Scheme 87) when a transmetallation with zinc chloride failed. Zinc cyanide can be utilized to furnish the cyanide adduct of caffeine (Scheme 88).[175] In this reaction, both cyanides are transferred, as only 0.6 equiv. of zinc cyanide is utilized. The combination of zinc bromide and a Grignard reagent (Scheme 89) allowed for installation of the isobutylene fragment in thiazole **191** in the first step of the fungicidal natural product hectochlorin.[176] Following an asymmetric dihydroxylation, both thiazole fragments of the natural product were constructed from this common intermediate.



Scheme 87.

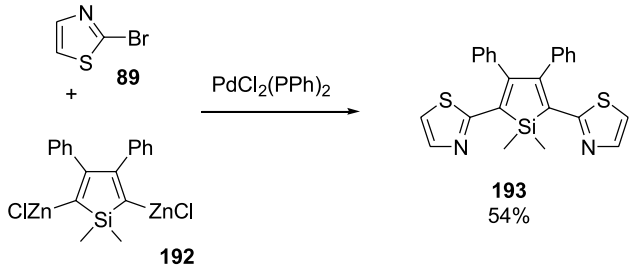


Scheme 88.

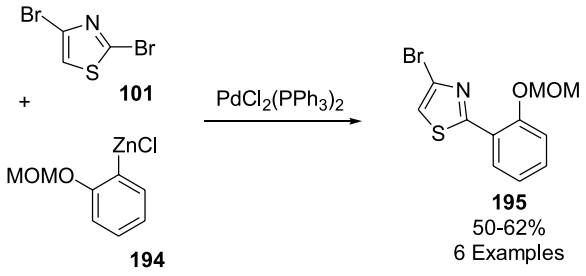


Scheme 89.

Negishi coupling with 2-bromothiazole **89** formed the symmetrical silole product **193** which has electroluminescent properties (Scheme 90).[177] Selective functionalization of dibromothiazole **101** was achieved by Bach (Scheme 91) with a variety of aryloxy zinc halides.[178] Bach also showed that the dibromide **101** couples selectively with isopropenyl zinc chloride (96%) and with a 4-thiazolyl zinc chloride (96%) in the synthesis of cystothiazole E.[179]



Scheme 90.



Scheme 91.

Thiazolyl and imidazolyl zinc reagents were coupled with the silyl-protected uridine derivative **198** (Scheme 92)[180] for the preparation of herpes simplex virus inhibitors. Likewise, the phosphorylated adduct **201** was prepared by Hocek via a Negishi coupling (Scheme 93).[181]

The use of active zinc generated by reduction of $ZnCl_2$ with potassium–naphthalide[182] was required to form **202** (Scheme 94) but resulted in a modest yield of the dicyano imidazole product **203**. The thiazole–aryl bond of **204** (Scheme 95) was derived from a selective Negishi coupling of thiazolyl zinc **196** with an aryl iodide, leaving the nonaflate moiety free for further coupling.[183] Both aryl halides and heteroaryl halides were effectively coupled with thiazolyl zinc bromide to afford the biaryl adducts (Scheme 96).[184] The application of a solid-supported organozinc species has been used[185] in the preparation of hydroxyimidazole products (Scheme 97).

Metallated 2-oxazoles are unique among the azoles in their relative instability (vide infra, Section 5.2). The stability of oxazoyl-zinc species **209** allowed for a modest yield[186] of unsymmetrical bisoxazole product **211** (Scheme 98). Similarly, oxazoyl zinc chlorides were reacted with a variety of iodide coupling partners to afford products in good yield (Scheme 99).[187,188]

Several methods for the coupling of thioether derivatives have been reported. Nickel catalysis in combination with both aryl and alkyl Grignard reagents (Scheme 100),[189] palladium with benzylzinc bromide (Scheme 101),[190] and zinc reagents with thioglycolic acid derivatives[191] catalyzed by nickel (Scheme 102) have all been introduced and expand upon the diversity of methods to construct substituted azoles.

The use of other organometallic reagents has also been demonstrated with halogenated azoles, and include organoaluminates (Scheme 103)[192,193] with palladium catalysis as well as Grignard reagents catalyzed by nickel (Scheme 104)[194,195] and iron (Scheme 105).[196]

5. Other substituted azoles

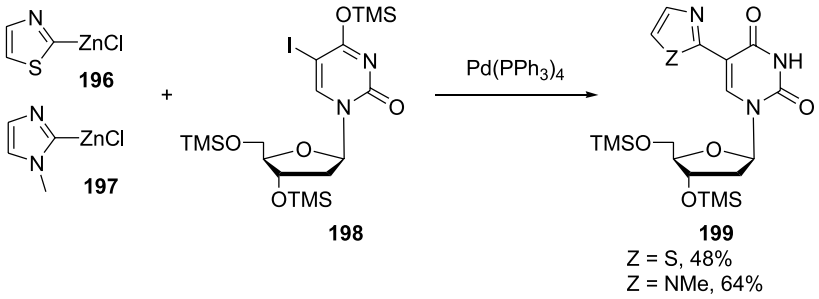
5.1. 2-Trimethylsilyl azoles

The substitution of 1,3-azoles in the 2-position with a trimethylsilyl group is known to give a species that readily adds to electrophiles. 2-Trimethylsilylthiazole (2-TST) (**226**) is the most widely utilized of the silylated azoles, serving to incorporate the thiazole substructure into targets which can also serve as a formyl anion equivalent after a methylation/reduction sequence. The ability of 2-TST to add to chiral aldehydes under mild conditions allows for the addition to occur without racemization of the aldehyde, and often with excellent diastereoselectivity. Scheme 106 depicts several aldehydes and the diastereomeric ratio obtained for recent examples which utilized 2-TST.[197–203]

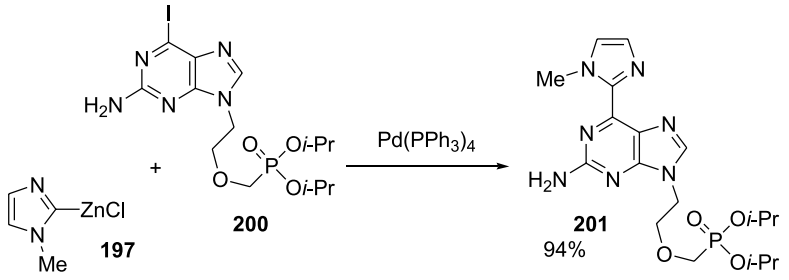
Dondoni has also demonstrated the use of 2-TST for the addition to fluorinated aryl and alkyl ketones (Scheme 107).[204] Acetophenones and other ketones have not been successful as electrophiles for 2-TST. Recently, Hosomi et al. have introduced a copper(I) mediated coupling reaction of aryl silanes[205] where the use of 1,3-dimethyl-2-imidazolidinone as solvent greatly improves the reaction yield. Copper pentafluorophenoxide is generated in situ as the active catalyst (Scheme 108).

5.2. Metalated azoles

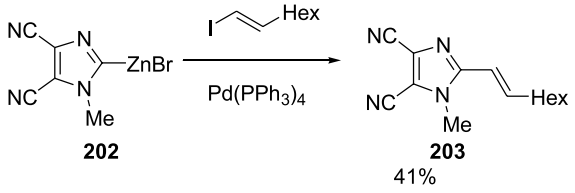
The acidity of the C2-proton of 1,3-azoles allows for facile, selective deprotonation and functionalization. Oxazole,



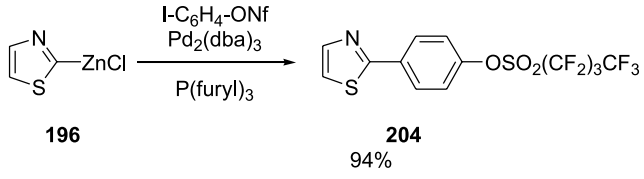
Scheme 92.



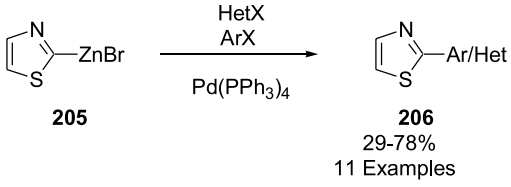
Scheme 93.



Scheme 94.



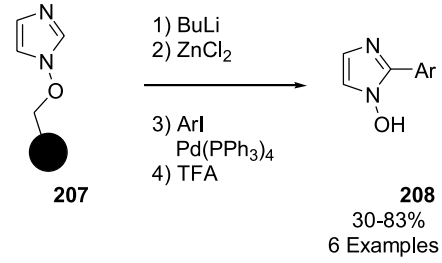
Scheme 95.



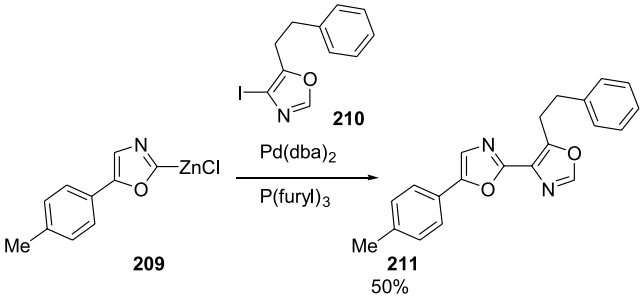
Scheme 96.

however, has been shown to undergo ring-opening and leads to substitution at both C2 and C4, as well as to give the isonitrile byproduct (Scheme 109) as the electrophile is varied.[206] Methods to circumvent this ambident nucleophilicity include transmetallation with zinc and inclusion of copper(I) iodide (Scheme 110),[207] and Vedejs' use of the borane adduct (Scheme 111).[208]

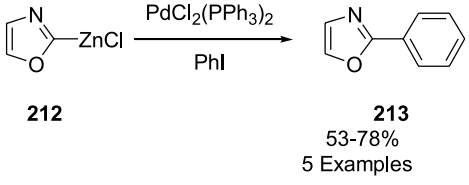
Other metallated azoles do not suffer from the propensity to



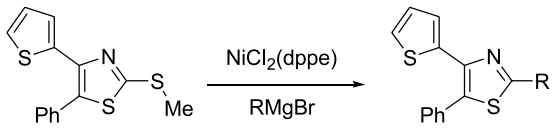
Scheme 97.



Scheme 98.

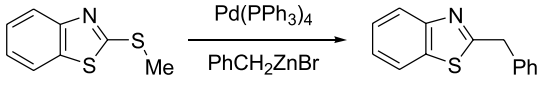


Scheme 99.



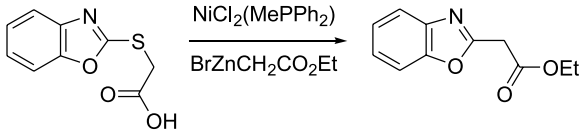
214 **215** 16-95% 6 Examples

Scheme 100.



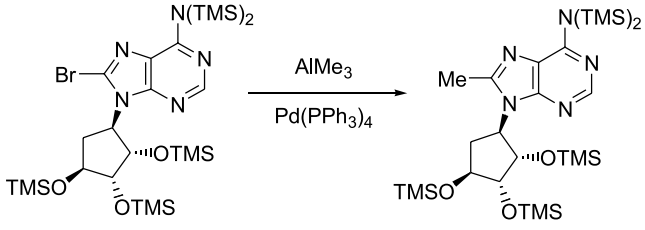
216 **217** 89%

Scheme 101.



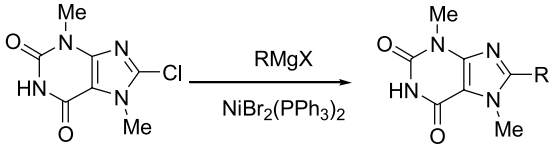
218 **219** 54%

Scheme 102.



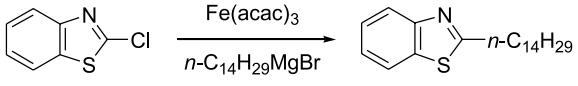
220 **221** 55%

Scheme 103.



222 **223** 60-94% 4 Examples

Scheme 104.



224 **225** 68%

Scheme 105.

rearrange, and have been widely used. Metallated imidazoles (Scheme 112)[209–220] and thiazoles (Scheme 113)[221–234] have been prepared, using a variety of metals (Li, Mg, Zn) and electrophiles as trapping agents.

Oxadiazoles **250** have been prepared in two steps from simple esters, metallated (Scheme 114) and trapped with Boc-L-valinal in a preparation of human neutrophil elastase inhibitors.[235] A hypervalent coupling reaction[236] is known to occur between lithiated thiazole and thionyl chloride, to provide a mixture of the desired coupling product **253** along with two side products (Scheme 115).

6. 2-Substituted azoles as electrophiles

Substitution at C2 of 1,3-azoles with a leaving group generates a heterocycle that can be functionalized via displacement of the C2 substituent. Heteroatom nucleophiles add either as the deprotonated species (i.e., alkoxides, thiolates) or under mildly basic conditions. Diazo salts can be displaced with bromide (Scheme 116),[237] arylated with benzene (Scheme 117) or displaced with alcohols.[238,239]

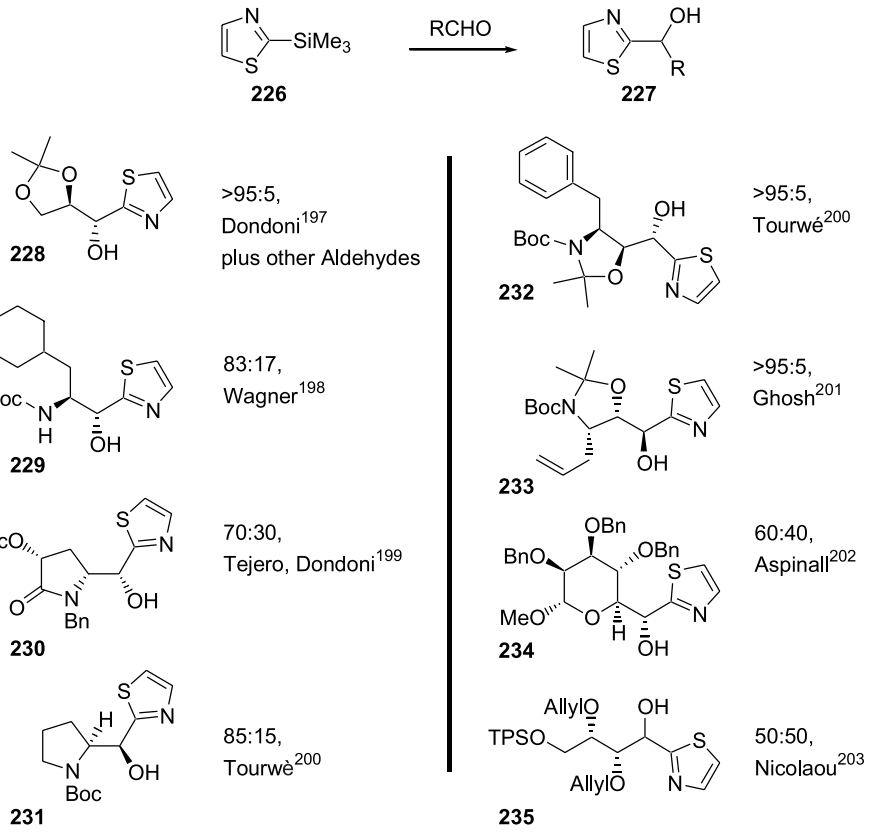
Addition of carbon nucleophiles to halogenated thiazoles include the use of sodium cyanide (Scheme 118),[240,241] indolyl Grignard reagent **262** (Scheme 119),[242] 2-lithio-2-nitropropane (Scheme 120)[243] and an ester enolate (Scheme 121).[244] Following saponification and decarboxylation, the isomeric 1-azabicyclo[2.2.1]heptanyl adducts derived from **266** were isolated in a combined 21% yield. Chlorobenzimidazole **268** has served as the arylating species (Scheme 122) when reacted with the dianion of 2,3′-biquinoline.[245]

2-Aminothiazole undergoes a fusion reaction with ester **270** to give the thiazoyl ester (Scheme 123).[246] Mourad et al. have investigated the reaction of a variety of 2-amino-1,3-azoles with activated quinones, giving products such as **274** in good yields (Scheme 124).[247,248]

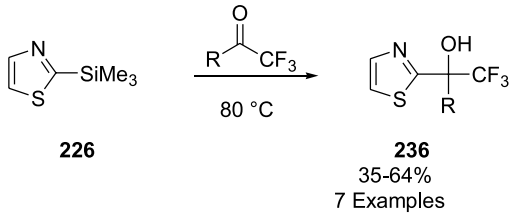
Imidazo[1,2-*b*]thiazolines[249] undergo nucleophilic displacement with allylic and benzylic Grignard reagents (Scheme 125); alkyl Grignard and alkyl or aryl lithium reagents result in nucleophilic attack on sulfur and loss of ethylene to furnish 2-thioalkyl-1*H*-imidazoles. The authors note the relief of ring strain via loss of ethylene to be a driving force in the latter cases.

2-Methylthio derivatives of oxazoles[250] and triazoles,[251] as well as the methylsulfonyl analogs of oxadiazole[252] and tetrazole[253] have been used as electrophiles with a variety of carbon and heteroatom nucleophiles.

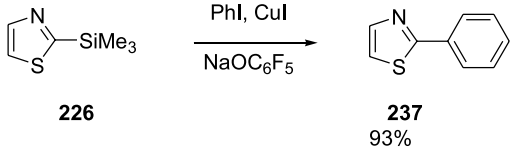
2-Thiophenoxybenzimidazole **277** is susceptible to intramolecular radical addition in the presence of cobaloxime (Scheme 126)[254] in higher yield than with Ph_3SnH/AIBN with less of the dehalogenated byproduct (81% and 11% vs. 64% and 35%). Dimsyl guanosine[255] was also generated in an attempt to synthesize the benzyl ether **280**, resulting from the generation of an iminyl radical under forcing reaction conditions. 5-Nitro-2-iodoimidazole has been reacted with arenes and thiophenes under photochemical conditions to give single products in high yields (Schemes 126–128).[256]



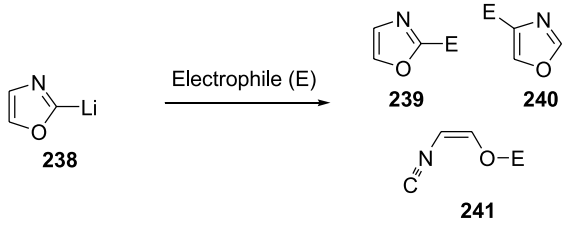
Scheme 106.



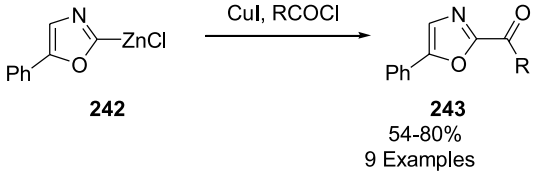
Scheme 107.



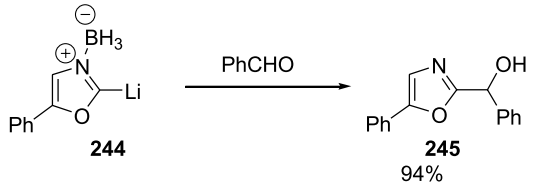
Scheme 108.



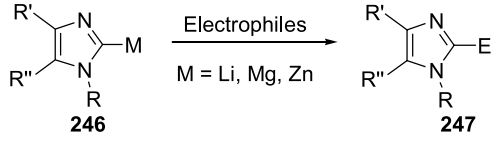
Scheme 109.



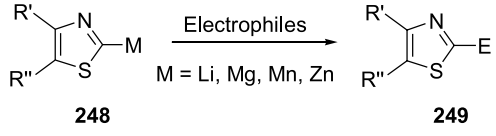
Scheme 110.



Scheme 111.

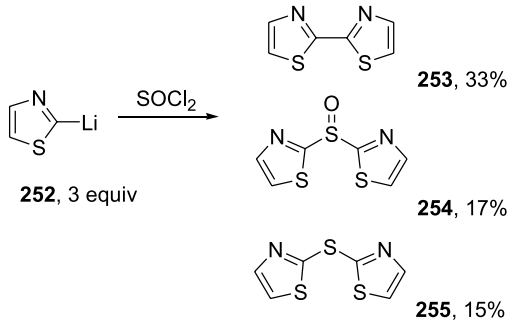


Scheme 112.

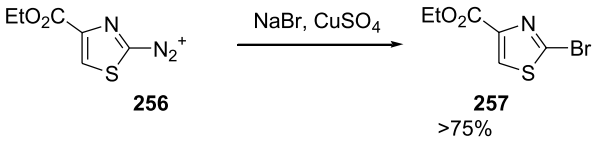


Scheme 113.

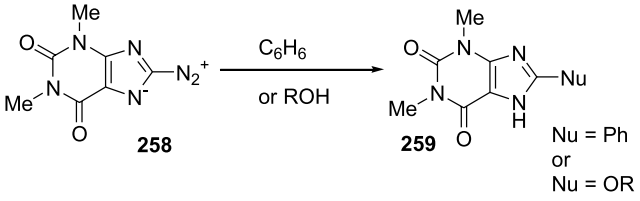
Scheme 114.



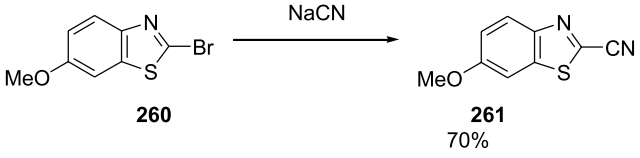
Scheme 115.



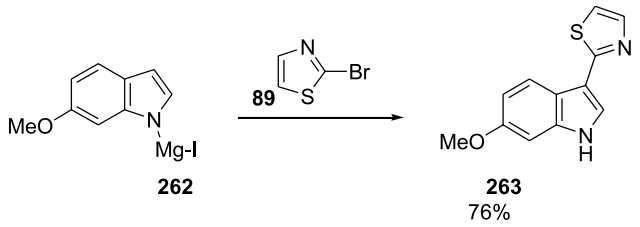
Scheme 116.



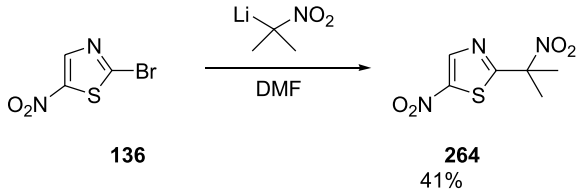
Scheme 117.



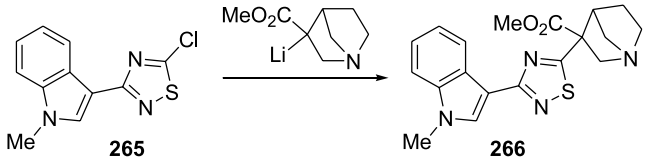
Scheme 118.



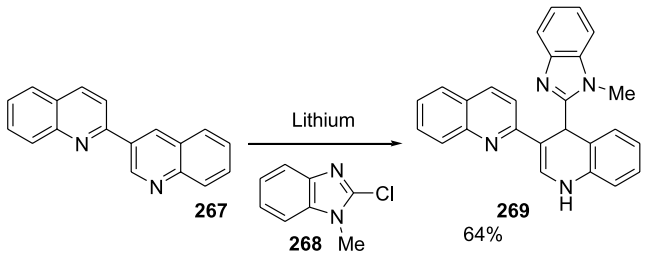
Scheme 119.



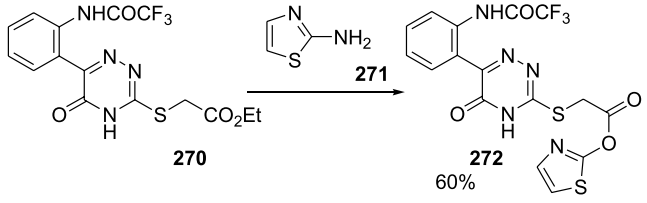
Scheme 120.



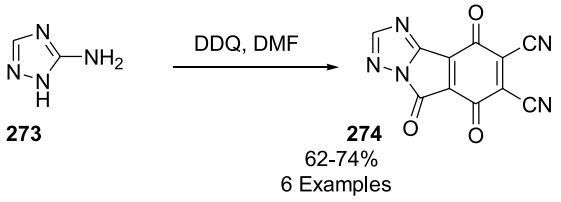
Scheme 121.



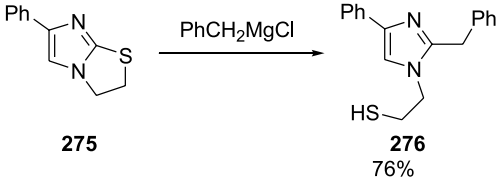
Scheme 122.



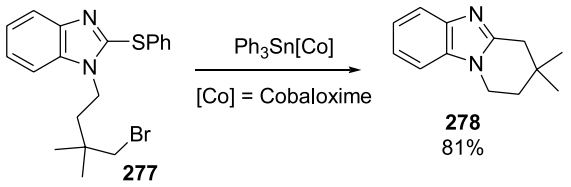
Scheme 123.



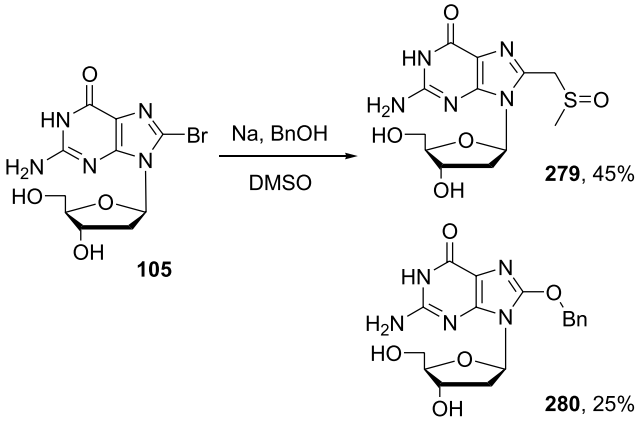
Scheme 124.



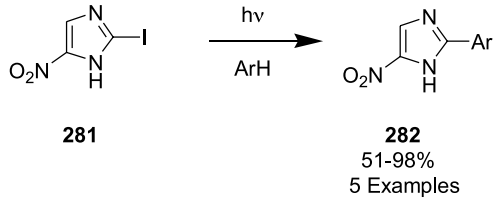
Scheme 125.



Scheme 126.



Scheme 127.



Scheme 128.

7. Conclusions

The synthesis of 2-substituted 1,3-azoles is a broad field of interest for synthetic organic and medicinal chemistry. Numerous methods for their synthesis from acyclic precursors exist.[1] However, this review has specifically focused on the functionalization chemistry of 1,3-azole systems in the literature over the last 10 years. Numerous additional examples can be found in the prior literature that is cited within the leading references provided in this review.

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Tetrahedron 60 (2004) 9017–9029
Tetrahedron

The *gem*-dimethyl effect: amphiphilic bilirubins

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Received 24 March 2004; revised 22 July 2004; accepted 3 August 2004

Abstract—New bilirubin congeners (**1a**–**1d**) with the central C(10) CH_2 replaced by $C(CH_3)_2$ were smoothly synthesized by coupling two identical dipyrrinones with 2,2-dimethoxypropane under acid catalysis. The new yellow pigments, with acid chains varying from acetic ($n=1$) to propionic ($n=2$) to butyric ($n=3$) to hexanoic ($n=5$), exhibit unusual amphiphilicity relative to the parent mesobilirubins without the *gem*-dimethyls and have highly favorable solubility in organic solvents ranging from nonpolar (benzene) to polar (CH_3OH). Like the parent rubins, **1a**–**1d** can easily bend about the middle but unlike the parents they cannot form mesobiliverdin analogs. NMR spectroscopic analysis and molecular dynamics calculations indicate that, like the parents, **1a**–**1d** adopt ridge-tile shapes that are stabilized by intramolecular hydrogen bonding. Confirmation of the conformation in **1b** comes from its X-ray crystallographic structure.

1. Introduction

Humans become jaundiced because they cannot efficiently eliminate bilirubin (Fig. 1), a yellow tetrapyrrole dicarboxylic acid formed in normal metabolism, principally from the heme of red cells, at the rate of 250–300 mg per day.[1,2] Perhaps the most important structural aspect of the bilirubin molecule, concluded from numerous investigations, is its strong propensity to adopt a shape like a half-opened book or ridge-tile,[3] with both carboxylic acid groups firmly engaged in intramolecular hydrogen bonding each to a dipyrrinone.[3–8] The intramolecularly hydrogen-bonded ridge-tile structure (Fig. 1) explains many of the chemical properties of the pigment, particularly its unexpected lipophilicity.[8] It also helps to understand why bilirubin is not excreted intact by the liver.[9,10] For hepatic excretion, a specific glucuronosyl transferase enzyme (UGT1A1) converts one or both of bilirubin's propionic acids to glucuronide esters in the livers of both humans and rats.[2,11]

An essential requirement for strong intramolecular hydrogen bonds between the bilirubin dipyrrinones and the carboxylic acid groups requires that the propionic acids (i) stem from C(8) and C(12) and (ii) be capable of orienting their CO_2H termini toward the dipyrrinones.[3,4] Mesobilirubin-XIIIα (Fig. 2) has these essential components and orientation, and its most stable conformation is the intramolecularly hydrogen-bonded ridge-tile (as in Fig. 1).[4] Molecular modeling studies indicates that a bilirubin with propionic acids replaced by other alkanoic acids, e.g. acetic, butyric, hexanoic, can adopt an intramolecularly hydrogen-bonded ridge-tile conformation, where the ridge-tile is pinched (acetic) or more opened (butyric, hexanoic).[12] In practice, we found that the mesobilirubin analog with butyric acids replacing propionic was still lipophilic, whereas those with acetic and hexanoic acid were more polar.[13] In the following we describe the syntheses of the *gem*-dimethyl analogs (Fig. 2) of mesobilirubin-XIIIα with varying alkanoic acid chain lengths and compare their polarity and spectroscopic properties and stereochemistry.

2. Results and discussion

2.1. Synthesis

The syntheses of *gem*-dimethyl bilirubins **1** (Scheme 1) are based on an earlier successful method, in which two 9-H dipyrrinones identical to **3** ($n=2$) except with two methyl groups on the lactam ring were condensed with 2,2-dimethoxypropane in TFA.[14] An improved method was developed in the current work by extending the reaction time to 1 h and maintaining the temperature at 0 °C. The yields were nearly 50%, based on one reaction cycle. The key intermediates, 9-H dipyrrinone alkanoic acids **3**, were prepared by either of two different routes: **3a** ($n=1$) was prepared in 6 steps by converting the previously reported monopyrrole **13**[15] to pyrrole aldehyde **8a** (Scheme 1), which was condensed with pyrrolinone **5**; similarly, **3c** was prepared from **8c**, reported previously.[16] Dipyrrinones **3b**[17] and **3d** were prepared by decarboxylation of 9-CO_2H

Keywords: Bilirubin; Conformation; Hydrogen bonding; Solubility.
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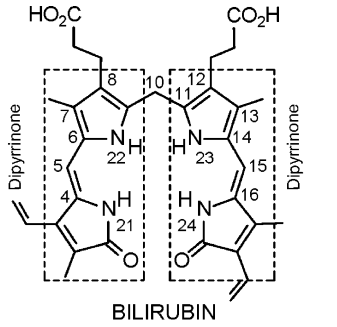
doi:10.1016/j.tet.2004.08.005



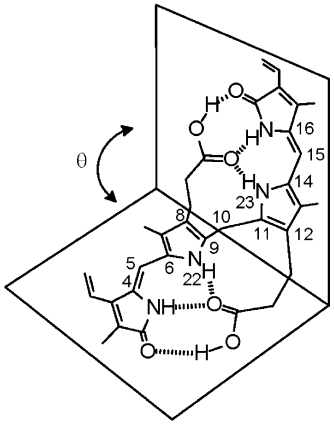


Figure 1. (Upper) Bilirubin in a porphyrin-like conformation. (Lower) The most stable (ridge-tile) conformation of bilirubin. The latter is one of many possible conformations accessible by rotation of the dipyrrinones about C(10), and it is the only conformation where nonbonded intramolecular steric interactions are minimized and where both carboxylic acid groups can engage in intramolecular hydrogen bonding to the opposing dipyrrinones. The ridge-tile conformation is defined by torsion angles about both C(10) C–C single bonds: ϕ_1=N(22)–C(9)–C(10)–C(11) and ϕ_2=C(9)–C(10)–C(11)–N(23). Limited rotations can also occur within the dipyrrinones about the C(5)–C(6) single bond: ψ_1=C(4)–C(5)–C(6)–N(22) and the C(14)–C(15) single bond: ψ_2=N(23)–C(14)–C(15)–C(16). More restricted rotations may occur about the C(4)–C(5) double bond: ψ_3=N(21)–C(4)–C(5)–C(6) and the C(15)–C(16) double bond: ψ_4=C(14)–C(15)–C(15)–C(16)–N(24). In the ridge-tile conformation shown, $\phi_1=\phi_2=-60°$ and $\psi_1=\psi_2=0°$. In the porphyrin-like shape of bilirubin (upper), $\phi_1=\phi_2=0°$. The interplanar angle (θ) determines the pitch of the ridge-tile and is determined by the angle of intersection of the average planes of the two dipyrrinones (θ_1) or the angle of intersection of the planes of two pyrrole rings (θ_2).

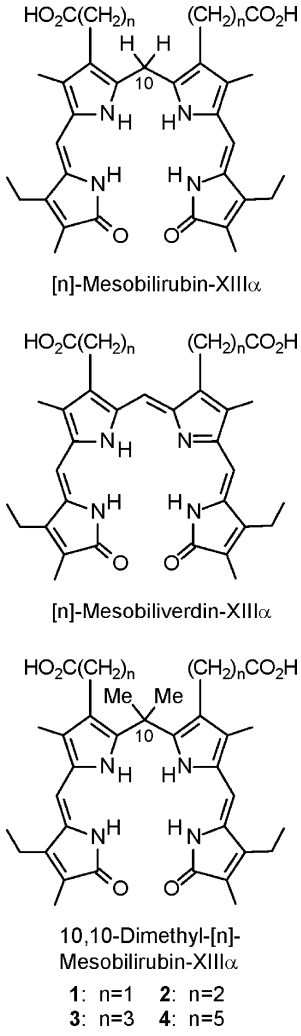
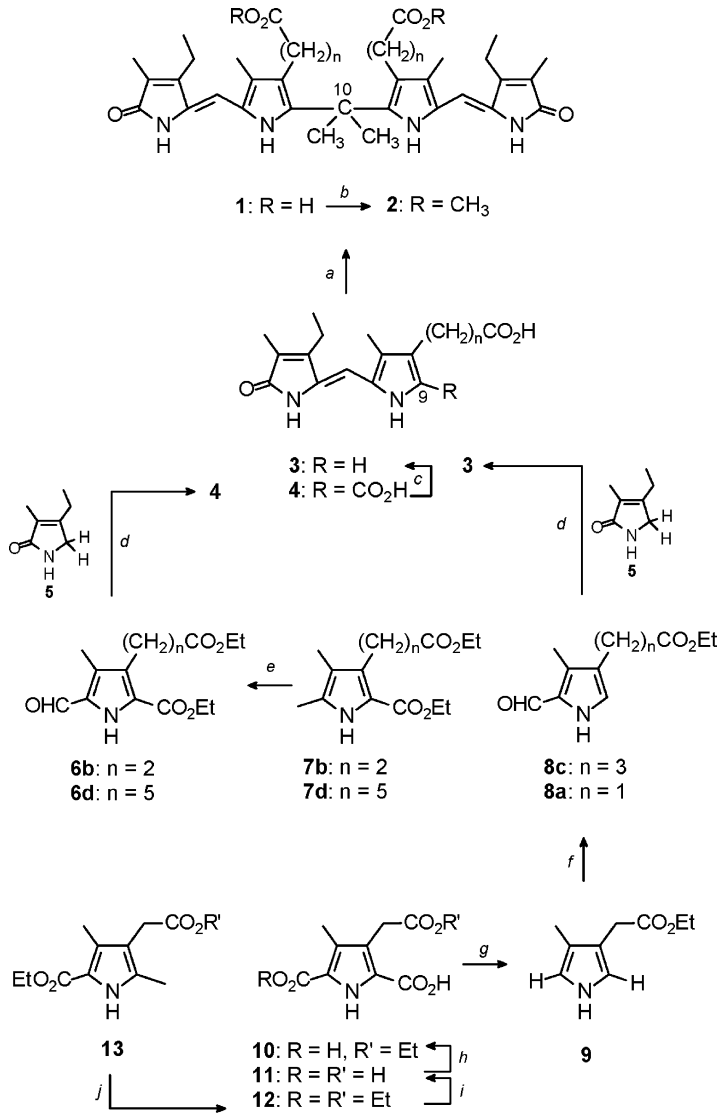


Figure 2. [*n*]-Mesobilirubins-XIIIα, their verdins, and their 10,10-*gem*-dimethyl analogs with chain lengths varying from $n=1$ to $n=5$. [$n=2$]-Mesobilirubin-XIIIα is mesobilirubin-XIIIα. While the former can be oxidized easily at C(10) to mesobiliverdin-XIIIα, the 10,10-*gem*-dimethyl rubins resist oxidation and cannot form verdins.

dipyrrinones **4b**[17] and **4d**, respectively, in molten NaOAc–KOAc.[18,19] Thus, 9-H dipyrrinone acids **3b** and **3d** were prepared in 2 steps in over 80% yield from pyrrole aldehydes **6b** and **6d**, which were prepared by CAN oxidation of the known 2-carboethoxy-4,5-dimethyl 3-alkanoic acid ethyl esters **7b**[19,20] and **7d**.[21]

We prepared **8a** and **8c** by a procedure developed for synthesis of its propionic acid analog.[14,18] As outlined in Scheme 1 for the acetic acid series (**a**), the α-methyl of pyrrole **13** was oxidized to carboxylic acid **12** by reaction with 3 mequiv of sulfuryl chloride in anhydrous ether, then treatment with aq. KOAc. After saponification of **12** to pyrrole triacid **11**, the acetic acid group was selectively esterified in 90% yield by treatment with absolute ethanol and TFA for 12 h followed by reaction with triethyl orthoformate for another 48 h at room temperature to afford **10**. The two α-carboxylic acids of **10** were removed by decarboxylation by heating in a Kugelrohr apparatus at 160 °C under 15 mm Hg vacuum (water aspirator) to distill **9** as an oil. A Vilsmeier reaction of **9** with $(CH_3)_2NCHO$ and $POCl_3$, followed by aq. NaOAc work-up gave an 81% yield of a 4:1 mixture of **8a** and its regio-isomer, from which the major isomer (**8a**) could not be separated by crystallization (as in the propionic ester analog[14]) but could be separated only partially using radial chromatography on silica gel, eluting with CH_2Cl_2–CH_3OH (50:1 by vol). This mixture of aldehydes, highly enriched in **8a**, was condensed with pyrrolinone **5** in the presence of methanolic KOH to afford 9-H dipyrrinone **3a** in 80% yield. In the crystallized dipyrrinone **3a**, we could detect no dipyrrinone isomer coming from the trace amounts of the regio-isomeric aldehyde contaminant in **8a**. Similarly, aldehyde **8c**, prepared in connection with an earlier study,[16] and similarly essentially regio-isomerically pure as determined by ^{13}C NMR, was condensed with **5** to afford dipyrrinone **3c**. To prepare **3b** and **3d**, aldehydes **6b** and **6d** were condensed separately with **5** to afford 9-CO_2H dipyrrinones **4b** and **4d**



Scheme 1. Reagents and conditions: for **1**, **2**, **3**: **a**: $n=1$, **b**: $n=2$, **c**: $n=3$, **d**: $n=5$. (a) $(CH_3)_2C(OCH_3)_2$, TFA, 0 °C; (b) CH_2N_2, CH_3OH; (c) KOAc–NaOAc·$3H_2O$, 160–180 °C; (d) KOH, then HOAc; (e) CAN; (f) DMF, $POCl_3$; then aq. KOAc; (g) Kugelrohr, 180 °C; (h) $HC(OEt)_3$, TFA, absol. EtOH, RT; (i) NaOH refl.; then HCl; (j) SO_2Cl_2, anhydr. Et_2O, −5 °C; then aq. KOAc.

in 90% yield. The 9-COOH of **4b** and **4d** was decarboxylated in a 1:1 molten mixture of KOAc–NaOAc·$3H_2O$ at 165 °C[18,19] to yield 9-H dipyrrinones **3b** and **3d** in 80% yield.

Treatment of the 9-H dipyrrinones **3a**–**3d** with 2,2′-dimethoxypropane in TFA at 0 °C for 1 h afforded the desired *gem*-dimethyl bilirubins **1a**–**1d**, each in nearly 50% yield. The corresponding methyl esters (**2**) were prepared in >90% yield from the acids (**1**) by reaction with excess CH_2N_2 in methanol at room temperature.

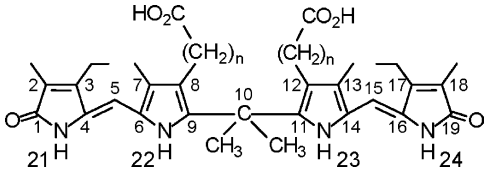
2.2. Constitutional structures

The constitutional structures of *gem*-dimethyl bilirubins **1a**–**1d** and their methyl esters **2a**–**2d** follow logically from the method of synthesis and the well-characterized mono and dipyrrole synthetic precursors. The tetrapyrrole structures were confirmed from their ^{13}C NMR spectral data in $(CD_3)_2SO$ and by comparisons with ^{13}C NMR data from the parent mesobilirubins without *gem*-dimethyl groups[13b] and with 10,10-dimethyl glaucorubin.[14] As expected, the ^{13}C NMR data for **1a**–**1d** are nearly identical, except for the differing number of carbon signals from the alkanoic acid chains and the C(8)/C(12) ring carbons to which they are attached (Table 1). They compare well with the ^{13}C NMR data of the corresponding [*n*]-mesobilirubins-XIIIα.[13b] The most significant difference between the *gem*-dimethyl series and the mesobilirubin parent is found at C(10) and the flanking carbons C(9/11), both of which are significantly more deshielded in the former. Similar trends were observed in comparing the ^{13}C NMR data of the methyl esters **2a**–**2d** (Table 2).

2.3. Solution and chromatographic properties

Like the bright yellow parent, mesobilirubin-XIIIα, *gem*-dimethyl mesobilirubins **1a**–**1d** and their dimethyl esters (**2a**–**2d**) are yellow solids that form bright yellow solutions. The *gem*-dimethyl rubin **1c**, with butyric acids, has excellent

Table 1. Comparison of the ^{13}C NMR chemical shift[a] assignments of *gem*-dimethyl bilirubin analogs **1a** ($n=1$), **1b** ($n=2$), **1c** ($n=3$), and **1d** ($n=5$) in $(CD_3)_2SO$ with those (italicized) of the corresponding [n]-mesobilirubins-XIIIα (see Fig. 2)[b]



Position	1a	1b	1c	1d
1,19-CO	172.8 (*172.6*)	172.3 (*171.9*)	172.9 (*172.5*)	172.8(*172.4*)
2,18	123.4 (*123.6*)	123.0 (*122.9*)	123.6 (*123.3*)	123.5(*123.6*)
2,18-CH_3	9.9 (*9.7*)	9.3 (*9.2*)	9.4 (*9.6*)	9.9 (*9.6*)
3,17	147.8 (*147.3*)	147.2 (*147.1*)	147.8 (*147.8*)	147.8 (*147.7*)
3,17-CH_2CH_3	17.6 (*17.7*)	17.2 (*17.2*)	17.8 (*17.6*)	17.6 (*17.6*)
3,17-CH_2CH_3	15.2 (*15.1*)	14.8 (*14.8*)	14.9 (*15.3*)	15.2 (*15.3*)
4,16	129.2 (*128.3*)	128.5 (*122.4*)	128.7 (*128.1*)	128.4 (*127.7*)
5,15-CH═	98.4 (*97.9*)	98.1 (*97.7*)	98.6 (*98.2*)	98.5 (*98.3*)
6,14	124.2 (*123.4*)	123.3 (*123.0*)	123.9 (*123.3*)	123.9 (*123.3*)
7,13	121.5 (*122.7*)	123.3 (*122.0*)	122.0 (*122.4*)	122.0 (*122.1*)
7,13-CH_3	8.5 (*8.4*)	8.1 (*8.1*)	8.0 (*8.5*)	8.5 (*8.5*)
8,12	114.2 (*114.7*)	118.4 (*119.3*)	120.3 (*120.7*)	120.8 (*121.4*)
8^1-CH_2	30.3	19.8 (*19.2*)	23.5 (*24.1*)	24.9 (*25.1*)
8^2-CH_2	—	34.2 (*34.6*)	24.9 (*26.1*)	29.6 (*29.5*)
8^3-CH_2	—	—	32.2 (*33.8*)	29.7 (*29.6*)
8^4-CH_2	—	—	—	30.4 (30.5)
8^5-CH_2	—	—	—	34.1 (*34.1*)
8,12-COOH	173.3 (*173.7*)	173.9 (*174.1*)	174.7 (*174.9*)	174.8 (*174.9*)
9,11	139.7 (*131.2*)	138.6 (*130.4*)	139.1 (*130.8*)	139.0 (*130.9*)
10	36.8 (*23.7*)	36.5 (*23.3*)	35.7 (*23.4*)	37.3 (*24.3*)
10-CH_3	29.1	29.0	28.2	29.6

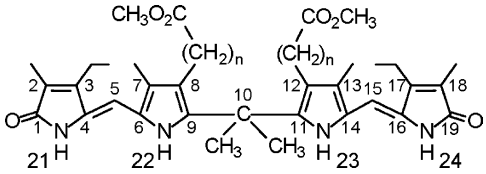
[a] In δ, ppm downfield from $(CH_3)_4Si$.
[b] Data from Ref. 22.

solubility in most organic solvents ranging from non-polar to polar, even in those in which bilirubin and mesobilirubin-XIIIα are insoluble: hexane and methanol. The other isomers, **1a**, **1b** and **1d** are somewhat less soluble than **1c** in CH_2Cl_2, $CHCl_3$ and CH_3OH, but they are much more soluble in organic solvents (order of solubility: **1b**>**1c**>**1a**>**1d**) than their respective parent rubins without *gem*-dimethyls.[13b] They also have good solubility in a mixture of CH_2Cl_2 and CH_3OH, which indicates better amphiphilicity than their parent mesobilirubins. This is unlike the intramolecularly hydrogen-bonded parent [$n=2$ and 3] mesobilirubins-XIIIα, which are insoluble in CH_3OH and in 1:1 CH_2Cl_2–CH_3OH. And it is unlike the [$n=1$, 4 and 5]-mesobilirubins-XIIIα, which have poor solubility in both CH_2Cl_2 and CH_3OH. On silica gel TLC using 4% by vol CH_3OH in CH_2Cl_2 as eluent, **1a** exhibited an $R_f\sim0.61$; **1b**, $R_f\sim0.77$; **1c**, $R_f\sim0.55$; and **1d**, $R_f\sim0.32$. By way of comparison, mesobilirubin-XIIIα exhibits an $R_f\sim0.85$, which suggests that **1a**–**1d** are more polar. The data indicate that **1c** and **1d** are more polar than **1a** and especially **1b**. In contrast, the dimethyl esters **2a**–**2d** of the *gem*-dimethyl rubins have lower R_f values compared with the corresponding acids: **2a**, 0.27; **2b**, 0.11; **2c**, 0.14; **2d**, 0.18. These data indicate that acids **1a**–**1d** are less polar than their dimethyl esters. Contrasting polarity between acids and their esters is not generally seen but is consistent with intramolecular hydrogen bonding that tethers the CO_2H and lactam groups and makes **1a**–**1d** much less polar than **2a**–**2d**. The HPLC retention times on a reverse phase column (**1a**: 27.37; **1b**: 8.44; **1c**: 6.47; **1d**: 6.31 min) vs. mesobilirubin-XIIIα (18.3 min) are consistent with the behavior on silica gel TLC except for **1a**, whose unusually long retention time is not understood and might be due to unusual ion pairing effects in the di-*n*-octylamine acetate–CH_3OH reverse phase eluent. (The parent [$n=1$]-mesobilirubin-XIIIα exhibited a retention time of ~60 min, vs. ~18 for the [$n=2$] analog.[12]) As with bilirubin and mesobilirubin-XIIIα, the *gem*-dimethyl mesobilirubin analogs are not extracted into 5% (or saturated) aqueous sodium bicarbonate from chloroform—a further indication that the change of C(10) CH_2 to $C(CH_3)_2$ does not have a large effect on the chloroform/bicarbonate partition coefficient. Taken collectively, the data are consistent with *gem*-dimethyl mesobilirubins **1a**–**1d** being intramolecularly hydrogen bonded.

2.4. Analysis of hydrogen bonding and conformation by ^1H NMR

Hydrogen bonding strongly perturbs dipyrrinone lactam and pyrrole N–H chemical shifts (~7.5 and 8 ppm, respectively, in monomers[22]) causing large deshieldings (~11 and 10 ppm, respectively) in intermolecularly hydrogen-bonded dipyrrinones in $CDCl_3$.[22,23] In bilirubins, dipyrrinone NH chemical shifts have been used to detect and distinguish dipyrrinone-to-carboxylic acid intramolecular hydrogen bonding[24] from dipyrrinone-to-dipyrrinone intermolecular hydrogen bonding. Thus, ^1H NMR studies have shown that in $CDCl_3$ solvent the carboxylic acid COOH signal appears near 13.5 δ and the lactam and pyrrole NH signals near 10.6 and 9.2 δ, respectively, in the former; whereas, in the latter,

Table 2. Comparison of ^{13}C NMR chemical shift[a] assignments of *gem*-dimethyl bilirubin dimethyl ester analogs **2a** ($n=1$), **2b** ($n=2$), **2c** ($n=3$), and **2d** ($n=5$) in $(CD_3)_2SO$ and (in italics) the corresponding [*n*]-mesobilirubin-XIIIα dimethyl esters (see Fig. 2)[b]



Position	2a	2b	2c	2d
1,19-CO	172.1 (*173.1*)	172.8 (*172.4*)	172.8 (*172.4*)	172.8 (*173.2*)
2,18	124.0 (*124.2*)	123.4 (*123.0*)	123.7 (*123.2*)	123.5 (*122.7*)
2,18-CH_3	9.8 (*9.4*)	9.6 (*9.5*)	9.7 (*9.6*)	9.8 (*9.3*)
3,17	147.8 (*147.6*)	147.7 (*147.6*)	147.7 (*147.7*)	147.7 (*147.2*)
3,17-CH_2CH_3	17.6 (*17.9*)	17.6 (*17.6*)	17.6 (*17.6*)	17.6 (*17.5*)
3,17-CH_2CH_3	15.1 (*14.8*)	15.1 (*15.3*)	15.1 (*15.3*)	15.4 (*14.6*)
4,16	129.5 (*129.4*)	129.3 (*128.2*)	128.8 (*128.1*)	128.5 (*127.6*)
5,15-CH═	98.2 (*97.7*)	98.4 (*98.0*)	98.4 (*98.1*)	98.4 (*99.1*)
6,14	124.4 (*124.2*)	123.9 (*123.4*)	123.8 (*123.3*)	123.9 (*123.2*)
7,13	122.2 (*122.0*)	122.2 (*122.3*)	122.0 (*122.3*)	121.9 (*122.6*)
7,13-CH_3	8.5 (*8.2*)	8.5 (*8.5*)	8.5 (*8.5*)	8.5 (*7.8*)
8,12	113.4 (*112.7*)	118.6 (*119.4*)	120.1 (*120.5*)	120.7 (*120.9*)
8^1-CH_2	29.8 (*30.0*)	20.1 (*19.6*)	24.2 (*24.1*)	24.8 (*24.1*)
8^2-CH_2	—	34.2 (*34.2*)	25.8 (*25.9*)	24.9 (24.6)
8^3-CH_2	—	—	33.9 (*33.4*)	29.6 (29.0)
8^4-CH_2	—	—	—	30.2 (30.6)
8^5-CH_2	—	—	—	33.7 (33.6)
8,12-$COCH_3$	51.6 (*54.0*)	51.4 (*51.4*)	51.4 (*51.5*)	51.4 (*51.0*)
8,12-COOH	172.8 (*175.5*)	173.1 (*173.2*)	173.2 (*173.6*)	173.6 (*173.6*)
9,11	139.7 (*131.8*)	138.9 (*130.8*)	139.1 (*130.8*)	139.0 (*130.6*)
10	36.9 (*22.7*)	36.9 (*24.0*)	37.0 (*23.5*)	37.2 (*23.4*)
10^1-CH_3	29.1	29.4	29.4	29.6

[a] In δ, ppm downfield from $(CH_3)_4Si$.
[b] Data from Ref. 13b.

when the carboxylic acids are esterified, the pyrrole NH becomes more deshielded.[25] In contrast, in $(CD_3)_2SO$, where the dipyrrinone NHs become hydrogen bonded to the solvent, and the pyrrole NH resonances are typically deshielded to ~10.2 δ, while COOH fall near 12 ppm and the lactam NH resonances lie near 9.58, both more shielded than in $CDCl_3$.

In Table 3, the ~8–9 ppm pyrrole NH chemical shift of rubins **1a**–**1d** in $CDCl_3$ is consistent with carboxylic acid to dipyrrinone intramolecular hydrogen bonding. The deshielding of COOH to 13.40 ppm provides added support to this conclusion. For rubins **1c** and **1d**, the pyrrole NH resonances of **1c** and **1d** are unusually shielded (compared to **1a** and **1b** and mesobilirubin-XIIIα) which suggests a somewhat weaker hydrogen bond between the pyrrole NH and the COOH carbonyl—a poorer match between dipyrrinone and CO_2H due to the longer alkanoic acid. For rubin **1b**, the lactam NH is somewhat more deshielded than **1a**, **1c** or **1d** (or mesobilirubin-XIIIα), consistent with a stronger hydrogen bond between the lactam NH and the COOH carbonyl. In contrast, the significantly more shielded lactam NH chemical shift in **1a** vs. that of **1b**–**1d** suggests a weaker hydrogen bond between the pyrrole NH and the COOH carbonyl, due to a longer or looser hydrogen bond—a distinction probably related to the inability of the short acetic acid chain to position its carbonyl effectively for hydrogen bonding. Yet the hydrogen-bonded COOH H NMR chemical shifts all lie between 13.2 and 13.9 ppm. (A non-hydrogen-bonded lactam N–H would be even more

Table 3. Comparison of the lactam and pyrrole NH carboxylic acid and carboxylic acid ^1H NMR chemical shifts[a] of **1a**, **1b**, **1c**, **1d** and (italicized entries)[b] [*n*]-mesobilirubins-XIIIα (see Fig. 2) in $CDCl_3$ and $(CD_3)_2SO$ solvents

Pigments	$CDCl_3$			$(CD_3)_2SO$		
	Lactam	pyrrole	COOH	Lactam	pyrrole	COOH
1a	9.28	9.01	13.21	9.56	10.14	11.85
				9.69	*10.22*	*11.89*
1b	11.08	8.93	13.92	9.50	10.09	11.88
	10.57	*9.15*	*13.62*	*9.74*	*10.28*	*11.87*
1c	10.26	8.40	13.41	9.42	10.15	11.86
				9.79	*10.28*	*11.50*
1d	10.49	8.35	13.43	9.40	10.18	11.89
				9.83	*10.33*	*11.83*

[a] δ, ppm downfield from $(CH_3)_4Si$.
[b] Data from Ref. 21.

Table 4. Comparison of the *gem*-dimethyl mesobilirubin dimethyl esters **2a**, **2b**, **2c**, **2d** and (in italics) the [*n*]-mesobilirubin-XIIIα dimethyl esters[a] (see Fig. 2) lactam and pyrrole NH chemical shifts in $CDCl_3$ and $(CD_3)_2SO$ solvents[b]

Pigments	$CDCl_3$		$(CD_3)_2SO$	
	Lactam	Pyrrole	Lactam	Pyrrole
2a	9.73	8.75	9.54	10.14
			8.84	*10.18*
2b	9.80	8.79	9.49	10.06
	10.50	*10.27*	*9.71*	*10.37*
2c	8.98	8.49	9.39	10.18
			9.79	*10.32*
2d	9.50	8.60	9.41	10.13
			9.80	*10.38*

[a] In δ, ppm downfield from $(CH_3)_4Si$.
[b] Data from Ref. 13b.

shielded, to ~7.5 ppm.[22]) In **1b** in $CDCl_3$, intramolecular hydrogen bonding is supported by the observation of an NOE effect between the COOH and lactam NH. Dimerization is excluded because the lactam and pyrrole chemical shifts typically lie at ~10.5–10.2 ppm,[22,28] which is not observed.

The ^{1}H NMR data of dimethyl esters **2a**–**2d** (Table 4) are normal for rubin esters in $(CD_3)_2SO$ solvent and match up well with the corresponding data from the parent [*n*]-mesobilirubin dimethyl esters. In contrast, in $CDCl_3$, intermolecular hydrogen bonded dimeric structures tend to prevail among bilirubin esters and bilirubin analogs without propionic or other alkanoic acids at C(8)/C(12).[25] In such dimers, the lactam and pyrrole NH chemical shifts typically lie near δ 10.5 and 10.2 ppm, respectively. While this is observed for mesobilirubin-XIIIα dimethyl ester, its *gem*-dimethyl analog (**2b**) shows more shielded NH signals, suggesting that the *gem*-dimethyl group interferes with self-association (dimer formation). Esters **2a**, **2c** and **2d** show a similar behavior.

2.5. Molecular conformation from molecular dynamics calculations

Substantial evidence from investigations of bilirubin stereochemistry has been marshaled to show that (i) the most stable conformation is shaped like a ridge-tile (Fig. 2), with the planes of the two dipyrrinones interesecting at an angle of ~100° and (ii) considerable conformational stabilization is achieved by intramolecular hydrogen bonding.[4] The computed (Sybyl)[26] global energy minimum conformations of **1a**–**1d** (Fig. 3) have extensive intramolecular hydrogen bonding and are shaped like ridge-tiles that differ considerably in pitch, determined by torsion angles about C(10) and C(5)/C(15) and dictated by the length of the acid chain. Thus, the following interplanar angles are found: $\theta_1 \sim 75°/\theta_2 \sim 73°$ in **1a**, $\theta_1 \sim \theta_2 \sim 91°$ in **1b**, $\theta_1 \sim 87°/\theta_2 \sim 89°$ in **1c**, and $\theta_1 \sim 43°/\theta_2 \sim 29°$ in **1d**; where in **1a**: $\phi_1 \sim \phi_2 \sim 80°$, $\psi_1 \sim \psi_2 \sim -31°$, and $\psi_3 \sim \psi_4 \sim 4°$; in **1b**: $\phi_1 \sim \phi_2 \sim 60°$, $\psi_1 \sim \psi_2 \sim -9°$ and $\psi_3 \sim \psi_4 \sim 0.4°$; in **1c**, $\phi_1 \sim \phi_2 \sim 61°$, $\psi_1 \sim \psi_2 \sim 27°$ and $\psi_3 \sim \psi_4 \sim 1°$; in **1d**, $\phi_1 \sim \phi_2 \sim 29°$, $\psi_1 \sim \psi_2 \sim -15°$ and $\psi_3 \sim \psi_4 \sim 4°$. While it may be noted that the representations of **1a**–**1d** all belong to the same molecular chirality, the helicity represented is opposite to that shown for bilirubin in Figure 1. In fact **1a**–**1d** as well as bilirubin all have isoenergetic nonsuperimposable mirror images.

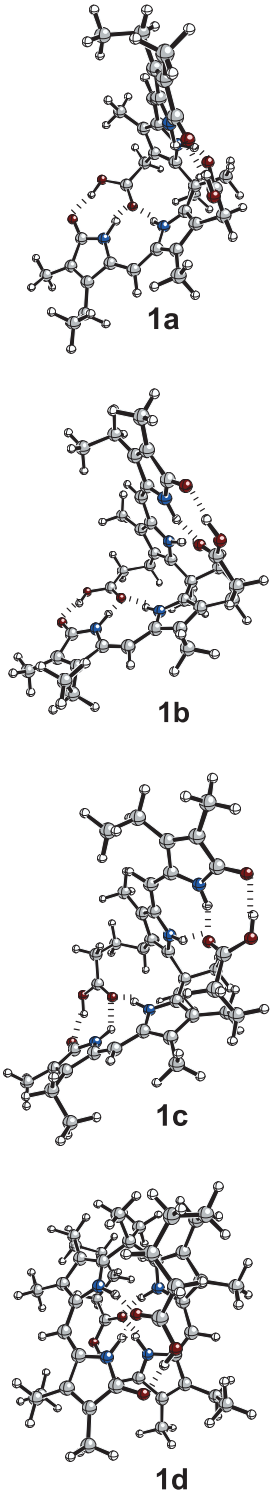


Figure 3. Global energy-minimum conformations of 10,10-dimethyl-[*n*]-mesobilirubins **1a**–**1d** showing intramolecular hydrogen bonds and the influence of alkanoic acid chain length on conformation.

2.6. Molecular geometry from X-ray crystallography

Few crystal structures of bilirubin have been reported[3,5] and none with 10,10-dimethyl groups. X-ray analysis of crystals

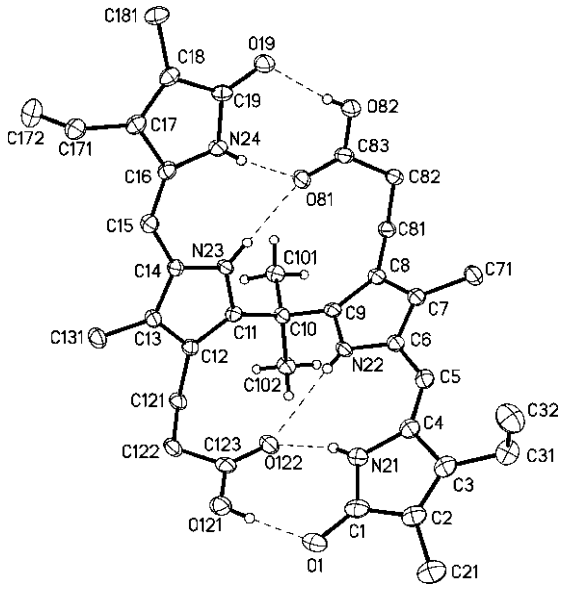


Figure 4. Perspective drawing of the *P*-helical enantiomer of **1b** with ring and atom labeling. Hydrogen bonds are denoted by dotted lines.

of **1b** clearly reveal a ridge-tile structure. Crystals of **1b** were grown from $CHCl_3$ by diffusion of hexane. Molecules of **1b** pack in a triclinic lattice with the propionic acid groups lying in close proximity for intramolecular hydrogen bonding to the opposing dipyrrinones. This conformation (Fig. 4) is also predicted by molecular mechanics calculations (see above) using Sybyl.[26] The dipyrrinone units in **1b** display essentially planar *syn-Z* conformations (Table 5) rotated into a half-opened book or ridge-tile shape. The pigment is thus quite similar in overall shape to that of bilirubin, which has planar dipyrrinones held at an interplanar angle of 98°. Mirror image (*M* and *P*-helical) intramolecularly hydrogen-bonded molecules of **1b** are stacked with their dipyrrinone systems parallel to one another, a stacking pattern very similar to that found in bilirubin.[27]

2.7. UV–visible spectral analysis

Additional evidence on the conformation of **1a–1d** comes from solvent-dependent UV–visible spectra. Over a wide range of solvents with varying polarity and hydrogen bonding ability (benzene, chloroform, acetone, methanol, acetonitrile and dimethylsulfoxide), the UV–visible spectra of **1a–1d** and **2a–2d** are rather similar—much more so than the parent [*n*]-mesobilirubins and their dimethyl esters. All showed exciton-type spectra, typically with a dominant band near 430 nm and a less intense band near 395 nm. In most examples, the latter appeared as a shoulder on the short wavelength side of the former, but in some of the parent esters, especially in $CHCl_3$, the shorter wavelength band was dominant. The long wavelength band and short wavelength band correspond to the two exciton components from electronic transition dipole-dipole interaction of the two dipyrrinone chromophores.[4] The uniformity of the position (nm) of the wavelength absorption of all of the rubins in $(CH_3)_2SO$ (Table 6) suggests a similar conformation and probably one where any intramolecular hydrogen bonding incorporates solvent. In contrast, although the long wavelength absorption λ_{max} of **2a–2d** in $CHCl_3$ do not differ much from those in $(CH_3)_2SO$, large differences in λ_{max} are found for **1b–1d**, with λ_{max} in $CHCl_3$ generally red-shifted by 10–20 nm. The data in $CHCl_3$ are consistent with the intramolecularly hydrogen-bonded structures predicted by molecular mechanics calculations of part 2.5 (Fig. 4). Taken collectively, the data for **1** are consistent with conformation in non-polar solvents that is stabilized by intramolecular hydrogen bonds.

2.8. Induced circular dichroism and conformation

In the presence of chiral complexation agents, such as human serum albumin (HSA) and quinine, bilirubin and mesobilirubin-XIIIα give well-defined, strong bisignate dichroism (CD) spectra for the long wavelength UV–visible transition near 430–450 nm.[27,28] The CD spectra have been

Table 5. Comparison of selected torsion (ϕ, ψ) and interplanar angles (θ) and hydrogen bond distances (*d*) and angles ($\angle$) in the structure of **1b** from X-ray crystallography and molecular dynamics calculations, as compared with those from the bilirubin crystallographic structure[a]

Angle (°) Distance (Å)	**1b** X-ray	**1b** Molec. dynamics	Bilirubin X-ray
ψ_3=N(21)–C(4)–C(5)–C(6)	−0.4	−6.5	17.5
ψ_1=C(4)–C(5)–C(6)–N(22)	1.0	−7	−2.7
ϕ_1=N(22)–C(9)–C(10)–C(11)	61.9	60	60
ϕ_2=C(9)–C(10)–C(11)–N(23)	63	60	64
ψ_2=N(23)–C(14)–C(15)–C(16)	−1.0	−10	10.7
ψ_4=C(14)–C(15)–C(16)–N(24)	−0.5	−0.4	5.8
θ_1 (dipyrrinones)	98.7	91.8	95.4
θ_2 (pyrroles)	101.2	91.3	99.3
d: L N(21)–H···O=C(OH)	1.95	1.77	1.80
d: P N(22)–H···O=C(OH)	2.36	1.50	1.80
d: P N(23)–H···O=C(OH)	2.13	1.73	1.80
d: L N(24)–H···O=C(OH)	1.98	1.52	1.80
d: C(1)=O···HO–C(=O)	1.83	1.52	1.50
d: C(19)=O···HO–C(=O)	1.95	1.52	1.50
$\angle$ N(21)–H···O=C(OH)	166	168	160
$\angle$ N(22)–H···O=C(OH)	176	159	157
$\angle$ N(23)–H···O=C(OH)	179	162	157
$\angle$ N(24)–H···O=C(OH)	172	172	162
$\angle$ C(1)=O···H–OC(12^3)=O	170	173	180
$\angle$ C(19)=O···H–OC(8^3)=O	170	171	180

[a] From the crystal coordinates of bilirubin from Ref. 3.

Table 6. Solvent-dependence of the UV–visible spectral data[a] of *gem*-dimethyl mesobilirubins **1a**, **1b**, **1c**, **1d** and their dimethyl esters **2a**, **2b**, **2c**, **2d**, as compared with data[b] (italicized) from the parent [*n*]-mesobilirubins-XIIIα

Compound	$\Delta\varepsilon^{max}$ (λ^{max}, nm)					
	Benzene	$CHCl_3$	$(CH_3)_2CO$	CH_3OH	CH_3CN	$(CH_3)_2SO$
1a	58,200 (421)	57,800 (423)	62,200 (417)	56,600 (421)	54,000 (409)	66,600 (422)
	54,300 (400)[c]	54,100 (399)[c]	57,200 (403)[c]			54,600 (397)[c]
		57,000 (423)[d]		*50,200 (422)*		*49,400 (424)*
				45,600 (390)		
1b	56,000 (435)	57,900 (435)	55,200 (423)	62,500 (429)	55,500 (421)	63,200 (425)
	52,900 (414)[c]					
		57,800 (431)[e]		*50,700 (426)*		*57,000 (426)*
				43,100 (401)		
1c	61,200 (447)	70,900 (445)	63,800 (437)	63,900 (435)	65,100 (439)	65,300 (428)
						46,600 (394)[c]
		59,700 (438)[e]		52,000 (428)		*58,200 (427)*
				54,500 (398)		*53,000 (398)*
1d	59,800 (431)	65,000 (443)	57,900 (425)	62,900 (435)	58,500 (426)	63,900 (428)
	43,900 (397)[c]		41,800 (392)[c]	43,100 (397)[c]		46,500 (393)[c]
		57,100 (439)		*54,000 (428)*		*67,000 (432)*
		39,600 (398)		*50,000 (400)*		*53,700 (399)*
2a	61,300 (417)	61,000 (415)	63,300 (412)	62,200 (418)	58,900 (408)	66,200 (420)
	56,200 (392)[c]	58,300 (396)[c]	57,300 (392)[c]			
		60,600 (413)		60,300 (414)		*57,800 (419)*
		56,900 (399)				*50,600 (395)*
2b	63,600 (424)	59,100 (419)	61,700 (418)	61,600 (428)	65,800 (416)	64,900 (425)
	52,300 (303)[c]					
		59,300 (382)		*61,100 (428)*		*58,800 (427)*
				51,800 (399)		*52,600 (398)*
2c	64,800 (427)	63,500 (423)	67,400 (421)	69,600 (433)	64,700 (419)	69,600 (427)
	50,700 (394)[c]	49,200 (390)[a]				
		59,000 (382)		*58,900 (428)*		*62,400 (427)*
				52,100 (397)		*51,600 (399)*
2d	64,300 (428)	61,200 (423)	65,800 (423)	67,700 (435)	60,500 (420)	67,700 (429)
	52,800 (394)[c]		50,600 (390)[c]		49,200 (391)[c]	50,300 (397)[a]
		68,700 (3789)		*62,500 (433)*		*64,100 (433)*
				48,800 (398)		*44,000 (399)*

[a] At 22 °C in concentrations $\sim 1.4\times10^{-5}$ M, λ^{max} in nm, ε^{max} in L mol^{-1} cm^{-1}.
[b] Data from Ref. 13b.
[c] Shoulders (or) inflections were determined by first and second derivative spectra.
[d] In $CHCl_3$–15% CH_3OH.
[e] In $CHCl_3$–2% CH_3OH.

interpreted in terms of exciton coupling[27] between the two dipyrrinone chromophores, and the exciton chirality rule[29] has been used to assign the absolute stereochemistry of the predominant ridge-tile enantiomer (*M* or *P*).

As may be seen in Table 3, bilirubin **1b**–**1d** in $CHCl_3$ solutions containing a 300:1 molar ratio of quinine:pigment exhibit weak positive Cotton effects near 390 nm and broad negative Cotton effects near 440 nm, with ($\Delta\varepsilon$(values 11–36. On the contrary, and for reasons unclear, bilirubin **1a** in $CHCl_3$ exhibits a more intense exciton chirality CD, with long wavelength positive Cotton effect near 440 nm ($\Delta\varepsilon+$ 109) and a short wavelength negative Cotton effect near 390 ($\Delta\varepsilon-80$).

The CD of **1a** and **1d** in pH 7.4 aqueous buffered human serum albumin (HSA) is identical in sign, both exhibit negative chirality bisignate CD curve with moderately intense Cotton effects. They exhibit broad positive Cotton effects near 430 nm (**1a**, $\Delta\varepsilon\sim+27$; **1d**, $\Delta\varepsilon\sim+24$), while broader negative Cotton effects near 380 nm (**1a**, $\Delta\varepsilon-13.0$) and near 456 nm (**1b**, $\Delta\varepsilon-26.2$). On the other hand, the CD of **1b** and **1c** in pH 7.4 aqueous buffered human serum albumin (HSA) is also identical in sign; both exhibit positive chirality bisignate CD curves with moderately intense Cotton effects. They exhibit broad positive Cotton effect near 390 nm (**1b**, $\Delta\varepsilon\sim+27$; **1d**, $\Delta\varepsilon\sim+23$), while broader negative Cotton effects near 430 nm (**1b**, $\Delta\varepsilon-15.3$) and near 456 nm (**1c**, $\Delta\varepsilon-16.6$) (Table 7).

3. Concluding comments

Synthetic *gem*-dimethyl rubins **1a**–**1d** are found to adopt preferentially a conformation shaped like a ridge-tile or half-opened book where the varying length acids are engaged in intramolecular hydrogen bonding to the pigment's dipyrrinone components. As in natural bilirubin, the yellow pigment of jaundice, such intramolecular hydrogen bonding stabilizes the ridge-tile conformation, but **1a**–**1d** all have considerably greater solubility in both nonpolar and polar organic solvents. This is due apparently to the presence of the *gem*-dimethyls because the corresponding mesobilirubins without the *gem*-dimethyls are more polar, especially **1a** and (counter-intuitively) **1d**. The length of the acid chain dictates the molecular shape, ranging from the higher-pitched ridge-tile of **1a** (acetic acid) to a helical shape in **1d**. The X-ray crystal structure of **1b** indicates a similar ridge-tile shape to that found in crystals of bilirubin, but with weaker (longer) hydrogen bonds, forced apparently by the *gem*-dimethyl group. This

Table 7. Comparison of circular dichroism (CD) and UV–visible spectroscopic data for **1a**, **1b**, **1c** and **1d** in $CHCl_3$ solutions containing quinine (I, II, II, IV pigment conc. $\sim 1.4\times10^{-5}$ M; quinine conc. $\sim 4.2\times10^{-3}$ M; pigment:quinine molar ratio $=\sim$1:300) and in HSA pH 7.4 tris buffer (V, VI, VII, VIII pigment conc. $\sim 1.4\times10^{-5}$ M, HSA conc. 2.8×10^{-5} M)

Pigment	Solution	CD			UV	
		$\Delta\varepsilon^{max}$ $(\lambda)_1$	λ_2 at $\Delta\varepsilon=0$	$\Delta\varepsilon^{max}$ $(\lambda)_3$	ε^{max}	λ (nm)
1a	$CHCl_3$	−80.8 (389)	410	+109.5 (438)	56,700	438
1b	$CHCl_3$	+15.0 (390)	410	−21.7 (442)	56,600	439
1c	$CHCl_3$	+7.5 (399)	416	−3.4 (440)	59,000	444
1d	$CHCl_3$	+13.9 (396)	406	−19.6 (435)	44,800	431
1a	HAS	−13.0 (381)	399	+27.0 (429)	50,000	432
1b	HSA	+27.3 (399)	407	−15.3 (431)	47,500	439
1c	HSA	+22.9 (392)	411	−16.1 (439)	51,700	441
1d	HSA	−26.2 (387)	405	+24 (431)	48,700	439

apparently accounts for the increased amphiphilicity of **1b** (and its homologs).

These new bilirubin analogs (**1a**–**1d**) might prove useful in studies of the mechanism of bilirubin acting as an antioxidant in vivo. It has been shown that bilirubin's potent antioxidant properties are enhanced by redox recycling during which peroxyl radicals are destroyed while bilirubin is converted to biliverdin (and biliverdin reductase reduces the verdin back to the rubin).[30] With the inability of **1a**–**1d** to form verdins, such recycling is not possible.

4. Experimental

4.1. General procedures

Nuclear magnetic resonance (NMR) spectra were obtained on a GE QE-300 300 MHz spectrometer in $(CD_3)_2SO$ solvent (unless otherwise specified), or on a Varian Unity Plus 500 MHz spectrometer. HMQC, HMBC and NOE NMR were obtained at 500 MHz. Chemical shifts are reported in δ ppm referenced to the residual $CHCl_3$ ^1H signal at 7.26 ppm and ^{13}C at 77.23 ppm. All ultraviolet–visible spectra were recorded on a Perkin–Elmer $\lambda-12$ spectrophotometer, and circular dichroism (CD) spectra were recorded on a JASCO J-600 instrument. Infrared spectra were recorded on a Perkin–Elmer model 1610-FT IR instrument. GC-MS analyses were carried out on a Hewlett-Packard GC-MS Model 5890A ion selective detector equipped with a DB-1 (100% dimethylpolysiloxane) column. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ. High-resolution mass spectra were obtained from the Nebraska Center for Mass Spectrometry (Univ. Nebraska). Analytical thin layer chromatography (TLC) was carried out on J.T. Baker silica gel IB-F plates (125 μm layers). Radial chromatography was carried out on Merck preparative layer grade silica gel PF_{254} with $CaSO_4$ binder using a Chromatotron (Harrison Research, Inc., Palo Alto, CA) with 1, 2 or 4 mm thick rotors. Flash column chromatography was carried out using silica gel, 60–200 mesh (M. Woelm). HPLC analyses were carried out on a Perkin–Elmer Series 4 high performance liquid chromatograph with a LC-95 UV/vis spectrophotometric detector (410 nm). The column was a Beckman-Altex ultrasphere-IP 5 μm C-18 ODS column (25×0.46 cm) fitted with a similarly-packed precolumn (4.5×0.46 cm). The flow rate was 0.75–1.0 cm^3/min; elution solvent was 0.1 M di-*n*-octylamine acetate in 5% aqueous CH_3OH, the column temperature was ~34 °C. Ceric ammonium nitrate (CAN) was from Alfa Aesar. Commercial reagents were used as received from Aldrich or Acros. HPLC grade CH_3OH was from Fisher, human serum albumin (defatted) was obtained from Sigma. Spectroscopic data were obtained in spectral grade solvents from Fisher and Acros. Deuterated chloroform and dimethylsulfoxide were from Cambridge Isotope Laboratories. 2-Carboethoxy-3,5-dimethyl-1*H*-pyrrole-3-acetic acid ethyl ester (**13**),[13b] 2-carboxy-5-carboethoxy-4-methyl-1*H*-pyrrole-3-acetic acid ethyl ester (**12**),[31] 2-formyl-3-methyl-1*H*-pyrrole-4-butanoic acid ethyl ester (**8c**)[16] and (4*Z*)-8-(2-carboxyethyl-2,7-dimethyl-3-ethyl-1,10-dihydro-11*H*-dipyrrin-1-one (**3b**)[17] were prepared as described in the literature.

4.1.1. 2,5-Dicarboxy-4-methyl-1*H*-pyrrole-3-acetic acid ethyl ester (10). 2-Carboxy-5-carboethoxy-4-methyl-1*H*-pyrrole-3-acetic acid ethyl ester **12**[31] (3.9 g, 13.75 mmol) was suspended in 20% sodium hydroxide solution (40 mL), and the mixture was heated at reflux under N_2 for 4 h. The clear solution was cooled to 0 °C and acidified carefully using HCl to pH ~3, the mixture was stirred for an addition 1 h at 0 °C until all solid had precipitated. The solid was filtered and washed with cold water to afford pyrrole triacid **11**, which was used directly in the next step.

To the solution of pyrrole triacid **11** in absolute ethanol (30 mL) was added trifluoracetic acid (3 mL), with stirring, during 10 min at 0 °C. The mixture was stirred for another 12 h; then triethyl orthoformate (1.8 mL) was added. The reaction was stirred for 48 h at room temperature, and the solvent was evaporated to afford the product as a red solid. An analytical sample could be prepared by chromatography through a short silica gel column by using CH_2Cl_2–CH_3OH (50:1 by vol) as eluent, followed by recrystallization from acetone and hexane to afford mono-ester **10** (3.0 g, 85%). It had mp 248–250 °C; IR (KBr, film) ν: 3413, 2595, 1664, 1470, 1415, 1275, 1204, 1028 cm^{-1}; ^1H NMR δ: 1.12 (3H, t, $J=7.05$ Hz), 2.11 (3H, s), 3.724 (3H, s), 3.99 (2H, q, $J=7.05$ Hz), 11.38 (1H, brs), 12.72 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 10.29, 14.54, 30.23, 60.14, 122.6, 123.1, 123.3, 126.6, 162.0, 162.3, 171.1 ppm. Anal. calcd for $C_{11}H_{13}NO_3$ (255.0): C, 51.77; H, 5.13; N, 5.49. Found: C, 51.44; H, 4.83; N, 5.85.

4.1.2. (4*Z*)-8-Carboxymethyl-2,7-dimethyl-3-ethyl-1,10-dihydro-11*H*-dipyrrin-1-one (3a). (a) Decarboxylative-distillation of pyrrole monoester diacid **10** (1.20 g, 4.7 mmol) was carried out in a Kugelrohr apparatus. The pyrrole product distilled as an oil at 160 °C under a vacuum of 15 mm Hg (water pump) during 40 min and was pure enough for the next step. The yield was 630 mg, 3.77 mmol (80%); IR (NaCl, film) ν: 3486, 2982, 2254, 2727, 1571, 1370, 1181, 908, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.26 (3H, t, $J=7.2$ Hz), 2.05 (3H, s), 3.45 (3H, s), 4.16 (2H, q, $J=7.2$ Hz), 6.53 (1H, d), 6.68 (1H, s), 7.88 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 300 Hz) δ: 9.89, 14.17, 31.39, 60.40, 115.2, 115.8, 116.7, 118.0, 172.3 ppm; GC-MS (*m*/*z*): 167, 138, 110, 94 (100%), 75, 65 amu.

(b) Next, 2-formyl-3-methyl-1*H*-pyrrole-4-acetic acid ethyl ester (**8a**) was prepared by a Vilsmeier reaction on pyrrole ester **9**, then **8a** was converted to **3a**. To a solution of ethyl ester **9** (600 mg, 3.6 mmol) in dry absolute diethyl ether (13 mL) containing N,N-dimethylformamide (0.33 g) was added dropwise phosphorous oxychloride (0.65 g) over 30 min at 0 °C. The mixture was stirred at room temperature overnight under N_2, and then the solvent was evaporated. The residue was dissolved in dichloroethane (10 mL) and to it was added aqueous sodium acetate (7.5 g in 35 mL H_2O). Then the mixture was heated at reflux for 30 min, after which it was poured into water (100 mL), and extracted with dichloromethane (3×50 mL). A brown solid was obtained after the solvent was evaporated. The solid, as shown by ^1H NMR, contained both the 2-formyl isomer (**8a**) and the 5-formyl regio-isomer in an $\sim$4:1 ratio. The predominant, 2-formyl isomer (**8a**) could be partly separated from the mixture using radial chromatography. The combined yield of the aldehydes was 81%, and **8a** was carried directly to the next step. Mono-pyrrole aldehyde **8a** had mp 82–83 °C; IR (NaCl, film) ν: 3453, 2986, 2254, 1730, 1642, 1425, 1096, 908, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.26 (3H, t, $J=7.2$ Hz), 2.30 (3H, s), 3.44 (3H, s), 4.17 (2H, q, $J=7.2$ Hz), 7.03 (1H, d), 9.48 (1H, brs), 9.61 (1H, brs) ppm; ^{13}C NMR ($CDCl_3$, 300 Hz) δ: 8.49, 14.1, 30.7, 60.8, 118.0, 125.0, 129.7, 130.6, 171.3, 177.5 ppm; GC-MS (*m*/*z*): 195, 166, 148, 122 (100%), 93, 77, 65 amu.

(c) To a solution of pyrrole aldehyde **8a** (1.28 mmol) and pyrrolinone **5** (1.28 mmol) in methanol (2.5 mL) was added 4 M NaOH solution (10 mL), and the mixture was heated at reflux under N_2 for 4 h. The reaction mixture was acidified carefully by using HOAc at 0 °C to pH $\sim$3, and the resulting precipitate was collected by filtration and washed with cold water to afford the yellow dipyrrinones **3a**. An analytical sample could be prepared by chromatography on a silica gel column, eluting with a mixture of CH_2Cl_2 and CH_3OH (30:1 by vol). The desired product, **3a**, was obtained in 79% yield. It had mp 210–1 °C; IR (KBr, film) ν: 3622, 3367, 3055, 2945, 1717, 1449, 1423, 1266, 896, 739 cm^{-1}; ^1H NMR, δ: 1.049 (2H, t, $J=7.5$ Hz), 1.742, (3H, s), 1.980 (3H, s), 2.457 (2H, q, $J=7.5$ Hz), 3.283 (2H, s), 5.92 (1H, s), 6.80 (1H, s), 9.68 (1H, brs), 10.55 (1H, brs), 12.05 (1H, brs) ppm; ^{13}C NMR, δ: 8.48, 9.56, 15.14, 17.60, 31.43,97.94, 117.13, 121.10, 122.14, 124.0, 124.2, 129.4, 147.8, 172.4, 173.2 ppm. Anal. calcd for $C_{15}H_{18}N_2O_3$ (274.3): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.46; H, 6.65; N, 10.35.

4.1.3. (4*Z*)-8-(4-Carboxybutyl)-2,7-dimethyl-3-ethyl-1,10-dihydro-11*H*-dipyrrin-1-one (3c). This dipyrrinone was prepared in 82% yield from aldehyde **8c**[16] as described above for **3a**. It had mp 198–9 °C; IR (KBr, film) ν: 3436, 3364, 2932, 1665, 1401, 1269, 1170, 980, 814, 681 cm^{-1}; ^1H NMR, δ: 1.03 (3H, t, $J=7.8$ Hz), 1.65 (2H, m), 1.74 (3H, s), 1.78 (3H, s), 2.18 (2H, t, $J=7.5$ Hz), 2.30 (2H, t, $J=7.5$ Hz), 2.46 (2H, q, $J=7.8$ Hz), 5.92 (1H, s), 6.70 (1H, s), 9.70 (1H, brs), 10.52 (1H, brs), 12.01 (1H, brs) ppm; ^{13}C NMR, δ: 8.5, 9.50, 15.22, 17.06, 24.59, 25.73, 33.72, 98.11, 120.0, 121.6, 123.2, 123.8, 124.2, 129.0, 147.7, 172.4, 174.8 ppm. Anal. calcd for $C_{17}H_{22}N_2O_3$ (302.4): C, 67.35; H, 7.33; N, 9.26; $C_{17}H_{22}N_2O_3\cdot1/4H_2O$ (306.9): C, 66.53; H, 7.39; N, 9.12. Found: C, 66.74; H, 7.08; N, 9.12.

4.1.4. 8-(6-Carboxyhexyl)-2,7-dimethyl-3-ethyl-1,10-dihydro-11*H*-dipyrrin-1-one-9-carboxylic acid (4d). As described above for **3a**, **6d** was condensed with pyrrolinone **5** to afford 9-CO_2H dipyrrinone **4d** in 92% yield. It had mp 214–6 °C; IR (KBr, film) ν: 3411, 3056, 2988, 2306, 1711, 1421, 1266, 1020, 896, 740 cm^{-1}; ^1H NMR, δ: 1.06 (3H, t, $J=7.5$ Hz), 1.248 (2H, m), 1.38 (2H, m), 1.47 (2H, m), 1.76 (3H, s), 1.989 (3H, s), 2.15 (2H, t, $J=7.2$ Hz), 2.47 (2H, q, $J=7.5$ Hz), 2.62 (2H, t, $J=7.05$), 5.90 (1H, s), 10.40 (1H, s), 10.92 (1H, s), 12.11 (2H, brs) ppm; ^{13}C NMR, δ: 8,52, 9.50, 15.02, 17.56, 24.61, 24.83, 28.95, 30.46, 34.10, 96.58, 121.7, 122.5, 126.0, 127.8, 131.3, 133.3, 147.9, 162.5, 173.1, 174.8 ppm. Anal. calcd for $C_{20}H_{26}N_2O_5$ (374.4): C, 64.15; H, 7.00; N, 7.48. Found: C, 64.35; H, 7.39; N, 7.17.

4.1.5. (4*Z*)-8-(6-Carboxyhexyl)-2,7-dimethyl-3-ethyl-1,10-dihydro-10*H*-dipyrrin-1-one (3d). Dipyrrinone **4d** (0.53 mmol) from the previous step was placed in a 200 mL round-bottom flask and mixed with potassium acetate (1 g) and sodium acetate trihydrate (1 g), which had been ground with a mortar and pestle until intimately mixed. The mixture was heated to $\sim$165 °C, at which time it melted with the evolution of CO_2. The temperature was maintained at $\sim$165 °C for 20 min until the evolution of CO_2 ceased. The mixture was cooled down to room temperature and water (100 mL) was added. The solid was collected by filtration and washed with cold water to afford 9-H dipyrrinone **3d** in 80% yield. It had 206–7 °C; IR (KBr, film) ν: 3468, 3217, 2948, 2530, 1663, 1450, 1115, 1044, 679 cm^{-1}; ^1H NMR, δ: 1.05 (3H, t, $J=7.5$ Hz), 1.25 (2H, m), 1.43 (4H, m), 1.74 (3H, s), 1.99 (3H, s), 2.14 (2H, t, $J=7.2$ Hz), 2.28 (2H, t, $J=7.05$ Hz), 2.43 (2H, q, $J=7.5$ Hz), 5.92 (1H, s), 6.68 (1H, s), 9.69 (1H, s); 10.47 (1H, s), 12.25 (1H, brs) ppm; ^{13}C NMR, δ: 8.48, 9.54, 15.17, 17.06, 25.09, 28.92, 30.07, 39.21, 98.14, 119.9, 121.6, 123.7, 123.9, 124,1, 129.0, 147.7, 172.4 ppm. Anal. calcd for $C_{19}H_{26}N_2O_3$ (330.4): C, 69.06; H, 7.93; N, 8.48; calcd for $C_{19}H_{26}N_2O_3\cdot3/4H_2O$ (343.94): C, 66.35; H, 8.06; N, 8.15. Found: C, 66.52; H, 7.88; N, 8.05.

4.2. General procedure for the synthesis of *gem*-dimethyl bilirubins 1a–1d

To a solution of 9-H dipyrrinone (0.3 mmol) in TFA (2 mL) was added dropwise dimethoxypropane (36.6 μL) over 15 min at 0 °C. The mixture was stirred at 0 °C for 1 h under N_2, and then poured into cold water (100 mL). The yellow precipitate was collected by filtration and washed

with cold water. Purification was achieved by chromatography through a column of silica gel eluting with a mixture of CH_2Cl_2 and CH_3OH (50:1 by vol) as eluent. A 10–20% yield of recovered starting material (**3**) could be recycled.

4.2.1. 10,10-Dimethyl-3,17-diethyl-1,10,19,22,23,24-hexahydro-2,7,13,18-tetramethyl-1,19-dioxo-21*H*-bilin-8,12-diacetic acid (1a). Was prepared from **3a** in 48% yield. It had mp 226–7 °C; IR (NaCl, film) ν: 3622, 3368, 2945, 2307, 1633, 1422, 1266, 896, 738 cm^{-1}; ^1H NMR, δ: 1.06 (6H, t, $J=7.65$ Hz), 1.65 (6H, s), 1.75 (6H, s), 1.87 (6H, s), 2.75 (4H, q, $J=7.65$ Hz), 3.26 (4H, s), 5.94 (2H, s), 9.52 (2H, s), 10.10 (2H, s), 11.79 (2H, s) ppm; ^1H NMR ($CDCl_3$, 500 Hz) δ: 1.12 (6H, t, $J=7.5$ Hz), 1.86 (6H, s), 2.03 (6H, s), 2.11 (6H, s), 2.47 (4H, q, $J=7.5$ Hz), 3.75 (4H, s), 6.02 (2H, s), 9.01 (2H, brs), 9.28 (2H, brs), 13.21 (2H, s) ppm. Anal. calcd for $C_{33}H_{40}N_4O_6$ (588.7): C, 67.33; H, 6.85; N, 9.52; calcd for $C_{33}H_{40}N_4O_6\cdot 2H_2O$ (606.7): C, 63.44; H, 7.10; N, 8.97. Found: C, 63.88; H, 6.68; N, 8.71.

4.2.2. 10,10-Dimethyl-3,17-diethyl-1,10,19,22,23,24-hexahydro-2,7,13,18-tetramethyl-1,19-dioxo-21*H*-bilin-8,12-dipropanoic acid (1b). Was prepared from **3b** in 51% yield. It had mp 236–7 °C; IR (NaCl, film) ν: 3623, 3360, 2947, 1635, 1422, 1211, 896, 738 cm^{-1}; ^1H NMR δ: 1.10 (6H, t, $J=7.75$ Hz), 1.73 (6H, s), 1.78 (6H, s), 1.96 (6H, s) 1.97 (4H, t, $J=8.25$ Hz), 2.20 (4H, t, $J=8.25$ Hz), 2.51 (4H, q, $J=7.75$ Hz), 5.97 (2H, s), 9.50 (2H, s), 10.09 (2H, s), 11.88 (2H, s) ppm; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.12 (6H, t, $J=7.5$ Hz), 1.85 (6H, s), 2.07 (6H, s), 2.14 (6H, s), 2.48 (4H, q, $J=7.5$ Hz), 2.50–3.49 (8H, unresolved m at 300 MHz), 6.04 (2H, s), 8.93 (2H, s), 11.08 (2H, s), 13.98 (2H, s) ppm. Anal. calcd for $C_{35}H_{44}N_4O_6$ (616.7): C, 68.16; H, 7.19; N, 9.08; $C_{35}H_{44}N_4O_6\cdot H_2O$ (634.7): C, 66.22; H, 7.30; N, 8.82. Found: C, 66.26; H, 7.33; N, 8.46.

4.2.3. 10,10-Dimethyl-3,17-diethyl-1,10,19,22,23,24-hexahydro-2,7,13,18-tetramethyl-1,19-dioxo-21*H*-bilin-8,12-dibutanoic acid (1c). Was prepared from **3c** in 52% yield. It had mp 174–5 °C; IR (NaCl, dichloromethane), ν: 3691, 3054, 2686, 1602, 1422, 1265, 896, 738 cm^{-1}; ^1H NMR, δ: 1.06 (6H, t, $J=7.5$ Hz), 1.27 (4H, m), 1.70 (6H, s), 1.75 (6H, s), 1.87 (4H, t, $J=7.2$ Hz), 1.93 (6H, s), 2.03 (4H, t, $J=7.2$ Hz), 2.48 (4H, q, $J=7.5$ Hz), 5.94 (2H, s), 9.42 (2H, s), 10.15 (2H, s), 11.86 (2H, brs) ppm; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.18 (6H, t, $J=7.5$ Hz), 1.80 (4H, m), 1.93 (6H, s), 2.04 (6H, s), 2.06 (6H, s), 2.39 (4H, t, $J=7.2$ Hz), 2.50 (4H, t, $J=7.2$), 2.62 (4H, q, $J=7.5$ Hz), 6.13 (2H, s), 8.42 (2H, s), 10.26 (2H, s), 13.41 (2H, brs) ppm. Anal. calcd for $C_{37}H_{48}N_4O_6$ (644.7): C, 68.92; H, 7.50; N, 8.69. Found: C, 68.93; H, 7.34; N, 8.68.

4.2.4. 10,10-Dimethyl-3,17-diethyl-1,10,19,22,23,24-hexahydro-2,7,13,18-tetramethyl-1,19-dioxo-21*H*-bilin-8,12-dihexanoic acid (1d). Was prepared from **3c** in 51% yield. It had 238–9 °C; IR (NaCl, film) ν: 3754, 3054, 2987, 1731, 1633, 1422, 979, 896, 740, 705 cm^{-1}; ^1H NMR, δ: 1.03 (6H, t, $J=7.5$ Hz), 1.07 (8H, m), 1.30 (4H, m), 1.71 (6H, s), 1.74 (6H, s), 1.93 (6H, s), 1.98 (4H, s, $J=7.0$ Hz), 2.03 (4H, t, $J=7.0$ Hz), 2.46 (4H, q, $J=7.5$ Hz), 5.94 (2H, s), 9.40 (2H, s), 10.18 (2H, s), 11.89 (2H, brs) ppm; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.18 (6H, t, $J=7.5$ Hz), 1.38 (4H, m), 1.45 (4H, m), 1.67 (4H, m), 1.86 (6H, s), 1.19 (4H, t, $J=7.2$ Hz), 1.92 (6H, s), 2.07 (6H, s) 2.37 (4H, t, $J=7.2$ Hz), 2.54 (4H, q, $J=7.5$ Hz), 6.15 (2H, s), 8.35 (2H, brs), 10.49 (2H, brs), 13.43 (2H, brs) ppm. Anal. calcd for $C_{41}H_{56}N_4O_6$ (700.8): C, 70.26; H, 8.05; N, 7.99. Found: C, 69.87; H, 7.83; N, 7.78.

4.3. General procedure for the synthesis of *gem*-dimethyl bilirubin dimethyl esters 2a–2d

To a solution of *gem*-dimethyl bilirubin (**3**) (0.21 mmol) in methanol (50 mL) was added excess ethereal diazomethane. The mixture became homogeneous and was stirred at room temperature for 30 min. After evaporation of the solvent, the residue was purified by radial chromatography on silica gel, eluting with a mixture of CH_2Cl_2 and CH_3OH (100:1 by vol). The isolated, purified esters were recrystallized from CH_2Cl_2-hexane to afford pure **2** as a yellow powder.

4.3.1. 10,10-Dimethyl-3,17-diethyl-1,10,19,22,23,24-hexahydro-2,7,13,18-tetramethyl-1,19-dioxo-21*H*-bilin-8,12-diacetic acid dimethyl ester (2a). Was isolated in 93% yield. It had mp 162–3 °C; IR (NaCl, film), ν: 3687. 3054, 2987, 2305, 1682, 1605, 1422, 1265, 896, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ: 1.12 (6H, t, $J=7.5$), 1.87 (6H, s), 1.88 (6H, s), 2.04 (6H, s), 2.49 (4H, q, $J=7.5$ Hz), 3.78 (4H, s), 4.05 (6H, s), 5.89 (2H, s), 9.73 (2H, s) ppm; ^{13}C NMR ($CDCl_3$, 300 MHz), δ: 8.16, 9.35, 14.58, 17.82, 29.16, 30.74, 39.50, 54.38, 97.09, 110.3, 122.4, 124.2, 124.5, 129.6, 139.4, 147.6, 172.7, 176.8 ppm. Anal. calcd for $C_{35}H_{44}N_4O_6$ (616.7) C, 68.16; H, 7.19; N, 9.08. Found: C, 68.02; H, 6.97; N, 9.22.

4.3.2. 10,10-Dimethyl-3,17-diethyl-1,10,19,22,23,24-hexahydro-2,7,13,18-tetramethyl-1,19-dioxo-21*H*-bilin-8,12-dipropanoic acid dimethyl ester (2b). Was prepared in 93% yield. It had 224–5 °C; IR (NaCl, film) ν: 3696, 3054, 1762, 1603, 1421 978, 894, 705 cm^{-1}; ^1H NMR, δ: 1.03 (6H, t, $J=7.5$ Hz), 1.69 (6H, s), 1.75 (6H, s), 1.91 (6H, s), 1.97 (4H, t, $J=7.2$ Hz), 2.20 (4H, t, $J=7.2$), 2.48 (4H, q, $J=7.5$ Hz), 3.29 (6H, s), 5.92 (2H, s), 9.48 (2H, s), 10.06 (2H, s) ppm; ^{13}C NMR, δ: 8.50, 9.69. 15.15 17.64, 20.19, 29.42, 34.27, 36.97, 51.43, 98.40, 118.6, 122.2, 123.4, 124.0, 129.3, 139.0, 147.7, 172.8, 173.2 ppm. FAB HRMS (3-NBA): calcd for $C_{38}H_{42}N_4O_6$, 650.3104. Found 650.3116 (error −1.8 ppm). Anal. calcd for $C_{37}H_{48}N_4O_6$ (644.7): C, 68.92; H, 7.50; N, 8.69; calcd for $C_{37}H_{48}N_4O_6\cdot 1/2H_2O$ (653.8): C, 67.97; H, 7.55; N, 8.56. Found: C, 68.36; H, 7.56; N, 8.18.

4.3.3. 10,10-Dimethyl-3,17-diethyl-1,10,19,22,23,24-hexahydro-2,7,13,18-tetramethyl-1,19-dioxo-21*H*-bilin-8,12-dibutanoic acid dimethyl ester (2c). Was prepared in 95% yield. It had 180–1 °C; IR (NaCl, film), ν: 3691, 3054, 2987, 1661, 1422, 1265 896, 705 cm^{-1}; ^1H NMR, δ: 1.06 (6H, t, $J=7.2$ Hz), 1.27 (4H, m), 1.69 (6H, s), 1.75 (6H, s), 1.83 (4H, t, $J=7.05$ Hz), 1.92 (6H, s), 2.03 (4H, t, $J=7.05$ Hz), 2.484 (4H, q, $J=7.2$ Hz), 3.46 (6H, s), 9.41 (2H, s), 10.13 (2H, s) ppm; ^{13}C NMR, δ: 8.52, 9.76, 15.19, 17.65, 24.29, 25.87, 29.45, 33.97, 37.01, 51.41, 98.46, 120.1, 122.0, 123.7, 123.8, 128.8, 139.1 147.7, 172.8, 173.5 ppm. Anal. calcd for $C_{39}H_{52}N_4O_6$ (672.7): C, 69.62; H, 7.79; N, 8.33. Found: C, 69.73; H, 7.76; N, 8.37.

4.3.4. 10,10-Dimethyl-3,17-diethyl-1,10,19,22,23,24-hexahydro-2,7,13,18-tetramethyl-1,19-dioxo-21*H*-bilin-8,12-dihexanoic acid dimethyl ester (2d). Was isolated in 90% yield. It had mp 204–5 °C; IR (NaCl, film), ν: 3754, 3054, 2987, 1731, 1633, 1422, 979, 896, 740, 705 cm^{-1}; ^1H NMR, δ: 1.008 (8H, m), 1.05 (6H, t, $J=7.5$ Hz), 1.32 (4H, m), 1.70 (6H, s), 1.74 (6H, s), 1.89 (4H, t, $J=6.9$ Hz), 1.92 (6H, s), 2.09 (4H, t, $J=7.35$ Hz), 2.43 (4H, q, $J=7.5$ Hz), 3.49 (6H, s), 5.93 (2H, s), 9.38 (2H, s), 10.18 (2H, s) ppm; ^{13}C NMR, δ: 8.51, 9.83, 15.18, 17.64, 24.80, 24.95, 29.60, 29.64, 30.27, 33.75, 37.23, 51.47, 98.47, 120.7, 121.9, 123.5, 123.9, 128.4, 139.0, 147.7, 172.8, 173.6 ppm. Anal. calcd for $C_{43}H_{60}N_4O_6$ (728.8): C, 70.85; H, 8.30; N, 7.69. Found: C, 71.13; H, 8.25; N, 7.72.

4.4. UV and CD measurements

A stock solution of **1** ($\sim 7.0\times10^{-4}$ M) was prepared by dissolving an appropriate amount of the desired pigment in 2 mL of DMSO. Next, a 100 μL aliquot of the stock solution was diluted to 5 mL (volumetric flask) with an HSA solution ($\sim 2.8\times10^{-5}$ M in pH 7.4 Tris buffer). The final concentration of the solution was $\sim 1.4\times10^{-5}$ M in pigment. Up to four 5 mL solutions of each pigment were prepared, as needed, in 5 mL volumetric flasks.

4.5. X-ray structure and solution

Crystals of **1b** were grown by slow diffusion of *n*-hexane into a solution of chloroform. Suitable crystals were coated with epoxy cement, mounted on a glass fiber and placed on the diffractometer. The handedness of the molecule shown in Figure 4 is therefore arbitrarily chosen.

Crystal structure data are filed with the Cambridge Crystallographic Data Centre, CCDC No. 227 598.

Acknowledgements

We thank the U.S. National Institutes of Health (HD 17779) for generous support of this work. Special thanks are accorded to Professor V. J. Catalano for his assistance with the X-ray crystallographic measurements and to the National Science Foundation for providing the funds to purchase the Bruker SMART Apex diffractometer used.

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Calcium phosphate-vanadate apatite (CPVAP)-catalyzed aerobic oxidation of propargylic alcohols with molecular oxygen

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Received 21 June 2004; revised 4 August 2004; accepted 4 August 2004

Available online 1 September 2004

Abstract—Calcium phosphate-vanadate apatite (CPVAP) works effectively as a catalyst for the aerobic oxidation of propargylic alcohols to the corresponding carbonyl compounds under an atmospheric pressure of molecular oxygen. Moreover, CPVAP can be readily separated by filtration and reused at least 10 times without appreciable loss of the catalytic activity.

1. Introduction

For the increasing environmental and economical concerns in recent years, it is now essential for chemists to search environmentally benign catalytic reactions as many as possible. The organic reaction using heterogeneous catalyst is one of the suitable methods for realizing green and sustainable chemistry and much attention has been paid to it because of its reusability and the ability to minimize the toxic wastes.[1,2] Recently, metal-immobilized hydroxyapatite has been developed by Kaneda and co-workers, in which the aerobic oxidation of organic compounds was well studied.[3] Especially, ruthenium and palladium-hydroxyapatite (RuHAP or PdHAP) were revealed to be excellent catalysts for the aerobic oxidation of alcohols, amines, and silanes.[3a–d]

We have so far studied the oxidation of alcohols using molecular oxygen as a sole reoxidant, in which both homogeneous and heterogeneous Pd-catalytic systems were disclosed to be quite effective for the oxidation of various kinds of alcohols.[2d,e,4] We also found the effective oxidation system for propargylic alcohols consisting of an oxovanadium complex such as $VO(acac)_2$, molecular sieves 3 Å (MS3A), and molecular oxygen in acetonitrile,[5,6] the oxidation of which was unsuccessful with Pd catalysts. We have now tried to heterogenize this vanadium system for reuse of the catalyst from the viewpoint of green and sustainable chemistry, and eventually we disclosed that calcium phosphate-vanadate apatite (we abbreviate this as CPVAP), prepared by the reported method,[7] could be used as a recyclable catalyst for the aerobic oxidation of propargylic alcohols. The CPVAP has been known to be formed by partial substitution of PO_4^{3-} by VO_4^{3-} in hydroxyapatite as a highly stable, isomorphic compound $Ca_{10}(PO_4)_{6-x}(VO_4)_x(OH)_2$.[7] Herein, we report the CPVAP-catalyzed oxidation of propargylic alcohols under an atmospheric pressure of oxygen.

2. Results and discussion

First, the oxidation of 1-phenyl-2-propyn-1-ol (**1a**) (0.5 mmol) was examined using the catalytic amount of CPVAP (25 mg, 0.073 mmol (15 mol% to **1a**) as vanadium) in acetonitrile (1 mL) at 80 °C under an atmospheric pressure of oxygen similar to the reaction conditions of homogeneous catalytic system that we previously reported.[5] The reaction, however, did not proceed efficiently to give the corresponding ketone **2a** even after a longer reaction time (Table 1, entries 1–3). On the other hand, **2a** was obtained in high yield at higher temperature using benzonitrile as solvent in the presence of the doubled amount of CPVAP (50 mg, 0.15 mmol as vanadium) (entry 4). Other solvents such as toluene, chlorobenzene, and *n*-butyronitrile were also examined (entries 5–7), because benzonitrile was not easy to be removed after the reaction due to its high boiling nature. When *n*-butyronitrile was used as solvent, **2a** was obtained in a similar high yield as in

Keywords: Vanadium; Oxidation; Propargylic alcohols; Molecular oxygen; Hydroxyapatite.
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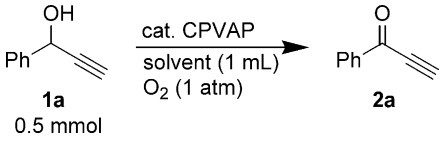
doi:10.1016/j.tet.2004.08.004

Table 1. Optimization of the reaction



Entry	Solvent	Temperature (°C)	Reaction time (h)	CPVAP (mg)	Conversion of **1a** (%)	Yield of **2a** (%)[a]
1	Acetonitrile	80	3	25[b]	16	10
2	Acetonitrile	80	24	25	24	16
3	Acetonitrile	80	72	25	35	34
4	Benzonitrile	100	20	50[c]	99	82
5	Toluene	100	20	50	38	38
6	Chlorobenzene	100	20	50	78	53
7	*n*-Butyronitrile	100	20	50	92	85
8[d]	*n*-Butyronitrile	100	20	50	0	0

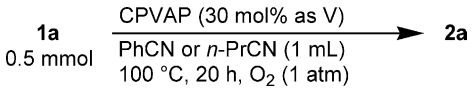
[a] Based on **1a** employed.
[b] 15 mol% as V to **1a**.
[c] 30 mol% as V to **1a**.
[d] Under N_2 (1 atm).

the use of benzonitrile (entry 7). The reaction under nitrogen atmosphere did not proceed at all (entry 8), showing that the presence of oxygen is essential for this reaction.

Next, we examined recycling of the catalyst. At first, the oxidation of **1a** in benzonitrile was carried out in the presence of CPVAP (50 mg, 0.15 mmol as vanadium) at 100 °C for 20 h under oxygen atmosphere. After the reaction, CPVAP was separated by filtration from the reaction mixture, and the collected CPVAP was washed with diethyl ether and dried under vacuum at room temperature before use for the next run. The yield of **2a** was determined by GLC analysis. As a result, CPVAP could be reused at least 10 times keeping in high catalytic activity (Table 2). Similar phenomenone was also observed using *n*-butyronitrile as solvent also shown in Table 2.

The oxidation of some propargylic alcohols was examined in *n*-butyronitrile as solvent. Typical results are listed in Table 3. When the reaction was carried out under an atmospheric pressure of air, **1a** was also converted to **2a** in good yield although it proceeded slower than the same reaction under molecular oxygen (entry 2). Among 1-aryl-2-propyn-1-ols, those having a chloro or methyl substituent at *m*- or *p*-position on aromatic nuclei (**1e–1h**) were efficiently oxidized to give the corresponding ketones in high yields (entries 6–9), while the oxidation of the alcohols having a substituent at *o*-position (**1b–1d**) was slower (entries 3–5). This tendency was also observed when propargylic alcohol having a 1-naphthyl substituent (**1i**) was compared with that having 2-naphthyl one (**1j**) (entries 10 and 11). Propargylic alcohol having a vinylic substituent at the α-position (**1k**) gave the corresponding ketone in low yield under this condition (entry 12). Primary propargylic alcohol **1l** was converted to the corresponding aldehyde in good yield (entry 13). The oxidation of propargylic alcohols having an alkyl substituent at the α-position (**1m–1o**) gave the corresponding ketones in low yields (entries 14, 17, and 18). Longer reaction time and higher reaction temperature did not improve much the product yields (entries 15 and 16).

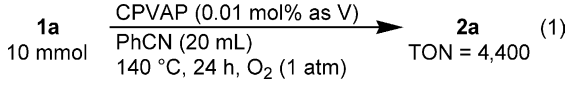
Table 2. Recycling of the catalyst



Run	Conversion of **1a** (%)[a]	Yield of **2a** (%)[a,b]
1	99 (92)	82 (85)
2	99 (84)	78 (82)
3	99 (84)	83 (80)
4	99 (84)	86 (81)
5	99 (83)	87 (82)
6	95 (79)	92 (74)
7	95	91
8	92	88
9	94	92
10	86	86
11	88	87

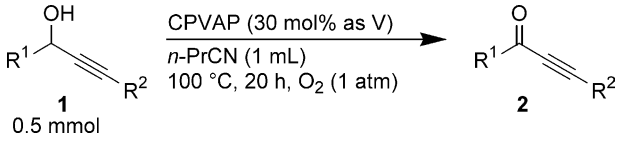
[a] The results using *n*-butyronitrile as solvent are shown in parentheses.
[b] Based on **1a** employed.

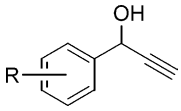
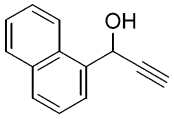
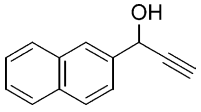
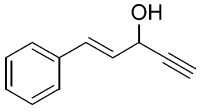
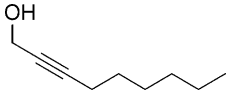
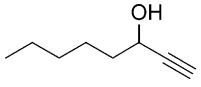
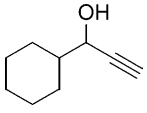
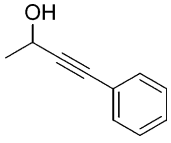
The amount of the catalyst could be reduced in the oxidation of some propargylic alcohols listed in Table 3 which smoothly reacted to give the corresponding carbonyl compounds in good yields (Table 4). Although the higher reaction temperature was needed, the turnover number (TON) reached to 4,400 when the reaction was carried out in benzonitrile at 140 °C under S/C = 10,000 for 24 h (Eq (1)).



We next investigated a time profile of the oxidation of **1a** under the conditions shown in Table 4. The product yield gradually increased and reached to maximum after ca. 20 h (Fig. 1). When CPVAP was removed by filtration from the reaction mixture after 9 h and the heating of the filtrate was continued under the same conditions, the yield of **2a** did not improve at all. Further, no leaching of vanadium into the filtrate was detected by ICP (inductivity coupled plasma) atomic emission analysis. These results clearly show that

Table 3. CPVAP-catalyzed aerobic oxidation of propargylic alcohols



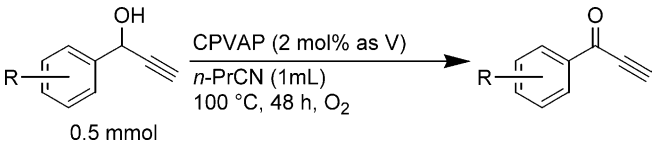
Entry	Substrate		Conversion of **1** (%)	Yield of **2** (%)[a]
1		**1a** R=H	89	85[b]
2[c]		**1a** R=H	73	64[b]
3		**1b** R=2-Cl	59	56
4		**1c** R=2-Me	80	53
5		**1d** R=2-OMe	55	41
6		**1e** R=3-Cl	89	79
7		**1f** R=3-Me	99	99
8		**1g** R=4-Cl	99	91
9		**1h** R=4-Me	98	87
10		**1i**	72	52
11		**1j**	87	87
12		**1k**	99	31[d]
13		**1l**	74	66
14		**1m**	31	20[b]
15[e]		**1m**	79	41[b,d]
16[f,g]		**1m**	—	31[b,d]
17		**1n**	89	37
18		**1o**	50	24

[a] Based on an alcohol employed.
[b] GLC yield.
[c] Under air (1 atm).
[d] Many unidentified products were also observed.
[e] For 48 h.
[f] For 96 h.
[g] Benzonitrile was used as solvent at 120 °C.

any vanadium species do not leach to the solution and the oxidation may proceed on the surface of the solid catalyst.

Lastly, we investigated the catalytic activity of other transition metal-containing hydroxyapatites. The results are summarized in Table 5. The use of vanadium hydroxyapatite (VHAP) prepared by Kaneda's method[8] as a catalyst gave **2a** in moderate yield (entry 2). When RuHAP and PdHAP, which were known to be efficient catalysts for the aerobic oxidation of alcohols,[3a,c] were used as catalysts, **2a** was not obtained at all (entries 3–6).

Table 4. Reducing of the catalyst



Entry	Substrate	Yield of **2** (%)[a]	TON
1[b]	**1a**	97	48.5
2	**1e**	78	39
3	**1f**	72	36
4	**1g**	89	44.5
5	**1h**	82	42

[a] Based on an alcohol employed.
[b] For 24 h.

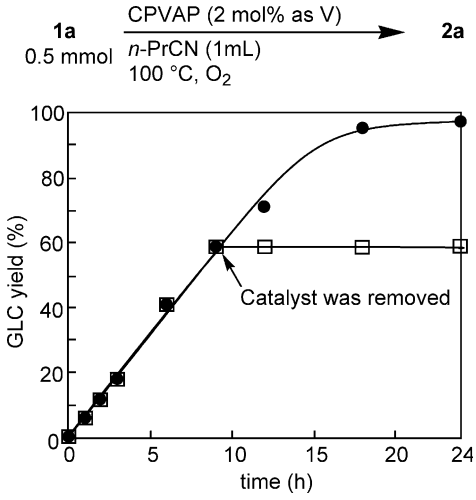


Figure 1. Time profile of CPVAP-catalyzed aerobic oxidation of **1a**.

3. Conclusion

In summary, we found that calcium phosphate-vanadate apatite (CPVAP) worked effectively as a catalyst for the aerobic oxidation of propargylic alcohols to the corresponding carbonyl compounds under an atmospheric pressure of molecular oxygen. Moreover, CPVAP was readily separated by filtration and could be reused at least 10 times.

4. Experimental

4.1. General

NMR spectra were recorded on JEOL EX-400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz) instruments for solutions in $CDCl_3$ with Me_4Si as an internal standard: the following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet. GLC analyses were performed on a Shimadzu GC-14A instrument (25 m×0.33 mm, 5.0 mm film thickness, Shimadzu fused silica capillary column HiCap CBP10-S25-050) with a flame-ionization detector and helium as carrier gas. Analytical thin-layer chromatography (TLC) was performed with Merck silica gel 60 F-254 plates. Column chromatography was performed with Merck silica gel 60. ICP atomic emission analysis for the vanadium content in the CPVAP was performed with a Shimadzu ICPS-1000 sequential plasma spectrometer.

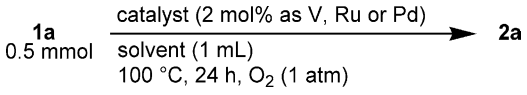
4.2. Materials

Commercially available organic and inorganic compounds were used without further purification except for the solvent. Alcohols **1a**, **1m**, **1o** are commercial products and purified by normal methods just before use. Alcohols **1b**–**1l** and **1n** were prepared from the corresponding aldehydes and lithium acetylides or alkynylmagnesium bromides, purified by column chromatography on silica gel (eluent; *n*-hexane–ethyl acetate) and identified by ^{1}H NMR and ^{13}C NMR. All propargylic alcohols and the corresponding aldehydes and ketones are known compounds. Ketone **2m** is commercial products. Selected spectral data of alcohols and carbonyl compounds are shown below. Spectral data of other alcohols and carbonyl compounds were shown in the previous report.[5b]

4.2.1. 1-(*o*-Tolyl)-2-propyn-1-ol.[9] (1c, Table 3, entry 4) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (br s, 1H (OH)), 2.44 (s, 3H), 2.64 (d, J=2.4 Hz, 1H), 5.61 (d, J=2.4 Hz, 1H), 7.17–7.27 (m, 3H), 7.65–7.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 62.2, 74.7, 83.2, 126.2, 126.3, 128.5, 130.7, 135.8, 137.7.

4.2.2. 1-(2-Methoxyphenyl)-2-propyn-1-ol.[10] (1d, Table 3, entry 5) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60

Table 5. Comparison with results using other transition metal containing hydroxyapatite as catalyst



Entry	Catalyst	Solvent	Conversion of **1a** (%)	Yield of **2a** (%)[a]
1	CPVAP	*n*-Butyronitrile	97	97
2	VHAP[b]	*n*-Butyronitrile	49	39
3	RuHAP[b]	Toluene	62	2[c]
4	RuHAP[b]	*n*-Butyronitrile	10	5
5	PdHAP[b]	Benzotrifluoride	100	0[c]
6	PdHAP[b]	*n*-Butyronitrile	100	0[c]

[a] Based on alcohol employed.
[b] Prepared by following the method described by Kaneda et al.[3a,3c,8]
[c] Many unidentified products were also observed.

(d, J=2.4 Hz, 1H), 3.15 (br s, 1H (OH)), 3.88 (s, 3H), 5.69 (d, J=2.4 Hz, 1H), 6.90 (d, J=8.3 Hz, 1H), 6.97 (td, J=8.3, 1.5 Hz, 1H), 7.31 (td, J=7.8, 1.5 Hz, 1H), 7.56 (dd, J=7.8, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 60.9, 74.0, 83.0, 110.7, 120.7, 127.7, 128.1, 129.7, 156.5.

4.2.3. 1-(3-Chlorophenyl)-2-propyn-1-ol.[11] (1e, Table 3, entry 6) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (br s, 1H (OH)), 2.70 (d, J=2.2 Hz, 1H), 4.54 (d, J=2.2 Hz, 1H), 7.31–7.44 (m, 3H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.7, 75.3, 82.7, 124.6, 126.7, 128.6, 129.8, 134.4, 141.7.

4.2.4. 1-(*m*-Tolyl)-2-propyn-1-ol.[9] (1f, Table 3, entry 7) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.37 (br s, 1H (OH)), 2.65 (d, J=2.4 Hz, 1H), 5.41 (s, 1H), 7.15 (d, J=7.3 Hz, 1H), 7.25–7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 64.4, 74.7, 85.6, 123.6, 127.2, 128.5, 129.2, 138.3, 139.8.

4.2.5. 1-(4-Chlorophenyl)-2-propyn-1-ol.[10] (1g, Table 3, entry 8) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (d, J=2.4 Hz, 1H), 2.87 (br s, 1H (OH)), 5.40 (d, J=2.4 Hz, 1H), 7.33 (dt, J=8.3, 2.2 Hz, 2H), 7.45 (dt, J=8.3, 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.5, 75.1, 83.0, 127.8, 128.6, 134.2, 138.3.

4.3. General procedure for the preparation of calcium phosphate-vanadate apatite (CPVAP)

Calcium phosphate-vanadate apatite (CPVAP) $Ca_{10}(PO_4)_{6-x}(VO_4)_x(OH)_2$ (x=3.1) was prepared by following the method described by Boechat et al.[7] To a solution of $Ca(NO_3)_2\cdot 4H_2O$ (15.8 g, 66.7 mmol) in H_2O (60 mL) in a 500 mL three-necked round bottomed flask was added a solution of VCl_3 (8.6 g, 54.4 mmol) in H_2O (brown solution, 30 mL). The mixture was then brought to pH 11–12 with 28% ammonia solution in H_2O (dark brown solution) and thereafter diluted to 120 mL. In a separate flask, a solution of $(NH_4)_2HPO_4$ (5.3 g, 40.0 mmol) in H_2O (100 mL) was brought to pH 11–12 with 28% ammonia solution in H_2O and then diluted to 160 mL. This $(NH_4)_2HPO_4$ solution was added dropwise from dropping funnel to the above $Ca(NO_3)_2/VCl_3$ solution with stirring for 30 min. After the addition, the mixture was heated to 95 °C for 10 min. After cooling, it was filtered and the separated solid was washed with water (20 mL×7). This solid was dried at 80 °C for 15 h and calcined at 500 °C for 3 h to give 9.1 g of CPVAP as a pale brown solid. The vanadium content in the CPVAP was 2.9 mmol g^{-1} estimated by ICP atomic emission analysis.

Hydroxyapatite-supported vanadium, ruthenium and palladium were prepared by treatment of hydroxyapatite (HAP)[12] with VCl_3, $RuCl_3$ and $PdCl_2(MeCN)_2$ at room temperature in water or acetone by following the methods described by Kaneda et al.[3a,c,8]

4.4. General procedure for the CPVAP-catalyzed oxidation of porpargylic alcohols with molecular oxygen

To a suspension of CPVAP (50 mg, 0.15 mmol as vanadium) in benzonitrile or *n*-butyronitrile (1 mL) in a 20 mL Schlenk flask was added a propargylic alcohol (0.5 mmol). Oxygen gas was then introduced into the flask from an O_2 balloon under atmospheric pressure and then the mixture was stirred vigorously for 20 h at 100 °C under oxygen. After the reaction, the mixture was cooled to room temperature and CPVAP was separated by filtration through a glass filter. The amount of the product was determined by GLC analysis using bibenzyl as an internal standard. For isolation of the product the solvent was evaporated and the residue was purified by column chromatography on SiO_2 (*n*-hexane–ethyl acetate as an eluent) and identified by ^{1}H NMR and ^{13}C NMR.

4.4.1. 1-(*o*-Tolyl)-2-propyn-1-one.[13] (2c, Table 3, entry 4) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H), 3.38 (s, 1H), 7.27 (d, J=7.1 Hz, 1H), 7.35 (t, J=7.1 Hz, 1H), 7.48 (td, J=7.5, 1.5 Hz, 1H), 8.27 (dd, J=7.5, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 79.5, 81.6, 125.9, 132.1, 133.2, 133.7, 134.6, 140.8, 178.7 (C=O).

4.4.2. 1-(2-Methoxyphenyl)-2-propyn-1-one.[14] (2d, Table 3, entry 5) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (s, 1H), 3.93 (s, 3H), 7.00–7.06 (m, 2H), 7.55 (ddd, J=8.3, 7.3, 2.0 Hz, 1H), 8.06 (dd, J=7.8, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 79.3, 82.1, 112.1, 120.1, 125.7, 133.1, 135.4, 159.9, 175.8 (C=O).

4.4.3. 1-(3-Chlorophenyl)-2-propyn-1-one.[15] (2e, Table 3, entry 6) Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 1H), 7.45 (t, J=7.8 Hz, 1H), 7.61 (ddd, J=7.8, 2.0, 1.0 Hz, 1H), 8.04 (td, J=7.8, 1.0 Hz, 1H), 8.12 (t, J=2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.8, 81.5, 127.7, 129.5, 129.9, 134.3, 135.0, 137.4, 175.8 (C=O).

4.4.4. 1-(*m*-Tolyl)-2-propyn-1-one.[14] (2f, Table 3, entry 7) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.42 (s, 1H), 7.39 (t, J=7.8 Hz, 1H), 7.45 (d, J=7.8 Hz, 1H), 7.95 (s, 1H), 7.98 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 80.3, 80.5, 127.1, 128.5, 129.9, 135.2, 136.1, 138.5, 177.4 (C=O).

4.4.5. 1-(4-Chlorophenyl)-2-propyn-1-one.[15] (2g, Table 3, entry 8) Orange solid; mp: 96.0–97.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 1H), 7.48 (dt, J=8.8, 2.0 Hz, 2H), 8.10 (dt, J=8.8, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.9, 81.2, 129.0, 130.9, 134.4, 141.1, 175.9 (C=O).

4.5. General procedure for recycling of the catalyst

Recovered CPVAP by filtration from the former run of the oxidation of porpargylic alcohols was washed with diethyl ether and dried under vacuum at room temperature before use for the next run.

Acknowledgements

We thank Professor Masashi Inoue and Dr. Shinji Iwamoto (Kyoto University) for their help in ICP atomic emission analysis to measure vanadium contents in CPVAP. The financial support from Japan Science and Technology Corporation (JST) is also acknowledged.

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Enantioselective oxidative coupling of methyl 3-hydroxy-2-naphthoate using mono-*N*-alkylated octahydrobinaphthyl-2,2′-diamine ligand

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Received 8 July 2004; revised 28 July 2004; accepted 30 July 2004

Available online 27 August 2004

Abstract—Mono-*N*-alkylated octahydrobinaphthyl-2,2′-diamine (H_8-BINAM) chiral ligands were employed in the catalytic and asymmetric oxidative coupling of methyl 3-hydroxy-2-naphthoate to the corresponding binaphthol derivative. The diamine ligand with one *N*-(3-pentyl) group shows highest enantioselectivity in the biaryl coupling among other BINAM derivatives, and the coupling reaction proceeds faster than the reactions using alkanediamine ligands.

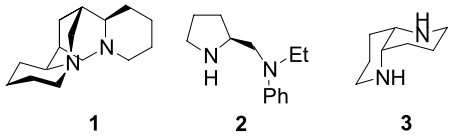
1. Introduction

Chiral 1,1′-bi-2-naphthol (BINOL) and its derivatives have been very successful as chiral ligands in asymmetric transformations and catalyses.[1] Efforts to obtain these versatile ligands in enantiopure forms were mainly focused on the optical resolutions of racemic compounds.[2] However, significant developments were also made in the last decade on the oxidative asymmetric homocoupling of achiral 2-naphthols to chiral BINOL derivatives. Oxidative coupling of 2-naphthol to BINOL utilizing chiral oxovanadium(IV) complexes has been reported with reasonably high enantioselectivities.[3] Another area of intensive study is the oxidative coupling of 3-hydroxy-2-naphthoate ester catalyzed by copper-amine complexes. The ester group on the naphthol is essential for a better asymmetric induction through a bidentated chelation to the copper catalyst. Initial asymmetric study was reported by Smrcina et al. using stoichiometric copper(II) complex of chiral amines, such as sparteine (**1**) and α-methylbenzylamine.[4] Further development was made by Nakajima et al. using catalytic amount CuCl and proline-derived diamine **2** to give an improved, but still moderate, enantiselectivity.[5] Better enantioselectivity, up to 93%, was achieved using *cis*-1,5-diazadecalin (**3**) as a chiral diamine ligand and CuI as a copper(I) source.[6] The slow reaction rates of the oxidative biaryl couplings using the diamine ligands **1**–**3**, requiring heating at 40 °C for one to several days, and the formation of the *ortho*-iodinated naphthol byproduct in the case of using CuI as a copper ion source are demanding further improvements of the catalyst activity and enantioselectivity in this versatile catalytic reaction (Fig. 1).

The chiral diamines previously studied for the biaryl coupling reaction were mostly aliphatic diamines, and the use of chiral aryldiamines derived from 1,1′-binaphthyl-2,2′-diamine (BINAM) has not been reported yet. Thus, we studied the Cu-catalyzed enantioselective oxidative coupling of naphthol **4** to binaphthol **5** in the presence of BINAM derivatives.[7,8]

2. Results and discussion

The use of (*R*)-BINAM (**6a**) itself for the copper-catalyzed oxidative coupling of 3-hydroxy-2-naphthoate ester provided **5** in almost quantitative yield at room temperature under oxygen atmosphere in two days, and the reaction was slowed down, without affecting the enantioselectivity, when powdered 4 Å molecular sieves were not added (entries 1 and 2, Table 1).[6a] The coupling reaction was almost



1 2 3

Figure 1. Chiral diamine ligands for the asymmetric oxidative coupling of methyl 3-hydroxy-2-naphthoate

Keywords: Catalytic; Asymmetric; Oxidation; Biaryl; Coupling; Binaphthol.
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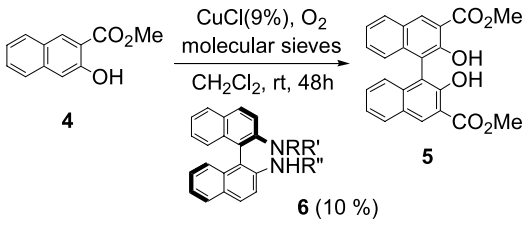
doi:10.1016/j.tet.2004.07.086

Table 1. Enantioselective oxidative coupling of **4** catalyzed by complexes between (*R*)-BINAM derivative and CuCl



Entry	Ligand	R, R′	R″	Yield[a,b] (%)	ee[c,d] (%)
1	**6a**	H, H	H	99	20 (*S*)
2	**6a**[e]	H, H	H	76	20 (*S*)
3	**6b**	*i*-Pr, H	*i*-Pr	11	11 (*S*)
4	**6c**	$-(CH_2)_4-$	H	56	23 (*S*)
5	**6d**	*i*-Pr, H	H	95	58 (*R*)
6	**6e**	*c*-Hex, H	H	82	51 (*R*)
7	**6f**	3-Pentyl, H	H	8	30 (*R*)

[a] Isolated yields.
[b] 0.5 M substrate concentration.
[c] Determined by chiral HPLC (Chiralpak AD-H column).
[d] Absolute configuration assigned by comparison to the literature.
[e] Without powdered molecular sieves.

completed in a day and is apparently much faster than the reported cases using aliphatic diamines. It was proposed by Kozlowski et al. that the slow step of the catalytic cycle of this oxidative coupling is the reduction of copper(II) to copper(I), and a more electrophilic copper(II) coordinates to the substrate more strongly and can undergo more facile reduction to copper(I).[6d] Thus, the decreased basicity of the biaryl diamine ligand **6a**, compared with aliphatic diamines **1**–**3**, can be the major reason for the relative rate increase. We screened a number of *N*-substituted BINAMs for an optimum *N*-substitution pattern for better enantiselectivity. *N*,*N*′-Dialkylated BINAM **6b** and *N*,*N*-dialkylated BINAM **6c** provided low reaction yields and enantioselectivities under the same condition (entries 3 and 4, Table 1). *N*-Monoalkylated BINAMs showed improved results. *N*-Isopropyl BINAM **6d** showed an improved enantioselectivity, but the change of the isopropyl group to cyclohexyl or 3-pentyl decreases the reaction yield and enantioselectivity (entries 5–7, Table 1). Racemic **5** was observed in low yield with the use of ligand **6d** in CH_3CN as a solvent, and only trace amounts of **5** were observed with the use of CuI, instead of CuCl, in CH_2Cl_2.

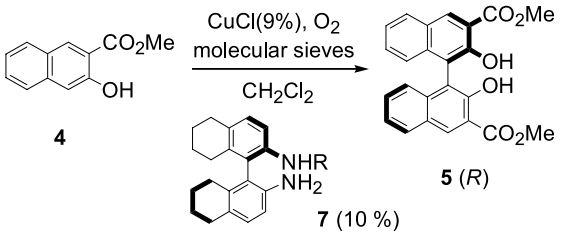
With the results that mono-*N*-alkylated derivatives are showing better enantioselectivity than other BINAM derivatives, we studied the use of enantiopure mono-*N*-alkylated 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (H_8-BINAM) derivatives for the coupling reaction. (*R*)-H_8-BINAM (**7a**) can be easily obtained by partial reduction of **6a** with Ni–Al alloy in dilute aqueous alkaline solution or with Pd/C catalyst under hydrogen pressure at elevated temperature.[9] With this steric tuning, much an enhancement in the enantioselectivity was observed in the case of **7a** (entry 1, Table 2) compared with **6a** (entry 1, Table 1). *N*-Benzyl and *N*-aryl derivatives were inferior to **7a** (entries 2 and 3, Table 2), and *N*-isopropyl **7d** gave a better, but much less than desired, enantioselectivity (entry 4, Table 2). Lowering the reaction temperatures gradually improved the enantioselectivities, but with decreasing reaction yields (entries 5–7, Table 2). Unexpectedly, considering the result with ligand **6f** (entry 7, Table 1), *N*-3-pentyl derivative **7e** showed an improved result with 73% ee and 99% isolated yield in 24 h at ambient temperature. The reaction temperature was lowered to 0 °C and, much gratifyingly, the enantioselectivity was improved to 94% with 95% isolated yield which is the best result so far reported to date for the catalytic enantioselective oxidative coupling of **4** using CuCl catalyst (entry 9, Table 2). Decreasing the substrate concentration of the reaction under the same condition slowed down the coupling reaction without deteriorating the enantioselectivity of the coupling reaction (entries 10 and 11, Table 2).

The stereochemical result of this oxidative biaryl coupling can be rationalized with a tentative monomeric model of the substrate-catalyst complex (Fig. 2). The in situ generated Cu(II)–binaphthol complex from **4** and **7e** would undergo electron transfer to form a radical intermediate coordinated to tetrahedral Cu(I) center, as shown with the intermediate **8** (Fig. 2). The ketoester–Cu(I) complex **8** is likely favored over the more congested **9** due to the steric interaction between the *N*-3-pentyl group and the substrate. The approach of the second substrate in the carbon–carbon bond formation step is preferred from the top *si*-face since the bottom face is blocked by the *N*-3-pentyl group. Subsequent transformation of the central chirality of the coupling product to axial chirality through keto-enol tautomerization would provide the binaphthol (*R*)-**5**.

3. Conclusions

In conclusion, enantiopure *N*-(3-pentyl)-octahydrobinaphthyl-2,2′-diamine [*N*-(3-pentyl)-H_8-BINAM] has shown to be a highly selective diamine ligand in Cu(I)-catalyzed asymmetric oxidative biaryl coupling of

Table 2. Enantioselective oxidative coupling of **4** with the use of monoalkylated (*R*)-H_8-BINAM ligands



7a R = H **7d** R = *i*-Pr
7b R = $PhCH_2$ **7e** R = 3-pentyl
7c R = 3,5-xylyl

Entry	Ligand	Conc.(M)[a]	Temp. (time)	Yield[b] (%)	ee[c,d] (%)
1	**7a**	0.5	rt (24 h)	98	42
2	**7b**	0.5	rt (24 h)	95	4
3	**7c**	0.5	rt (24 h)	60	12
4	**7d**	0.5	rt (24 h)	92	66
5	**7d**	0.5	0 °C (48 h)	97	71
6	**7d**	0.5	−20 °C (48 h)	83	78
7	**7d**	0.5	−40 °C (24 h)	10	90
8	**7e**	0.5	rt (24 h)	99	73
9	**7e**	0.5	0 °C (48 h)	95	94
10	**7e**	0.4	0 °C (48 h)	88	94
11	**7e**	0.2	0 °C (48 h)	72	94

[a] Substrate concentration.
[b] Isolated yields.
[c] Determined by chiral HPLC (Chiralpak AD-H column).
[d] Absolute configuration assigned by comparison to the literature.

methyl 3-hydroxy-2-naphthoate to the corresponding binaphthol derivative. This catalytic system using the easily available chiral binaphthyl-based aryldiamine ligand provides an excellent enantioselectivity and a much improved catalytic activity in the biaryl coupling reaction compared with the other alkanediamine ligands. Further studies to address the scope of this catalyst in the other biaryl couplings are in progress.

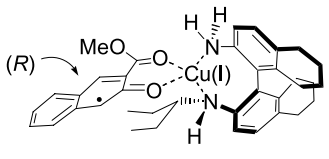
4. Experimental

4.1. General

IR spectra were recorded on a Bomem MB-104 spectrophotometer. Optical rotations were measured with a Rudolph Research Autopol III polarimeter. ^{1}H NMR spectra were recorded on a Varian Germini 300 (300 MHz) with TMS as an internal reference. ^{13}C NMR spectra were recorded on a Bruker AMX 400 (100 MHz) with TMS or $CDCl_3$ as an internal reference. Elemental analyses were obtained from Sogang Organic Chemistry Research Center, Seoul. Chiral HPLC analysis was performed on a Jasco LC-1500 Series HPLC system with a UV detector. TLC was performed on Merck silica gel 60 F_{254} precoated glass backed plates. All reactions were carried out in oven-dried glassware under an argon or oxygen atmosphere. Dichloromethane (CaH_2), THF (Na, benzophenone), toluene (CaH_2) were dried by distillation before use.

4.2. General procedure for the synthesis of diamine ligands 6d–f and 7d–e

To a solution of the corresponding ketone (21.9 mmol) in THF was added 20% H_2SO_4 (2 ml per 1 mmol of diamine). The reaction mixture was stirred for 30 min at rt, and the binaphthyl diamine[10] (1.37 mmol, 0.1 M substrate concentration) was added slowly followed by the addition of $NaBH_4$ (21.9 mmol). The resulting mixture was stirred for 1 h at room temperature and quenched by the addition of 1 N KOH (40 ml). The mixture was extracted with ethyl acetate (40 ml×3), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel



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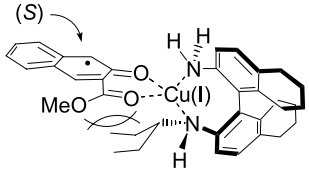

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Figure 2. Tentative stereochemical models for the coupling of **4** using the diamine ligand **7e**.

eluted with ethyl acetate/hexanes to give the enantiomerically pure *N*,*N*′-dialkylated diamines and *N*-monoalkylated diamines.

4.2.1. (*R*)-*N*-Isopropyl-1,1-binaphthyl-2,2′-diamine (6d). 74% yield as a white solid (mp 158–159 °C); $[\alpha]_D^{25}$ 137.3 (*c* 1.33, THF) {lit.[8] $[\alpha]_D$137 (*c* 0.2, THF)}; IR ($CHCl_3$) 3473, 3380 (NH_2), 1620, 1596 (C=C, aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, J=6.3 Hz, 3H), 1.08 (d, J=6.3 Hz, 3H), 3.44 (br, 1H), 3.68 (br, 2H), 3.83 (m, 1H), 6.99 (d, J=7.5 Hz, 1H), 7.07 (d, J=8.1 Hz, 1H), 7.15–7.24 (m, 4H), 7.31 (d, J=9.0 Hz, 2H), 7.78–7.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.45, 23.60, 45.02, 112.53, 113.09, 115.55, 118.48, 122.17, 122.62, 124.06, 124.35, 126.90, 126.95, 127.89, 128.28, 128.32, 128.68, 129.72, 129.81, 133.96, 134.17, 143.15, 144.28. Anal. Calcd for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58. Found: C, 84.57; H, 6.88; N, 8.60.

4.2.2. (*R*)-*N*-Cyclohexyl-1,1-binaphthyl-2,2′-diamine (6e). 32% yield as a white solid (mp 223–224 °C); $[\alpha]_D^{25}$ 121.9 (*c* 1.0, THF) {lit.[8] $[\alpha]_D$122 (*c* 0.4, THF)}; IR ($CHCl_3$) 3475, 3377 (NH_2), 1618, 1597 (C=C, aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.76–1.11 (m, 3H), 1.19–1.37 (m, 2H), 1.52–1.66 (m, 3H), 1.86–1.98 (m, 2H), 3.41 (m, 1H), 3.65 (br, 3H), 6.98 (d, J=6.6 Hz, 1H), 7.06 (d, J=8.1 Hz, 1H), 7.13–7.31 (m, 6H), 7.76–7.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.19, 25.26, 25.90, 33.85, 34.02, 52.39, 112.59, 112.90, 115.51, 118.47, 122.07, 122.60, 124.00, 124.39, 126.86, 126.93, 127.84, 128.26, 128.28, 128.67, 129.64, 129.64, 134.01, 134.18, 143.13, 144.00.

4.2.3. (*R*)-*N*-(3-Pentyl)-1,1-binaphthyl-2,2′-diamine (6f). 61% yield as a yellowish solid (mp 133–134 °C); $[\alpha]_D^{25}$ 174.8 (*c* 1.0, THF); IR ($CHCl_3$) 3460, 3376 (NH_2), 1617, 1594 (C=C, aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (t, J=7.5 Hz, 3H), 0.88 (t, J=7.2 Hz, 3H), 1.24–1.60 (m, 4H), 3.46 (m, 1H), 3.61 (br, 1H), 3.71 (br, 1H), 7.01 (d, J=6.6 Hz, 1H), 7.14–7.31 (m, 7H), 7.81–7.92 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.15, 10.36, 27.37, 27.50, 55.64, 111.93, 112.72, 114.75, 118.51, 121.80, 122.65, 123.90, 124.54, 126.93, 126.96, 127.52, 128.29, 128.35, 128.71, 129.71, 129.77, 134.16, 134.29, 143.30, 144.59. Anal. Calcd for $C_{25}H_{26}N_2$: C, 84.70; H, 7.39; N, 7.90. Found: C, 84.77; H, 7.36; N, 7.75.

4.2.4. (*R*)-*N*-Isopropyl-5,5′,6,6′,7,7′,8,8′-octahydro-1,1-binaphthyl-2,2′-diamine (7d). 79% yield as a pale yellow oil; $[\alpha]_D^{25}$ 80.7 (*c* 0.32, THF); IR ($CHCl_3$) 3461, 3369 (NH_2), 1680, 1597 (C=C, aromatic) cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 1.07 (d, J=3.0 Hz, 3H), 1.09 (d, J=3.1 Hz, 3H), 1.62–1.77 (m, 8H), 2.16–2.30 (m, 4H), 2.74 (m, 4H), 3.28 (br, 3H), 3.62 (m, 1H), 6.61 (d, J=9.0 Hz, 1H), 6.64 (d, J=8.1 Hz, 1H), 6.94 (d, J=8.1 Hz, 1H), 7.01 (d, J=8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.38, 23.40, 23.57, 23.63, 23.72, 23.82, 27.21, 27.41, 29.56, 29.63, 44.48, 109.78, 113.31, 121.93, 122.09, 126.15, 127.77, 129.40, 129.47, 136.33, 136.61, 142.04, 143.03. Anal. Calcd for $C_{23}H_{32}N_2$: C, 82.59; H, 9.04; N, 8.37. Found: C, 82.40; H, 9.15; N, 8.17.

4.2.5. (*R*)-*N*-(3-Pentyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1-binaphthyl-2,2′-diamine (7e). 63% yield as a pale yellow oil; $[\alpha]_D^{25}$ 88.5 (*c* 0.37, THF); IR ($CHCl_3$) 3459, 3367 (NH_2), 1619, 1597 (C=C, aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (td, J=7.2, 2.1 Hz, 6H), 1.23–1.38 (m, 4H), 1.47 (m, 1H), 1.58–1.75 (m, 8H), 2.11–2.30 (m, 4H), 2.72 (m, 4H), 3.19 (br, 3H), 6.51 (d, J=8.1 Hz, 1H), 6.63 (d, J=8.4 Hz, 1H), 6.91 (d, J=8.1 Hz, 1H), 6.99 (d, J=8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.16, 10.34, 23.56, 23.67 (2C), 23.84, 26.99, 27.01, 27.19, 27.37, 29.51, 29.65, 54.99, 108.31, 113.26, 121.31, 122.05, 127.37, 127.79, 129.30, 129.44, 136.42, 136.79, 142.08, 143.23. Anal. Calcd for $C_{25}H_{34}N_2$: C, 82.82; H, 9.45; N, 7.73. Found: C, 82.961; H, 9.61; N, 7.79.

4.3. Procedures for the synthesis of diamine ligands 6c, 7b and 7c.

4.3.1. (*R*)-2-Amino-2′-(1-pyrrolinyl)-1,1′-binaphthyl (6c). To a solution of (*R*)-BINAM (**6a**)[10a] (300 mg, 1.056 mmol), NaI (16 mg, 0.1056 mmol), and potassium carbonate (365 mg, 2.64 mmol) in DMF (22 ml) was added 1,4-dibromobutane (126 μl, 1.506 mmol) slowly. The reaction mixture was stirred for 36 h at 70 °C. After cooling the mixture to room temperature, the reaction mixture was added with brine followed by extraction with dichloromethane (30 ml×3). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluted with ethyl acetate/hexanes (1:16) to give **6c** (71 mg, 20% yield) as a white solid (mp 99–100 °C): $[\alpha]_D^{25}$ 180.0 (*c* 1.0, THF); IR ($CHCl_3$) 3464, 3374 (NH_2), 1618, 1596 (C=C, aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62–1.70 (m, 4H), 2.90 (m, 2H), 3.14 (m, 2H), 3.75 (br, 2H), 7.03–7.27 (m, 6H), 7.32 (d, J=9.0 Hz, 2H), 7.75–7.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.01 (2C), 49.99 (2C), 112.70, 117.50, 117.99, 118.07, 122.00, 122.26, 124.29, 125.59, 126.61, 126.78, 127.84, 128.03, 128.09, 128.11, 129.01, 129.27, 134.65, 135.42, 142.96, 146.46. Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.18; H, 6.54; N, 8.18.

4.3.2. (*R*)-*N*-Benzyl-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (7b). To a solution of the diamine **7a**[10b] (300 mg, 1.019 mmol) in 10 ml of dichloromethane was added a solution of acetic anhydride (0.11 ml, 1.12 mmol) in 10 ml of dichloromethane slowly for 2 h. The reaction mixture was stirred for another 1 h and quenched with 1 N NaOH (20 ml). The mixture was extract with dichloromethane (20 ml×3), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluted with ethyl acetate/hexanes (1:3) to give (*R*)-*N*-acetyl-H_8-BINAM (202.6 mg, 68%). The (*R*)-*N*-acetyl-(H_8)-BINAM (100 mg, 0.3 mmol) was dissolved with DMF (3 ml), and K_2CO_3 (42 mg, 0.3 mmol) was added to the reaction mixture. Benzyl bromide (36 μl, 0.3 mmol) was added slowly to the reaction mixture, and the mixture was stirred overnight. The mixture was added with 1 N NaOH (10 ml) and extracted with ethyl acetate (20 ml×3). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved with MeOH (5 ml) and 4 N HCl (5 ml) and the reaction mixture was heated to reflux overnight. The reaction mixture was quenched by 1 N NaOH (20 ml),

extracted with ethyl acetate (20 ml×3). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluted with ethyl acetate/hexanes (1:7) to give **7b** (40.5 mg, 71% yield based on the (*R*)-*N*-acetyl-H_8-BINAM) as a pale yellow oil: $[\alpha]_D^{25}$ 70.7 (*c* 0.35, THF); IR ($CHCl_3$) 3459, 3360 (NH_2), 1677, 1597 (C=C, aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63–1.78 (m, 8H), 2.14–2.34 (m, 4H), 2.69–2.75 (m, 4H), 3.37 (br, 2H), 3.89 (br, 1H), 4.29 (s, 2H), 6.50 (d, J=8.1 Hz, 1H), 6.64 (d, J=7.8 Hz, 1H), 6.94 (d, J=8.1 Hz, 2H), 7.17–7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.50, 23.58, 23.66, 23.76, 27.27, 27.33, 29.53, 29.61, 48.07, 109.07, 113,37, 121.80, 121.85, 126.61, 126.98, 127.10, 127.15, 127.37, 127.92, 128.63, 129.37, 129.59, 136.25, 136.77, 140.56, 142.07, 143.19. Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.90; N, 7.32. Found: C, 84.86; H, 7.86; N, 7.26.

4.3.3. (*R*)-*N*-(3,5-Xylyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (7c). (*R*)-*N*-Acetyl-1,1′-binaphthyl-2,2′-diamine (prepared during the synthesis of **7b**) in toluene (0.5 ml) was added to a solution of $Pd(OAc)_2$ (2 mg, 9×10^{-3} mmol), (*o*-biphenyl)P(*t*-Bu)$_2$[11] (3.6 mg, 1.2×10^{-2} mmol), bromo-*m*-xylene (40 μl, 0.30 mmol) in toluene (0.5 ml). The reaction mixture was stirred for 12 h and diluted with ethyl acetate. The organic layer was washed with brine (10 ml), dried (Na_2SO_4), and concentrated in vacuo. After the deacetylation as above, the desired product was purified by flash column chromatography on silca gel eluted with ethyl acetate/hexanes (1:6) to give **7c** (51 mg, yield: 43%) as a pale yellow oil: $[\alpha]_D^{25}$ 47.3 (*c* 0.34, THF); IR ($CHCl_3$) 3464, 3371 (NH_2), 1615, 1589 (C=C, aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63–1.74 (m, 8H), 2.14–2.33 (m, 10H), 2.68–2.78 (m, 4H), 3.31 (br, 2H), 5.16 (br, 1H), 6.52–6.63 (m, 4H), 6.91 (d, J=6.6 Hz, 1H), 7.01 (d, J=8.1 Hz, 1H), 7.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.58(2C), 23.07, 23.30, 23.34, 23.51, 27.39, 27.57, 29.63, 29.77, 110.36, 116.71, 123.40, 123.67, 124.75, 124.90, 127.75, 127.95, 129.78, 129.94, 130.03, 130.13, 131.59, 133.65, 136.33, 139.14, 139.43, 143.16. Anal. Calcd for $C_{28}H_{32}N_2$: C, 84.80; H, 8.13; N, 7.06.Found: C, 84.75; H. 8.17; N, 7.15.

4.4. General procedure for the oxidative biaryl coupling

CuCl (0.09 equiv) and the diamine ligand (0.1 equiv) were dissolved in dichloromethane and stirred for 30 min. The color of solution was changed to dark brown. Substrate **4** (0.5 M substrate concentration) was added and the mixture was stirred for 48 h in O_2 atmosphere. The reaction mixture was treated with aqueous ammonia to decompose the copper complexes. The reaction mixture was extracted with dichloromethane (20 ml×3), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluted with ethyl acetate/hexanes (1:8) to give **5**: IR ($CHCl_3$) 3207 (OH), 1680 (carbonyl), 1599, 1577 (C=C, aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06 (s, 6H), 7.17–7.39 (m, 6H), 7.92–7.95 (m, 2H), 8.71 (s, 2H), 10.76 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.99, 114.38, 117.21, 124.22, 124.92, 127.42, 129.70, 130.03, 133.13, 137.42, 154.24, 170.81. Anal. Calcd for $C_{24}H_{18}O_6$: C, 71.64; H, 4.51; O, 23.86. Found: C, 71.61; H, 4.66; N, 0.00.

4.4.1. Asymmetric synthesis of 5 from the coupling of 4 using ligand 7e. 95% yield; $[\alpha]_D^{25}$ 161.5 (*c* 1.0, THF) {lit.[5b] $[\alpha]_D$ −125.0 (*c* 1.0, THF) for 78% (*S*) of ee}, 94% ee by HPLC analysis (Chiralpak AD-H column, hexane:2-propanol=9:1, 1 ml/min, 254 nm UV detector), t_R=11.47 min for (*S*) and t_R=20.56 min for (*R*).

Acknowledgements

This work was financially supported by the Center for Molecular Design and Synthesis (CMDS) at KAIST.

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Efficient solution phase parallel synthesis of norstatine analogs

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Received 8 April 2004; revised 29 June 2004; accepted 29 July 2004

Available online 27 August 2004

Abstract—The reaction of glycidic amides with various functionalized nitriles to afford norstatine analogs in a regio- and diastereoselective fashion (43–99% yield) is described. Utilizing this chemistry, a 20 membered solution phase library was prepared in two steps featuring three points of diversity.

1. Introduction

Since the discovery of the inhibitory activity of (hydroxymethyl)carbonyl isosteres against aspartyl proteases, the norstatine analogs **1** have become a popular target for medicinal chemists.[1,2] Amongst the various synthetic approaches to these analogs, the reaction of glycidic esters **3** with acetonitrile to afford the desired 3-*N*-acylamino-2-hydroxy compounds **2** via the oxazoline intermediate **4**, appears to be the most straightforward (Fig. 1).[3] Surprisingly, the scope of this reaction has been largely unexplored: glycidic esters have been reported to react with only a few simple unfunctionalized nitriles (i.e. acetonitrile and propionitrile), and only a single glycidic amide[3c] has been described as an alternative to the ester. However, in all of the published examples, the transformation proceeds with remarkably high regio- and diastereoselectivity, which would be a crucial feature for the efficient preparation of a diverse solution phase library. Herein, we present our investigations into expanding the reaction scope and describe the preparation of a small library of norstatine analogs.[4]

2. Results and discussion

2.1. Chemical approaches

Our initial approach to the library synthesis was based on the results published by Zvonkova and others.[3] For our initial synthetic studies, we used racemic glycidic acid **5a** available via a simple *m*CPBA epoxidation of the commercially available olefin.[5] When the epoxy-acid **5a** reacted with acetonitrile in the presence of an excess of $BF_3 \cdot OEt_2$, the corresponding 3-*N*-acyl-2-hydroxyacid **6a** was isolated upon base hydrolysis of the oxazoline **4a** (Fig. 2). We found that this transformation can be efficiently performed using only a single equivalent of the nitrile and also that a number of functionalities on the nitrile are tolerated. However, numerous attempts to couple the

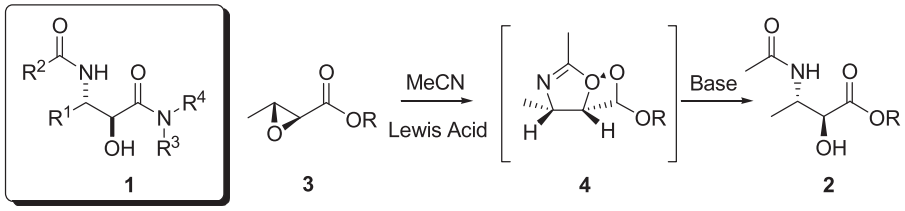

Figure 1. Proposed synthesis of norstatine analogues.

Keywords: Epoxide; Nitrile; Norstatine; Solution phase combinatorial chemistry.
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doi:10.1016/j.tet.2004.07.085

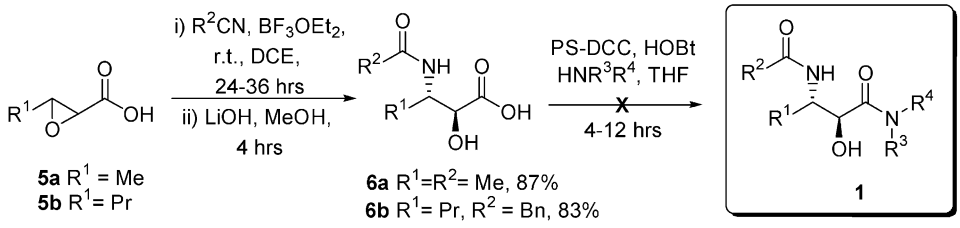


Figure 2. Initial route to norstatine analogues.

product **6a** with amines in the presence of resin-bound DCC and HOBt according to published procedures[6,7] failed to produce the desired norstatine analog **1**.

To circumvent the deleterious influence of the functionalities in **6** on the DCC coupling step, the sequence of steps was reversed (Fig. 3). The amides **7** and **8** were prepared in 35–81% yields (Table 1) from the epoxy-acids **5** and the corresponding amines via resin-bound DCC coupling in the presence of HOBt.

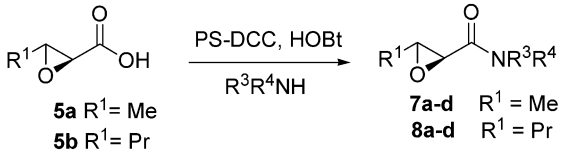
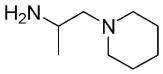
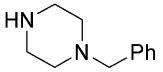
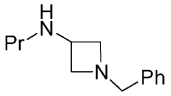
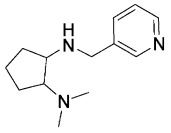
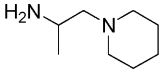
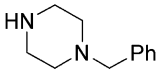
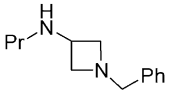
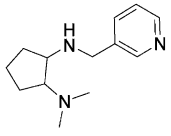


Figure 3. Resin bound amide bond formation.

We then studied the influence of various conditions on the epoxide opening of glycidic amides **7** and **8**. Use of a stoichiometric amount of $BF_3 \cdot OEt_2$ and nitrile in dichloroethane afforded **1** in low yield accompanied by considerable amounts of recovered starting material. This can be rationalized by formation of an amine–borane complex, leaving only a small amount of the uncomplexed Lewis acid available in solution to mediate the desired transformation.

In addition, the nitrile opening of the glycidic amides **7** and **8** mediated by an excess of $BF_3 \cdot OEt_2$ proceeded considerably more slowly than the previously examined reactions of the glycidic acids **5**. The desired products **1** were isolated in low yields, after $NaHCO_3$ hydrolysis[3c]of the oxazoline intermediates, and no starting material was detected in the reaction mixture. This suggested that competing reactions such as the facile opening of the epoxide by other nucleophiles present in the reaction mixture such as traces of water were effectively competing with the desired reaction leading to the observed attrition in yield. In fact,

Table 1. Preparation of glycidic amides **7** and **8**

Entry	Product	Epoxide	NHR^3R^4	Yield (%)
1	**7a**	**5a**		74
2	**7b**	**5a**		81
3	**7c**	**5a**		62
4	**7d**	**5a**		35
5	**8a**	**5b**		66
6	**8b**	**5b**		85
7	**8c**	**5b**		48
8	**8d**	**5b**		Traces

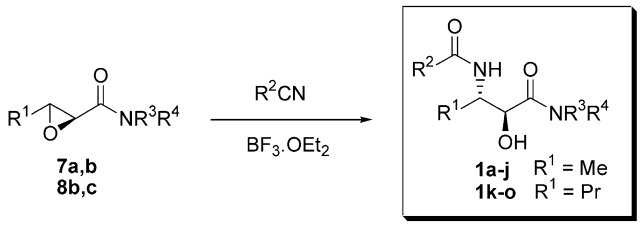


Figure 4. Synthesis of a library of norstatine analogues.

LC/MS analysis identified the corresponding diol as the major impurity. Use of other chlorinated solvents (CH_2Cl_2, $CHCl_3$) gave similar results, while reactions in ethers (Et_2O, THF) or NMP resulted in multiple products. Other Lewis acids (TfOH, $Mg(ClO_4)_2$ and $LiClO_4$) gave also inferior results.

The optimized conditions for the desired transformation was found to be the reaction of glycidic amides **7** and **8** with a 5-fold excess of the nitrile in the presence of an excess of $BF_3 \cdot OEt_2$ in dichloroethane under strictly anhydrous conditions. This consistently put the yields of the desired product in 90% range with little or no undesired by-products being formed (Fig. 4). After 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and stirred for an additional 12 h to break the trifluoroborane–amine complexes and hydrolyze the oxazoline ring.[3c] The products were isolated by utilizing the 'catch-and-release' technique with acidic SCX resin taking advantage of the basicity of the tertiary amine moiety within the target molecules.[8]

The relative stereochemistry of the C2 and C3 substituents was established by NMR analysis of oxazoline **4a** isolated from the reaction mixture.[3c] The ^1H NMR spectrum of **4a** revealed the characteristic $J_{H2}=9.4$ Hz coupling constant for a doublet at 5.01 ppm (H2 signal) which is consistent with a *syn* geometry of the substituents.[3b,c]

Therefore, upon base hydrolysis of oxazoline **4a**, the resulting 3-*N*-acylamino-2-hydroxyamide **1a** would have the desired *anti*-relationship between the substituents at C2 and C3 positions. Indeed, the characteristic *anti* ($J_{H2}=$ 6.6 Hz) coupling constant for H2 was observed in the ^1H NMR spectrum of isolated **1a** (a doublet at 5.04 ppm) (Fig. 5).

Thus, the stereoselectivity of reaction of nitriles with glycidic amides is thought to arise from preferential S_N2 attack on the C3 position since the C2 positive charge is somewhat destabilized by the adjacent carboxylate group similarly to the reaction with glycidic esters.[3b,c,10]

2.2. Library synthesis and analysis

For library preparation, chiral glycidic amides **7a**,**b** and **8b**,**c** were prepared from commercial optically active precursors. The reaction of these glycidic amides with a series of nitriles in dichloroethane in the presence of the excess $BF_3 \cdot OEt_2$ afforded the desired products **1** (Table 2). The adducts formed utilizing cyclohexanecarbonitrile and acetonitrile were isolated by simple removal of excess reagent under reduced pressure. When non-volatile nitriles were used, the final products were captured on acidic SCX resin and then released with methanolic ammonia to afford **1** in yields ranging from 43–99%. Generally, secondary amides gave both higher yield and purity than tertiary amides. Amongst the tertiary amides, both glycidic amides **7d** and **8d** gave low purity of the corresponding products **1**, and as such were discarded. As expected, adducts of chiral nitriles (entries 4, 10 and 15) were obtained as equimolar mixtures of diastereomers. Similarly, adducts of glycidic amide **7a** also afforded diastereomeric mixtures.

The purity of all the library members was ascertained by LC/MS analysis (UV and LSD detection). The structures of the representative library members was further confirmed by proton and carbon NMR experiments. According to LC/MS analysis, compounds **1c**, **1j**, **1g** and **1q** cyclize spontaneously upon isolation and exist as equilibrium mixtures of the corresponding oxazolines with the open-chain amido-alcohols; compounds **1d**, **1i** and **1o** were isolated as the corresponding oxazolines. All compounds analyzed by ^1H NMR consistently showed the H2 signal as a doublet at 4.71–5.15 ppm with a coupling constant $J_{H2}=$ 6.4–6.7 Hz. This is consistent with the expected *anti* geometry of the norstatine analogues. There were no other regioisomers observed.

In conclusion, the scope of the epoxide ring opening with nitriles in the presence of $BF_3 \cdot OEt_2$ has been significantly extended to reactions of functionalized nitriles with glycidic acids, and secondary and tertiary amides. These reactions proceed with high regio and diastereoselectivity and afford **1** in 43–99% yields. This transformation was used as the key step in a solution-phase preparation of a 20-membered combinatorial library of norstatine analogs.

3. Experimental

3.1. General comments

NMR experiments were conducted with a Bruker ARX300 spectrometer at 75 MHz for ^{13}C and 300 MHz for ^1H

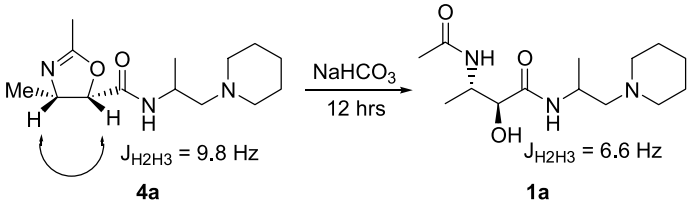
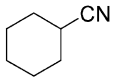
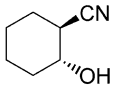
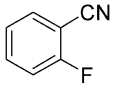
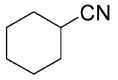
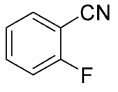
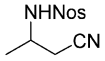
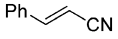
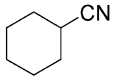
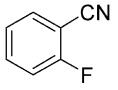
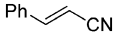
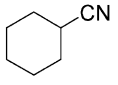
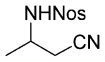


Figure 5. Confirmation of stereochemistry via hydrolysis of the oxazoline.

Table 2. Characterization of solution phase library of norstatine analogues, **1**

Entry	Product	Amide	R^2CN	Purity[a] (%)	ES-MS calc'd	Anal. obs'd	Yield (%)
1	**1a**	**7a**	MeCN	91	286.1	286.1	99
2	**1b**	**7a**	BnCN	97	362.2	362.2	90
3	**1c**	**7a**		93	354.3	354.3, 336.4	99
4	**1d**	**7a**		95	370.2[b]	352.2	60
5	**1e**	**7a**		96	366.2	366.2	95
6	**1f**	**7b**	MeCN	93	320.2	320.2	99
7	**1g**	**7b**	BnCN	95	396.1	396.1, 378.1	85
8	**1h**	**7b**		95	388.1	388.1	77
9	**1i**	**7b**		78	400.1[b]	382.1	78
10	**1j**	**7b**		97	548.2	548.2, 530.2	60
11	**1k**	**8b**	MeCN	91	347.6	347.6	71
12	**1l**	**8b**	BnCN	75	423.6	423.6	68
13	**1m**	**8b**		83	435.6	435.6	61
14	**1n**	**8b**		93	415.6	415.6	58
15	**1o**	**8b**		91	427.5[b]	409.5	43
16	**1p**	**8c**	MeCN	86	376.2	376.2	46
17	**1q**	**8c**	BnCN	77	452.2	452.2, 434.2	52
18	**1r**	**8c**		83	464.2	464.2	67
19	**1s**	**8c**		85	444.3	444.3	61
20	**1t**	**8c**		86	604.2	604.2	43

[a] Determined by UV at 220 nm.
[b] Isolated as corresponding oxazolines.

spectra. Samples were dissolved in $CDCl_3$ with TMS as the internal reference. Affinity chromatography was carried out using Bondesil (SCX 40 μm). Reactions were carried out under dry nitrogen with magnetic stirring. LC/MS analysis was conducted on HP1100 with Polaris C18 A-5μ column. Thin layer chromatographic (TLC) analyses were performed using 10×20 cm Analtech Silica Gel GF plates (25 mm thick). The TLC plate was developed in the appropriate EtOAc/hexanes mixture and visualized by UV light (254 nm).

Ethyl (2*S*)-*trans*-2,3-epoxybutanoate was purchased from

Acros. (2*S*)-*trans*-2,3-epoxyhexanol [lit.[11] bp 100 °C/17 mm] was prepared in accordance with the literature methods. 1-Methyl-2-piperidinoethylamine (**a**), *N*-*3*-propyl-1-benzyl-3-azetanamine (**c**), *N1*,*N1*-dimethyl-*N*2-(3-pyridylmethyl)-2,1-cyclopentanediamine (**d**), 2-hydroxy-1-cyclo hexanecarbonitrile (**E**) and *N*-1-(2-cyano-1-methylethyl)-3-nitro-1-benzenesulfonamide (**G**) were obtained as single racemic diastereomers from Coelacanth Corporation's available inventory of building blocks. All other chemicals were obtained from commercial sources and were used without further purification.

3.1.1. Preparation of (2*S*)-*trans*-2,3-epoxybutanoic acid (5a). To a cooled solution of ethyl (2*S*)-*trans*-2,3-epoxybutanoate (2.8 g, 24 mmol) in ethanol (25 mL) was added ethanolic KOH (1.8 g, 26 mmol, 25 mL of ethanol) dropwise at 0 °C over 30 min. The reaction mixture was stirred at room temperature for 6 h. Potassium *trans*-2,3-epoxybutanoate was isolated by filtration, washed with cold ethanol (25 mL) and dried in vacuo overnight. The potassium salt was mixed with dichloroethane (20 mL) cooled to 0 °C and HCl (1,4-dioxane solution, 4 M, 5.5 mL) was added dropwise over 10 min. The reaction mixture was stirred for an additional 2 h, filtered and concentrated to yield **5a** (1.4 g, 58%) as a viscous oil which solidified upon standing. ^{1}H (300 MHz; $CDCl_3$): δ 1.41 (d, 3H, J=6.2 Hz), 3.22 (d, 1H, J=2.2 Hz), 3.31–3.37 (m, 1H), 9.80 (br s, 1H); ^{13}C (75 MHz; $CDCl_3$): δ 17.5, 53.9, 55.5, 175.2.

3.1.2. Preparation of (2*S*)-*trans*-2,3-epoxyhexanoic acid (5b). (2*S*)-*trans*-2,3-Epoxyhexanol (10 mmol) was dissolved in acetonitrile (20 mL) and CCl_4 (20 mL) followed by addition of water (40 mL). To the vigorously stirred solution, $RuCl_3$ (0.03 g) and $NaIO_4$ (8 g) were added at room temperature. The reaction was monitored by TLC (9:1 hexanes/EtOAc, developed in PMA). After 10 h, TLC indicated full consumption of the starting material and the reaction mixture was diluted with 100 mL of dichloroethane. The aqueous phase was saturated with NaCl, and extracted twice with dichloromethane. The organic phases were combined, filtered through Celite, dried over magnesium sulfate and concentrated to give **5b** as a clear oil. ^{1}H (300 MHz; $CDCl_3$): δ 1.12 (d, 3H, J=6.2 Hz), 1.64–1.82 (m, 4H), 3.28–3.30 (m, 1H), 3.37 (d, 1H, J=1.5 Hz), 10.22 (br s, 1H); ^{13}C (75 MHz; $CDCl_3$): δ14.1, 19.2, 33.7, 52.9, 59.2, 175.3.

3.2. General procedure for the preparation of compounds 6

To a vigorously stirred solution of **2** (0.1 mmol) in 2 mL of dichloroethane, the corresponding nitrile (0.1 mmol) was added, followed by dropwise addition of $BF_3 \cdot OEt_2$ (0.1 mmol) over 5 min at 0 °C. After stirring at room temperature for 12 h, TLC indicated that no starting material remained, and the reaction mixture was quenched with 2 mL of saturated aqueous $NaHCO_3$ and stirred for an additional 12 h. The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo to afford the desired product **6**.

3.2.1. Compound 6a. Colorless oil. ^{1}H (300 MHz; DMSO-d_6): δ 1.12 (d, 3H, J=7.4 Hz), 1.32 (d, 3H, J=7.2 Hz), 4.11 (dq, 1H, J=6.5, 7.2 Hz), 4.56 (d, 1H, J=6.5 Hz); ^{13}C (75 MHz; DMSO-d_6): δ 16.8, 17.9, 46.9, 84.2, 170.1, 175.6.

3.2.2. Compound 6b. Colorless oil. ^{1}H (300 MHz; $CDCl_3$): δ 1.16 (t, 3H, J=7.4 Hz), 1.39–1.71 (m, 4H), 3.64 (s, 2H), 4.03 (d, 1H, J=6.5 Hz), 4.62 (d, 1H, J=6.5 Hz), 7.18–7.34 (m, 5H); ^{13}C (75 MHz; $CDCl_3$): δ 14.7, 18.5, 32.3, 46.8, 83.1, 127.5, 128.5, 129.4, 137.7, 169.8, 172.7.

3.3. General procedure for preparation of epoxy amides 7 and 8

To a solution of the glycidic acid **5** (4.8 mmol) in THF (10 mL) was added PS-DCC (14.4 mmol) and HOBt (4.8 mmol). The mixture was shaken for 20 min, and then a solution of the corresponding amine (4 mmol) in 10 mL of THF was added. The reaction was monitored by LC/MS. Depending on the nature of the amine, the reaction went to a completion in 12–36 h. Upon completion, the reaction was diluted with 20 mL of ethyl acetate and filtered. The filtrate was washed with saturated $NaHCO_3$ solution, dried over magnesium sulfate and concentrated in vacuo to yield the desired glycidic amides **7** or **8** in 46–92% yields.

3.3.1. Compound 7a. Colorless oil.[9] ^{1}H (300 MHz; $CDCl_3$): δ 1.22 (d, 3H, J=7.4 Hz), 1.32 (d, 3H, J=6.2 Hz), 1.54–1.62 (m, 6H), 2.16–2.45 (m, 6H), 2.98–3.05 (m, 1H), 3.17 (d, 1H, J=1.5 Hz), 6.32 (br s, 1H); ^{13}C (75 MHz; $CDCl_3$): δ 17.9, 19.5, 24.7, 26.3, 42.6, 54.9, 56.0, 56.7, 63.8, 168.7.

3.3.2. Compound 7b. Amorphous solid. ^{1}H (300 MHz; $CDCl_3$): δ 1.32 (d, 3H, J=7.2 Hz), 2.31–2.45 (m, 4H), 3.15 (dq, 1H, J=1.5 Hz, 7.2 Hz), 3.27 (d, 1H, J=1.5 Hz), 3.52 (s, 2H), 3.59–3.74 (m, 4H), 7.16–7.32 (m, 5H); ^{13}C (75 MHz; $CDCl_3$): δ 17.7, 45.3, 52.9, 53.5, 55.3, 63.2, 127.7, 128.8, 129.5, 137.9, 166.3.

3.3.3. Compound 7c. Amorphous solid. ^{1}H (300 MHz; $CDCl_3$): δ 1.12 (t, 3H, J=7.2 Hz), δ 1.32 (d, 3H, J=6.8 Hz), 1.64–1.82 (m, 2H), 3.17–3.30 (m, 2H), 3.31–3.52 (m, 6H), 3.57 (d, 1H, J=1.5 Hz), 3.72 (s, 2H) 7.25–7.47 (m, 5H); ^{13}C (75 MHz; $CDCl_3$): δ 14.2, 19.6, 23.9, 33.9, 48.0, 48.8, 53.9, 58.6, 62.7, 128.1, 128.9, 129.3, 137.9, 168.7.

3.3.4. Compound 8a. Colorless oil.[9] ^{1}H (300 MHz; $CDCl_3$): δ 1.25 (t, 3H, J=7.2 Hz), 1.32 (d, 3H, J=6.2 Hz), 1.58–1.82 (m, 10H), 2.16–2.45 (m, 6H), 3.11–3.17 (m, 1H), 3.21 (d, 1H, J=1.7 Hz), 6.22 (br s, 1H); ^{13}C (75 MHz; $CDCl_3$): δ 17.9, 19.4, 20.3, 24.1, 24.7, 26.3, 42.6, 54.9, 56.2, 56.7, 63.9, 167.1.

3.3.5. Compound 8b. Amorphous solid. ^{1}H (300 MHz; $CDCl_3$): δ 1.26 (t, 3H, J=7.4 Hz), 1.59–1.81 (m, 4H), 2.33–2.47 (m, 4H), 3.12 (dq, 1H, J=1.5 Hz, 7.4 Hz), 3.21 (d, 1H, J=1.5 Hz), 3.42 (s, 2H), 3.44–3.64 (m, 4H), 7.18–7.31 (m, 5H); ^{13}C (75 MHz; $CDCl_3$): δ 17.7, 19.6, 20.3, 44.6, 52.7, 53.5, 54.8, 63.1, 127.5, 128.5, 129.4, 137.7, 167.3.

3.3.6. Compound 8c. Amorphous solid. ^{1}H (300 MHz; $CDCl_3$): δ 1.02 (t, 3H, J=7.4 Hz), δ 1.24 (d, 3H, J=6.2 Hz), 1.59–1.82 (m, 6H), 3.07–3.21 (m, 2H), 3.32–3.49 (m, 6H), 3.52 (d, 1H, J=1.5 Hz), 3.69 (s, 2H) 7.22–7.42 (m,

5H); ^{13}C (75 MHz; $CDCl_3$): δ 14.1, 19.7, 23.3, 34.0, 48.0, 48.8, 53.9, 58.6, 62.7, 128.2, 128.9, 129.1, 137.8, 167.7.

3.4. Preparation of oxazoline 4a

To a vigorously stirred solution of **7a** (23 mg, 0.1 mmol) in 2 mL of acetonitrile was added $BF_3 \cdot OEt_2$ (0.5 mmol) over 5 min at 0 °C. The resulting solution was stirred at room temperature for 7 h, at which point TLC indicated that no starting material remained. The reaction mixture was concentrated, re-dissolved in 10 mL of ethanol, heated at a gentle reflux for 3 h, then filtered through a silica gel plug and concentrated in vacuo to yield 24 mg (89%) of **4a**.

3.4.1. Compound 4a. Clear oil.[9] ^{1}H (300 MHz; DMSO-d_6): δ 0.92–1.27 (m, 6H), 1.35–1.61 (m, 6H), 1.72 (s, 3H), 2.24–2.72 (m, 6H), 3.41–3.47 (m, 1H), 4.19 (dt, 1H, J=6.6, 7.4 Hz), 5.04 (d, 1H, J=6.6 Hz); ^{13}C (75 MHz; DMSO-d_6): δ 13.9, 17.9, 19.2, 19.7, 23.7, 26.8, 43.2, 54.6, 54.7, 63.8, 71.5, 75.4, 171.2, 174.1.

3.5. General procedure for the preparation of the library set 1

To a vigorously stirred solution of **7** or **8** (0.1 mmol) in 2 mL of dichloromethane, 0.5 mmol of the corresponding nitrile was added, followed by dropwise addition of 0.5 mmol of $BF_3 \cdot OEt_2$ over 5 min at 0 °C. The reaction mixture was stirred at room temperature for 24 h, at which point TLC indicated no starting glycidic amides remained. The reaction mixture was quenched with 2 mL of saturated aqueous $NaHCO_3$ and stirring was continued for 12 h. The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo. Purification of the product was accomplished 'catch and release technique': the solution of the crude product mixture in methanol was passed through a column packed with SCX modified silica. The non-basic impurities were washed off the column with excess of methanol and the retained product was then released with 1 M methanolic ammonia.

3.5.1. Compound 1a. Colorless amorphous solid.[9] ^{1}H (300 MHz; DMSO-d_6): δ 0.98–1.32 (m, 6H), 1.54–1.67 (m, 6H), 1.98 (s, 3H), 2.24–2.72 (m, 6H), 3.41–3.47 (m, 1H), 3.97–4.11 (m, 1H), 4.91 (br s, 1H), 5.04 (d, 1H, J=6.6 Hz), 8.11 (br s, 1H); ^{13}C (75 MHz; DMSO-d_6): δ 13.2, 17.9, 19.5, 19.6, 23.8, 25.4, 42.0, 54.6, 54.7, 63.5, 71.5, 74.2, 170.2, 171.3.

3.5.2. Compound 1j. Off-white amorphous solid.[9] ^{1}H (300 MHz; $CDCl_3$): δ 1.17 (d, 3H, J=6.4 Hz), 1.37 (d, 3H, J=6.2 Hz), 1.31–1.38 (m, 1H), 1.92–1.98 (m, 1H), 2.37–2.46 (m, 4H), 3.52 (s, 2H), 3.49–3.70 (m, 4H), 3.79 (dq, 1H, J=6.6 Hz, 6.2 Hz), 4.31–4.39 (m, 1H), 5.08 (d, 1H, J=6.6 Hz), 7.18–7.27 (m, 5H), 7.65–7.72 (m, 2H), 7.81–7.84 (m, 1H), 8.14–8.19 (m, 1H); ^{13}C (75 MHz; $CDCl_3$): δ 17.6, 20.7, 34.9, 42.3, 46.2, 54.6, 63.9, 64.5, 78.6, 125.4, 127.8, 128.8, 129.5, 133.5, 133.6, 137.9, 148.2, 166.3, 171.2.

3.5.3. Compound 1n. Amorphous solid. ^{1}H (300 MHz; $CDCl_3$): δ 1.02 (t, 3H, J=7.4 Hz), 1.22–129 (m, 6H), 1.52–1.75 (m, 8H), 2.33–2.47 (m, 5H), 3.42 (s, 2H), 3.44–3.51 (m, 1H), 3.59–3.74 (m, 4H), 4.95 (d, 1H, J=6.5 Hz), 7.22–7.35 (m, 5H); ^{13}C (75 MHz; $CDCl_3$): δ 17.2, 19.6, 20.3, 23.9, 26.4, 27.4, 42.2, 44.6, 52.7, 53.5, 63.8, 64.1, 81.1, 127.5, 128.5, 129.4, 137.7, 167.3, 177.7.

3.5.4. Compound 1r. Amorphous solid. ^{1}H (300 MHz; $CDCl_3$): δ 0.81–1.24 (m, 6H), 1.58–1.74 (m, 6H), 3.07–3.36 (m, 4H), 3.49–3.82 (m, 3H), 3.69 (s, 2H), 4.23–4.50 (m, 2H), 4.71 (d, 1H, J=6.7 Hz), 6.56 (d, 1H, J=14.2 Hz), 7.25–7.41 (m, 7H), 7.51–7.65 (m, 3H); ^{13}C (75 MHz; $CDCl_3$): δ 14.6, 17.3, 23.9, 34.4, 47.3, 48.5, 58.9, 59.8, 63.4, 68.9, 78.5, 114.9, 127.6, 127.9, 128.5, 128.8, 128.9, 129.0, 135.6, 137.5, 141.2, 167.9, 193.2.

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Tetrahedron 60 (2004) 9049–9060

Aerobic oxidative dimerization of 1-naphthols to 2,2′-binaphthoquinones mediated by $SnCl_4$ and its application to natural product synthesis

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Received 1 July 2004; revised 28 July 2004; accepted 28 July 2004

Available online 25 August 2004

Abstract—We developed a simple method for the direct synthesis of 2,2′-binaphthoquinones, utilizing oxidative dimerization via electron donor–acceptor complex formation of 1-naphthols with $SnCl_4$ in the presence of dioxygen. This oxidation involves a catalytic cycle of $SnCl_4$, and the reaction mechanism is discussed. As an application of this method to natural products synthesis, we describe facile biomimetic syntheses of the binaphthoquinones 3,3′-bijuglone, 3,3′-biplumbagin and elliptinone.

1. Introduction

Quinone derivatives, including biarylquinones, are not only versatile compounds for organic synthesis, but also intermediates in the biosynthesis of various natural products, and several applications of quinone derivatives as synthons for the synthesis of natural products have been reported.[1] Among natural biaryls, 2,2′-binaphthoquinones, including 3,3′-bijuglone (**1**),[1d–e] 3,3′-biplumbagin (**2**)[1f–g] and biramentaceone (**3**),[1h] and 2,2′-binaphthols, such as elliptinone (**4**), gossypol[1l–p] and michellamine A,[1q] have been isolated from several plants and show various biological activities. It is considered that the biogenetic pathway to the 2,2′-binaphthoquinones (BNPQ) involves oxidative biaryl coupling of 1-naphthols (NPOH) and subsequent oxidation of the resulting 2,2′-binaphthols (BNPOH). We are interested in the oxidative reactions of 1-naphthols in order to develop a method for constructing these biaryl substructures, aiming at biomimetic synthesis of various natural products (Fig. 1).

In general, the synthesis of the BNPQ framework requires two steps, namely, the biaryl coupling of NPOH and subsequent oxidation of the resulting BNPOH. Although a number of authors have obtained the above framework in two steps,[2] only a few examples of synthesis in one step have been recorded.[3] In most cases, however, the coupling reactions are not catalytic but require a more than stoichiometric amount of oxidant. These methods suffer from drawbacks such as the use of an expensive oxidant and the production of copious amounts of heavy metal-containing wastes. In addition, they are not always suitable for large-scale reaction.

The replacement of current stoichiometric oxidations for the production of fine chemicals with environmentally benign catalytic oxidations is one of the major goals of so-called green chemistry. Dioxygen (O_2) is an attractive oxidant and the development of synthetic methodologies using dioxygen is a rewarding goal from both economic and environmental points of view. Thus, aerobic catalytic oxidative dimerization with air or dioxygen has been extensively studied for many years. For instance, several methods using the combination of oxovanadium(IV)-amino acid complex, Ru(II)-salen complex, Cu(II)-amine complex, Fe (III) complex, $VO(acac)_2$, $CuSO_4/Al_2O_3$ or CuCl as a catalyst and dioxygen or air as an oxidant have been developed for oxidative coupling of 2-naphthols.[4]

Alternatively, stannic chloride ($SnCl_4$; SC) as an inorganic metal halide is used extensively in organic synthesis as a Lewis acid for enhancing a variety of organic reactions.[5a–d] However, to our knowledge there have been only a few reports to date on oxidative reactions using SC as a catalyst.[5e–f] Recently, we reported that BNPOH **6** and dinaphtho[1,2-*b*;2′,1′-*d*]furans (**9**; DNF) were obtained in excellent yields through the catalytic oxidative coupling reaction of NPOH **5** with the SC system in the absence of

Keywords: Naphthols; Binaphthoquinones; Dimerization; Tin chloride; Dioxygen.
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doi:10.1016/j.tet.2004.07.073

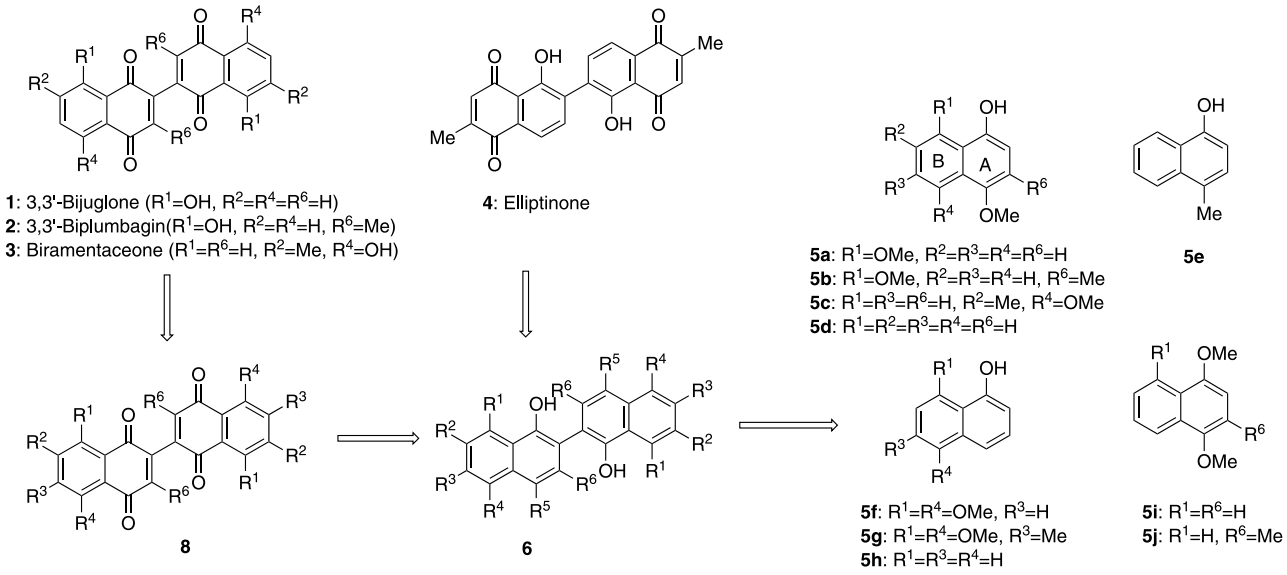


Figure 1.

O_2.[6a,b] Furthermore, in a preliminary communication,[6c] we reported a simple and convenient method for oxidative dimerization of **5** to the corresponding BNPQ **8** in one step, without the formation of DNF **9**, by using SC as a catalyst in the presence of O_2.

These results showed that the present SC/O_2 system has different reactivity from the SC system[6b] reported previously by us. We now present a detailed study of the aerobic oxidative reaction of **5** with the SC/O_2 system, including further additional experiments, and its application to the biomimetic synthesis of naturally occurring **1**, **2** and **4**.

2. Results and discussion

2.1. Oxidative reactions of NPOH 5 with the $SnCl_4/O_2$ system

First, we investigated the reaction of **5**[7] with the SC/O_2 system with the aim of achieving a facile synthesis of naturally occurring **1**–**4** under various conditions. The results are shown in Table 1 and Scheme 1. The optimum conditions were NPOH (1 mmol) with a catalytic amount of SC (0.25 equiv.). We found that the nature of the major products changed drastically with the passage of time at room temperature (23 °C). In the cases of **5a**,**b**, BNPOH **6a**,**b** were obtained as major products in the reaction for a short time (1–7 h) (entries 3, 6). Prolonged reaction (20–71 h) under the same conditions selectively afforded BNPQ **8a**,**b**, synthetic intermediates to the desired natural products **1** and **2**, in one step from **5a**,**b** (entries 4, 7).

On the contrary, prolonged reaction of **5a** with the SC system did not afford **8a**, but gave DNF **9a**, as reported previously by us[6a,b] (refer to Table 1, entry 2). The reason for this is discussed below. We also used another Lewis acid for the formation of **8**. However, the reaction of **5a** with the $TiCl_4/O_2$ system in CH_2Cl_2 gave **8a** in very low yield (entry 5). With the naphthol ethers **5i**,**j**, the oxidation reaction almost did not proceed (entries 9, 10). These results show that the hydroxyl group in **5a**,**b** is required for the coupling reaction. Furthermore, in order to extend the range of applicability of the SC/O_2 system, the reaction of several NPOHs under the same conditions was carried out. In the case of **5c**, which might be a precursor for the synthesis of **3**, the expected coupling product **8c** was not obtained (entry 8).

Next, the reaction of **5d** with the SC/O_2 system was examined (Scheme 2). Surprisingly, the reaction for a short time (0.5 h) did not afford BNPOH **6d** at all, but gave the O–C_{para} coupled product, the novel dinaphthofuranone (**11**; DNFO) in 88% yield (Table 2, entry 1). Prolonged reaction (67 h) under the same conditions selectively afforded BNPQ **8d** (59%), in one step from **5d** (entry 2). We also used another Lewis acid for the formation of **8d**. The reaction of **5d** with the $TiCl_4/O_2$ system gave **8d** in 51% yield (entry 3). The formation of **11** in entry 1 was different from the result (entry 4) with the SC system. DNFO **11** is an analogous to the skeleton of the known Pummerer's ketone **14** (C_{ortho}–C_{para} coupled product).[8] The oxidative C_{ortho}–C_{para} coupling reaction of *p*-cresol having a methyl group at the *para* position has been often cited as an analogue to usnic acid and morphine biosyntheses (Scheme 3).[9]

Furthermore, we examined the reaction of **5e**, having a methyl group in place of a methoxyl group, for comparison with the above reaction of **5d** (entries 6–8). The result differed from that of **5d**; only **6e** (68%) was obtained, without the formation of **8d** and **15** (entry 6).

The structure of **11** was elucidated by analyses of the IR, ^1H, and ^{13}C NMR spectra with the aid of 2D NMR analyses (^1H–^1H COSY, ^{13}C–^1H COSY, HMBC and NOESY experiments), and also by chemical transformation as shown in Scheme 2. The formation of the dihydrofuran ring in **11** was confirmed by observation of the long-range correlations of 7-H and C-6a, and 6-H and C-6b in the HMBC spectrum of **11** (Fig. 2). The stereochemistry of **11** was confirmed by the NOESY spectrum, showing that structure **1** has the *trans*-configuration between C-13a and C-6a (Fig. 3). Treatment of **11** in methanol (MeOH)

Table 1. Reactions of naphthols with $SnCl_4$ in the presence of dioxygen (O_2) at 23 °C[a]

Entry	Substrate	Acceptor	Solvent	Temp. (°C)	Time (h)	Product (isolated yield, %)					Recovered (%)
						6	**7**	**8**	**9**	**10**	**5**
1[b]	**5a**	$SnCl_4$	CH_2Cl_2	100	24	97			Trace		—
2[b]	**5a**	$SnCl_4$	CH_2Cl_2	100	56				92		—
3	**5a**	$SnCl_4/O_2$	CH_2Cl_2	23	1	75	5				15
4	**5a**	$SnCl_4/O_2$	CH_2Cl_2	23	20		22	76			—
5[c]	**5a**	$TiCl_4/O_2$	CH_2Cl_2	23	48	82		2	4		8
6	**5b**	$SnCl_4/O_2$	$MeNO_2$	100	7	52	Trace				20
7	**5b**	$SnCl_4/O_2$	$MeNO_2$	100	71		Trace	48			—
8	**5c**	$SnCl_4/O_2$	CH_2Cl_2	23	0.25					25	—
9	**5i**	$SnCl_4/O_2$	CH_2Cl_2	23	139					2	88
10	**5j**	$SnCl_4/O_2$	CH_2Cl_2	23	150						98
11	**6a**	$SnCl_4/O_2$	CH_2Cl_2	23	0.5	41	46	1			—
12[d,e]	**6a**	$SnCl_4/H_2O_2$	CH_2Cl_2	23	1.5	49	37	7			—
13	**7a**	$SnCl_4/O_2$	CH_2Cl_2	23	26		8	25			—
14[d,e]	**7a**	$SnCl_4/H_2O_2$	CH_2Cl_2	23	0.5			75			—
15[f]	**5a**	$SnCl_4$/air	CH_2Cl_2	23	20		4	7			—

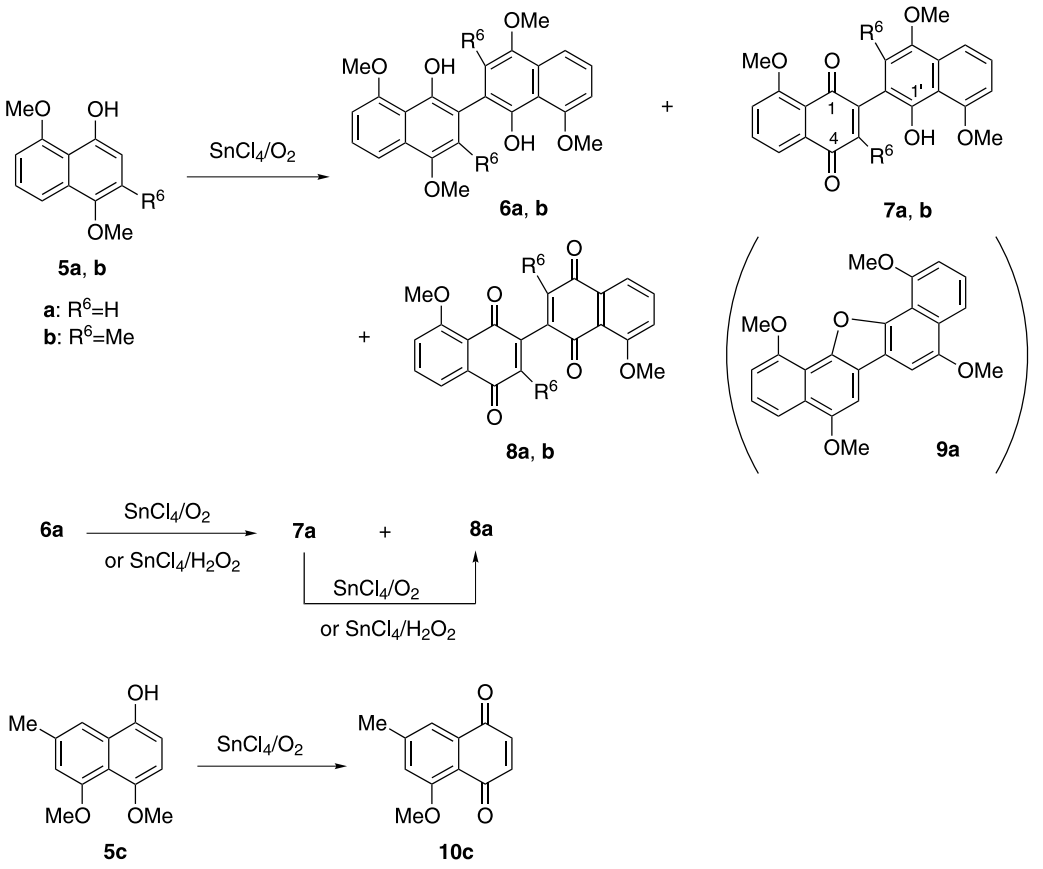
[a] The reactions of naphthols (1 mmol) with $SnCl_4$ (0.25 equiv.) were carried out using dioxygen (O_2)-saturated solvent in a sealed tube with stirring under normal laboratory light. Similar results were obtained in the dark.
[b] $SnCl_4$ (1.3 equiv.) at 100 °C. This result was reported previously by us (see Ref. 6a,b).
[c] This reaction was carried out with $TiCl_4$ (0.25 equiv.) in place of $SnCl_4$ under otherwise the same conditions as above.
[d] $SnCl_4$ (1 equiv.) at 23 °C.
[e] With 30% H_2O_2 (1 mmol) in place of dioxygen.
[f] This reaction was carried out under air. Polymer was also formed.

containing concentrated HCl gave the dinaphthofuran **12** (27%) and dinaphthofuranol **13** (24%).[10] Furthermore, the reaction of **11** with the $SnCl_4/O_2$ system afforded **8d** in 36% yield.

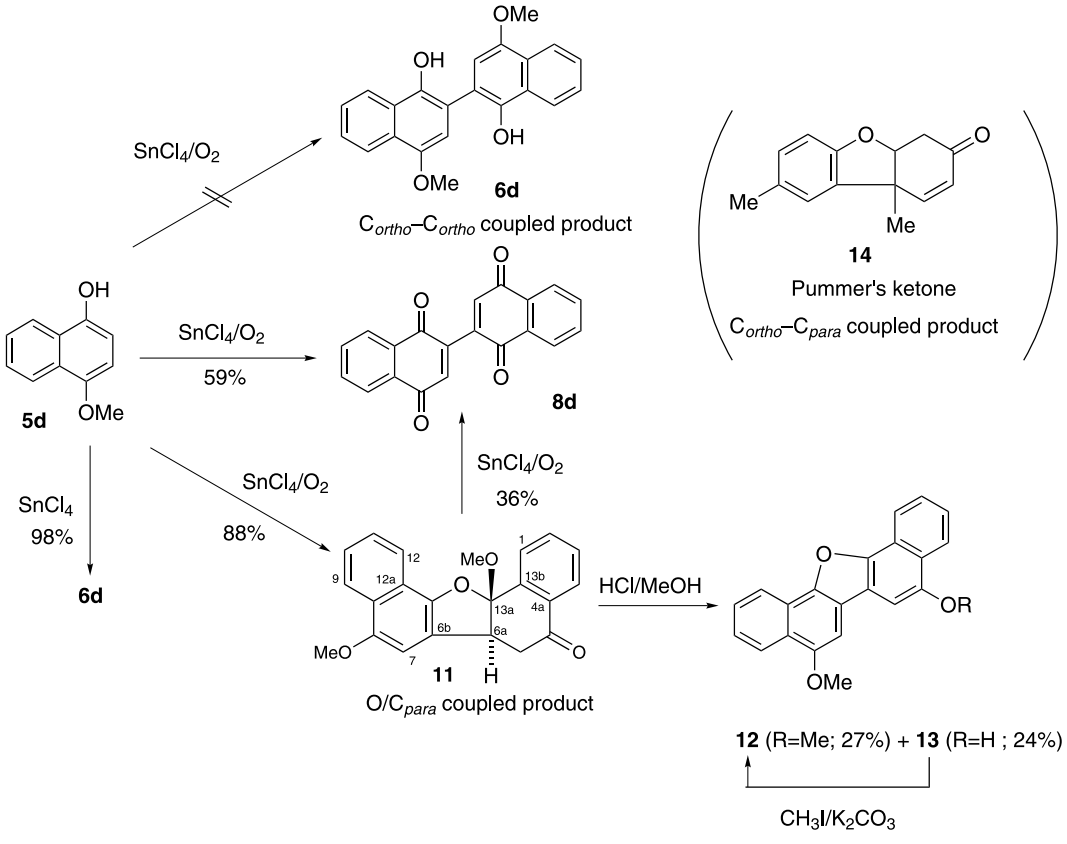
Although oxidative coupling reactions of naphthols using several metal oxidants[1q,11] in the absence or presence of O_2 have been studied extensively, mixtures of dimeric, polymeric and quinoid compounds were usually generated. In addition, regioselective *ortho*/*ortho* coupling is more difficult to control in the reaction of NPOHs such as **5f–h**, which lack a methoxyl group on ring A. In order to obtain **6g** as a synthetic intermediate for **4**, the *ortho*/*ortho* coupling reaction of **5f** as a model substrate with SC in the absence of O_2 was tried first, but the yield of **6f** was low,[6b] partly because of the formation of a polymeric mixture. We then studied the reaction of **5g** with the SC/O_2 system (Scheme 4, Table 3). In this reaction, *ortho*/*ortho*-coupled BNPOH **6g** was obtained along with the trimeric furan **16g**, without the formation of BNPQ (Table 3, entry 3). In the case of **5h**, the desired dimer was obtained in a lower yield (entry 5). Physical data for the compounds **16f** and **16g** were identical with those of the corresponding compounds reported previously by us.[6b]

The noteworthy features of the present reactions with the SC/O_2 system were as follows, as compared with the SC system reported previously by us[6b] (Scheme 5).

(1) The prolonged catalytic reactions of NPOH **5a**,**b** with SC (0.25 equiv.) in the presence of dioxygen afforded BNPQ **8a**,**b** in one step via the formation of BNPOH **6a**,**b**. The prolonged reaction of **5d** under the same conditions gave **8d** via **11**.
(2) The formation of **8** can be conveniently performed with electron-rich NPOH **5** having a methoxyl group at the R^5 position on ring A. However, there is an exception: in the case of **5c** as a substrate, the coupling reaction to **6c** did not take place. The reason for this may be that **5c** is much more oxidizable than the other compounds because it has the lowest oxidation potential (0.82 V vs. Ag/AgCl), as reported by us previously.[6b]
(3) NPOHs **5e**, **5f** and **5g** having a methyl group on ring A or B could not be converted to the corresponding BNPQs **8e**, **8f** and **8g**.
(4) When using **5d** as a substrate, a particular difference between oxidation with the SC/O_2 system and the SC system was observed. Among NPOHs **5**, only oxidation of **5d** with the SC/O_2 system for a short time (0.5 h) afforded DNF **11** having a different framework from other products, without the formation of the BNPOH framework. In contrast with this result, the reaction with the SC system gave only **6d**. Although the reason for this difference is unclear, it may be related to the influence or participation of dioxygen (O_2). Some structural difference of the electron donor–acceptor (EDA) complex formed between SC and **5d** in the presence of O_2 or in absence of O_2 in the reaction process may be involved.
(5) In all reactions of **5** with the SC/O_2 system, formation of DNFs **9** obtained in the reaction in the SC system was not observed at all. The reason for this is discussed below.



Scheme 1.

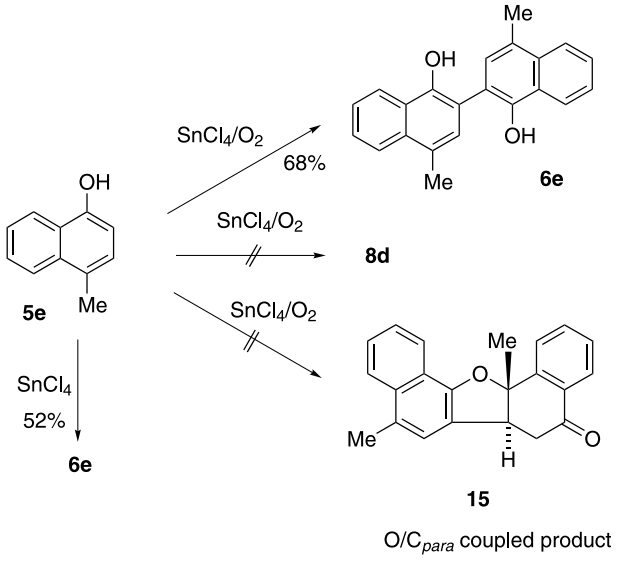


Scheme 2.

Table 2. Reactions of the naphthols **5d**,**e** with the $SnCl_4/O_2$ system at 23 °C[a]

Entry	NPOH	Reagent	Time (h)	Product (%)[b]			Recovered
				6	**8**	**11**	**5** (%)
1	**5d**	$SnCl_4/O_2$	0.5	—	—	88	—
2	**5d**	$SnCl_4/O_2$	67	—	59	—	—
3[c]	**5d**	$TiCl_4/O_2$	72	—	51	—	—
4[d]	**5d**	$SnCl_4$	18	98	—	—	—
5	**5e**	$SnCl_4/O_2$	9	68	—	—	—
6	**5e**	$SnCl_4/O_2$	24	59	—	—	—
7	**5e**	$SnCl_4/O_2$	115	61	—	—	—
8[d]	**5e**	$SnCl_4$	48	52	—	—	38

[a] The reactions of **5d**,**e** (1 mmol) with $SnCl_4$ (0.25 equiv.) were carried out using dioxygen (O_2)-saturated solvent in a sealed tube with stirring under normal laboratory light. Similar results were obtained in the dark.
[b] Isolated yield.
[c] This reaction was carried out with $TiCl_4$ (0.25 equiv.) in place of $SnCl_4$ under the same conditions as above.
[d] $SnCl_4$ (1.3 equiv.) at 100 °C. This result was reported previously by us (see Ref. 6b).



Scheme 3.

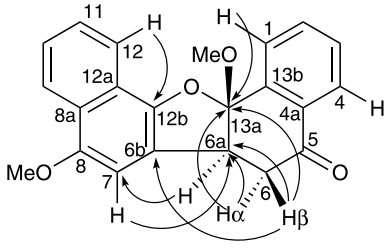


Figure 2. The Main HMBC correlations of **11**.

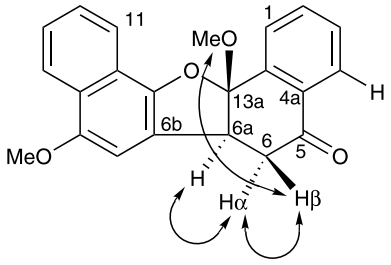


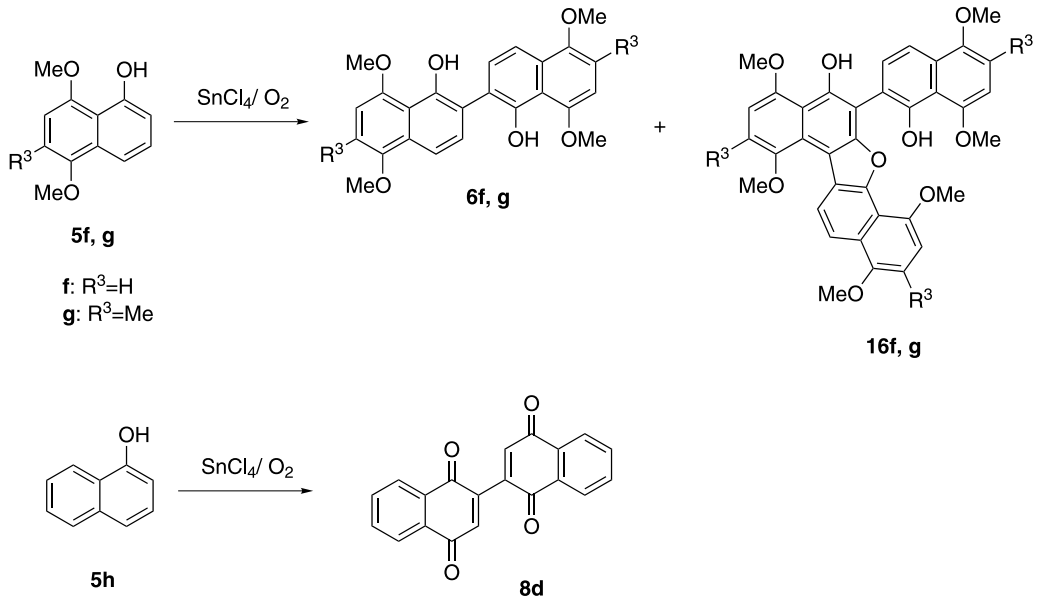
Figure 3. The main NOESY correlations of **11**.

2.2. Proposed mechanism for oxidative reaction of 1-naphthols 5 with $SnCl_4$ in the presence of O_2

To throw light on the formation of **7** and **8** in the reactions of **5a**,**b** with the SC/O_2 system in CH_2Cl_2, the reactions of **6a** or **7a** with the SC/H_2O_2 (hydrogen peroxide) and SC/O_2 reagent systems in CH_2Cl_2 were examined. In the case of **6a**, **7a** and **8a** were obtained with both reagent systems (refer to Table 1, entries 11 and 12). The reaction of **7a** afforded **8a** as a major product in both cases (entries 13 and 14). These results suggest the participation of H_2O_2 or O_2. In addition, the present reaction of NPOH **5** (1 mmol) involves a catalytic cycle of SC (0.25 equiv.) in all cases. Furthermore, there are a number of reports on the generation of H_2O_2 via the hydroperoxy radical ($HO_2\cdot$) by reduction of O_2 in aprotic solvents in the presence of Brønsted acids such as phenol and perchloric acid ($HClO_4$) as proton sources, by means of chemical and electrochemical methods.[12]

The above results and information are consistent with the mechanism illustrated in Scheme 6 for the oxidative reaction of NPOH **5** with SC in the presence of O_2. This reaction is initiated by the formation of the EDA complex **B** via the complex **A** of NPOH **5** with SC ($SnCl_4$) and O_2. The O_2 site in the complex **B** receives one-electron transfer from the anion radical species (SC–$\cdot$) and subsequent one-proton transfer from the NPOH site to reform SC, with the generation of the radical **C** and $HO_2\cdot$. Then, H_2O_2 and O_2 are generated by the disproportionation of two $HO_2\cdot$.[13] The complex **E** or **F** can be formed by the interaction of H_2O_2 or O_2 with complex **D** generated from SC and BNPOH **6**, which is produced by *ortho*/*ortho* radical coupling of two **C** (route b). In the reaction of **5a**,**b**, the quinones **7a**,**b** can be formed via Fenton-like reaction[14a] of **E** or radical autoxidation type reaction[14b] of **F**. The formation of BNPQ **8a**,**b** takes place similarly (route e). On the other hand, the trimeric furan **16** is formed by *para*/*ortho* radical coupling between **H** and **C**, followed by oxidative radical chain reaction in the case of **5f**,**g** (route f).

Although DNF **9a** was obtained in the prolonged reaction of NPOH **5a** with the SC system in the absence of O_2 (Table 1, entry 2), the formation of **9** was not observed at all in the case with the SC/O_2 system in the presence of O_2 (Table 1, entries 3 and 4). The reason for this is considered to be as follows. It is known that SC forms six-coordination complexes (σ-type EDA complexes) with hydroxyarenes,



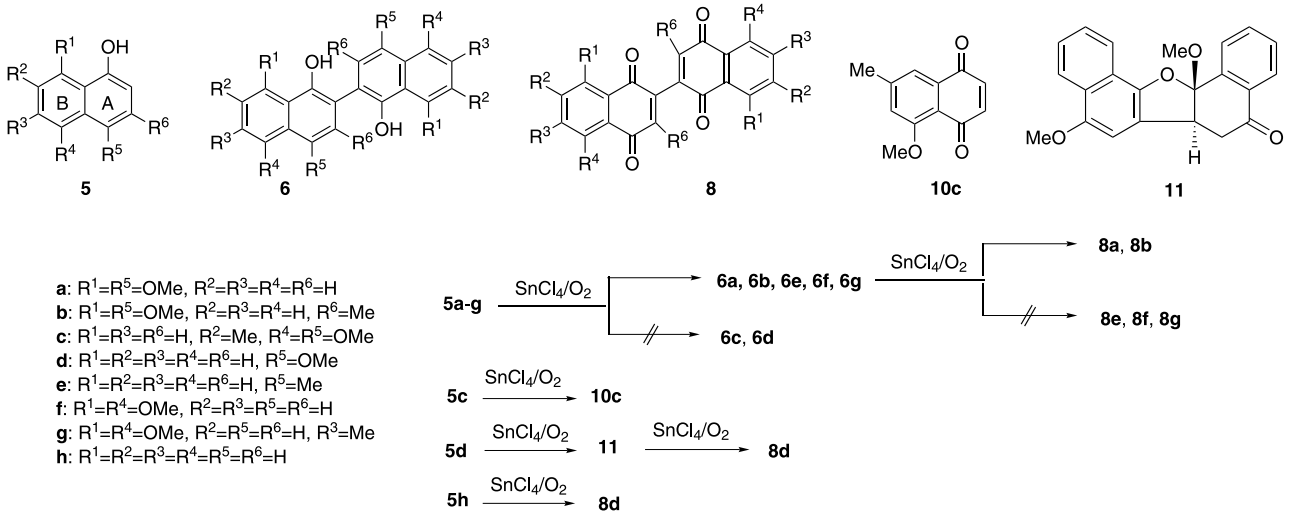
Scheme 4.

Table 3. Reactions of naphthols **5f–h** with the $SnCl_4/O_2$ system at 23 °C[a]

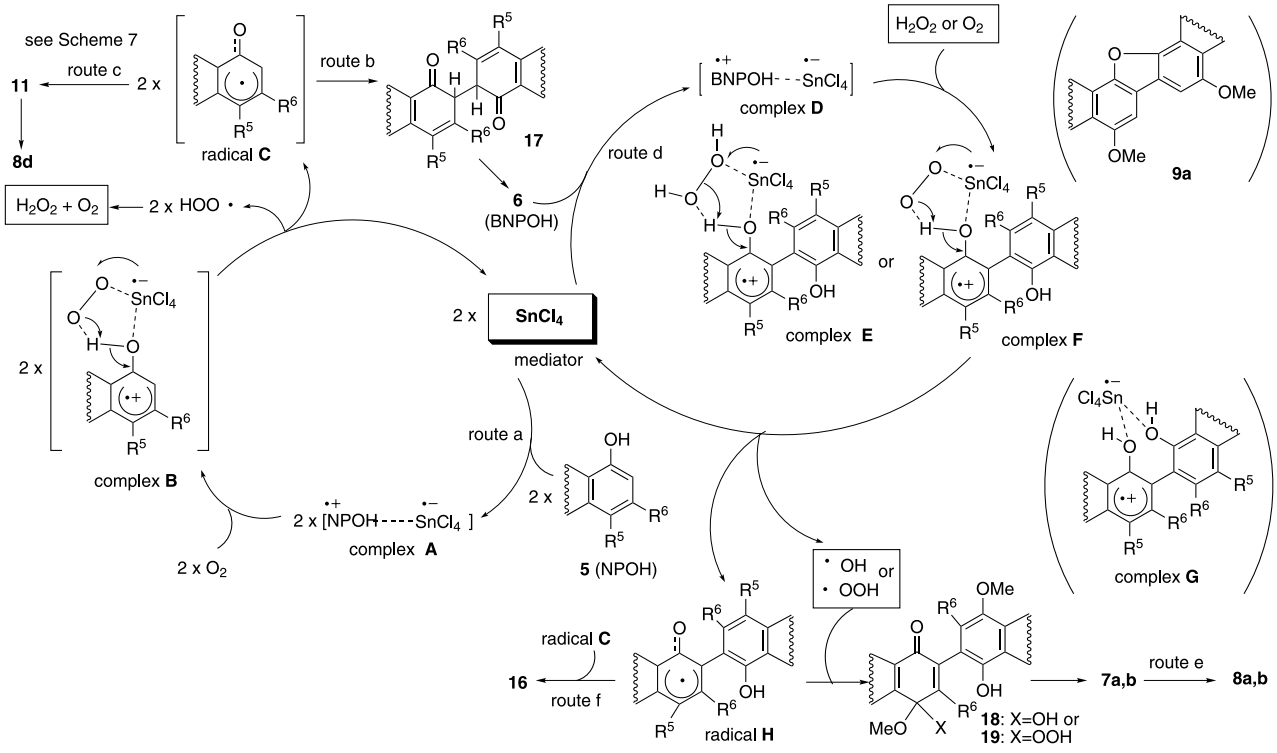
Entry	NPOH	Reagent	Time (h)	Product (%)[b]			Recovered
				6	**16**	**8**	**5** (%)
1	**5f**	$SnCl_4/O_2$	1	20	24	—	33
2	**5f**	$TiCl_4/O_2$	1	20	16	—	47
3	**5g**	$SnCl_4/O_2$	5	8	19	—	53
4[c]	**5g**	$TiCl_4/O_2$	5	5	—	—	60
5	**5h**	$SnCl_4/O_2$	43	—	—	7	3
6[d]	**5f**	$SnCl_4$	4.3	16	—	—	24

[a] The reactions of naphthols (1 mmol) with $SnCl_4$ (0.25 equiv.) were carried out using dioxygen (O_2)-saturated solvent in a sealed tube with stirring under normal laboratory light. Similar results were obtained in the dark.
[b] Isolated yield.
[c] This reaction was carried out with $TiCl_4$ (0.25 equiv.) in place of $SnCl_4$ under otherwise the same conditions as above.
[d] The reaction with $SnCl_4$ (1.3 equiv.) at 100 °C was carried out to afford **6f** along with 1,5,8,12-tetramethoxydinaphtho[1,2-*b*:1′,2′-*d*]furan (8%). This result was reported previously by us (see Ref. 6b).

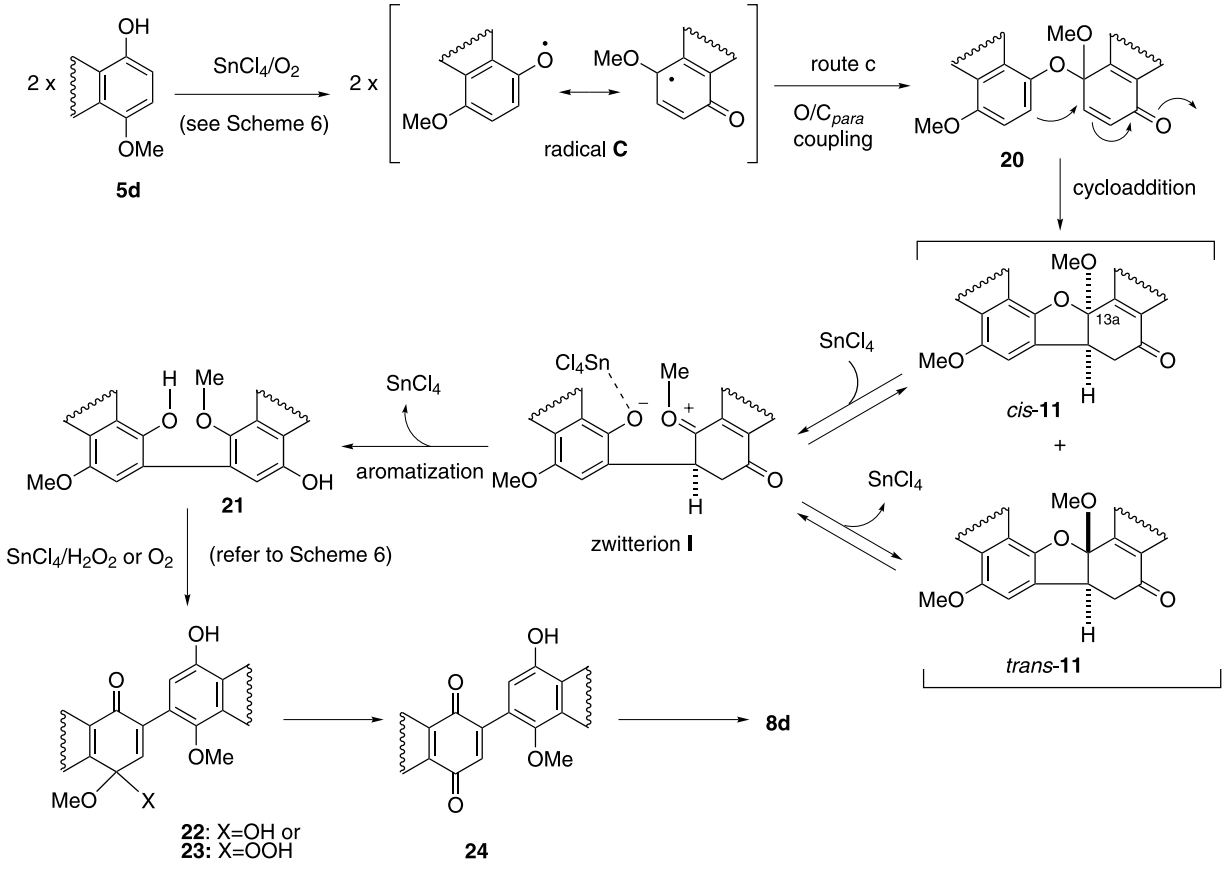
aromatic aldehydes and 1,1′-binaphthols as *O*-donors.[15] In our preceding paper,[6b] we proposed a mechanism for the formation of **9a** via six-coordination complexes **G** between SC and two hydroxyl moieties of BNPOH **6** in the absence of O_2. However, in the case with the SC/O_2 system, the presence of O_2 or H_2O_2 inhibits the formation of the complex **G**. The formation of the complex **E** or **F** of O_2 or H_2O_2 with SC and **6** may be favored over that of the



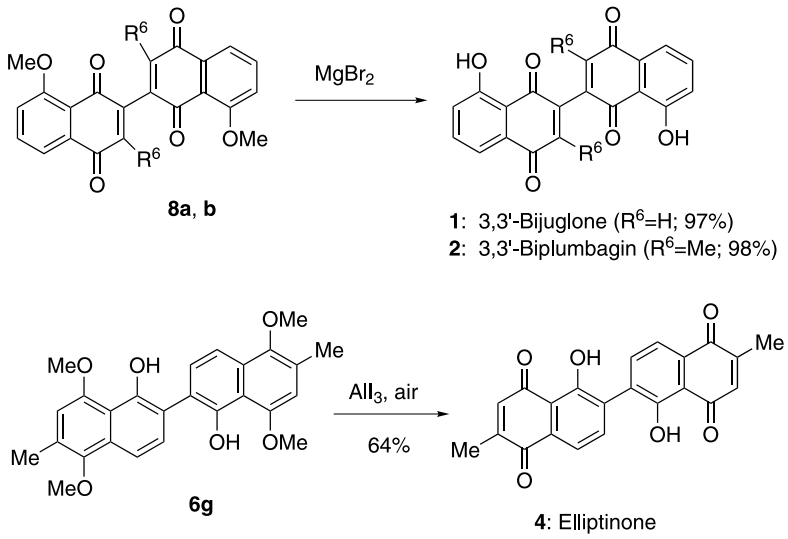
Scheme 5.



Scheme 6. Proposed mechanism for oxidative reaction of 1-naphthols **5** with the $SnCl_4/O_2$ system.



Scheme 7. Proposed mechanism for the formation BNPQ **8d** by the reaction of NPOH **5d** with the SC/O_2 system.



Scheme 8.

complex **G**. Accordingly, the DNF framework, such as **9a**, is not formed in the prolonged reaction of **5** with the SC/O_2 system.[6a,b]

The formation mechanism of **8d** via **11** (route c) by the reaction of **5d** with the SC/O_2 system is postulated to proceed as shown in Scheme 7, based on (i) Table 2 (entries 1, 2) and (ii) the formation of **8d** by the reaction of *trans*-**11** with the same reagent (refer to Scheme 2). The diastereomeric ketals, *cis*-**11** and *trans*-**11** could be first formed by O–C_{para} coupling between two naphthoxyradicals **C**, generated by the SC-mediated oxidative reaction of NPOH **5d**, followed by intramolecular cycloaddition of **20**. Furthermore, the epimerization at C13a of *cis*-**11** is initiated by the opening of the furan ring induced by Lewis acid ($SnCl_4$). The formed zwitterion **I** can undergo ring closure again by nucleophilic attack from the opposite side, thus shifting the equilibrium towards the thermodynamically more stable epimer (*trans*-**11**). BNPQ **8d** could be formed through aromatization of **I** followed by further SC-mediated oxidative reaction of BNPOH **22** (refer to Scheme 6).

SC plays an important role in the oxidative reactions of NPOH in the presence of O_2: it acts not only as a characteristic Lewis acid catalyst, but also as a mediator of the oxidative reaction. On the other hand, O_2 acts as one-electron acceptor from the anion radical species (SC–·) and a one-proton acceptor from NPOH, and as an oxygen source for the formation of BNPQ.

2.3. Biomimetic syntheses of natural products 1, 2 and 4

Finally, we investigated the synthesis of 3,3′-bijuglone (**1**), 3,3′-biplumbagin (**2**) and elliptinone (**4**) from the corresponding **8a**, **8b** and **6g**, prepared by means of the reactions of NPOHs with the SC/O_2 system as shown in Scheme 8. The demethylation of **8a** and **8b** with $MgBr_2$[7c] led to the corresponding 3,3′-bijuglone (**1**; mp 265–267 °C) in 97% yield and 3,3′-biplumbagin (**2**; mp 212–214 °C) in 98% yield. Furthermore, elliptinone (**4**; mp 302–305 °C) was synthesized in 64% yield by the demethylation of **6g** with AlI_3[16] followed by air auto-oxidation. Physical data for the synthetic compounds **1**,[1d–e] **2**[1f–g] and **4**[1i–k] were identical with those of the corresponding natural products.

3. Conclusion

In conclusion, we found a simple method for the synthesis of BNPQ **8** in one step by means of aerobic oxidative dimerization of NPOH **5** with the SC/O_2 system. We have established a facile and biomimetic synthesis of several natural products, 3,3′-bijuglone (**1**), 3,3′-biplumbagin (**2**) and elliptinone (**4**), by utilizing BNPQs **8a**,**b** and BNPOH **6g** prepared by means of the above reactions. The present aerobic oxidative reaction provides a new methodology for constructing 2,2′-binapthoquinones with potential as intermediates for biomimetic synthesis of natural products.

4. Experimental

4.1. General

All melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IR-700 spectrometer, and ^1H and ^{13}C NMR spectra with JEOL JNM-AL300 and JNM-alpha 500 spectrometers, using tetramethylsilane as an internal standard ($CDCl_3$, CD_3COCD_3 and CD_3SOCD_3 solutions). Mass spectra were recorded on a JEOL JMS-D300 or Shimadzu QP-5000 spectrometer. Elemental analyses were done using a Yanaco CHN-MT-3 apparatus. Merck Kieselgel 60 (230–400 mesh), Wako silica gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254} were used for flash column chromatography, column chromatography and thin-layer chromatography, respectively. Each organic extract was dried over $MgSO_4$ or Na_2SO_4. Oxidation potential was measured on a Yanaco P-1100 voltammetric analyzer by cyclic voltammetry in argon-saturated CH_2Cl_2, $MeNO_2$ or MeCN solutions with an Ag/AgCl reference electrode. Tetrabutylammonium perchlorate (0.1 M solution) was used as a supporting electrolyte. Storage and handling of $SnCl_4$: $SnCl_4$ should be stored in a container with silica gel, blue,

medium granule to minimize exposure to moisture. The container should be flushed with N_2 or Ar and tightly sealed. Perform all manipulations under N_2 or argon. All reactions were carried out in an anhydrous state.

4.2. Synthesis of 1-naphthols 5a–j

1-Naphthols **5a**,[7a,b] **5b**,[7c] **5c**,[7d–f] **5e**,[6b] **5f**,[7g] and **5g**[7h] were synthesized according to the protocol reported previously, and **5d** and **5h** are commercially available (Tokyo Kasei Chemical Industries, Ltd, Japan).

4.3. General procedure A for oxidative reaction of NPOHs 5a–j, DNF 11, BNPOHs 6a–7a with $SnCl_4/O_2$ or $TiCl_4/O_2$ system in the presence of dioxygen

$SnCl_4$ or $TiCl_4$ (0.25 equiv.) was added to a solution of the selected substrate (1 mmol) in dioxygen (O_2)-saturated solvent (CH_2Cl_2 or $MeNO_2$; 20 ml) and the mixture was stirred for 5 min with bubbling of O_2 gas at room temperature under normal laboratory light. Then, the reaction mixture was stirred in a sealed tube until disappearance of the substrate (1-naphthols and 2,2′-binaphthyls), except in cases where the starting material was recovered. The reaction mixture was poured into ice water, 10% HCl was added, and the mixture was extracted with $CHCl_3$. The organic layer was washed with H_2O, then dried and concentrated. The residue was purified by flash column chromatography on silica gel.

4.4. General procedure B for oxidative reaction of 6a and 7a with the $SnCl_4/H_2O_2$ system

$SnCl_4$ (1 equiv.) was added to a solution of the selected naphthol (1 mmol) and 30% H_2O_2 (1 mmol) in CH_2Cl_2 (20 ml) and the mixture was stirred for 10 min at room temperature under normal laboratory light in an argon atmosphere. Then, the reaction mixture was stirred for 1.5 h in a sealed tube under the same conditions. The reaction mixture was poured into ice water, 10% HCl was added, and the mixture was extracted with $CHCl_3$. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to flash column chromatography on silica gel. The eluate with AcOEt–hexane (1:6, v/v) gave **7a** and **8a** along with recovered **6a**. Yields are listed in Table 1.

4.5. General procedure C for oxidative reactions of 1-naphthols 5d and 5e with $SnCl_4$ in the absence of dioxygen

$SnCl_4$ (1.3 equiv.) was added to a solution of the selected naphthol (1 mmol) in CH_2Cl_2 (20 ml) and the mixture was stirred for 20 min at room temperature under normal laboratory light in an argon atmosphere. Then, the reaction mixture was heated at 100 °C in a sealed tube with stirring. The reaction mixture was poured into ice water, 10% HCl was added, and the mixture extracted with $CHCl_3$. The organic layer was washed with H_2O, then dried with Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel.

4.5.1. 4,4′,8,8′-Tetramethoxy-2,2′-di-1,1′-naphthol (6a), 1′-hydroxy-4′,8,8′-trimethoxy[2,2′]binaphthalenyl-1,4-dione (7a) and 5,5′-dimethoxy-3,3′-bi-1,4-naphthoquinone (8a).

These compounds were obtained from **5a** by the above general procedure A (with the $SnCl_4/O_2$ system). The residue was subjected to flash column chromatography on silica gel. The eluate with AcOEt–hexane (1:6, v/v) gave **7a** and **8a** along with the recovered **5a**. Yields are listed in Table 1. **6a**: Colorless needles ($CHCl_3$–hexane), mp 207–209 °C. LR-MS *m/z*: 406 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[6b] **7a**: Deep purple needles (hexane–AcOEt), mp 120–122 °C. IR (KBr) cm^{-1}: 3394, 1607. ^1H NMR ($CDCl_3$) δ: 3.95 (3H, s, OMe), 3.99 (3H, s, OMe), 4.01 (3H, s, OMe), 6.72 (1H, s, 3′-H), 6.86 (1H, d, J=7.9 Hz, 7′-H), 7.04 (1H, s, 3-H), 7.30 (1H, d, J=8.2 Hz, 7-H), 7.37 (1H, t, J=7.9, 8.5 Hz, 6′-H), 7.66 (1H, t, J=7.6, 8.2 Hz, 6-H), 7.76 (1H, dd, J=0.9, 7.6 Hz, 5-H), 7.86 (1H, dd, J=1.1, 8.5 Hz, 5′-H), 9.41 (1H, s, OH). ^{13}C NMR ($CDCl_3$) δ: 55.9 (C4′-O*Me*), 56.1 (C8-O*Me*), 56.5 (C8′-O*Me*), 105.6 (C7′), 107.1 (C3′), 114.9 (C2′), 115.3 (C8a′), 115.9 (C5′), 117.8 (C7), 118.6 (C5), 121.1 (C8a), 126.3 (C6′), 128.9 (C4a′), 134.35 (C3), 134.38 (C6), 134.41 (C4a), 146.3 (C1′), 147.8 (C4′), 150.9 (C2), 156.4 (C8′), 159.6 (C8), 183.2 (C1), 185.3 (C4). LR-MS *m/z*: 390 (M^+). HR-MS Calcd for $C_{23}H_{18}O_6$: 390.1100, Found: 390.1170. Anal. Calcd for $C_{23}H_{18}O_6$: C, 70.76; H, 4.65. Found: C, 70.56; H, 4.62. **8a**: yellow needles ($CHCl_3$–hexane), mp 202–204 °C. IR (KBr) cm^{-1}: 1644, 1604, 1570. ^1H NMR ($CDCl_3$) δ: 3.99 (6H, s, 5 and 5′-OMe), 6.95 (2H, s, 2 and 2′-H), 7.33 (2H, d, J=8.2 Hz, 6 and 6′-H), 7.71 (2H, t, J=7.9, 8.2 Hz, 7 and 7′-H), 7.76 (2H, d, J=7.9 Hz, 8 and 8′-H). ^{13}C NMR ($CDCl_3$) δ: 56.5 (C5 and C5′-O*Me*), 118.2 (C6 and C6′), 119.1 (C8 and C8′), 119.8 (C5a and C5′a), 134.2 (C8a and C8a′), 134.8 (C2 and C2′), 135.2 (C7 and C7′), 146.8 (C3 and C3′), 160.1 (C5 and C5′), 182.1 (C4 and C4′), 184.4 (C1 and C1′). LR-MS *m/z*: 374 (M^+). HR-MS Calcd for $C_{22}H_{14}O_6$: 374.0790, Found: 374.0762. Anal. Calcd for $C_{22}H_{14}O_6$: C, 70.59; H, 3.77. Found: C, 70.49; H, 3.78.

4.5.2. 1,5,8,12-Tetramethoxydinaphtho[1,2-*b*:1′,2′-*d*]furan (9a).

This compound was obtained as colorless needles ($CHCl_3$–hexane), mp over 300 °C from **5a** by the above general procedure A (with the $SnCl_4/O_2$ or $TiCl_4/O_2$ system). LR-MS *m/z*: 388 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[6b]

4.5.3. 4,4′,8,8′-Tetramethoxy-3,3′-dimethyl[2,2′]di-1,1′-naphthol (6b), 1′-hydroxy-8,4′,8′-trimethoxy-3,3′-dimethyl[2,2′]binaphthalenyl-1,4-dione (7b) and 5,5′-dimethoxy-2,2′-dimethyl[3,3′]binaphthoquinone (8b).

These compounds were obtained from **5b** by the above general procedure A (with the $SnCl_4/O_2$ system). **6b**: Colorless needles ($CHCl_3$–MeOH), mp 251–252 °C. LR-MS *m/z*: 434 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[6b] **7b**: Orange amorphous powder ($CHCl_3$–MeOH), mp 261–263 °C. IR (KBr) cm^{-1}: 3384, 1654, 1582. ^1H NMR ($CDCl_3$) δ: 1.59 (3H, s, Me), 2.17 (3H, s, Me), 3.84 (3H, s, OMe), 3.96 (3H, s, OMe), 4.00 (3H, s, OMe), 6.78 (1H, d, J=8.4 Hz, Ar-H), 7.29 (1H, dd, J=1.1, 7.5 Hz, Ar-H), 7.37 (1H, t, J=7.5 Hz, Ar-H), 7.68 (1H, t, J=8.4 Hz, Ar-H), 7.71 (1H, d, J=8.4 Hz, Ar-H), 7.84 (1H, dd, J=1.1, 7.5 Hz, Ar-H), 9.29 (1H, s, OH). LR-MS *m/z*: 418 (M^+). HR-MS Calcd for $C_{25}H_{22}O_6$: 418.1417, Found: 418.1441. Anal. Calcd for

$C_{25}H_{22}O_6$: C, 71.76; H, 5.30. Found: C, 71.46; H, 5.32. **8b**: yellow needles ($CHCl_3$–hexane), mp 261–263 °C. LR-MS *m/z*: 402 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[6b]

4.5.4. 5-Methoxy-7-methyl-1,4-naphthoquinone (10c). This compound was obtained as yellow needles ($CHCl_3$–hexane), mp 169.5–170 °C (lit.[17a] 166.5–167.5 °C) from **5c** by the above general procedure A (with the $SnCl_4/O_2$ system). LR-MS *m/z*: 202 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[6b]

4.5.5. 8,13a-Dimethoxy-6a,13a-dihydro-6H-dinaphtho-[1,2-*b*;2′,1′-*d*]furan-5-one (11). This compound was obtained as yellowish-green amorphous powder (benzene–hexane), mp 228–229 °C from **5d** by the above general procedure A (with the $SnCl_4/O_2$ system). IR (KBr) cm^{-1}: 1686, 1598. ^1H NMR ($CDCl_3$) δ: 2.63 (1H, dd, J=2.6, 12.9 Hz, 6α-H), 2.76 (1H, dd, J=3.7, 12.9 Hz, 6β-H), 3.69 (3H, s, 13a-OMe), 3.91 (3H, s, 8-OMe), 4.14 (1H, dd, J=2.6, 3.7 Hz, 6a-H), 6.71 (1H, s, 7-H), 7.43–7.52 (3H, m, Ar-H), 7.71 (1H, dt, J=1.5, 7.5 Hz, 2-H), 7.84 (1H, dd, J=1.5, 7.7 Hz, 4-H), 7.96–8.05 (3H, m, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 28.11 (C6), 46.93 (C6a), 49.66 (C13a–O*Me*), 55.55 (C8–O*Me*), 97.23 (C13a), 103.59 (C7), 110.39 (C6b), 120.29 (C9 or C12), 121.17 (C9 or C12), 124.64 (C12a), 124.82 (C1), 125.29 (C8a), 125.48 (C4), 125.66 (C10 or C11), 126.03 (C10 or C11), 128.91 (C3), 129.24 (C12b), 134.03 (C2), 141.15 (C4a), 141.83 (C13b), 148.98 (C8), 193.64 (C5). LR-MS *m/z*: 346 (M^+). HR-MS Calcd for $C_{22}H_{18}O_4$: 346.1200, Found: 346.1224. Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.39; H, 5.27.

4.5.6. 2,2′-Binaphthalenyl-1,4,1′,4′-tetraone (8d). This compound was obtained as yellow needles ($CHCl_3$), mp 288 °C (decomp) (lit.[17b,17c] 270 °C, decomp.) from **5d** by the above general procedure A (with the $SnCl_4/O_2$ system). IR (KBr) cm^{-1}: 1664, 1613, 1587. ^1H NMR ($CDCl_3$) δ: 7.07 (2H, s, 3 and 3′-H), 7.75–7.80 (4H, m, Ar-H), 8.12–8.16 (4H, m, Ar-H). LR-MS *m/z*: 314 (M^+). HR-MS Calcd for $C_{20}H_{10}O_4$: 314.0576, Found: 314.0561. Anal. Calcd for $C_{20}H_{10}O_4$: C, 76.43; H, 3.21. Found: C, 76.23; H, 3.19.

4.5.7. 4,4′-Dimethoxy[2,2′]binaphthalenyl-1,1′-diol (6d). This compound was obtained as colorless needles (benzene), mp 223–224 °C from **5d** by the above general procedure D (with $SnCl_4$). LR-MS *m/z*: 346 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[6b]

4.5.8. Reaction of 11 with *c*-HCl in MeOH. A solution of **11** (50 mg, 0.15 mmol) and conc. HCl (6.3 ml) in MeOH (6.3 ml) was refluxed with stirring at 110 °C for 5 h. The reaction mixture was poured into ice–water and extracted with CH_2Cl_2. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to flash column chromatography on silica gel using AcOEt–hexane (1:10, v/v) as an eluent to give 5,8-dimethoxydinaphtho[1,2-*b*;2′,1′-*d*]furan (**12**) (27%) and 8-methoxy-dinaphtho[1,2-*b*;2′,1′-*d*]furan-5-ol (**13**) (24%). **12**: Pale blue needles (benzene), mp 215.5–216.5 °C (lit.[10] 216–217 °C). IR (KBr) cm^{-1}: 1598, 1583. ^1H NMR ($CDCl_3$) δ: 4.12 (6H, s, 5 and 8-OMe), 7.23 (2H, s, 6 and 7-H), 7.54 (2H, ddd, J=1.3, 7.0, 8.4 Hz, 2 and 11-H, or 3 and 10-H), 7.67 (2H, ddd, J=1.3, 7.0, 8.4 Hz, 2 and 11-H, or 3 and 10-H), 8.37 (2H, broad d, J=8.5 Hz, 1 and 12-H, or 4 and 9-H), 8.47 (2H, broad d, J=7.7 Hz, 1 and 12-H, or 4 and 9-H). LR-MS *m/z*: 328 (M^+). HR-MS Calcd for $C_{22}H_{16}O_3$: 328.1095, Found: 328.1146. Anal. Calcd for $C_{22}H_{16}O_4$: C, 80.47; H, 4.91. Found: C, 80.57; H, 4.95. **13**: Colorless needles (AcOEt–hexane), mp 222–223 °C (lit.[10] 307 °C). IR (KBr) cm^{-1}: 3316, 1633, 1599. ^1H NMR ($CDCl_3$) δ: 4.01 (3H, s, 5-OMe), 7.41 (1H, s, 7-H), 7.43 (1H, s, 6-H), 7.44–7.65 (5H, m, Ar-H), 8.23–8.38 (3H, m, Ar-H), 9.01 (1H, s, 8-OH). LR-MS *m/z*: 314 (M^+). HR-MS Calcd for $C_{21}H_{14}O_3$: 314.33, Found: 314.33. Anal. Calcd for $C_{21}H_{14}O_3$: C, 80.24; H, 4.49. Found: C, 80.20; H, 4.50.

4.6. Oxidation of 11 with the SC/O_2 system

The reaction of **11** with the SC/O_2 system was carried out at 23 °C for 12 h according to the above general procedure A (with the $SnCl_4/O_2$ system) to give **8d** (36%).

4.7. Methylation of 13

CH_3I (12 μl, 0.02 mmol) was added to a solution of **13** (15 mg, 0.05 mmol) and anhydrous K_2CO_3 (66 mg) in dry DMF (6 ml), and the solution was stirred at 23 °C for 4 h with vigorous stirring. The reaction mixture was poured into ice–water, neutralized with 10% HCl, and extracted with ether. The organic layer was washed with H_2O, dried and concentrated. The residue was purified by recrystallization from MeOH to yield **12** (91%).

4.7.1. 4,4′-Dimethyl[2,2′]binaphthalenyl-1,1′-diol (6e). This compound was obtained as a colorless amorphous powder ($CHCl_3$–hexane), mp 219–220 °C from **5e** by the above general procedure A (with the $SnCl_4/O_2$ system) or the general procedure D (with $SnCl_4$). LR-MS *m/z*: 314 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[6b]

4.7.2. 5,5′,8,8′-Tetramethoxy[2,2′]di-1,1′-naphthol (6f) and 12-(1′-hydroxy-5′,8′-dimethoxy-naphthalen-2′-yl)-1,4,7,10-tetramethoxy-13-oxadibenzo[a,g]fluoren-11-ol (16f). These compounds were obtained from **5f** according to the above general procedure A (with the $SnCl_4/O_2$ system). **6f**: Colorless needles (hexane–AcOEt), mp 257–260.5 °C. LR-MS *m/z*: 406 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[6b] **16f**: Light brown amorphous powder ($CHCl_3$–MeOH), mp 263–265 °C. IR (KBr) cm^{-1}: 3346, 1612, 1449. ^1H NMR (CD_3SOCD_3) δ: 3.53 (3H, s, 7-OMe), 3.96 (3H, s, 10-OMe), 3.99 (3H, s, 5′-OMe), 4.01 (3H, s, 8′-OMe), 4.10 (6H, s, 1- and 4-OMe), 6.87 (1H, d, J=8.5 Hz, 9-H), 6.89 (1H, d, J=8.5 Hz, 8-H), 6.92 (1H, d, J=8.6 Hz, 6′-H), 6.96 (1H, d, J=8.6 Hz, 7′-H), 7.14 (1H, d, J=8.6 Hz, 2-H), 7.20 (1H, d, J=8.6 Hz, 3-H), 7.59 (1H, d, J=8.6 Hz, 3′-H), 7.74 (1H, d, J=8.6 Hz, 4′-H), 8.06 (1H, d, J=9.2 Hz, 5-H), 8.71 (1H, d, J=9.2 Hz, 6-H), 9.94 (1H, s, 1′-OH), 10.63 (1H, s, 11-OH). ^{13}C NMR (CD_3SOCD_3) δ: 55.34 (4-O*Me*), 55.64 (5′-O*Me*), 55.66 (10-O*Me*), 56.28 (7-O*Me*), 56.31 (8′-O*Me*), 57.00 (1-O*Me*), 104.15 (C6′ or C7′), 104.17 (C6′ or C7′), 104.19 (C9), 105.12 (C2), 106.74 (C3), 107.39 (C2′), 107.53 (C8), 108.23 (C12), 111.03 (C4′), 113.48 (C13b), 113.73 (C10a), 114.93 (C6c), 115.09 (C8a′), 115.78 (C5), 121.46 (C4a), 122.09 (C6a), 123.48

(C6), 123.52 (C6b), 127.19 (C4a′), 130.29 (C3′), 148.28 (C7), 149.05 (C10), 149.27 (C5′), 149.31 (C13a), 149.73 (C8′), 150.09 (C4), 150.54 (C1), 151.20 (C11), 151.75 (C1′), 154.08 (C12a). LR-MS *m/z*: 606 (M^+). HR-MS Calcd for $C_{36}H_{30}O_9$: 606.1881, Found: 606.1887. Anal. Calcd for $C_{36}H_{30}O_9$: C, 71.28; H, 4.98. Found: C, 70.98; H, 5.05.

4.7.3. 5,5′,8,8′-Trimethoxy-6,6′-dimethyl[2,2′]di-1,1′-naphthol (6g) and 12-(1-hydroxy-5,8-dimethoxy-6-methylnaphthalen-2-yl)-1,4,7,10-tetramethoxy-3,8-dimethyl-13-oxadibenzo[a,g]fluoren-11-ol (16g). These compounds were obtained from **5g** by the above general procedure A (with the $SnCl_4/O_2$ system). **6g**: Colorless needles (ether–hexane), mp 229–232 °C. LR-MS *m/z*: 434 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[6b] **16g**: Pale green amorphous powder ($CHCl_3$–hexane), mp 249–251 °C. IR (KBr) cm^{-1}: 3372, 1619, 1581. ^1H NMR (CD_3SOCD_3) δ: 2.45 (3H, s, 3-Me), 2.49 (3H, s, 6′-Me), 2.62 (3H, s, 8-Me), 3.64 (3H, s, 1-OMe), 3.71 (3H, s, 7-OMe), 3.90 (3H, s, 4-OMe), 3.91 (3H, s, 5′-OMe), 4.08 (3H, s, 8′-OMe), 4.17 (3H, s, 10-OMe), 6.85 (1H, s, 2-H), 6.93 (1H, s, 7′-H), 7.12 (1H, s, 9-H), 7.63 (1H, d, J=8.5 Hz, 4′-H), 7.66 (1H, d, J=8.5 Hz, 3′-H), 7.99 (1H, d, J=9.2 Hz, 5-H), 8.80 (1H, d, J=9.2 Hz, 6-H), 9.73 (1H, s, 1′-OH), 10.35 (1H, s, 11-OH). ^{13}C NMR (CD_3SOCD_3) δ: 15.50 (C6′-*Me*), 15.59 (C3-*Me*), 15.88 (C8-*Me*), 55.88 (C1-O*Me*), 56.21 (C8′-O*Me*), 56.82 (C10-O*Me*), 60.21 (C7 or C5′-O*Me*), 60.25 (C7 or C5′-O*Me*), 60.48 (C4-O*Me*), 106.43 (C6b), 107.21 (C12), 107.31 (C7′), 107.97 (C9), 109.92 (C2), 110.87 (C4′), 112.28 (C10a), 112.45 (C13b), 113.67 (C2′), 114.10 (C8a′), 116.07 (C5), 120.36 (C6a), 123.67 (C6), 123.69 (C6c), 125.05 (C3), 125.43 (C6′), 126.30 (C4a), 127.96 (C8), 129.77 (C4a′), 131.03 (C3′), 146.84 (C4), 147.14 (C5′), 147.81 (C7), 149.82 (C13a), 150.29 (C1), 151.41 (C11), 151.75 (C8′), 152.10 (C1′), 152.59 (C10), 154.48 (C12a). LR-MS *m/z*: 648 (M^+). HR-MS Calcd for $C_{39}H_{36}O_9$: 648.2349, Found: 648.2386. Anal. Calcd for $C_{39}H_{36}O_9$: C, 72.21; H, 5.59. Found: C, 72.41; H, 5.60. Anal. Calcd for $C_{39}H_{36}O_9$: C, 72.21; H, 5.59. Found: C, 72.15; H, 5.61.

4.7.4. Synthesis of 3,3′-bijuglone (1) from 8a. Magnesium bromide (anhydrous)[7c] (2.2 g, 12 mmol) was added to a solution of **8a** (182 mg, 0.5 mmol) dissolved in absolute toluene (50 ml) and the whole was refluxed for 12 h. The reaction was quenched with cooled water and saturated NH_4Cl solution, and the whole was stirred for 30 min. The mixture was extracted with $CHCl_3$. The organic layer was washed with H_2O, dried with Na_2SO_4 and concentrated. The residue was subjected to flash chromatography ($CHCl_3$–AcOEt–hexane=3:1:4) to yield 183 mg (98%) of 8,8′-dihydroxy[2,2′]binaphthalenyl-1,4,1′,4′-tetraone (**1**) as an orange amorphous powder (benzene), mp 265–267 °C (decomp.) (lit.[1e] 270 °C), 173 mg (97%). IR (KBr) cm^{-1}: 1663, 1627, 1454, 1293. ^1H NMR ($CDCl_3$) δ: 7.04 (2H, s, 2 and 2′-H), 7.34 (2H, m, Ar-H), 7.70 (4H, m, Ar-H), 11.76 (2H, s, 5 and 5′-OH). LR-MS *m/z*: 346 (M^+). HR-MS Calcd for $C_{20}H_{10}O_6$: 346.0478, Found: 346.0472. Anal. Calcd for $C_{20}H_{10}O_6$: C, 69.37; H, 2.91. Found: C, 69.27; H, 2.90.

4.7.5. Synthesis of 3,3′-biplumbagin (2) from 8b. 8,8′-Dihydroxy-3,3′-dimethyl[2,2′]binaphthalenyl-1,4,1′,4′-tetraone (**2**) was synthesized as yellow needles ($CHCl_3$–hexane), mp 212–214 °C (lit.[1g] 214–217 °C) from **8b** in 98% yield by a procedure similar to that used for **1**. IR (KBr) cm^{-1}: 1665, 1645, 1455, 1280, 1244, 1200, 1057, 1023, 741. ^1H NMR ($CDCl_3$) δ: 2.08 (6H, s, C3 and C3′-Me), 7.29 (2H, dd, J=1.3, 8.3 Hz, 7 and 7′-H), 7.66 (2H, t, J=8.3 Hz, C 6 and C6′ H), 7.73 (2H, dd, J=1.3, 8.3 Hz, C5 and C5′-H), 11.73 (2H, s, 5 and 5′-H). MS *m/z*: 374 (M^+). HR-MS Calcd for $C_{22}H_{14}O_6$: 374.0790. Found 374.0783. Anal. Calcd for $C_{22}H_{14}O_6$: C, 70.59; H, 3.77. Found: C, 70.79; H, 3.75.

4.7.6. Synthesis of elliptinone (4) from 6g. A solution[16] of Al powder (416.2 mg, 15.4 mmol) and I_2 (2936 mg, 11.6 mmol) in absolute benzene (6.7 ml) was stirred under an argon atmosphere for 3 h. A solution of **6g** (21.7 mg, 0.05 mmol) in absolute benzene (16.7 ml) was added to the above solution (AlI_3) and the whole was stirred at ambient temperature for 3 h, then further stirred under air for 1 h. The reaction mixture was poured into ice water and acidified with 10% HCl. The whole was extracted with $CHCl_3$. The organic layer was washed with H_2O, then dried with Na_2SO_4 and concentrated. The residue was subjected to flash chromatography (AcOEt–hexane=1:2) to yield 12 mg (64%) of 1,1′-dihydroxy-6,6′-dimethyl[2,2′]binaphthalenyl-5,8,5′,8′-tetraone (**4**) as orange red needles ($CHCl_3$–hexane), mp 302–305 °C (lit.[1k] 300–305 °C). IR (KBr) cm^{-1}: 3426, 1640, 1603, 1417, 1353, 1258. ^1H NMR ($CDCl_3$) δ: 2.23 (6H, d, C6 and C6′-Me), 6.85 (2H, q, J=1.5 Hz, C7 and C7′-H), 7.73 (4H, s, C 3, 4 and C3′, 4′-H), 12.50 (2H, s, C1 and C1′-OH). ^{13}C NMR ($CDCl_3$) δ: 16.5, 115.3, 118.7, 131.2, 131.9, 135.5, 137.7, 149.8, 158.9, 184.5, 190.5. MS *m/z*: 374 (M^+). HR-MS Calcd for $C_{22}H_{14}O_6$: 374.0790. Found 374.0769. Anal. Calcd for $C_{22}H_{14}O_6$: C, 70.59; H, 3.77. Found: C, 70.49; H, 3.80.

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Allyl protecting group mediated intramolecular aglycon delivery (IAD): synthesis of α-glucofuranosides and β-rhamnopyranosides

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Received 8 June 2004; revised 6 July 2004; accepted 28 July 2004

Available online 27 August 2004

Abstract—The use of allyl protecting group mediated intramolecular aglycon delivery (IAD) as a strategy for intramolecular glycosylation has been extended to allow the stereoselective synthesis of α-glucofuranosides and β-rhamnopyranosides, in a totally stereoselective fashion. The efficiency of intramolecular glycosylation is dependent on the protecting group pattern of the glycosyl donor, and on the steric bulk of the glycosyl acceptor.

1. Introduction

The formal sub-division of glycosidic linkages into two categories depending on whether the 2-hydroxyl group is formally *cis* or *trans* to the anomeric substituent is strategically useful when planning the synthesis of a particular oligosaccharide. The use of participating protecting groups on the 2-hydroxyl of a glycosyl donor readily allows the stereoselective formation of 1,2-*trans* glycosidic linkages,[1] and therefore the construction of glycosides and oligosaccharides containing 1,2-*trans* linkages may be readily achieved by employing monosaccharide building blocks which posses 2-*O*-acyl protection. However, the stereoselective synthesis of glycosides and oligosaccharides containing 1,2-*cis* linkages is considerably more difficult. At the very least, the presence of such 1,2-*cis* linkages necessitates the use of glycosyl donors with non-participating protecting groups at the 2-position. However, in general, intermolecular glycosylation reactions of such donors are very rarely completely stereoselective,[2] and the undesired anomer must be separated, if possible, and discarded.

One of the most ingenious approaches to overcome this problem of stereoselectivity is to temporarily attach, or 'tether', the glycosyl acceptor to the C-2 hydroxyl of the glycosyl donor. This process can then be followed by a stereospecific intramolecular glycosylation, or Intramolecular Aglycon Delivery (IAD), wherein the aglycon is delivered to the same face of the glycosyl donor as the C-2 hydroxyl, hence forming a 1,2-*cis* linkage. The most notable applications of IAD to the synthesis of β-mannosides have arisen from the laboratories of Hindsgaul,[3] Stork,[4] and Ogawa,[5] whilst Bols extended the Stork 'silicon tether' approach to the synthesis of α-glucosides.[6] Following on from methodological developments[7] of the original Hindsgaul IAD approach,[3] we recently reported the development of an IAD strategy based on the use of glycosyl donors possessing allyl protection of the 2-hydroxyl group.[8] Herein the 2-*O*-allyl protecting group is isomerised to yield an enol ether, which can then undergo iodonium ion mediated tethering of a range of aglycon alcohols. Subsequent intramolecular glycosylation then yields the 1,2-*cis* glycoside product, with complete control of

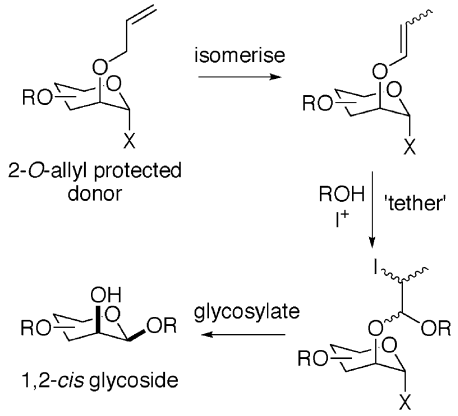

Figure 1.

Keywords: Carbohydrates; Glycosylation; Stereocontrol; Thioglycosides; Intramolecular aglycon delivery (IAD).
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doi:10.1016/j.tet.2004.07.083

anomeric stereochemistry (Fig. 1). This strategy has been applied to allow the synthesis of a variety of β-mannnopyranosides and α-glucopyranosides, using either thioglycosides[9] or glycosyl fluorides[10] as donors, and in addition, both steps have also been achieved in a one-pot reaction.[9]

Despite considerable methodological investigation into the development of IAD, this type of intramolecular glycosylation approach has not yet become a widely and generally used approach for glycoside and oligosaccharide synthesis. This is perhaps in part due to the limited number of examples of the different types of 1,2-*cis* glycosidic linkages that have so far been prepared by this strategy.[11] In particular, the vast majority of work published to date[12] has focused on the synthesis of the notorious β-*manno* linkage, which, although it forms part of the core *N*-glycan pentasaccharide, does not otherwise have particularly widespread occurrence in nature. In order to begin to address this problem, and hopefully expand the utility of IAD as a method for stereoselective glycosylation in a more general context, we detail herein extensions of the allyl IAD approach to other 1,2-*cis* glycosides, namely α-glucofuranosides and β-rhamnopyranosides.

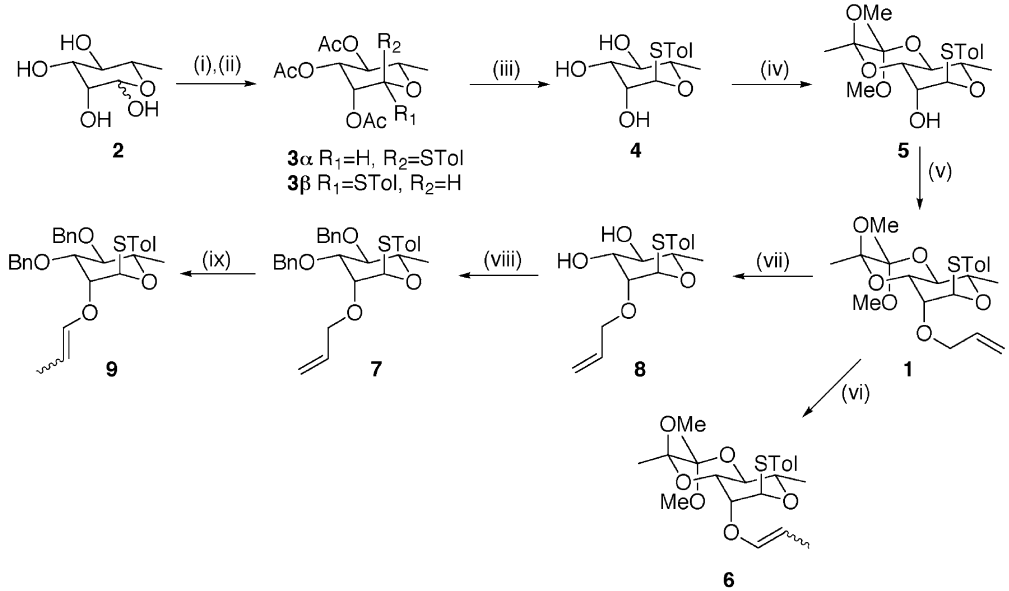
2. Results and discussion

2.1. Synthesis of β-rhamnopyranosides

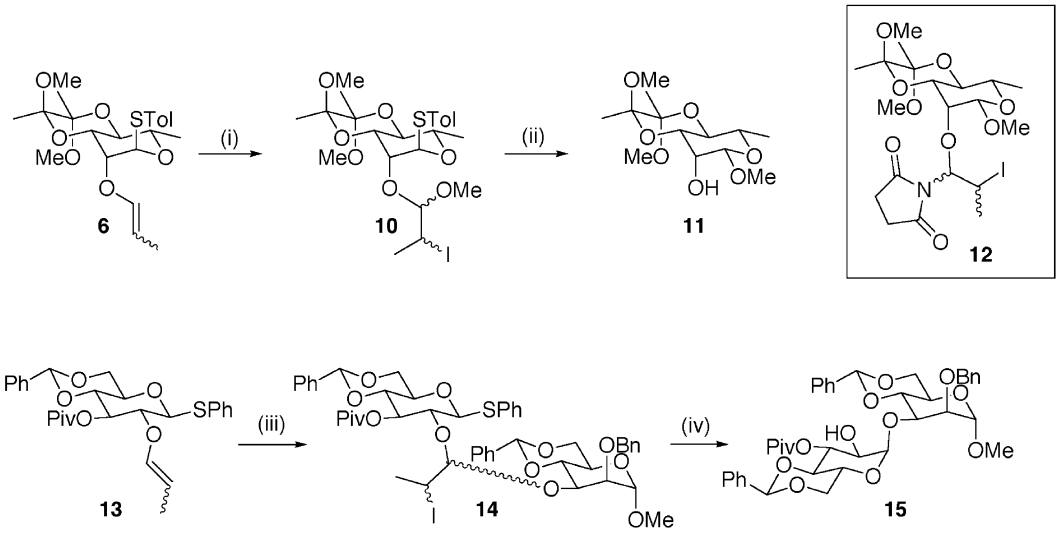
2.1.1. Synthesis of glycosyl donors. The allyl IAD approach requires selective access to the 2-hydroxyl of the glycosyl donor. As rhamnose is a 6-deoxy sugar, any protecting group strategy therefore only requires differentiation of the axial 2-hydroxyl from the equatorial 3- and 4-hydroxyl groups, and this may be most readily achieved by the use of a butane diacetal (BDA) protecting group.[13] The BDA protected rhamnose thioglycoside **1** was therefore chosen as an initial donor for study. L-Rhamnose **2** was peracetylated using acetic anhydride in combination with iodine[14] to give a tetraacetate which was then directly treated with *para*-thiocresol and $BF_3 \cdot OEt_2$ to give thioglycosides **3α/3β** as a separable 3.6:1 α/β mixture (76% yield over two steps, Scheme 1). Zemplen deacetylation of the pure α-anomer **3α** gave the triol **4** (97% yield). Treatment of triol **4** with butanedione and trimethyl orthoformate in methanol, in the presence of an acid catalyst as described by Ley,[13b] afforded the selectively 3,4-protected derivative **5** (74% yield). Allylation with sodium hydride and allyl bromide gave the fully protected sugar **1** (83% yield). Finally, isomerisation of the allyl group by treatment with Wilkinson's catalyst[15] yielded the enol ethers **6** as substrates for tethering and glycosylation of aglycon alcohols (95% yield).

Protection by 1,2-diacetal groups, such as BDA, is known to reduce the reactivity of a glycosyl donor, and indeed such torsional deactivation has been successfully applied in a reactivity tuning approach to one-pot oligosaccharide synthesis.[16] In order to investigate any potential effect of BDA protection on the efficiency of the intramolecular glycosylation reaction inherent in the IAD approach, glycosyl donor **1** was also elaborated into the dibenzylated donor **7**. Thus, BDA protected donor **1** was treated with aqueous trifluroacetic acid to afford the diol **8** (95% yield), which was then benzylated by treatment with sodium hydride and benzyl bromide to give the benzyl-protected donor **7** (88% yield). Finally, **7** was isomerised by treatment with Wilkinson's catalyst, as before, to give the required enol ethers **9** as substrates for subsequent tethering and glycosylation (80% yield, Scheme 1).

2.1.2. Tethering and intramolecular glycosylation reactions. Investigations initially focused on the use of the more readily available BDA protected donors. Enol ethers **6** were treated with *N*-iodosuccinimide (NIS) and methanol, and the desired mixed acetals **10** were obtained in good yield



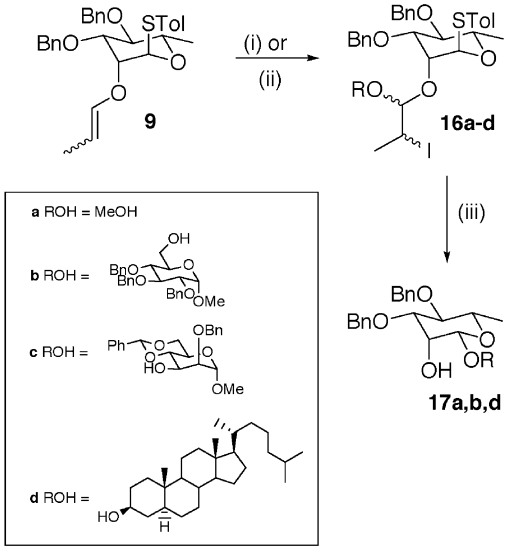
Scheme 1. (i) I_2, Ac_2O, rt; (ii) TolSH, $BF_3 \cdot OEt_2$, DCM, rt, 76% over 2 steps (**3α**:**3β**, 3.6:1); (iii) Na, MeOH, rt, 97%; (iv) $CH_3C(O)C(O)CH_3$, $CH(OMe)_3$, CSA, MeOH, 75 °C, 74%; (v) allyl bromide, DMF, NaH, 0 °C, 83%; (vi) Wilkinson's catalyst, BuLi, THF, 70 °C, 95%; (vii) TFA/H_2O (9:1), 95%; (viii) BnBr, DMF, NaH, 0 °C, 88%; (ix) Wilkinson's catalyst, BuLi, THF, 70 °C, 80%.



Scheme 2. (i) NIS, MeOH, DCE, −40 °C→rt, 96%; (ii) NIS, DTBMP, AgOTf, DCE, 50 °C, 29%; (iii) NIS, methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside, DTBMP, CH_2Cl_2, −40 °C→rt, 60%; (iv) NIS, DTBMP, AgOTf, DCE, rt, 70%.

(Scheme 2). However, when tethered material **10** was treated under a range of reaction conditions commonly used for the activation of thioglycosides, the desired methyl β-rhamnoside **11** was only obtained in poor yield: the best yield (30%) was obtained by the use of NIS and silver triflate in the presence of di-*tert*-butylmethyl pyridine (DTBMP) in dichloroethane (DCE) as solvent, at 50 °C; all reactions required heating to proceed at an appreciable rate indicating torsional deactivation of the glycosyl donor. In all reactions in which NIS was used as activator, succinimide-trapped products, such as **12**, were observed to a varying degree, which was found to be concentration dependent. Despite the disappointing efficiency of this intramolecular glycosylation process, it was noted that no α-rhamnoside products were observed in any reaction, and the low yields were perplexing as no other major products were isolated. This observation that allyl-mediated IAD does not work efficiently for BDA-protected donors in the *rhamno* series, is particularly interesting in light of results obtained by Ogawa which indicated that *para*-methoxybenzyl (PMB) mediated IAD worked more efficiently for glycosyl donors that possessed cyclic 4,6-protection,[5c] and which could therefore also be considered as torisionally deactivated. It was therefore thought prudent at this juncture to investigate if allyl-mediated IAD was actually compatible with cyclic 4,6-protection of the glycosyl donor. To this end, the enol ethers **13**[17] were tethered to a secondary carbohydrate alcohol to give mixed acetals **14**. Intramolecular glycosylation of **14**, mediated by NIS and silver triflate, proceeded smoothly to give the α-*gluco* disaccharide **15** in good yield as the sole product (Scheme 2). This result therefore indicates that whilst allyl mediated IAD is apparently not compatible with 3,4-BDA protection of the donor, it is indeed compatible with 4,6-benzylidene protection.

In light of the failure of the BDA protected donor to undergo efficient intramolecular glycosylation, the enol ethers **9**, derived from the benzylated donor **7**, were investigated. Iodonium-mediated tethering of a range of aglycon alcohols with the enol ethers **9** was undertaken either using NIS or alternatively by using iodine, silver triflate and DTBMP, and good yields of the mixed acetals **16a**−**d** were obtained in all cases (Scheme 3). Intramolecular glycosylation of the methanol (**16a**) and the primary carbohydrate (**16b**) tethered materials, mediated by NIS and silver triflate, cleanly furnished the desired β-rhamnosides[18] **17a** and **17b** in good yield in a totally stereoselective fashion. Attempted alternative activation of **16b** with MeOTf resulted in no appreciable glycosylation, indicating that in this system NIS/AgOTf is a more potent activator. In contrast to the BDA-protected glycosylations outlined above, which required heating in order for efficient reaction to be seen, these reactions did proceed at an appreciable rate at room temperature, in line with the expected higher reactivity of these 'armed' benzylated donors over the torsionally deactivated BDA-protected counterparts. However, when the steroid-tethered material **16d** was treated under the same conditions, only a relatively poor 29% yield of the

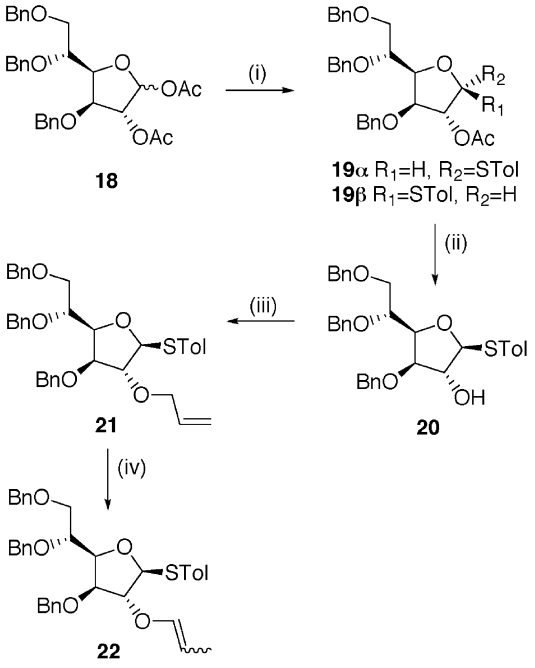


Scheme 3. (i) ROH, NIS, DCE, −40 °C→rt; **16a**, 88%; **16b**, 75%; (ii) ROH, I_2, AgOTf, DTBMP, CH_2Cl_2, −78 °C→rt; **16c**, 82%; **16d**, 69%; (iii) NIS, DTBMP, AgOTf, DCE, 50 °C; **17a**, 54%; **17b**, 62%; **17c**, –; **17d**, 29%.

β-rhamnoside **17d** was obtained. Moreover for the case of the tethered material derived from the secondary carbohydrate alcohol **16c**, only decomposition and no appreciable glycosylation was observed.

2.2. Synthesis of α-glucofuranosides

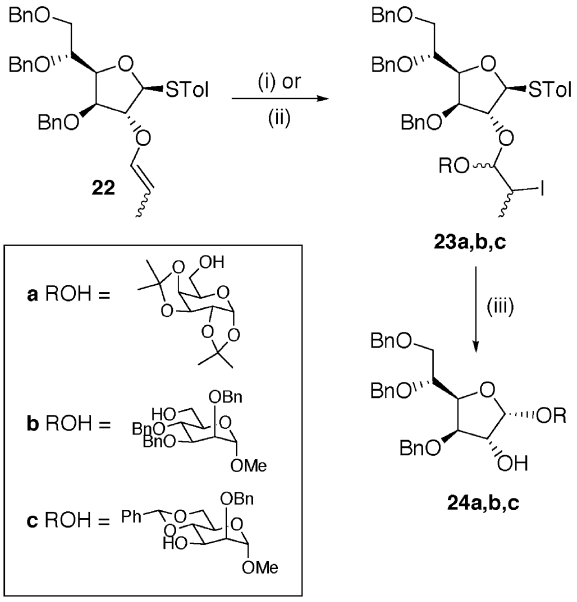
2.2.1. Synthesis of the glycosyl donor. Investigations required access to a glucofuranosyl donor bearing 2-*O*-allyl protection, which was readily available from diacetone glucose via the known diacetate **18**.[19] Treatment of diacetate **18** with *para*-thiocresol at room temperature in the presence of $BF_3 \cdot OEt_2$ gave the desired thioglycoside **19α/β** as a disappointing anomeric mixture (1.3:1, **19β**:**19α**,[20] in a poor overall yield (31%). However, conducting the reaction at lower temperature (−30 °C) increased both the yield and selectivity (58%, 50:1 **19β**:**19α**, Scheme 4). Subsequent studies focused on the major β-product as a donor for IAD.[21] Amine-mediated deacetylation of **19β** gave the alcohol **20** (91% yield). Subsequent allylation with sodium hydride and allyl bromide gave the glycosyl donor **21** (94% yield) and finally Wikinson's catalyst mediated isomerisation gave the required enol ethers **22** (96% yield, Scheme 4).



Scheme 4. (i) HSTol, $BF_3 \cdot OEt_2$, CH_2Cl_2, −30 °C, 58%, **19β**:**α**, 50:1; (ii) $^nPrNH_2$, MeOH, THF, rt, 91%; (vi) allyl bromide, DMF, NaH, 0 °C, 94%; (vii) Wilkinson's catalyst, BuLi, THF, 70 °C, 96%.

2.2.2. Tethering and intramolecular glycosylation reactions. Iodonium ion-mediated tethering reactions of a selection of carbohydrate aglycon alcohols to the β-glucofuranose enol ethers **22** were undertaken, both using NIS as a source of I^+, and also by the use of iodine, silver triflate and di-*tert*-butylmethylpyridine, to form mixed acetals **23a–c** in good yield in all cases (Scheme 5).

Treatment of the mixed acetals derived from diacetone galactose **23a** with NIS and silver triflate in the presence of



Scheme 5. (i) ROH, NIS, DCE, −40 °C→rt; **23a**, 75%; **23b**, 53%; (ii) ROH, I_2, AgOTf, DTBMP, CH_2Cl_2, −78 °C→rt; **23b**, 64%; **23c**, 88%; (iii) NIS, DTBMP, AgOTf, DCE, rt; **24a**, 70%; **24b**, 39%; (iv) MeOTf, Me_2S_2, DTBMP, CH_2Cl_2, rt; **24c**, 32%.

DTBMP resulted in the formation of the desired α-glucofuranoside **24a**, as a single anomer,[22] in a good 75% yield. When mixed acetals **23b**, derived from the more hindered primary *manno* alcohol, were treated under the same conditions again only a single α anomer of the desired glycosylated product **24b** was formed, but in a rather poor 35% yield. Moreover, treatment of mixed acetals **23c**, derived from the hindered secondary *manno* alcohol with NIS, siver triflate and DTBMP resulted in a complex mixture of products.[23] However, the use of dimethyl(thiomethyl)sulfonium triflate (DMTST) as an alternative activator[11c] gave a much cleaner glycosylation reaction, and the 1,2-*cis* disaccharide **24c** was isolated without any formation of the aglycon alcohol, albeit in a very modest overall yield (32%, Scheme 5).

3. Summary and conclusion

The potential of allyl-mediated IAD as a tool for the synthesis of α-glucofuranosyl and β-rhamnosyl bonds has been investigated with a range of substrates. In all cases, tethering reactions of aglycon alcohols to enol ethers derived from 2-*O*-allyl protected glycosyl donors by Wilkinson's catalyst mediated isomerisation has been efficiently achieved. However the efficacy of the subsequent intramolecular glycosylation reaction has been demonstrated to depend markedly both on the protecting group pattern of the glycosyl donor, and on the steric bulk of the glycosyl acceptor. Importantly, intramolecular glycosylation was completely stereoselective in all cases, and only the 1,2-*cis* isomer of glycosylated product was isolated from all glycosylation reactions. However, in the rhamnopyranose series, butane diacetal protection (BDA) of the 3- and 4-hydroxyls of the donor is seen to be currently incompatible with high yielding intramolecular glycosylation. Since efficient intramolecular glycosylation of a 4,6-*O*-benzylidene

protected *gluco* donor was observed using identical reaction conditions, this implies that the effect may not be simply due to torsional deactivation of the glycosyl donor. In the glucofuranose series, intramolecular glycosylation of mixed acetals derived from a simple unhindered primary alcohol aglycon is efficient. However, the yield of intramolecular glycosylation is seen to decrease with increasing bulk of the aglycon alcohol, and only low yields were achieved for a hindered secondary carbohydrate alcohol. It is clear that in order for allyl IAD to become a useful and widely applicable technique for the stereoselective synthesis of di- and higher oligosaccharides, the efficiency of the intramolecular glycosylation step requires substantial improvement. Investigations into the improvement and optimisation of allyl mediated IAD in the cases of hindered secondary carbohydrate alcohols are currently in progress, and the results will be reported in due course.

4. Experimental

4.1. General

Melting points were recorded on a Kofler hot block and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on Bruker DPX 400 or AV 400 (400 MHz), Bruker AMX 500 or DRX 500 (500 MHz) or Bruker DPX 200, AC 200 or Varian Gemini 200 (200 MHz) spectrometers. Spectra were assigned using COSY, edited HSQC, HMQC and/or HMBC experiments. Carbon nuclear magnetic resonance spectra were recorded on Bruker DPX 400 or AV 400 (100.6 MHz), Bruker AMX 500 or DRX 500 (125.7 MHz) or Bruker DPX 200, AC 200 or Varian Gemini 200 (50.3 MHz) spectrometers. Multiplicities were assigned using APT or DEPT sequence. Proton-carbon coupling constants were measured either from proton-coupled carbon spectra (125.7 MHz) or from carbon-coupled HSQC spectra (400 MHz). Fluorine nuclear magnetic resonance spectra were recorded on a Bruker DPX 250 (235 MHz) spectrometer. All chemical shifts are quoted on the δ scale in ppm and coupling constants are quoted once. Residual signals from the solvents were used as an internal reference. Infrared spectra were recorded on a Perkin–Elmer 150 Fourier transform spectrophotometer. Low resolution mass spectra were obtained by atmospheric pressure chemical ionisation (APCI) on a Micromass Platform 1 APCI spectrometer; or by electrospray ionisation (ES) on a Micromass Platform 1 APCI spectrometer, or on a Micromass LCT spectrometer, or on a VG BioQ spectrometer, or by on a Micromass ZMD spectrometer, or by the EPSRC Mass Spectrometry Service Centre, Department of Chemistry, University of Wales, Swansea, on a Micromass Quattro II spectrometer; or using chemical ionisation (CI) on a Micromass AutoSpec-oa Tof spectrometer, or by the EPSRC Mass Spectrometry Service Centre on a Micromass Quattro II spectrometer; or using solid probe temperature programmed field ionisation (TOF FI) on a Micromass GCT Tof spectrometer by the Inorganic Chemistry Laboratory, Oxford University, UK. High-resolution mass spectra were performed on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer, or by the EPSRC Mass Spectrometry Service Centre on a MAT900 XLT electrospray ionisation mass spectrometer, or by the Inorganic Chemistry Laboratory using solid probe temperature programmed field ionisation (TOF FI) on a Micromass GCT Tof spectrometer. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. Microanalyses were performed by the microanalytical services of Elemental Microanalysis Ltd., Devon. Thin layer chromatography (TLC) was carried out on Merck Kieselgel 0.22–0.25 mm thickness glass-backed sheets pre-coated with $60F_{254}$ silica. Plates were developed using 5% w/v ammonium molybdate in 2 M sulfuric acid. Flash column chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and reagents were dried and purified before use according to standard procedures; dichloromethane was distilled from CaH_2 immediately before use; methanol was distilled from NaH or anhydrous methanol was purchased from Acros; THF and ether were distilled from solutions of sodium benzophenone ketal immediately before use; anhydrous DMF and anhydrous dichloroethane were purchased from Aldrich or Acros. Petrol refers to the fraction of light petroleum ether boiling in the range 40–60 °C. Reactions performed under an atmosphere of argon or hydrogen gas were maintained by an inflated balloon.

4.1.1. *para*-Tolyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranoside 3α and *para*-tolyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-rhamnopyranoside 3β. L-Rhamnose **2** (10.0 g, 61 mmol) was suspended in acetic anhydride (40 ml). Iodine (250 mg, 0.98 mmol) was dissolved in acetic anhydride (10 ml). The mixture was warmed until an exothermic reaction was initiated, then added to the sugar suspension. The reaction mixture was kept cool in a water bath. After 10 min, TLC (petrol/ethyl acetate, 1:1) indicated formation of major (R_f 0.5) and minor (R_f 0.45) products and the absence of starting material (R_f 0). The reaction was diluted with CH_2Cl_2 (200 ml), washed with $Na_2S_2O_3$ (200 ml of a 10% aqueous solution) and $NaHCO_3$ (200 ml of a saturated aqueous solution), dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude tetraacetate (20.1 g, 99%) as a pale yellow oil which was used without further purification. Crude tetraacetate (18.7 g, 56 mmol) and *para*-thiocresol (10.7 g, 86.2 mmol) were dissolved in CH_2Cl_2 (50 ml). $BF_3{\cdot}OEt_2$ (9.1 ml, 74.7 mmol) was added and the reaction mixture stirred at rt under Ar. After 3 h, TLC (petrol/ethyl acetate, 3:2) indicated formation of two products (R_f 0.5 and 0.45) complete consumption of starting materials (R_f 0.35 and 0.3). The reaction mixture was diluted with CH_2Cl_2 (300 ml) and washed with $NaHCO_3$ (300 ml of a saturated aqueous solution), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 4:1) and recrystallised from ether/petrol to afford thioglycoside **3** (α/β ratio 3.6:1 determined by ^{1}H NMR spectroscopy) (17.0 g, 76%). Separation of the anomers by flash column chromatography gave pure α-thioglycoside **3α** as white crystals, mp 112–114 °C (ether/petrol); $[\alpha]_D^{25} = -87.2$ (*c*, 3.4 in $CHCl_3$); ν_{max} 1749 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, $J_{5,6}=6.1$ Hz, CH_3-6), 2.00, 2.07, 2.13 (9H, 3×s, 3×$COCH_3$), 2.32 (3H, s, $ArCH_3$), 4.36 (1H, dq, $J_{4,5}=9.7$ Hz, H-5), 5.13 (1H, at, $J=10.0$ Hz, H-4), 5.28 (1H, dd, $J_{2,3}=3.5$ Hz, $J_{3,4}=10.1$ Hz, H-3), 5.32 (1H, d, $J_{1,2}=1.3$ Hz, H-1), 5.48 (1H, dd, H-2), 7.11, 7.35 (4H, 2× d, $J=8.1$ Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 17.3 (q, C-6),

20.6, 20.8, 20.9, 21.1 (4×q, $ArCH_3$, 3×$COCH_3$), 67.6, 69.3, 71.1, 71.2 (4×d, C-2, C-3, C-4, C-5), 86.0 (d, $^1J_{C\text{-}1,H\text{-}1}$= 168.2 Hz, C-1), 129.3, 138.2 (2×s, Ar-C), 129.9, 132.4 (2×d, Ar-CH), 169.9, 170.0, 170.0 (3×s, 3×C=O); *m/z* (CI^+) 414 ($M+NH_4^+$, 76), 273 (M-STol, 100%). (HRMS calcd for $C_{19}H_{28}NO_7S$ (MNH_4^+) 414.1586. Found 414.1581). (Found: C, 57.49; H, 6.27. $C_{19}H_{24}O_7S$ requires C, 57.56; H, 6.10%); and pure β-thioglycoside **3β** as white crystals, mp 103–107 °C (ether/petrol); $[\alpha]_D^{25}=+23.5$ (*c*, 1.5 in $CHCl_3$); ν_{max} 1749 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, $J_{5,6}$=6.1 Hz, CH_3-6), 1.98, 2.04, 2.21 (9H, 3×s, 3×$COCH_3$), 2.34 (3H, s, $ArCH_3$), 3.52 (1H, dq, $J_{4,5}$=9.6 Hz, H-5), 4.83 (1H, d, $J_{1,2}$=1.2 Hz, H-1), 4.99 (1H, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=10.1 Hz, H-3), 5.11 (1H, at, *J*= 9.8 Hz, H-4), 5.64 (1H, dd, H-2), 7.13, 7.40 (4H, 2×d, *J*= 8.0 Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 17.7 (q, C-6), 20.6, 20.6, 20.7, 21.1 (4×q, $ArCH_3$, 3×$COCH_3$), 70.2, 70.9, 71.8, 74.9 (4×d, C-2, C-3, C-4, C-5), 85.7 (d, $^1J_{C\text{-}1,H\text{-}1}$= 153.4 Hz, C-1), 129.4, 138.4 (2×s, Ar-C), 129.9, 132.7 (2×d, Ar-CH) 169.8, 170.2, 170.3 (3×s, 3×C=O); *m/z* (CI^+) 414 ($M+NH_4^+$, 100), 273 (M-STol, 96%). (HRMS calcd for $C_{19}H_{28}NO_7S$ (MNH_4^+) 414.1586. Found 414.1586). (Found: C, 57.65; H, 6.30. $C_{19}H_{24}O_7S$ requires C, 57.56; H, 6.10%).

4.1.2. *para*-Tolyl 1-thio-α-L-rhamnopyranoside 4. Pure α-thioglycoside **3α** (9.4 g 23.7 mmol) was suspended in methanol (70 ml). Sodium (60 mg, 2.6 mmol) was dissolved in methanol (10 ml) and then added to the sugar solution. The reaction mixture was stirred at rt. After 1 h 40 min, TLC (petrol/ethyl acetate, 1:1) indicated formation of a major product (R_f 0.1) and no remaining starting material (R_f 0.7). The reaction mixture was concentrated in vacuo and the residue purified by flash column chromatography (ethyl acetate/methanol, 9:1) to afford the triol **4** (6.23 g, 97%) as a white solid which was recrystallised from ether to give white crystals, mp 95–96 °C (ether); $[\alpha]_D^{25}=-207$ (*c*, 0.25 in $CHCl_3$); ν_{max} 3342 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, $J_{5,6}$=6.2 Hz, CH_3-6), 2.34 (3H, s, $ArCH_3$), 3.57 (1H, at, *J*=9.4 Hz, H-4), 3.81 (1H, dd, $J_{2,3}$=2.9 Hz, $J_{3,4}$= 9.3 Hz, H-3), 4.12–4.19 (1H, m, H-5), 4.22 (1H, d, H-2), 5.41 (1H, s, H-1), 7.04, 7.30 (4H, 2×d, *J*=8.0 Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 17.5 (q, C-6), 21.0 (q, $ArCH_3$), 69.3, 72.1, 72.5, 73.2 (4×d, C-2, C-3, C-4, C-5), 88.2 (d, C-1), 129.8, 131.9 (2×d, Ar-CH), 130.1, 137.4 (2×s, Ar-C); *m/z* (CI^+) 288 ($M+NH_4^+$, 42), 271 ($M+H^+$, 4%). (HRMS calcd for $C_{13}H_{22}NO_4S$ (MNH_4^+) 288.1270. Found 288.1269). (Found: C, 57.61; H, 6.71. $C_{13}H_{18}O_4S$ requires C, 57.76; H, 6.71%).

4.1.3. (2′*S*, 3′*S*) *para*-Tolyl 3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-1-thio-α-L-rhamnopyranoside 5. Triol **4** (145 mg 0.54 mmol) was suspended in anhydrous methanol (5 ml). 2,3-Butanedione (0.15 ml, 1.72 mmol), trimethyl orthoformate (0.50 ml, 4.62 mmol) and camphorsulfonic acid (15 mg, 0.064 mmol) were added and the reaction mixture stirred under Ar at 75 °C. After 16 h, TLC (petrol/ethyl acetate, 1:1) indicated formation of a major product (R_f 0.6) and no remaining starting material (R_f 0.1). Triethylamine (4 ml) was added and the mixture was concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 3:1) to afford alcohol **5** (153 mg, 74%) as a colourless oil; $[\alpha]_D^{25}=-262$ (*c*, 1.0 in $CHCl_3$); ν_{max} 3410 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, $J_{5,6}$=6.5 Hz, CH_3-6), 1.32, 1.34 (6H, 2×s, 2×$C(O)_2CH_3$), 2.33 (3H, s, $ArCH_3$), 2.69 (1H, d, $J_{OH,2}$=1.8 Hz, OH-2), 3.25, 3.31 (6H, 2×s, 2×OCH_3), 3.78 (1H, at, *J*=9.7 Hz, H-4), 3.99 (1H, dd, $J_{2,3}$=3.1 Hz, $J_{3,4}$=10.0 Hz, H-3), 4.18 (1H, br s, H-2), 4.26–4.30 (1H, m, H-5), 5.43 (1H, s, H-1), 7.11, 7.35 (4H, 2×d, *J*=8.0 Hz, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 16.3, 17.5, 17.7 (3×q, 2×$C(O)_2CH_3$, C-6), 21.0 (q, $ArCH_3$), 47.6, 48.0 (2×q, 2×OCH_3), 67.5, 68.5, 68.6, 71.2 (4×d, C-2, C-3, C-4, C-5), 88.0 (d, C-1), 99.7, 100.1 (2×s, 2×$C(O)_2CH_3$), 129.7, 131.9 132.0 (3×d, Ar-CH), 130.2, 137.5 (2×s, Ar-C); *m/z* (ES^+) 786 ($2M+NH_4^+$, 5), 402 ($M+NH_4^+$, 41), 353 (M−OMe, 100%). (HRMS calcd for $C_{19}H_{32}NO_6S$ (MNH_4^+) 402.1950. Found 402.1949).

4.1.4. (2′*S*, 3′*S*) *para*-Tolyl 2-*O*-allyl-3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-1-thio-α-L-rhamnopyranoside 1. Alcohol **5** (118 mg 0.31 mmol) was dissolved in anhydrous DMF (2 ml) and cooled to 0 °C. Allyl bromide (0.053 ml, 0.62 mmol) then sodium hydride (60% in mineral oil) (25 mg, 0.62 mmol) were added. After 2 h, TLC (petrol/ethyl acetate, 3:1) indicated formation of a single product (R_f 0.6) and almost complete consumption of starting material (R_f 0.3). The reaction was quenched with water (50 ml) and extracted with ether (50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 8:1) to afford the BDA protected donor **1** (108 mg, 83%) as a colourless oil; $[\alpha]_D^{25}=-289$ (*c*, 0.25 in $CHCl_3$); ν_{max} no significant peaks; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, $J_{5,6}$=6.3 Hz, CH_3-6), 1.32, 1.33 (6H, 2×s, 2×$C(O)_2CH_3$), 2.33 (3H, s, $ArCH_3$), 3.26, 3.31 (6H, 2×s, 2×OCH_3), 3.81 (1H, at, *J*=9.9 Hz, H-4), 3.89 (1H, dd, $J_{1,2}$=1.3 Hz, $J_{2,3}$=3.0 Hz, H-2), 3.97 (1H, dd, $J_{3,4}$=10.2 Hz, H-3), 4.16 (1H, ddat, J_{gem}= 13.5 Hz, *J*=5.8, 1.4 Hz, $OCHH'CH=CH_2$), 4.20–4.29 (2H, m, H-5, $OCHH'CH=CH_2$), 5.16 (1H, dd, J_{gem}= 1.7 Hz, J_Z=10.4 Hz, $CH=CH_EH_Z$), 5.29 (1H, daq, *J*= 1.7 Hz, J_E=17.3 Hz, $CH=CH_EH_Z$), 5.42 (1H, d, H-1), 5.92 (1H, ddat, $CH=CH_2$), 7.11, 7.34 (4H, 2×d, *J*=8.1 Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 16.6, 17.7, 17.8 (3×q, 2×$C(O)_2CH_3$, C-6), 21.1 (q, $ArCH_3$), 47.6, 47.9 (2×q, 2×OCH_3), 67.9, 68.9, 68.9, 77.5 (4×d, C-2, C-3, C-4, C-5), 71.7 (t, $OCH_2CH=CH_2$), 87.2 (d, C-1), 99.5, 99.8 (2×s, 2×$C(O)_2CH_3$), 117.1 (t, $CH=CH_2$), 129.7, 131.7 (2×d, Ar-CH), 131.0, 135.0 (2×s, Ar-C) 137.4 (d, $CH=CH_2$); *m/z* (ES^+) 483 ($M+NH_4^+$ +MeCN, 15), 442 ($M+NH_4^+$, 40), 425 ($M+H^+$, 100), 393 (M−OMe, 81%). (HRMS calcd for $C_{22}H_{36}NO_6S$ (MNH_4^+) 442.2263. Found 442.2265).

4.1.5. (2′*S*, 3′*S*) *para*-Tolyl 3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-2-*O*-prop-1″-enyl-1-thio-α-L-rhamnopyranoside 6. Wilkinson's catalyst (471 mg, 0.51 mmol) was dissolved in freshly distilled THF (6 ml) and degassed. Butyl lithium (1.6 M solution in hexanes) (0.48 ml, 0.76 mmol) was added and the mixture stirred for 10 min. BDA protected donor **1** (2.16 g, 5.09 mmol) was dissolved in freshly distilled THF (6 ml) and heated to 70 °C. The catalyst solution was added by cannula under Ar. After 30 min, TLC (petrol/ether, 8:1) indicated formation of two products (R_f 0.2 and R_f 0.25) and complete consumption of

starting material (R_f 0.1). The reaction was allowed to cool then diluted with CH_2Cl_2 (20 ml) and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ether, 8:1) to afford enol ethers **6** (2.04 g, 95%) as a colourless oil. (*Z*/*E*, 1.8:1). The isomers were separated by flash column chromatography (petrol/ether, 8:1) for characterisation purposes. *E* isomer, a colourless oil; $[\alpha]_D^{25}=-254$ (*c*, 0.5 in $CHCl_3$); ν_{max} 1673 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, $J_{5,6}=6.3$ Hz, CH_3-6), 1.32, 1.35 (6H, 2×s, $2\times C(O)_2CH_3$), 1.52 (3H, dd, $J=1.5$, 6.8 Hz, OCH=CHCH_3), 2.34 (3H, s, $ArCH_3$), 3.27, 3.31 (6H, 2×s, $2\times OCH_3$), 3.80 (1H, at, $J=9.9$ Hz, H-4), 4.03 (1H, dd, $J_{2,3}=3.1$ Hz, $J_{3,4}=10.1$ Hz, H-3), 4.18 (1H, d, H-2), 4.25 (1H, dq, $J_{4,5}=9.6$ Hz, H-5), 4.88 (1H, dq, $J_E=12.7$ Hz, OCH=C*H*), 5.49 (1H, s, H-1), 6.14 (1H, dd, OC*H*=CH), 7.12, 7.36 (4H, 2×d, $J=8.1$ Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 12.4 (q, CH=CH*C*H_3), 16.6, 17.7, 17.8 (3×q, $2\times C(O)_2CH_3$, C-6), 21.0 (q, $ArCH_3$), 47.6, 47.9 (2×q, $2\times OCH_3$), 67.7, 67.8, 68.8, 77.6 (4×d, C-2, C-3, C-4, C-5), 85.6 (d, C-1), 99.6, 100.2 ($2\times$s, $2\times C(O)_2CH_3$), 102.5 (d, OCH=*C*H), 129.8, 131.9 (2×d, Ar-CH), 130.6, 137.6 (2×s, Ar-C) 144.7 (d, O*C*H=CH); *Z* isomer, a colourless oil; $[\alpha]_D^{25}=-366$ (*c*, 1.0 in $CHCl_3$); ν_{max} 1668 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, $J_{5,6}=6.1$ Hz, CH_3-6), 1.32, 1.34 (6H, 2×s, $2\times C(O)_2CH_3$), 1.61 (3H, dd, $J=1.7$ Hz, $J=6.7$ Hz, OCH=CHCH_3), 2.33 (3H, s, $ArCH_3$), 3.27, 3.32 (6H, 2×s, $2\times OCH_3$), 3.86 (1H, at, $J=9.9$ Hz, H-4), 4.03 (1H, dd, $J_{2,3}=3.1$ Hz, $J_{3,4}=10.1$ Hz, H-3), 4.08 (1H, d, H-2), 4.26 (1H, dq, $J_{4,5}=9.6$ Hz, H-5), 4.58 (1H, aquint, $J=6.7$ Hz, OCH=C*H*), 5.38 (1H, s, H-1), 5.96 (1H, dd, $J_Z=6.0$ Hz, OC*H*=CH), 7.12, 7.35 (4H, 2×d, $J=8.1$ Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 9.5 (q, CH=CH*C*H_3), 16.7, 17.7, 17.8 (3×q, $2\times C(O)_2CH_3$, C-6), 21.1 (q, $ArCH_3$), 47.6, 48.0 (2×q, $2\times OCH_3$), 67.9, 68.1, 68.9, 79.5 (4×d, C-2, C-3, C-4, C-5), 86.8 (d, C-1), 99.6, 100.0 ($2\times$s, $2\times C(O)_2CH_3$), 105.6 (d, OCH=*C*H), 129.8, 132.1 (2×d, Ar-CH), 130.5, 137.7 (2×s, Ar-C) 143.8 (d, O*C*H=CH); For the *E*/*Z* mixture; *m*/*z* (ES^+) 483 ($M+NH_4^+$ + MeCN, 27), 442 ($M+NH_4^+$, 29), 425 ($M+H^+$, 64), 393 (M−OMe, 100%). (HRMS calcd for $C_{22}H_{36}NO_6S$ (MNH_4^+) 442.2263. Found 442.2261).

4.1.6. *para*-Tolyl 2-*O*-allyl-1-thio-α-L-rhamnopyranoside 8. The BDA protected donor **1** (159 mg 0.38 mmol) was dissolved in trifluoroacetic acid (1.8 ml) and water (0.2 ml) and stirred at rt. After 10 min, TLC (petrol/ethyl acetate, 3:1) indicated formation of a single product (R_f 0.2) and disappearance of starting material (R_f 0.7). The reaction mixture was concentrated in vacuo and the residue purified by flash column chromatography (petrol/ethyl acetate, 5:2→1:1) to afford the triol **8** (110 mg, 95%) as a colourless oil; $[\alpha]_D^{25}=-289$ (*c*, 0.25 in $CHCl_3$); ν_{max} 3392 (br, OH), 1646 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, $J_{5,6}=6.2$ Hz, CH_3-6), 2.34 (3H, s, $ArCH_3$), 2.70 (2H, br s, OH), 3.50 (1H, at, $J=9.5$ Hz, H-4), 3.77 (1H, dd, $J_{2,3}=3.7$ Hz, $J_{3,4}=9.5$ Hz, H-3), 3.92 (1H, dd, $J_{1,2}=1.2$ Hz, H-2), 4.00 (1H, ddat, $J_{gem}=12.6$ Hz, $J=6.2$ Hz, $J=1.2$ Hz, OC*H*H′CH=CH_2), 4.12 (1H, dq, $J_{4,5}=9.4$ Hz, H-5), 4.19 (1H, ddat, $J=5.5$, 1.4 Hz, OCH*H*′CH=CH_2), 5.21 (1H, dd, $J_{gem}=1.4$ Hz, $J_Z=10.3$ Hz, CH=CH_EH_Z), 5.29 (1H, daq, $J=1.5$ Hz, $J_E=17.3$ Hz, CH=CH_EH_Z), 5.50 (1H, d, H-1), 5.90 (1H, ddat, C*H*=CH_2), 7.13, 7.36 (4H, 2×d, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 17.4 (q, C-6), 21.1 (q, $ArCH_3$), 68.9, 71.9, 74.2, 79.2 (4×d, C-2, C-3, C-4, C-5), 71.3 (t, $OCH_2CH=CH_2$), 85.1 (d, C-1), 118.3 (t, CH=*C*H_2), 129.8, 132.0, 133.8 (3×d, Ar-CH, *C*H=CH_2), 130.4, 137.7 (2×s, Ar-C); *m*/*z* (TOF FI^+) 310 (M^+, 100%). (HRMS calcd for $C_{16}H_{22}O_4S$ (M^+) 310.1239. Found 310.1237).

4.1.7. *para*-Tolyl 2-*O*-allyl-3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside 7. The triol **8** (500 mg 1.61 mmol) was dissolved in anhydrous DMF (15 ml) and cooled to 0 °C. Benzyl bromide (0.57 ml, 4.84 mmol) then sodium hydride (60% in mineral oil) (258 mg, 6.44 mmol) were added. After 14 h 30 min, TLC (petrol/ethyl acetate, 4:1) indicated formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.1). The reaction mixture was quenched with methanol (4 ml) and partitioned between ether (100 ml) and water (100 ml). The aqueous layer was re-extracted with ether (50 ml) and the combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ether, 8:1) to afford the benzylated donor **7** (693 mg, 88%) as a colourless oil; $[\alpha]_D^{25}=-120.7$ (*c*, 0.75 in $CHCl_3$); ν_{max} no significant peaks; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, $J_{5,6}=6.3$ Hz, CH_3-6), 2.34 (3H, s, $ArCH_3$), 3.63 (1H, at, $J=9.4$ Hz, H-4), 3.85 (1H, dd, $J_{2,3}=3.2$ Hz, $J_{3,4}=9.3$ Hz, H-3), 3.95 (1H, dd, $J_{1,2}=1.6$ Hz, H-2), 4.09–4.20 (3H, m, OCH_2CH=CH_2, H-5), 4.65, 4.97 (2H, ABq, $J_{AB}=10.9$ Hz, $PhCH_2$), 4.73 (2H, s, $PhCH_2$), 5.20 (1H, dd, $J_{gem}=1.6$ Hz, $J_Z=10.2$ Hz, CH=CH_EH_Z), 5.28 (1H, daq, $J=1.5$ Hz, $J_E=17.2$ Hz, CH=CH_EH_Z), 5.43 (1H, d, H-1), 5.92 (1H, ddat, C*H*=CH_2), 7.11–7.42 (14H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 17.8 (q, C-6), 21.1 (q, $ArCH_3$), 69.1, 76.4, 77.2, 79.8 (4×d, C-2, C-3, C-4, C-5), 71.5, 72.2, 75.5 (3×t, $OCH_2CH=CH_2$, $2\times PhCH_2$), 86.1 (d, C-1), 118.0 (t, CH=*C*H_2), 127.6, 127.7, 127.9, 128.0, 128.3, 128.4, 129.8, 131.8, 134.7 (9×d, Ar-CH, *C*H=CH_2), 130.9, 137.4, 138.1, 138.5 (4×s, Ar-C); *m*/*z* ($APCI^+$) 546 (M+56, 100), 508 ($M+NH_4^+$, 5), 491 ($M+H^+$, 10%); (CI^+) 508 ($M+NH_4^+$, 100%). (HRMS calcd for $C_{30}H_{38}NO_4S$ (MNH_4^+) 508.2522. Found 508.2524). (Found: C, 73.60; H, 7.12. $C_{30}H_{34}O_4S$ requires C, 73.44; H, 6.98%).

4.1.8. *para*-Tolyl 3,4-di-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-α-L-rhamnopyranoside 9. Wilkinson's catalyst (120 mg, 0.13 mmol) was dissolved in freshly distilled THF (3 ml) and degassed. Butyl lithium solution in hexanes (0.12 ml, 0.20 mmol) was added and the mixture stirred for 10 min. Benzylated donor **7** (640 mg, 1.31 mmol) was dissolved in freshly distilled THF (3 ml) and heated to 75 °C. The catalyst solution was added by cannula under Ar. After 1 h 30 min, TLC (petrol/ether, 4:1) indicated formation of two products (R_f 0.5 and R_f 0.55) and complete consumption of starting material (R_f 0.45). The reaction was allowed to cool then diluted with CH_2Cl_2 (4 ml) and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ether, 8:1) to afford the enol ethers **9** (513 mg, 80%) as a colourless oil; ν_{max} 1671 (C=C) cm^{-1}; partial data: δ_H (400 MHz, $CDCl_3$) (*E*/*Z*, 1.4:1), *E* isomer 1.35 (3H, d, $J_{5,6}=6.1$ Hz, CH_3-6), 1.54 (3H, dd, $J=1.6$, 6.9 Hz, OCH=CHCH_3), 3.63 (1H, at, $J=9.3$ Hz, H-4), 4.92 (1H, dq, $J_E=12.5$ Hz, OCH=C*H*CH_3), 5.45 (1H, d, $J_{1,5}=1.5$ Hz, H-1), 6.09 (1H, dq, OC*H*=CHCH_3); *Z* isomer 1.36 (3H, d, $J_{5,6}=6.2$ Hz, CH_3-6), 1.65 (3H, dd, $J=1.5$,

6.7 Hz, OCH=CHCH_3), 3.67 (1H, at, J=9.3 Hz, H-4), 4.10 (1H, dd, $J_{1,2}$=1.8 Hz, $J_{2,3}$=2.8 Hz, H-2), 4.58 (1H, aquin, J=6.6 Hz, OCH=CHCH$_3$), 5.37 (1H, d, H-1), 5.91 (1H, dq, J_Z=6.1 Hz, OCH=CHCH$_3$); δ_C (100.6 MHz, $CDCl_3$) *E* isomer 12.4 (q, OCH=CHCH$_3$), 17.8 (q, C-6), 21.1 (q, ArCH_3), 72.2, 75.5 (2×t, 2×PhCH_2), 85.4 (d, C-1), 102.4 (d, OCH=CHCH$_3$), 144.0 (d, OCH=CHCH$_3$); Z isomer 9.5 (q, OCH=CHCH$_3$), 17.9 (q, C-6), 21.1 (q, ArCH_3), 72.2, 75.5 (2×t, 2×PhCH_2), 86.3 (d, C-1), 104.8 (d, OCH=CHCH$_3$), 144.9 (d, OCH=CHCH$_3$); *m/z* (APCI$^+$) 546 (M+56, 100), 491 (M+H$^+$, 11%); (CI$^+$) 508 (M+NH_4^+, 100), 491 (M+H$^+$, 17%). (HRMS calcd for $C_{30}H_{38}NO_4S$ (MNH_4^+) 508.2522. Found 508.2526). (Found: C, 73.56; H, 7.11. $C_{30}H_{34}O_4S$ requires C, 73.44; H, 6.98%).

4.1.9. (2′*S*, 3′*S*) para-Tolyl 3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-2-*O*-(2-iodo-1-methoxypropyl)-1-thio-α-L-rhamnopyranoside 10. *N*-Iodosuccinimide (239 mg, 1.1 mmol) and 4 Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to −40 °C under Ar. (2′S, 3′S) Enol ethers **6** (150 mg, 0.35 mmol, *E*/*Z*, 68:32) and methanol (0.022 ml, 0.53 mmol) were dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to 0 °C over 55 min. After this time, the reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2× 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ether, 8:1) to afford mixed acetals **10** (197 mg, 96%) as a colourless oil. *m/z* (ES$^+$) 641 (M+NH_4^++MeCN, 12), 600 (M+NH_4^+, 3), 583 (M+H$^+$, 3%). (HRMS calcd for $C_{23}H_{39}NO_7SI$ (MNH_4^+) 600.1492. Found 600.1496). Data for the individual 4 diastereomers (relative %): Diastereomer 1 (17%): δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, $J_{5,6}$=6.0 Hz, CH_3-6), 1.31, 1.34 (6H, 2×s, 2×C(O)$_2$CH$_3$), 1.87 (3H, d, J=6.9 Hz, CHICH_3), 2.33 (3H, s, ArCH_3), 3.24, 3.32, 3.37 (9H, 3×s, 3×OCH_3), 3.74 (1H, at, J=10.0 Hz, H-4), 3.99 (1H, dd, $J_{2,3}$=2.5 Hz, $J_{3,4}$=10.3 Hz, H-3), 4.07 (1H, dd, $J_{1,2}$=1.4 Hz, H-2), 4.24 (1H, dq, $J_{4,5}$=9.6 Hz, H-5), 4.65 (1H, d, J=2.6 Hz, (O)$_2$CHCHI), 4.67 (1H, dq, CHI), 5.46 (1H, d, H-1), 7.11–7.13, (2H, m, Ar-H), 7.34–7.36 (2H, m, Ar-H); Diastereomer 2 (8%): δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, $J_{5,6}$=6.2 Hz, CH_3-6), 1.29, 1.31 (6H, 2×s, 2×C(O)$_2$CH$_3$), 1.92 (3H, d, J=6.8 Hz, CHICH_3), 2.33 (3H, s, ArCH_3), 3.27, 3.31, 3.33 (9H, 3×s, 3×OCH_3), 3.79 (1H, at, J=10.0 Hz, H-4), 3.98 (1H, dd, $J_{2,3}$=2.6 Hz, $J_{3,4}$=10.4 Hz, H-3), 4.17 (1H, dd, $J_{1,2}$=1.3 Hz, H-2), 4.24 (1H, dq, $J_{4,5}$=9.7 Hz, H-5), 4.42 (1H, d, J=5.7 Hz, (O)$_2$CHCHI), 4.51 (1H, dq, CHI), 5.44 (1H, d, H-1), 7.11–7.13, (2H, m, Ar-H), 7.34–7.36 (2H, m, Ar-H); Diastereomer 3 (25%): δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, $J_{5,6}$=6.2 Hz, CH_3-6), 1.28, 1.30 (6H, 2×s, 2×C(O)$_2$CH$_3$), 1.88 (3H, d, J=7.2 Hz, CHICH_3), 2.34 (3H, s, ArCH_3), 3.23, 3.31, 3.50 (9H, 3×s, 3×OCH_3), 3.82 (1H, at, J=9.9 Hz, H-4), 3.98 (1H, dd, $J_{2,3}$=3.0 Hz, $J_{3,4}$=10.3 Hz, H-3), 4.18 (1H, dd, $J_{1,2}$=1.2 Hz, H-2), 4.20 (1H, dq, J=5.8 Hz, CHI), 4.25 (1H, dq, $J_{4,5}$=9.7 Hz, H-5), 4.31 (1H, d, (O)$_2$CHCHI), 5.41 (1H, s, H-1), 7.11–7.14, (2H, m, Ar-H), 7.34–7.37 (2H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 16.5, 17.6, 17.8 (3×q, 2×C(O)$_2$$CH_3$, C-6), 21.1 (q, Ar$CH_3$), 23.0 (q, CHI$CH_3$), 27.1 (q, CHICH$_3$), 47.6, 47.9 (2×q, 2×OCH_3), 54.8 (q, OCH_3), 68.0, 68.4, 68.7, (3×d, C-3, C-4, C-5), 74.4 (d, C-2), 88.0 (d, C-1), 99.6, 99.9 (2×s, 2×C(O)$_2$CH$_3$), 105.1 (d, (O)$_2$$C$HCHI), 129.9, 132.3 (2×d, Ar-CH), 130.5, 137.8 (2×s, Ar-C); Diastereomer 4 (50%): δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, $J_{5,6}$=6.0 Hz, CH_3-6), 1.29, 1.31 (6H, 2×s, 2×C(O)$_2$CH$_3$), 1.81 (3H, d, J=6.8 Hz, CHICH_3), 2.34 (3H, s, ArCH_3), 3.24, 3.32, 3.55 (9H, 3×s, 3×OCH_3), 3.85 (1H, at, J=9.5 Hz, H-4), 3.98–4.02 (2H, m, H-2, H-3), 4.06 (1H, dq, J=4.0 Hz, CHI), 4.24 (1H, dq, $J_{4,5}$=9.7 Hz, H-5), 4.78 (1H, d, (O)$_2$CHCHI), 5.36 (1H, s, H-1), 7.12–7.14, (2H, m, Ar-H), 7.34–7.36 (2H, m, Ar-H).

4.1.10. (2′*S*, 3′*S*) Methyl 3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-β-L-rhamnopyranoside 11. Mixed acetals **10** (114 mg, 0.25 mmol), were dissolved in anhydrous dichloroethane (9 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (138 mg, 0.67 mmol), *N*-iodosuccinimide (227 mg, 1.0 mmol) and silver trifluoromethanesulfonate (87 mg, 0.34 mmol) were added. The reaction mixture was stirred at 50 °C under Ar. After 19 h, TLC (petrol/ethyl acetate, 1:1) indicated the formation of a product (R_f 0.2). The reaction mixture was partitioned between CH_2Cl_2 (60 ml) and $Na_2S_2O_3$ (50 ml of a 10% aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 1:2) to afford the β-rhamnoside **11** (21 mg, 29%) as a colourless oil; $[\alpha]_D^{25}$=−122.7 (*c*, 1.0 in $CHCl_3$); ν_{max} 3472 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.30, 1.35 (6H, 2×s, 2×C(O)$_2$CH$_3$), 1.33 (3H, d, $J_{5,6}$=6.1 Hz, CH_3-6), 2.46 (1H, br s, OH-2), 3.25, 3.27 (6H, 2×s, 2×OCH_3), 3.46 (1H, dq, $J_{4,5}$=9.3 Hz, H-5), 3.55 (3H, s, OCH_3-1), 3.66 (1H, dd, $J_{2,3}$=3.0 Hz, $J_{3,4}$=10.1 Hz, H-3), 4.01 (1H, br s, H-2), 3.75 (1H, at, J=9.6 Hz, H-4), 4.41 (1H, d, $J_{1,2}$=0.8 Hz, H-1); δ_C (125.7 MHz, $CDCl_3$) 16.4, 17.5, 17.7 (3×q, 2×C(O)$_2$$CH_3$, C-6), 47.5, 47.9 (2×q, 2×OCH_3), 56.8 (q, OCH_3-1), 67.8, 69.4, 70.0, 70.4 (4×d, C-2, C-3, C-4, C-5), 99.6, 100.1 (2×s, 2×C(O)$_2$CH$_3$), 100.8 (d, $^1J_{C\text{-}1,H\text{-}1}$=156.6 Hz, C-1); *m/z* (ES$^+$) 315 (M+Na$^+$, 14), 310 (M+NH_4^+, 62), 261 (M−OMe, 100%). (HRMS calcd for $C_{13}H_{28}NO_7$ (MNH_4^+) 310.1866. Found 310.1867).

4.1.11. Phenyl 4,6-*O*-benzylidene-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-3-*O*-pivaloyl-1-thio-β-D-glucopyranoside 14. *N*-Iodosuccinimide (163 mg, 0.23 mmol), 2,6-di-*tert*-butyl-4-methyl pyridine (99 mg, 0.48 mmol), methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (90 mg, 0.282 mmol) and 4 Å molecular sieves were added to anhydrous dichloromethane (2 ml) and cooled to −40 °C under Ar. Phenyl 4,6-*O*-benzylidene-3-*O*-pivaloyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucopyranoside **13** (234 mg, 0.484 mmol) was dissolved in anhydrous dichloromethane (2 ml) and added to the reaction vessel by cannula under N_2. The reaction was allowed to warm to rt. After 16 h, TLC (cyclohexane/ethyl acetate, 4:1) indicated the complete consumption of starting material (R_f 0.7). After a further 24 h, the solvent had all evaporated off. TLC (cyclohexane/ethyl acetate, 4:1) indicated the formation of two major products (R_f 0.45 and 0.5), plus some remaining starting alcohol (R_f 0.4). The reaction was quenched with Et_3N (2 ml) and stirred for 5 min. Sodium thiosulfate (50 ml of a

10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (2×50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate, 6:1) to afford mixed acetals **14**. (142 mg, 60%) as a white foam. *m/z* (ES^+) 1000 ($M+NH_4^+$, 53%), which was used directly in the next step without further characterisation.

4.1.12. Methyl 4,6-*O*-benzylidene-3-*O*-pivaloyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside 15. The mixed acetals **14** prepared above (133 mg, 0.136 mmol) were dissolved in anhydrous dichloroethane (4 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (56 mg, 0.272 mmol), silver trifluoromethanesulfonate (35 mg, 0.136 mmol) and *N*-iodosuccinimide (92 mg, 0.409 mmol) were added. After 14 h 30 min, TLC (petrol/ethyl acetate, 4:1) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0.4). The reaction mixture was partitioned between CH_2Cl_2 (2× 50 ml) and $Na_2S_2O_3$ (50 ml of a 10% aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 3:1) to afford the α-*gluco* disaccharide **15** (67 mg, 70%) as a colourless oil; $[\alpha]_D^{22}=+40.6$ (*c*, 0.65 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, $C(CH_3)_3$), 2.56 (1H, d, $J_{OH,2}=11.5$ Hz, OH-2_b), 3.37 (3H, s, OCH_3), 3.59 (1H, at, $J=9.6$ Hz, H-4_b), 3.67 (1H, ddd, $J_{1,2}=3.8$ Hz, $J_{2,3}=9.7$ Hz, H-2_b), 3.72 (1H, at, $J=10.3$ Hz, H-6_b), 3.79–3.90 (3H, m, H-2_a, H-5_a, H-5_b), 3.89 (1H, at, $J=10.3$ Hz, H-6_a), 4.20–4.26 (3H, m, H-3_a, H-4_a, H-$6'_b$), 4.28 (1H, dd, $J_{5,6'}=4.5$ Hz, $J_{6,6'}=9.9$ Hz, H-$6'_a$), 4.74 (1H, d, $J_{1,2}=1.4$ Hz, H-1_a), 4.77 (2H, s, PhC*H*$_2$), 5.28 (1H, d, H-1_b), 5.42 (1H, at, $J=9.7$ Hz, H-3_b), 5.50, 5.62 (2H, 2×s, 2×PhC*H*), 7.27–7.48 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 27.6 (q, $C(CH_3)_3$), 37.8 (s, $C(CH_3)_3$), 55.4 (q, OCH_3), 63.9, 64.3, 72.1, 72.2, 75.7, 77.8, 78.9, 79.3 (8×d, C-2_a, C-3_a, C-4_a, C-5_a, C-2_b, C-3_b, C-4_b, C-5_b), 69.1, 69.3, (2×t, C-6_a, C-6_b), 73.9 (t, PhC*H*$_2$), 100.1, 101.2, 101.5, 101.9 (4×d, C-1_a, C-1_b, 2×PhC*H*), 126.4, 126.7, 127.9, 128.4, 128.5, 128.7, 129.1, 129.3, 129.5 (9×d, Ar-CH), 136.4 (s, Ar-C), 176.9 (s, C=O); *m/z* (ES^+) 729 ($M+Na^+$, 30), 724 ($M+NH_4^+$, 100%). (HRMS calcd for $C_{39}H_{50}NO_{12}$ (MNH_4^+) 724.3333. Found 724.3331).

4.1.13. *para*-Tolyl 3,4-di-*O*-benzyl-2-*O*-(2-iodo-1-methoxypropyl)-1-thio-α-L-rhamnopyranoside 16a. *N*-Iodosuccinimide (138 mg, 0.61 mmol) and 4 Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to −40 °C under Ar. Vinyl ethers **9** (100 mg, 0.20 mmol) and methanol (0.013 ml, 0.30 mmol) were dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to rt over 1 h. After this time, the reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2×30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ether, 8:1) to afford mixed acetals **16a** (117 mg, 88%) as a colourless oil; *m/z* ($APCI^+$) 704 (M+56, 100), 666 ($M+NH_4^+$, 10%); (ES^+) 671 ($M+Na^+$, 100%). (HRMS calcd for $C_{31}H_{41}NO_5SI$ (MNH_4^+) 666.1750. Found 666.1760).

4.1.14. *para*-Tolyl 3,4-di-O-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-O-benzyl-α-D-glucopyranosid-6-*O*-yl)propyl)-1-thio-α-L-rhamnopyranoside 16b. *N*-Iodosuccinimide (138 mg, 0.61 mmol) and 4 Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to −40 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (189 mg, 0.41 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. Vinyl ethers **9** (99 mg, 0.20 mmol) were dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to rt. After 21 h, TLC (petrol/ether, 4:1) indicated complete consumption of the enol ether (R_f 0.5). TLC (petrol/ethyl acetate, 3:1) indicated formation of a major (R_f 0.7) and two minor (R_f 0.6 and 0.4) products and remaining aglycon (R_f 0.3). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2×30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ether, 3:1) to afford mixed acetals **16b** (164 mg, 75%) as a colourless oil; *m/z* ($APCI^+$) 1136 (M+56, 20%); (ES^+) 1139 ($M+NH_4^+$+MeCN, 11), 1098 ($M+NH_4^+$, 14%). (HRMS calcd for $C_{58}H_{69}NO_{10}SI$ (MNH_4^+) 1098.3687. Found 1098.3678).

4.1.15. *para*-Tolyl 3,4-di-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-1-thio-α-L-rhamnopyranoside 16c. Iodine (61 mg, 0.24 mmol), silver trifluoromethanesulfonate (61 mg, 0.24 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (100 mg, 0.48 mmol), methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (72 mg, 0.19 mmol) and 4 Å molecular sieves were added to freshly distilled CH_2Cl_2 (2 ml) and cooled to −78 °C under Ar. Vinyl ethers **9** (90 mg, 0.18 mmol) were dissolved in freshly distilled CH_2Cl_2 (3 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to rt. After 6 h 30 min, TLC (petrol/ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.8) and formation of a major product (R_f 0.7). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2×30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ether, 3:1) to afford mixed acetals **16c** (148 mg, 82%) as a white foam; *m/z* (ES^+) 1027 ($M+K^+$, 62), 1011 ($M+Na^+$, 100), 1006 ($M+NH_4^+$, 65%).

4.1.16. *para*-Tolyl 3,4-di-*O*-benzyl-2-*O*-(1-(cholestan-3-β-yloxy)-2-iodopropyl)-1-thio-α-L-rhamnopyranoside 16d. Iodine (57 mg, 0.22 mmol), silver trifluoromethanesulfonate (57 mg, 0.22 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (91 mg, 0.44 mmol), cholestan-3-β-ol (70 mg, 0.18 mmol) and 4 Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to −78 °C under Ar. Vinyl ethers **9** (90 mg, 0.18 mmol) were dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to rt. After 6 h 45 min, TLC (petrol/ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.8) and formation of a major product (R_f 0.9). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous

solution) then extracted with CH_2Cl_2 (2×30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ether, 11:1) to afford mixed acetals **16d** (118 mg, 69%) as a white foam; *m/z* (ES^+) 1027 ($M+Na^+$, 22%).

4.1.17. Methyl 3,4-di-*O*-benzyl-β-L-rhamnopyranoside 17a. Mixed acetals **16a** (114 mg, 0.18 mmol) was dissolved in anhydrous dichloroethane (3 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (73 mg, 0.35 mmol), *N*-iodosuccinimide (119 mg, 0.53 mmol) and silver trifluoromethanesulfonate (46 mg, 0.18 mmol) were added. The reaction mixture was stirred at rt for 30 min under Ar and then heated to 50 °C. After 3 h, TLC (petrol/ether, 4:1) indicated the absence of starting material (R_f 0.5). TLC (petrol/ethyl acetate, 3:1) indicated formation of several products (R_f 0.55, 0.5 and 0.1). The reaction mixture was allowed to cool and then trifluoroacetic acid (2 ml) and water (1 ml) were added, and the mixture stirred further. After 2 h, TLC (petrol/ethyl acetate, 3:1) indicated formation of a major product (R_f 0.1). The reaction mixture was partitioned between $NaHCO_3$ (30 ml of a saturated aqueous solution) and CH_2Cl_2 (2× 30 ml). The combined organic extracts were washed with sodium thiosulfate (30 ml of a 10% aqueous solution) dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 2:1) to afford β-rhamnoside **17a** (34 mg, 54%) as a colourless oil; $[\alpha]_D^{25}=+27.0$ (*c*, 1.5 in $CHCl_3$); ν_{max} 3480 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, $J_{5,6}=$ 6.2 Hz, CH_3-6), 2.39 (1H, br s, OH-2), 3.33 (1H, dq, $J_{4,5}=$ 9.2 Hz, H-5), 3.51–3.60 (2H, m, H-3, H-4), 3.55 (3H, s, OCH_3), 4.11 (1H, br s, H-2), 4.31 (1H, d, $J_{1,2}=1.0$ Hz, H-1), 4.66, 4.95 (2H, ABq, $J_{AB}=10.9$ Hz, PhCH_2), 4.69, 4.78 (2H, ABq, $J_{AB}=12.2$ Hz, PhCH_2), 7.28–7.41 (10H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 17.7 (q, C-6), 56.7 (q, OCH_3), 68.2, 71.3, 79.6, 81.3 (4×d, C-2, C-3, C-4, C-5), 71.3, 75.3 (2×t, $PhCH_2$), 100.5 (d, $^1J_{C\text{-}1,H\text{-}1}=156.0$ Hz, C-1), 127.6, 127.7, 127.8, 128.0, 128.3, 128.4 (6×d, Ar-CH), 137.7, 138.2 (2×s, Ar-C); *m/z* (ES^+) 739 ($2M+Na^+$, 7), 734 ($2M+NH_4^+$, 11), 417 ($M+MeCN+NH_4^+$, 46), 381 ($M+Na^+$, 15), 376 ($M+NH_4^+$, 100%). (HRMS calcd for $C_{21}H_{30}NO_5$ (MNH_4^+) 376.2124. Found 376.2124).

4.1.18. Methyl 3,4-di-*O*-benzyl-β-L-rhamnopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 17b. Mixed acetals **16b** (70 mg, 0.065 mmol) were dissolved in anhydrous dichloroethane (3 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (27 mg, 0.13 mmol), *N*-iodosuccinimide (44 mg, 0.20 mmol) and silver trifluoromethanesulfonate (17 mg, 0.065 mmol) were added and the mixture stirred under Ar at rt. After 17 h 30 min, TLC (petrol/ethyl acetate, 3:1) indicated the complete consumption of starting material (R_f 0.6) and the formation of a major product (R_f 0.1). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) and extracted with CH_2Cl_2 (2× 30 ml). The organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 3:1→1:1) to afford β-*rhamno* disaccharide **17b** (32 mg, 62%) as a colourless oil; $[\alpha]_D^{24}=+32.6$ (*c*, 1.4 in $CHCl_3$); ν_{max} 3452 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, $J_{5,6}=$ 6.4 Hz CH_3-6_b), 2.26 (1H, br s, OH-2_b), 3.32 (1H, dq, $J_{4,5}=$ 8.7 Hz, H-5_b), 3.37 (3H, s, OCH_3), 3.49–3.56 (3H, m, H-2_a, H-3_b, H-4_b), 3.64 (1H, at, $J=9.5$ Hz, H-4_a), 3.71–3.76 (2H, m, H-5_a, H-6_a), 4.00 (1H, at, $J=9.3$ Hz, H-3_a), 4.14 (1H, br d, $J=1.9$ Hz, H-2_b), 4.23 (1H, dd, $J_{5,6'}=3.6$ Hz, $J_{6,6'}=$ 11.5 Hz, H-$6'_a$), 4.44 (1H, s, H-1_b), 4.61 (1H, d, $J_{1,2}=$ 3.5 Hz, H-1_a), 4.64, 4.96 (2H, ABq, $J_{AB}=10.8$ Hz, PhCH_2), 4.66, 4.82 (2H, ABq, $J_{AB}=12.5$ Hz, PhCH_2), 4.69, 4.77 (2H, ABq, $J_{AB}=11.5$ Hz, PhCH_2), 4.76, 4.87 (2H, ABq, $J_{AB}=10.3$ Hz, PhCH_2), 4.87, 5.00 (2H, ABq, $J_{AB}=$ 10.7 Hz, PhCH_2), 7.27–7.40 (25H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 17.8 (q, C-6_b), 55.1 (q, OCH_3), 66.9, 71.0, 73.3, 75.0, 75.4, 75.6 (6×t, 5×PhCH_2, C-6_a), 68.2, 69.7, 71.4, 77.2, 79.5, 79.6, 81.0, 81.9 (8×d, C-2_a, C-3_a, C-4_a, C-5_a, C-2_b, C-3_b, C-4_b, C-5_b), 98.1 (d, $^1J_{C\text{-}1,H\text{-}1}=$ 167.9 Hz, C-1_a), 99.3 (d, $^1J_{C\text{-}1,H\text{-}1}=157.1$ Hz, C-1_b), 127.5, 127.6, 127.7, 127.8, 127.8, 127.9, 127.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.3 (13×d, Ar-CH), 137.7, 138.0, 138.2, 138.3, 138.7 (5×s, Ar-C); *m/z* ($APCI^+$) 846 (M+ 56, 12), 808 ($M+NH_4^+$, 7%); ($APCI^-$) 825 ($M+Cl^-$, 32), 699 (M−Bn, 95%). (HRMS calcd for $C_{48}H_{58}NO_{10}$ (MNH_4^+) 808.4061. Found 808.4069).

4.1.19. Cholestan-3′-β-yl 3,4-di-*O*-benzyl-β-L-rhamnopyranoside 17d. Mixed acetals **16d** (102 mg, 0.10 mmol) were dissolved in anhydrous dichloroethane (9 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (42 mg, 0.20 mmol), *N*-iodosuccinimide (69 mg, 0.31 mmol) and silver trifluoromethanesulfonate (26 mg, 0.10 mmol) were added and the mixture stirred under Ar at rt. After 2 h 20 min, TLC (petrol/ethyl acetate, 3:1) indicated the absence of starting material (R_f 0.9) and the formation of a various products (R_f 0.5–0.9). The reaction mixture was partitioned between CH_2Cl_2 (2× 40 ml) and sodium thiosulfate (40 ml of a saturated aqueous solution). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 4:1) to afford β-rhamnosyl steroid **17d** (21 mg, 29%) as a colourless oil; $[\alpha]_D^{24}=+25.4$ (*c*, 0.8 in $CHCl_3$); ν_{max} 3469 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.65, 0.80 (6H, 2×s, 2×steroid CH_3), 0.86 (3H, d, $J=6.3$ Hz, steroid CH_3), 0.90 (3H, d, $J=6.9$ Hz, steroid CH_3), 0.90 (3H, d, $J=$ 6.4 Hz, steroid CH_3), 0.93–1.99 (31H, m, steroid CH, CH_2), 1.34 (3H, d, $J_{5,6}=6.2$ Hz, CH_3-6), 2.44 (1H, br s, OH-2), 3.30 (1H, dq, $J_{4,5}=8.8$ Hz, H-5), 3.51–3.57 (2H, m, H-3, H-4), 3.63–3.69 (1H, m, steroid OCH), 4.05 (1H, br s, H-2), 4.52 (1H, s, H-1), 4.65, 4.95 (2H, ABq, $J_{AB}=10.9$ Hz, PhCH_2), 4.68, 4.78 (2H, ABq, $J_{AB}=11.9$ Hz, PhCH_2), 7.27–7.40 (10H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 12.0, 12.3, 18.6, 22.5, 22.8 (5×q, 5×steroid CH_3), 17.9 (q, C-6), 21.2, 23.8, 24.2, 27.7, 28.2, 28.7, 32.1, 35.8, 36.1, 36.8, 39.5, 40.0 (12×t, 12×steroid CH_2), 28.0, 35.5, 35.8, 44.9, 54.4, 56.3, 56.5 (7×d, 7×steroid CH), 35.6, 42.6 (2×s, 2×steroid C), 69.0, 71.3, 77.7, 79.6, 81.5 (5×d, C-2, C-3, C-4, C-5, steroid O*C*H), 71.2, 75.5 (2×t, 2×PhCH_2), 97.2 (d, $^1J_{C\text{-}1,H\text{-}1}=158.3$ Hz, C-1), 127.7, 127.8, 127.9, 128.1, 128.4, 128.4 (6×d, Ar-CH), 137.9, 138.6 (2×s, Ar-C); *m/z* (ES^+) 737 ($M+Na^+$, 24), 732 ($M+NH_4^+$, 100%). (HRMS calcd for $C_{47}H_{74}NO_5$ (MNH_4^+) 732.5567. Found 732.5563).

4.1.20. *para*-Tolyl 2-*O*-acetyl-3,5,6-tri-*O*-benzyl-1-thio-α-D-glucofuranoside 19α and *para*-tolyl 2-*O*-acetyl-3,5,6-tri-*O*-benzyl-1-thio-β-D-glucofuranoside 19β. *Method 1 (reaction carried out at 0 °C).* Diacetate **18**

(1.0 g, 1.87 mmol) and *para*-thiocresol (348 mg, 2.81 mmol) were dissolved in freshly distilled CH_2Cl_2 (5 ml) and cooled to 0 °C. $BF_3{\cdot}OEt_2$ (0.3 ml, 2.43 mmol) was added and the mixture stirred under Ar. After 45 min, TLC (petrol/ethyl acetate, 2:1) indicated complete consumption of starting material (R_f 0.5) and formation of two major products (R_f 0.6 and 0.65). After a further 2 h, the reaction mixture was partitioned between CH_2Cl_2 (2× 100 ml) and $NaHCO_3$ (100 ml of a saturated aqueous solution). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 5:1) to afford α-thioglycoside **19α** (154 mg, 13%) as a colourless oil; $[\alpha]_D^{24}=+60.5$ (*c*, 1.0 in $CHCl_3$); ν_{max} 1749 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, $COCH_3$), 2.34 (3H, s, $ArCH_3$), 3.71 (1H, dd, $J_{5,6}=5.5$ Hz, $J_{6,6'}=10.6$ Hz, H-6), 3.91 (1H, dd, $J_{5,6'}=1.8$ Hz, H-6′), 4.06 (1H, ddd, $J_{4,5}=9.3$ Hz, H-5), 4.15 (1H, dd, $J_{2,3}=0.6$ Hz, $J_{3,4}=3.4$ Hz, H-3), 4.42 (1H, dd, H-4), 4.49, 4.80 (2H, ABq, $J_{AB}=11.2$ Hz, $PhCH_2$), 4.56, 4.76 (2H, ABq, $J_{AB}=11.6$ Hz, $PhCH_2$), 4.62 (2H, s, $PhCH_2$), 5.54 (1H, dd, $J_{1,2}=4.6$ Hz, H-2), 5.72 (1H, d, H-1), 7.09–7.40 (19H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.7, 21.1 (2×q, $ArCH_3$, $COCH_3$), 71.0, 72.0, 72.7, 73.4 (4×t, 3×$PhCH_2$, C-6), 75.5, 77.2, 78.8, 81.5 (4×d, C-2, C-3, C-4, C-5), 89.6 (d, C-1), 127.4, 127.5, 127.6, 127.7, 127.7, 127.7, 127.8, 128.3, 128.3, 128.4, 129.7, 131.9 (12×d, Ar-CH), 131.1, 137.3, 137.4, 138.4, 138.6 (5×s, Ar-C), 169.8 (s, C=O); *m/z* (ES^+) 657 ($M+NH_4^+$ +MeCN, 34), 621 ($M+Na^+$, 21), 616 ($M+NH_4^+$, 100), 599 ($M+H^+$, 3%). (HRMS calcd for $C_{36}H_{42}NO_6S$ (MNH_4^+) 616.2733. Found 616.2727); and β-thioglycoside **19β** (213 mg, 18%) as a colourless oil; $[\alpha]_D^{24}=-88.9$ (*c*, 1.0 in $CHCl_3$); ν_{max} 1748 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.09 (3H, s, $COCH_3$), 2.33 (3H, s, $ArCH_3$), 3.73 (1H, dd, $J_{5,6}=4.8$ Hz, $J_{6,6'}=10.7$ Hz, H-6), 3.90 (1H, dd, $J_{5,6'}=1.9$ Hz, H-6′), 4.11 (1H, d, $J_{3,4}=3.8$ Hz, H-3), 4.18 (1H, ddd, $J_{4,5}=9.3$ Hz, H-5), 4.30 (1H, dd, H-4), 4.44, 4.71 (2H, ABq, $J_{AB}=11.1$ Hz, $PhCH_2$), 4.53, 4.85 (2H, ABq, $J_{AB}=11.5$ Hz, $PhCH_2$), 4.61, 4.65 (2H, ABq, $J_{AB}=12.4$ Hz, $PhCH_2$), 5.34 (1H, d, $J_{1,2}=1.4$ Hz, H-1), 5.44 (1H, d, H-2), 7.09–7.42 (19H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.9, 21.1 (2×q, $ArCH_3$, $COCH_3$), 70.1, 71.8, 72.5, 73.7 (4×t, 3×$PhCH_2$, C-6), 75.8, 80.2, 80.7, 81.2 (4×d, C-2, C-3, C-4, C-5), 91.0 (d, C-1), 127.4, 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 128.3, 129.6, 129.7, 131.9 (11×d, Ar-CH), 131.5, 137.4, 137.5, 138.5, 138.6 (5×s, Ar-C), 169.8 (s, C=O); *m/z* (ES^+) 657 ($M+NH_4^+$ +MeCN, 33), 616 ($M+NH_4^+$, 60%). (HRMS calcd for $C_{36}H_{42}NO_6S$ (MNH_4^+) 616.2733. Found 616.2732), together with a further α/β mixture (223 mg, 19%) as a colourless oil.

Method 2 (reaction carried out at −30 °C). Diacetate **18** (2.99 g, 5.61 mmol) and *para*-thiocresol (836 mg, 6.74 mmol) were dissolved in freshly distilled CH_2Cl_2 (15 ml) in a flame-dried flask and cooled to −30 °C under Ar. $BF_3{\cdot}OEt_2$ (1.04 ml, 8.42 mmol) was added and the mixture stirred under Ar. After 40 min, the mixture had warmed to −20 °C. At this time, TLC (petrol/ethyl acetate, 2:1) indicated little remaining starting material (R_f 0.5) and formation of a major product (R_f 0.6). The reaction was quenched with Et_3N (2 ml), and the mixture partitioned between CH_2Cl_2 (120+60 ml) and water (100 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 5:1) to afford α-thioglycoside **19α** (37 mg, 1%) as a colourless oil identical to that described above, and β-thioglycoside **19β** (1.93 g, 58%) as a colourless oil identical to that described above.

4.1.21. *para*-Tolyl 3,5,6-tri-*O*-benzyl-1-thio-β-D-glucofuranoside 20. β-Thioglycoside **19β** (195 mg, 0.33 mmol) was dissolved in methanol (5 ml), THF (10 ml) and *n*-propylamine (5 ml) and stirred at rt. After 14 h, TLC (petrol/ethyl acetate, 2:1) indicated complete consumption of starting material (R_f 0.7) and formation of a major product (R_f 0.6). The reaction mixture was concentrated in vacuo and the residue purified by flash column chromatography (petrol/ethyl acetate, 4:1→3:1) to afford alcohol **20** (2.10 g, 91%) as a colourless oil; $[\alpha]_D^{25}=-132.2$ (*c*, 1.25 in $CHCl_3$); ν_{max} 3406 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, $ArCH_3$), 2.40 (1H, d, $J_{OH,2}=3.8$ Hz, OH-2), 3.75 (1H, dd, $J_{5,6}=5.2$ Hz, $J_{6,6'}=10.7$ Hz, H-6), 3.91 (1H, dd, $J_{5,6'}=2.0$ Hz, H-6′), 4.04 (1H, dd, $J_{2,3}=1.2$ Hz, $J_{3,4}=4.3$ Hz, H-3), 4.17 (1H, ddd, $J_{4,5}=9.0$ Hz, H-5), 4.37 (1H, br s, H-2), 4.39 (1H, dd, H-4), 4.46, 4.62 (2H, ABq, $J_{AB}=11.6$ Hz, $PhCH_2$), 4.50, 4.76 (2H, ABq, $J_{AB}=11.2$ Hz, $PhCH_2$), 4.61 (2H, s, $PhCH_2$), 5.19 (1H, d, $J_{1,2}=2.4$ Hz, H-1), 7.09–7.40 (19H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 21.1 (q, $ArCH_3$), 70.6 (t, C-6), 72.0, 72.6, 73.4 (3×t, 3×$PhCH_2$), 76.3 (d, C-5), 79.5 (d, C-2), 80.7 (d, C-4), 83.2 (d, C-3), 93.2 (d, C-1), 127.4, 127.6, 127.7, 128.2, 128.3, 128.4, 129.7, 131.4 (8×d, Ar-CH), 131.8, 137.1, 137.7, 138.5, 138.7 (5×s, Ar-C); *m/z* (ES^+) 615 ($M+NH_4^+$ +MeCN, 8), 574 ($M+NH_4^+$, 18), 557 ($M+H^+$, 6%). (HRMS calcd for $C_{34}H_{40}NO_5S$ (MNH_4^+) 574.2627. Found 574.2627).

4.1.22. *para*-Tolyl 2-*O*-allyl-3,5,6-tri-*O*-benzyl-1-thio-β-D-glucofuranoside 21. Alcohol **20** (2.1 g, 3.78 mmol) was dissolved in anhydrous DMF (10 ml) and cooled to 0 °C. Allyl bromide (0.65 ml, 7.55 mmol) then sodium hydride (60% in mineral oil) (300 mg, 7.55 mmol) were added. After 1 h, TLC (petrol/ethyl acetate, 3:1) indicated formation of a single product (R_f 0.5) and little remaining starting material (R_f 0.2). The reaction mixture was partitioned between ether (100+50 ml) and water (100 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ether, 4:1) to afford glycosyl donor **21** (2.12 g, 94%) as a colourless oil; $[\alpha]_D^{23}=-99.9$ (*c*, 2.0 in $CHCl_3$); ν_{max} no significant peaks; δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, $ArCH_3$), 3.74 (1H, dd, $J_{5,6}=5.3$ Hz, $J_{6,6'}=10.7$ Hz, H-6), 3.93 (1H, dd, $J_{5,6'}=2.0$ Hz, H-6′), 3.97–4.00 (2H, m, $OCHH'CH=CH_2$), 4.10–4.12 (2H, m, H-2, H-3), 4.20 (1H, ddd, $J_{4,5}=9.1$ Hz, H-5), 4.31 (1H, dd, $J_{3,4}=3.8$ Hz, H-4), 4.52, 4.62 (2H, ABq, $J_{AB}=11.6$ Hz, $PhCH_2$), 4.52, 4.80 (2H, ABq, $J_{AB}=11.6$ Hz, $PhCH_2$), 4.62 (2H, s, $PhCH_2$), 5.20 (1H, dq, $J_Z=10.4$ Hz, $J=1.5$ Hz, $CH=CH_EH_Z$), 5.26 (1H, dq, $J_E=17.3$ Hz, $J=1.7$ Hz, $CH=CH_EH_Z$), 5.30 (1H, d, $J_{1,2}=1.7$ Hz, H-1), 5.84 (1H, ddt, $J=5.5$ Hz, $CH=CH_2$), 7.09–7.42 (19H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 21.1 (q, $ArCH_3$), 70.6, 70.8, 72.0, 72.5, 73.4 (5×t, C-6, 3×$PhCH_2$, $OCH_2CH=CH_2$), 76.2, 81.2, 81.3, 86.3 (4×d, C-2, C-3, C-4, C-5), 91.0 (d, C-1), 117.6 (t, $CH=CH_2$), 127.4, 127.4,

127.6, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 129.6, 131.4, 133.9 (12×d, Ar-CH, *C*H=CH_2), 131.9, 137.0, 137.7, 138.6, 138.9 (5×s, Ar-C); *m/z* (ES^+) 619 ($M+Na^+$, 33), 614 ($M+NH_4^+$, 100), 597 ($M+H^+$, 7%). (HRMS calcd for $C_{37}H_{44}NO_5S$ (MNH_4^+) 614.2940. Found 614.2938).

4.1.23. *para*-Tolyl 3,5,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucofuranoside 22. Wilkinson's catalyst (320 mg, 0.35 mmol) was dissolved in anhydrous THF (6 ml) and degassed. Butyl lithium (1.6 M solution in hexanes) (0.32 ml, 0.52 mmol) was added and the mixture stirred for 10 min. Glycosyl donor **21** (2.07 g, 3.47 mmol) was dissolved in anhydrous THF (6 ml) and heated to 70 °C. The catalyst solution was added by cannula under Ar. After 2 h, TLC (CH_2Cl_2/petrol, 4:1) indicated formation of a two products (R_f 0.45 and 0.5) and complete consumption of starting material (R_f 0.4). The reaction was allowed to cool then diluted with CH_2Cl_2 (*ca* 5 ml) and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 8:1) to afford enol ethers **22** (1.99 g, 96%) as a colourless oil. Partial data: δ_H (400 MHz, $CDCl_3$) (*E*/*Z*, 1:1.7), *E* isomer 1.50 (3H, dd, $J=1.5$ Hz, $J=6.7$ Hz, OCH=CHCH_3), 2.33 (3H, s, $ArCH_3$), 4.83 (1H, dq, $J_E=12.5$ Hz, OCH=C*H*), 5.31 (1H, d, $J_{1,2}=1.2$ Hz, H-1), 5.97 (1H, daq, $J=1.5$ Hz, OC*H*=CH); *Z* isomer 1.53 (3H, dd, $J=1.9$ Hz, $J=6.7$ Hz, OCH=CHCH_3), 2.33 (3H, s, $ArCH_3$), 5.30 (1H, d, $J_{1,2}=1.8$ Hz, H-1), 5.84 (1H, daq, $J_Z=6.2$ Hz, $J=1.7$ Hz, OC*H*=CH); δ_C (100.6 MHz, $CDCl_3$) *E* isomer 12.4 (q, OCH=CH*C*H_3), 21.1 (q, $ArCH_3$), 90.8 (d, C-1), 102.6 (d, OCH=*C*H), 143.8 (d, O*C*H=CH); *Z* isomer 9.3 (q, OCH=CH*C*H_3), 21.1 (q, $ArCH_3$), 91.1 (d, C-1), 104.4 (d, OCH=*C*H), 142.9 (d, O*C*H=CH); *m/z* (ES^+) 619 ($M+Na^+$, 100), 614 ($M+NH_4^+$, 67), 597 ($M+H^+$, 23%). (HRMS calcd for $C_{37}H_{41}O_5S$ (MH^+) 597.2675. Found 597.2674).

4.1.24. *para*-Tolyl 3,5,6-tri-*O*-benzyl-2-O-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-1-thio-β-D-glucofuranoside 23a. *N*-Iodosuccinimide (68 mg, 0.30 mmol), and 4 Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to −40 °C under Ar. 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose (52 mg, 0.20 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. Vinyl ethers **22** (60 mg, 0.1 mmol) were dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred and allowed to warm to rt. After 1 h 35 min, TLC (petrol/ethyl acetate, 6:1) indicated formation of a major product (R_f 0.2), and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2×30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 5:1 with 1% Et_3N) to afford mixed acetals **23a** (107 mg, 75%) as a colourless oil. *m/z* (ES^+) 1005 ($M+Na^+$, 41), 1000 ($M+NH_4^+$, 5), 877 (M-STol+NH_4^+, 25%). (HRMS calcd for $C_{49}H_{63}NO_{11}SI$ (MNH_4^+) 1000.3167. Found 1000.3170).

4.1.25. *para*-Tolyl 3,5,6-tri-O-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-1-thio-β-D-glucofuranoside 23b. Iodine (55 mg, 0.22 mmol), silver trifluoromethanesulfonate (56 mg, 0.22 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (116 mg, 0.57 mmol) and 4 Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to −78 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (82 mg, 0.18 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added by cannula under Ar. Enol ethers **22** (100 mg, 0.17 mmol) were dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to rt. After 18 h, TLC (petrol/ethyl acetate, 6:1) indicated formation of a single major product (R_f 0.7), and little remaining starting material (R_f 0.8). The reaction was quenched with sodium thiosulfate (40 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2×40 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 7:1) to afford mixed acetals **23b** (128 mg, 64%) as a colourless oil; *m/z* (ES^+) 1245 ($M+NH_4^+$+MeCN, 55), 1209 ($M+Na^+$, 100), 1204 ($M+NH_4^+$, 92%).

4.1.26. *para*-Tolyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-1-thio-β-D-glucofuranoside 23c. Iodine (55 mg, 0.22 mmol), silver trifluoromethanesulfonate (56 mg, 0.22 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (116 mg, 0.57 mmol) and 4 Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to −78 °C under Ar. Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (65 mg, 0.18 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added by cannula under Ar. Enol ethers **22** (100 mg, 0.17 mmol) were dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to rt. After 17 h, TLC (petrol/ethyl acetate, 3:1) indicated formation of a two major products (R_f 0.55 and 0.5), and little remaining starting material (R_f 0.6). The reaction was quenched with sodium thiosulfate (40 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2×40 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 7:1→3:1) to afford mixed acetals **23c** (161 mg, 88%) as a colourless oil; *m/z* (ES^+) 1153 ($M+NH_4^+$+MeCN, 22), 1117 ($M+Na^+$, 58%).

4.1.27. 3,5,6-Tri-*O*-benzyl-α-D-glucofuranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose 24a. Mixed acetals **23a** (85 mg, 0.087 mmol) were dissolved in anhydrous dichloroethane (7 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (35 mg, 0.17 mmol), *N*-iodosuccinimide (59 mg, 0.26 mmol) and silver trifluoromethanesulfonate (22 mg, 0.087 mmol) were added and the mixture stirred under Ar at rt. After 6 h, TLC (petrol/ethyl acetate, 3:1) indicated the complete consumption of starting material (R_f 0.6) and the formation of a major product (R_f 0.3). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) and extracted with CH_2Cl_2 (2×30 ml). The organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash

column chromatography (petrol/ethyl acetate, 2:1) to afford α-*gluco* disaccharide **24a** (44 mg, 75%) as a colourless oil; $[\alpha]_D^{22} = -18.2$ (*c*, 0.55 in $CHCl_3$); ν_{max} 3467 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.33, 1.34, 1.46, 1.53 (12H, 4×s, 4×CH_3), 3.68 (1H, dd, $J_{5,6}=6.1$ Hz, $J_{6,6'}=10.5$ Hz, H-6_b), 3.79 (1H, dd, $J_{5,6}=7.9$ Hz, $J_{6,6'}=10.0$ Hz, H-6_a), 3.86–3.90 (2H, m, H-$6'_a$, H-$6'_b$), 4.03 (1H, ddd, $J_{4,5}=8.4$ Hz, $J_{5,6'}=2.0$ Hz, H-5_b), 4.06–4.11 (2H, m, H-5_a, H-3_b), 4.27–4.29 (2H, m, H-4_a, H-2_b), 4.33 (1H, dd, $J_{1,2}=5.1$ Hz, $J_{2,3}=2.3$ Hz, H-2_a), 4.37 (1H, dd, $J_{3,4}=4.3$ Hz,, H-4_b), 4.52, 4.70 (2H, ABq, $J_{AB}=11.8$ Hz, PhCH_2), 4.54, 4.80 (2H, ABq, $J_{AB}=11.6$ Hz, PhCH_2), 4.58 (2H, s, PhCH_2), 4.58–4.61 (1H, m, H-3_a), 5.21 (1H, d, $J_{1,2}=4.4$ Hz, H-1_b), 5.52 (1H, d, H-1_a), 7.16–7.37 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 24.4, 24.9, 25.9, 26.1 (4×q, 4×CH_3), 65.5 (d, C-5_a), 67.1 (t, C-6_a), 70.5, 70.5, 70.8, 75.5 (4×d, C-2_a, C-3_a, C-4_a, C-2_b), 71.3, 71.7, 72.6, 73.3 (4×t, 3×PhCH_2, C-6_b), 76.0 (d, C-5_b), 78.2 (d, C-4_b), 83.7 (d, C-3_b), 96.3 (d, C-1_a), 102.4 (d, C-1_b), 108.9, 109.3 (2×s, 2×$C(CH_3)_2$), 127.3, 127.4, 127.4, 127.5, 127.5, 127.6, 128.2, 128.3, 128.3 (9×d, Ar-CH), 137.9, 138.6, 138.9 (3×s, Ar-C); *m/z* (ES^+) 751 ($M+NH_4^+$ + MeCN, 22%), 715 ($M+Na^+$, 26), 710 ($M+NH_4^+$, 100%). (HRMS calcd for $C_{39}H_{52}NO_{11}$ (MNH_4^+) 710.3540. Found 710.3541).

4.1.28. Methyl 3,5,6-tri-*O*-benzyl-α-D-glucofuranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside 24b. Mixed acetals **23b** (103 mg, 0.087 mmol) were dissolved in anhydrous dichloroethane (7 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (35 mg, 0.17 mmol), *N*-iodosuccinimide (59 mg, 0.26 mmol) and silver trifluoromethanesulfonate (22 mg, 0.087 mmol) were added and the mixture stirred under Ar at rt. After 5 h, TLC (petrol/ethyl acetate, 3:1) indicated the complete consumption of starting material (R_f 0.7) and the formation of a major product (R_f 0.3). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) and extracted with CH_2Cl_2 (2× 30 ml). The organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 2:1) to afford α-*gluco* disaccharide **24b** (30 mg, 39%) as a colourless oil; $[\alpha]_D^{22} = +35.6$ (*c*, 0.5 in $CHCl_3$); ν_{max} 3383 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.31 (3H, s, OCH_3), 3.63 (1H, dd, $J_{5,6}=6.7$ Hz, $J_{6,6'}=10.5$ Hz, H-6_b), 3.68–3.71 (1H, m, H-5_a), 3.79–3.82 (2H, m, H-2_a, H-6_a), 3.84 (1H, dd, $J_{5,6'}=1.9$ Hz, H-$6'_b$), 3.89 (1H, dd, $J_{2,3}=2.9$ Hz, $J_{3,4}=9.6$ Hz, H-3_a), 4.01–4.07 (2H, m, H-4_a, H-5_b), 4.09 (1H, dd, $J_{2,3}=2.0$ Hz, $J_{3,4}=4.4$ Hz, H-3_b), 4.18 (1H, dd, $J_{5,6'}=3.6$ Hz, $J_{6,6'}=11.3$ Hz, H-$6'_a$), 4.25 (1H, dd, $J_{1,2}=4.3$ Hz, H-2_b), 4.34 (1H, dd, $J_{4,5}=8.0$ Hz, H-4_b), 4.46 (2H, s, PhCH_2), 4.49, 4.67 (2H, ABq, $J_{AB}=12.0$ Hz, PhCH_2), 4.55, 4.81 (2H, ABq, $J_{AB}=11.6$ Hz, PhCH_2), 4.63 (2H, s, PhCH_2), 4.67, 4.93 (2H, ABq, $J_{AB}=10.8$ Hz, PhCH_2), 4.69, 4.77 (2H, ABq, $J_{AB}=12.2$ Hz, PhCH_2), 4.70 (1H, s, H-1_a), 5.28 (1H, d, H-1_b), 7.23–7.38 (30H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 54.8 (q, OCH_3), 67.6 (t, C-6_a), 71.3 (d, C-5_a), 71.7, 72.1, 72.1, 72.7, 72.8, 73.2, 75.1 (7×t, 6×PhCH_2, C-6_b), 74.4, 74.5 (2×d, C-2_a, C-4_a), 75.6 (d, C-2_b), 76.3 (d, C-5_b), 78.4 (d, C-4_b), 79.9 (d, C-3_a), 83.7 (d, C-3_b), 99.0 (d, C-1_a), 102.6 (d, C-1_b), 127.2, 127.3, 127.4, 127.5, 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.3 (14×d, Ar-CH), 138.0, 138.1, 138.4, 138.4, 138.6, 139.0 (6×s, Ar-C); *m/z* (ES^+) 919 ($M+Na^+$, 54), 914 ($M+NH_4^+$, 100%). (HRMS calcd for $C_{55}H_{64}NO_{11}$ (MNH_4^+) 914.4479. Found 914.4467).

4.1.29. Methyl 3,5,6-tri-*O*-benzyl-α-D-glucofuranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside 24c. Dimethyl disulfide (24 μl, 0.26 mmol) and methyl trifluoromethanesulfonate (30 μl, 0.26 mmol) were dissolved in freshly distilled CH_2Cl_2 (1 ml) and stirred under Ar at rt. After 5 min, 2,6-di-*tert*-butyl-4-methylpyridine (68 mg, 0.33 mmol) was added and the mixture cooled to 0 °C. Mixed acetals **23c** (72 mg, 0.066 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added by cannula under Ar. After 5 h, TLC (petrol/ethyl acetate, 3:1) indicated very little remaining starting material (R_f 0.6) and the formation of major (R_f 0.4) and minor (R_f 0.4–0.5) products. The reaction was quenched with Et_3N and the mixture partitioned between ether (40 ml) and brine (40 ml). The aqueous layer was re-extracted with ether (20 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 7:2) to afford α-*gluco* disaccharide **24c** (17 mg, 32%) as a colourless oil; $[\alpha]_D^{22} = +12.8$ (*c*, 0.5 in $CHCl_3$); ν_{max} 3498 (br, OH) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.37 (3H, s, OCH_3), 3.67 (1H, dd, $J_{5,6}=5.7$ Hz, $J_{6,6'}=10.8$ Hz, H-6_b), 3.78–3.89 (4H, m, H-2_a, H-5_a, H-6_a, H-$6'_b$), 4.00 (1H, ddd, $J_{4,5}=8.0$ Hz, $J_{5,6'}=2.1$ Hz, H-5_b), 4.04 (1H, dd, $J_{2,3}=2.3$ Hz, $J_{3,4}=4.5$ Hz, H-3_b), 4.14 (1H, at, $J=9.5$ Hz, H-4_a), 4.23–4.28 (3H, m, H-3_a, H-$6'_a$, H-2_b), 4.35 (1H, dd, H-4_b), 4.48, 4.67 (2H, ABq, $J_{AB}=12.0$ Hz, PhCH_2), 4.52, 4.75 (2H, ABq, $J_{AB}=11.6$ Hz, PhCH_2), 4.52, 4.56 (2H, ABq, $J_{AB}=12.0$ Hz, PhCH_2), 4.59, 4.67 (2H, ABq, $J_{AB}=12.0$ Hz, PhCH_2), 4.67 (1H, d, $J_{1,2}=1.3$ Hz, H-1_a), 5.28 (1H, d, $J_{1,2}=4.5$ Hz, H-1_b), 5.59 (1H, s, PhC*H*), 7.23–7.47 (25H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 54.8 (q, OCH_3), 63.8 (d, C-5_a), 68.7 (t, C-6_a), 70.7 (t, C-6_b), 71.4, 72.3, 73.2, 73.8 (4×t, 4×PhCH_2), 75.2 (d, C-3_a), 75.9, 76.0 (2×d, C-2_b, C-5_b), 78.0, (d, C-2_a, C-4_a, C-4_b), 83.4 (d, C-3_b), 100.2 (d, C-1_a), 101.5 (d, PhC*H*), 102.8 (d, C-1_b), 125.9, 127.2, 127.3, 127.3, 127.4, 127.5, 127.7, 128.1, 128.1, 128.2, 128.3, 128.9 (12×d, Ar-CH), 137.2, 137.7, 137.9, 138.5, 138.8 (5×s, Ar-C); *m/z* (ES^+) 827 ($M+Na^+$, 46), 822 ($M+NH_4^+$, 100%). (HRMS calcd for $C_{48}H_{56}NO_{11}$ (MNH_4^+) 822.3853. Found 822.2863).

Acknowledgements

We gratefully acknowledge financial support from the EPSRC and GlaxoSmithKline (Quota and CASE Awards to I.C.). We also gratefully acknowledge the use of the EPSRC Mass Spectrometry Service (Swansea, UK) and the Chemical Database Service (CDS) at Daresbury, UK.

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21. Studies were in fact also carried out on the minor α-anomer **19α**, which was carried through an analogous reaction sequence to that undertaken for **19β** (Scheme 4). However, all subsequent IAD experiments on tethered materials derived from the α-donor, in which the leaving group is *syn* to the 2-hydroxyl group, revealed that whilst intramolecular glycosylation did occur that this was substantially less efficient than for the epimeric donor, in which the anomeric leaving group is *anti* to the 2-hydroxyl.
22. The anomeric stereochemistry of the α-glucofuranose disaccharides **24a–c** was determined by the $^{3}J_{H1,H2}$ coupling constant, which was between 4.3 and 4.5 Hz in all cases. See Ref. 19.
23. Whilst the desired 1,2-*cis* disaccharide **24c** was formed, as evidenced by ^{1}H NMR spectroscopy, this material could not be efficiently separated from the also-formed *manno* aglycon alcohol. In addition the overall reaction yield was low ($<31\%$), and many other unidentified products were also observed.

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Tetrahedron 60 (2004) 9075–9080
Tetrahedron

The absolute stereochemistry of anachelins, siderophores from the cyanobacterium *Anabaena cylindrica*

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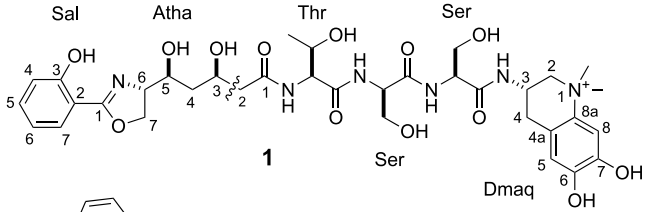
Received 7 June 2004; accepted 28 July 2004

Abstract—The absolute stereochemistry of anachelins (**1** and **2**), siderophores isolated from the freshwater cyanobacterium *Anabaena cylindrica*, was determined via the application of Boc-phenylglycine and Mosher's method. Consequently, it was revealed that a 1,1-dimethyl-3-amino-1,2,3,4-tetrahydro-6,7-dihydroxyquinolinium unit (Dmaq) has 3*S* (eq.) configuration, and a 6-amino-3,5,7-trihydroxy-heptanoic acid unit (Atha) has 3*R*, 5*S*, 6*S* configuration. The 6*S* configuration of Atha suggested that L-Ser was a biosynthetic precursor of Atha.

1. Introduction

Siderophores are low molecular weight and highly specific Fe(III) chelating agents synthesized by microorganisms to sequester iron from the iron-limited environment.[1] The structures of siderophores are diverse and several hundred structures have been reported from various microorganisms. Recently, the study of siderophore biosynthesis has been eagerly pursued, because the ability of siderophores from pathogenic microorganisms to efficiently assimilate Fe(III) from host cells has proven to be an important virulence factor. Therefore, proteins involved in the biosynthesis of siderophores have potential to be targets of therapeutic drugs.[2] In the view of application for the designed biosynthesis of natural-product-like molecules, siderophores are quite attractive molecules because many of them are peptide-like molecules[3] that are nonetheless biosynthesized non-ribosomally by large, multidomain enzymes termed non-ribosomal peptide synthetases (NRPS).[2,4] Furthermore, it has been recently elucidated that some siderophores, including yersiniabactin from *Yersinia pestis*,[5] are biosynthesized through the combination of NRPS and its biosynthetic cousin, polyketide synthase (PKS).[6]



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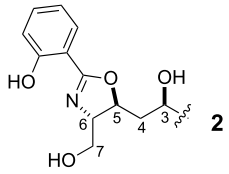

2

Anachelin and anachelin-2 (**1** and **2**) were isolated as the first genuine cyanobacterial siderophores from the freshwater cyanobacterium *Anabaena cylindrica*.[7,8] The structures of **1** and **2** have the sequence of three hydrophilic amino acids (L-Thr-D-Ser-L-Ser) in the middle of molecule and it has been assumed that D-Ser plays a role to resist hydrolysis by endogenous proteases. Two unique units responsible for binding iron are attached through amide bonds to each terminus of the sequence. One unit is a 6-amino-3,5,7-trihydroxyheptanoic acid unit (Atha). A 2-(2-hydroxyphenyl)-2-oxazoline ring of **1** and **2** functions as an iron-binding group formed from cyclization of 6-NH_2 and 7- or 5-OH of Atha, respectively, with salicylic acid (Sal). Although the ring system has been found in other siderophores such as the mycobactins of Mycobacteria,[9] it has usually been derived from cyclization of Ser or Thr.[10] In fact, the long-chain polyhydroxy unit Atha, which enhances the hydrophilic nature of the molecule, is quite unique in siderophores that usually consist of small endogenous

Keywords: Anachelin; Siderophore; Iron; Cyanobacteria; *Anabaena cylindrica*.
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doi:10.1016/j.tet.2004.07.105

organic moieties such as amino acids and diamines. Furthermore, the structure of Atha strongly suggests a hybrid of non-ribosomal peptide and polyketide biosynthetic origin. The other unit is a 1,1-dimethyl-3-amino-1,2,3,4-tetrahydro-6,7-dihydroxyquinolinium unit (Dmaq), of which a catechol group works as another iron-binding group. The structure of Dmaq is similar to the chromophore of the pyoverdines, the main siderophores of fluorescent pseudomonads,[11] but the dimethylated quaternary nitrogen seen in Dmaq has never been reported in any siderophores, and is reminiscent of quinoline alkaloids from plants.

Thus, Atha and Dmaq units of anachelins (**1** and **2**) have unique structural features and their biosynthetic pathway is also interesting, but the stereochemistry of **1** and **2** remained to be determined. Herein, we describe the absolute stereochemistry of Atha and Dmaq of **1** and **2**.

2. Results

Anachelins (**1** and **2**) were prepared from the iron-deficient culture supernatant of *A. cylindrica* NIES-19 as described previously.[8] Previous study reported that the oxazoline ring of **1** and **2** was sensitive to hydrolysis and easily opened to afford a 5- or 7-salicyl ester of Atha in acidic conditions, respectively.[7,8] Treatment with dilute alkali finally led the salicyl esters to a salicyl amide of Atha by the O→N acyl shift.[8,12] Since both salicyl amide derivatives prepared from **1** and **2** were identical in spectral analyses, including NMR (data not shown), the configuration of all chiral centers of **1** and **2** were determined to be identical. Therefore, we used a suitable sample of **1** or **2** for the determination of the stereochemistry of each chiral center.

2.1. Dmaq

The relative configuration at C-3 of Dmaq was elucidated by the combination of *J* values and NOESY correlations. Large vicinal coupling constants of H-2a/H-3 and H-3/H-4a (11.7 and 11.1 Hz, respectively) were observed in ^{1}H NMR spectrum of **1** and NOESY experiment of **1** showed the cross peak between H-2a and H-4a, indicating that the secondary amine group was equatorially connected to C-3 of Dmaq (Fig. 1). The absolute configuration at C-3 was determined by a Boc-phenylglycine (BPG) method,[13] because the BPG amides give rise to much higher $\Delta\delta$ values than those given by 2-methoxy-2-trifluoromethyl-2-phenylacetyl (MTPA) ester of Mosher's method. After treatment of **2** with excess trimethylsilyldiazomethane ($TMSCHN_2$) in dry MeOH to protect the catechol group,[14] **2** was hydrolysed in acid condition. HPLC purification of the hydrolysate furnished the 1,1-dimethyl-3-amino-1,2,3,4-tetrahydro-6,7-dimethoxyquinolinium unit (MeDmaq, **3**), which was subsequently converted to (*R*)- and (*S*)-BPG amides (**4** and **5**, respectively). ^{1}H NMR spectra of **4** and **5** were recorded for calculation of anisotropic chemical shift differences (the $\Delta\delta=\delta_R-\delta_S$) for each proton. The $\Delta\delta$ values for two *N*Me-1 and H-2 were positive, while negative $\Delta\delta$ values were observed for H-4, H-5, and *O*Me-6, which indicated that C-3 possessed *S* configuration (Fig. 2). Thus, the absolute configuration of Dmaq was assigned as 3*S* (eq).

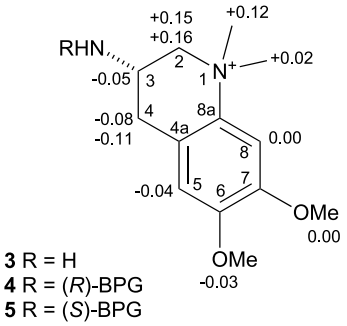


Figure 2. $\Delta\delta$ values [$\Delta\delta$ (in ppm)$=\delta_R-\delta_S$] obtained for (*R*)- and (*S*)-BPG amides of **3** (**4** and **5**, respectively).

2.2. Atha

To elucidate the relative configuration of C-3/C-5 of Atha, **1** was converted to a diacetonide derivative (**6**) with 2,2-dimethoxypropane in DMF. NOESY spectrum of **6** showed the cross peaks of H-3/H-5, H-3/H-4b, H-5/H-4b, H-3/Me (δ 1.42), and H-5/Me (δ 1.42) in Atha, indicating that the 1,3-dioxane ring in Atha existed in chair configuration to show the relative configuration of C-3/C-5 of Atha to be *syn* (Fig. 3). The oxazoline ring of **2** seemed to be convenient to determine the relative configuration of C-5/C-6 of Atha. Unfortunately, it was impossible to establish the configuration from the ^{1}H NMR spectrum of **2** recorded in DMSO-d_6, since the signals due to H-7 of Atha and H-3 of two Ser residues overlapped. After the trial of several solvents, however, the spectrum recorded in C_5D_5N gave the

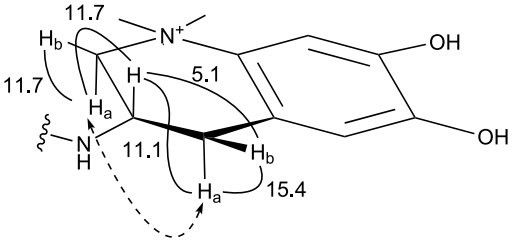


Figure 1. The relative stereochemistry of Dmaq of **1**. Coupling constants (Hz) and NOESY correlations are shown by plain lines and a dashed arrow, respectively.

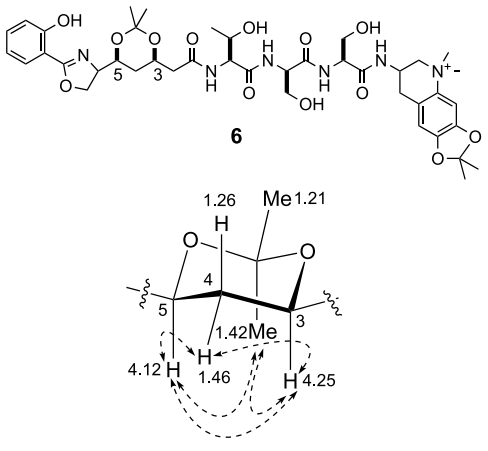


Figure 3. The relative stereochemistry of C3/C5 of Atha of a diacetonide derivative of **1** (**6**). NOESY correlations are shown by dashed arrows.

favorable separation between the signal of H-7 of Atha and other signals. The irradiation of the signal of H-7 of Atha changed that of H-6 to be a distinct doublet ($^3J_{H\text{-}5/H\text{-}6}=6.4$ Hz, Fig. 4). Previous study described that in a phenyl-oxazoline ring the large coupling constant ($^3J_{HH}=10.0$–11.0 Hz) corresponded to *cis* form and the small one ($^3J_{HH}=6.0$–7.0 Hz) to *trans* form.[15] Therefore, the conformation of the oxazoline ring of **2** was assigned to be *trans*, indicating the relative stereochemistry of C-5/C-6 of Atha to be *syn*.

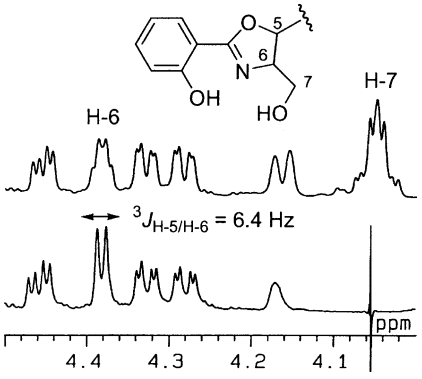


Figure 4. ^{1}H NMR spectra of **2** in C_5D_5N. Top: non-irradiation, bottom: irradiation of H-7 signal of Atha at δ_H 4.00.

The absolute stereochemistry of Atha was elucidated by Mosher's method.[16] It was found that acidic methanolysis of **1** gave a 7-*O*-salicyl-Atha methyl ester as a major degradation product (**7**, Scheme 1). Then, the methanolysate including **7** was treated in diluted NaOH solution to yield a *N*-salicyl Atha amide (**8**) by the O→N acyl shift.[12] Under acidic conditions, **8** was spontaneously cyclized to a delta lactone and therefore the application of Mosher's method for the secondary hydroxyl group at C-3 of the delta lactone was undertaken. However, the expected MTPA diester was not obtained because of the rapid dehydration between C-2 and C-3 of the delta lactone. Therefore, to prevent from the spontaneous cyclization, **8** was converted to a methyl ester (**9**) with $TMSCHN_2$ again, which also methylated the phenol group (Scheme 1). Then the methylester (**9**) was treated with 2 equiv of each (*R*)- and (*S*)-MTPACl in the presence of DMAP in dry C_5H_5N, followed by HPLC purification to furnish the 3,7-bis[(*S*)- and (*R*)-MTPA] esters of **9** (**10** and **11**, respectively, Scheme 1). The $\Delta\delta$ values ($\delta_S-\delta_R$) obtained from ^{1}H NMR data of **10** and **11** consistently fell into regions that lay to the left and right of the secondary MTPA ester group at C-3 except for that of Sal (Fig. 5), which was interpreted to be caused by turn of a branched Sal amide toward C-3. Thus the absolute stereochemistry at C-3 of Atha was confirmed to be *R* configuration. Consequently, the absolute stereochemistry at C-3, C-5, and C-6 of Atha unit were assigned as *R*, *S*, and *S*.

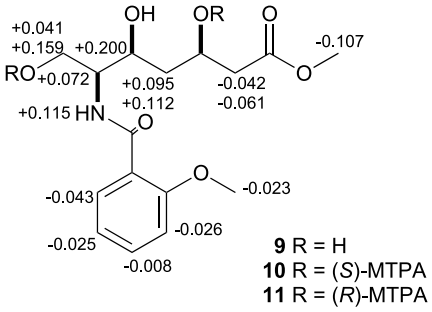
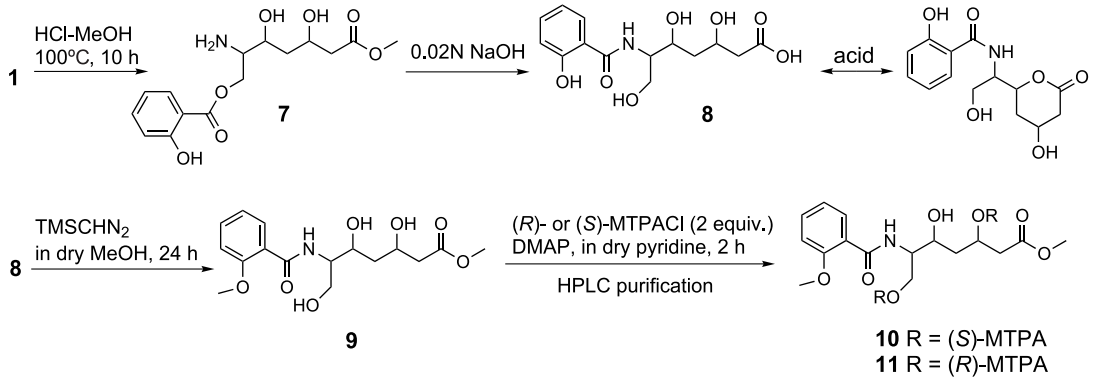


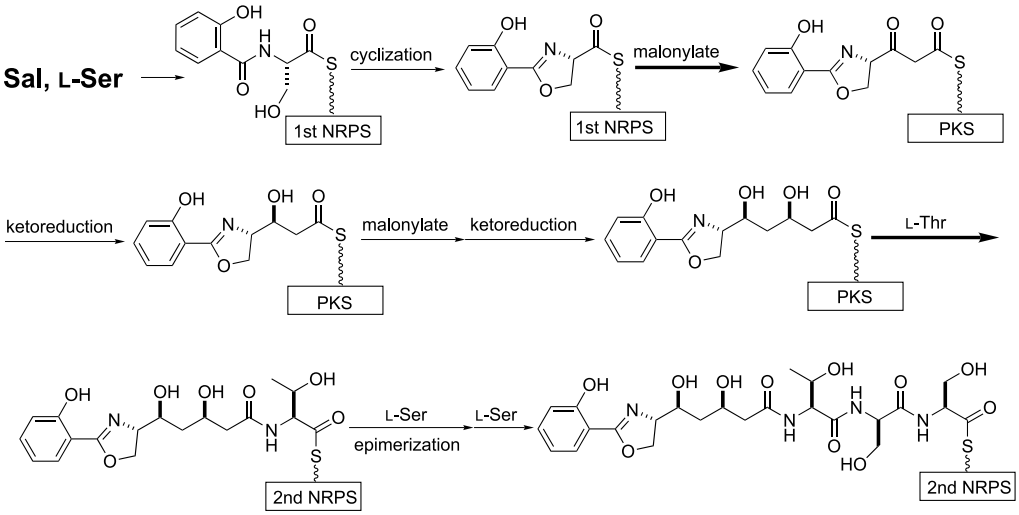
Figure 5. $\Delta\delta$ values [$\Delta\delta$ (in ppm)$=\delta_S-\delta_R$] obtained for 3,7-bis[(*S*)- and (*R*)-MTPA] esters of **9** (**10** and **11**, respectively).

3. Discussion

The stereochemistry of anachelins (**1** and **2**) was completely determined in this study. The heterocyclic oxazoline ring is a class of iron binding group in siderophores and it is usually derived from cyclization of L-Ser or L-Thr.[10] The *S* configuration at C-6 of Atha suggested that L-Ser was incorporated as a precursor in the biosynthesis of Atha. Furthermore, the structure of Atha also suggested that the carbon chain from C-1 to C-4 of Atha was incorporated by condensation of malonyl moieties by PKS. Recently, Walsh and co-workers revealed yersiniabactin, a siderophore containing three heterocycles (two thiazolines and a thiazolidine) from the plague bacterium *Yersinia pestis*,[5] to be produced by NRPS and PKS, which comprises Sal, three L-Cys, three methyl units from *S*-adenosyl-methionine, and a malonyl moiety.[6] Yersiniabactin synthetase was the first example of a NRPS/PKS hybrid assemble and involves two switching points from NRPS to PKS module. On the basis of suggested biosynthetic scheme of yersiniabactin, we propose the pathway to **1** that has two switching points from NRPS to PKS modules as follows (Scheme 2). At the beginning, L-Ser condenses to Sal on the first NRPS followed by cyclization to the oxazoline ring. The two-ring intermediate is elongated by condensation of



Scheme 1.



Scheme 2. Propose biosynthetic scheme for anachelin (**1**).

two malonyl groups on an intervening PKS module. Following ketone reduction, the molecule is transferred to the second NRPS module to attach the peptide sequence (L-Thr-D-Ser-L-Ser). However, one question arises from the scheme proposed above; when is the oxazoline of anachelin-2 (**2**) cyclized? If the carbon chain of Atha is elongated by the condensation of malonyl moieties on PKS, the oxazoline of **2** should be cyclized after the condensation of the first malonyl unit to Sal-Ser and the following reduction of its ketone to the hydroxyl group corresponding to 5-OH of Atha. However, some studies showed that cyclization to a phenyl-oxazoline or a phenyl-thiazoline occurred soon after the condensation of Sal and amino acids (L-Ser or L-Cys, respectively) on NRPS module.[2,6] Therefore, it is reasonable to surmise that **2** is an artificial compound formed from **1** during culture or purification. In our previous study, however, the conversion between **1** and **2** was not observed in the acidic solution used during HPLC purification and the culture supernatant in the fourth day showed the presence of both **1** and **2** in the ratio of 1:1.[8] Moreover, **1** dissolved in culture medium (pH 8.5) was incubated under a fluorescent light for 1 week, but the conversion from **1** to **2** was not observed (data not shown). Therefore, it is assumed that **2** is also a product of biosynthesis of *A. cylindrica* NIES-19, but we cannot exclude the possibility of the conversion between **1** and **2** in cell and other biosynthetic schemes. The structure of Dmaq is similar to the chromophore of pyoverdines, the main siderophore of fluorescent pseudomonads.[11] Feeding experiments and genetic studies revealed that Tyr was a precursor of the chromophore.[17] Therefore, it is possible that Tyr is also incorporated in Dmaq of **1** and **2**, and if so, its form could be L on the basis of the stereochemistry of the resulting siderophores.

4. Experimental

4.1. Instrumentation

NMR spectra were recorded on a JEOL JNM-A600 spectrometer at 27 °C. ^{1}H and ^{13}C NMR chemical shifts were referenced to residual solvent peaks of DMSO-d_6 at δ_H 2.49 and δ_C 39.5. FAB-MS spectra were measured using glycerol as matrix on a JEOL JMS SX-102 mass spectrometer.

4.2. Material

Anachelins (**1** and **2**) were prepared from the iron-deficient culture supernatant of *A. cylindrica* NIES-19 as described previously.[8] The obtained **1** and **2** were lyophilized completely and stored as powder at −20 °C. Boc-phenylglycine (BPG) was prepared from a commercial phenylglycine.

4.2.1. MeDmaq (3). To a solution of **2** (11.2 mg) in dry MeOH (100 μL) and dry benzene (500 μL), 8 equiv of $TMSCHN_2$ solution (68.8 μL) was added and stirred for 12 h under argon. The reacting mixture was dried in vacuo, followed by hydrolysis in 6 N HCl at 110 °C for 10 h. The solvent was removed in a stream of dry N_2, and the residue was applied to a YMC-ODS column (50×150 mm) and eluted with 0, 25, 50, and 100% MeOH. The concentrated H_2O fraction was purified by HPLC (Cosmosil C_{18} MS column, 10.0×250 mm; 0–20% MeCN containing 0.05% TFA in 20 min; flow rate 2 mL/min, UV detection at 210 nm) to yield MeDmaq (**3**, 2.4 mg). Retention time (min): **3** (25.6). HRFAB-MS *m/z* 237.1612 (M^+) calculated for $C_{13}H_{21}N_2O_2$ (Δ −0.8 mmu). ^{1}H NMR (DMSO-d_6), δ_H 3.56 (s, *N*Me-1a), 3.65 (s, *N*Me-1b), 3.66 (m, H-2a), 3.90 (m, H-2b), 4.45 (m, H-3), 2.75 (dd, J=16.2, 11.1 Hz, H-4a), 2.98 (s, J=16.2, 5.0 Hz, H-4b), 6.91 (s, H-5), 3.75 (s, *O*Me-6), 3.80 (s, *O*Me-7), 7.40 (s, H-8).

4.2.2. (*R*)-BPG amide of 3 (4). To solution of **3** (1.0 mg) in dehydrated DMF (1 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.0 mg), 1-hydroxybenzotriazole (HOBt, 2.0 mg) and (*R*)-BPG (2.0 mg) were added at 0 °C and stirred at room temperature for 10 h. The reacting mixture was dried in vacuo and redissolved in MeOH, and subjected to HPLC (Cosmosil C_{18} MS column, 10.0×250 mm; 32–37% MeCN containing 0.05% TFA in 10 min; flow rate 2 mL/min, UV detection at 210 nm) to afford (*R*)-BPG amide of **3** (**4**, 1.2 mg). Retention time (min): **4** (12.0). HRFAB-MS *m/z* 470.2647 (M^+) calculated for

$C_{26}H_{36}N_3O_5$ (Δ −0.8 mmu). ^{1}H NMR (DMSO-d_6), MeDmaq, δ_H 3.56 (s, *N*Me-1a), 3.65 (s, *N*Me-1b), 3.66 (m, H-2a), 3.90 (brd, J=12.0 Hz, H-2b), 4.45 (m, H-3), 2.78 (dd, J=16.2, 11.1 Hz, H-4a), 2.95 (dd, J=16.2, 5.0 Hz, H-4b), 6.91 (s, H-5), 3.75 (s, *O*Me-6), 3.80 (s, *O*Me-7), 7.40 (s, H-8), 7.40 (m, NH), BPG, 5.21 (d, J=4.2 Hz, H-2), 7.42 (d, J=7.5 Hz, H-4), 7.36 (t, J=7.5 Hz, H-5), 7.32 (t, J=7.5 Hz, H-6), 8.61 (d, J=4.2 Hz, NH), 1.40 (s, Me).

4.2.3. (*S*)-BPG amide of 3 (5). (*S*)-BPG amide of **3** (**5**, 1.0 mg) was prepared by the same manner as described above. Retention time (min): **5** (13.6). HRFAB-MS *m/z* 470.2652 (M^+) calculated for $C_{26}H_{36}N_3O_5$ (Δ −0.3 mmu). ^{1}H NMR (DMSO-d_6), MeDmaq, δ_H 3.54 (s, *N*Me-1a), 3.53 (s, *N*Me-1b), 3.51 (m, H-2a), 3.74 (brd, J=12.0 Hz, H-2b), 4.50 (m, H-3), 2.86 (dd, J=16.2, 11.1 Hz, H-4a), 3.06 (dd, J=16.2, 5.1 Hz, H-4b), 6.95 (s, H-5), 3.78 (s, *O*Me-6), 3.80 (s, *O*Me-7), 7.40 (s, H-8). 7.40 (m, NH), BPG, 5.21 (d, J=4.2 Hz, H-2), 7.41 (d, J=7.5 Hz, H-4), 7.36 (t, J=7.5 Hz, H-5), 7.32 (t, J=7.5 Hz, H-6), 8.61 (d, J=4.2 Hz, NH), 1.40 (s, Me).

4.2.4. Diacetonide derivative of 1 (6). To solution of **1** (10.4 mg) in dehydrated DMF (1.0 mL), *p*-TsOH (11.8 mg) and excess amount of 2,2-dimethoxypropane (500 μL) were added and stirred at room temperature for 24 h. The reacting mixture was dried in vacuo and dissolved in H_2O, and subjected to ODS open column chromatography, and eluted with 0, 20, 50 and 100% MeOH. The 50% MeOH fraction was lyophilized to obtain a diacetonide derivative (**6**, 7.5 mg). HRFAB-MS *m/z* 841.4024 (M^+) calculated for $C_{41}H_{57}N_6O_{13}$ (Δ +4.0 mmu). ^{1}H NMR (DMSO-d_6), Sal, δ_H 6.96 (d, J=7.7 Hz, H-4), 7.42 (t, J=7.7 Hz, H-5), 6.91 (t, J=7.7 Hz, H-6), 7.58 (d, J=7.7 Hz, H-7), Atha, 2.06 (m, H-2a), 2.35 (m, H-2b), 4.25 (m, H-3), 1.26 (m, H-4a), 1.46 (m, H-4b), 4.12 (m, H-5), 4.33 (m, H-6), 4.33 (m, H-7a), 4.46 (m, H-7b), 1.21 (s, Me), 1.42 (s, Me), Thr, 4.33 (m, H-2), 3.97 (m, H-3), 1.27 (m, H-4), 7.44 (m, NH), Ser (1), 4.16 (m, H-2), 3.65 (m, H-3a), 3.73 (m, H-3b), 8.50 (d, J=5.7 Hz, NH), Ser (2), 4.22 (m, H-2), 3.58 (m, H-3a), 3.64 (m, H-3b), 8.96 (d, J=5.6 Hz, NH), Dmaq, 3.51 (s, *N*Me-1a), 3.60 (s, *N*Me-1b), 2.97 (m, H-2a), 3.82 (m, H-2b), 4.50 (br, H-3), 2.85 (dd, J=15.4, 11.1 Hz, H-4a), 2.95 (dd, J=15.3, 5.1 Hz, H-4b), 6.56 (s, H-5), 7.27 (s, H-8), 7.83 (d, J=7.7 Hz, NH), 1.13 (s, Me), 1.29 (s, Me).

4.2.5. *N*-Salicyl-Atha amide (8). 10% HCl–MeOH solution (3.0 mL) containing **1** (10 mg) was heated to 100 °C in a sealed tube for 10 h and then cooled. The reaction mixture was evaporated and lyophilized to remove traces of HCl. The HPLC and following spectral analyses of a part of the resultant products showed that a 7-*O*-salicyl Atha methyl ester (**7**) was a major degradation compound **7**; FABMS *m/z* 328 $(M+H)^+$, ^{1}H NMR (DMSO-d_6). Sal, δ_H 6.88 (m, H-4), 7.35 (t, J=7.7 Hz, H-5), 6.88 (m, H-6), 7.91 (d, J=7.7 Hz, H-7), Atha, 2.16 (dd, J=15.0, 8.1 Hz, H-2a), 2.30 (dd, J=15.0, 3.9 Hz, H-2b), 4.00 (m, H-3), 1.48 (m, H-4a), 1.53 (m, H-4b), 3.98 (m, H-5), 3.62 (m, H-6), 4.44 (m, H-7a), 4.52 (m, H-7b). Then, the resultant compound was dissolved in 0.02 N NaOH solution and incubated at room temperature for 1 h, followed by resolution by HPLC (Cosmosil C_{18} MS column, 10.0×250 mm; 20–30% MeCN containing 0.05% TFA in 10 min; flow rate 2 mL/min, UV detection at 210 nm) to yield **8** (1.5 mg). Retention time (min): **8** (18.4). HRFAB-MS *m/z* 314.1263 $(M+H)^+$ calculated for $C_{14}H_{20}NO_7$ (Δ +2.3 mmu). ^{1}H NMR (DMSO-d_6), Sal, δ_H 6.88 (m, H-4), 7.35 (t, J=7.7 Hz, H-5), 6.88 (m, H-6), 7.91 (d, J=7.7 Hz, H-7), Atha, 2.16 (dd, J=15.0, 8.1 Hz, H-2a), 2.32 (dd, J=15.0, 3.9 Hz, H-2b), 4.00 (m, H-3), 1.48 (m, H-4a), 1.53 (m, H-4b), 3.98 (m, H-5), 3.99 (m, H-6), 3.44 (m, H-7a), 3.52 (m, H-7b), 8.34 (d, J=8.5 Hz, NH).

4.2.6. Methylester of 8 (9). To solution of **8** (1.5 mg) in dehydrated MeOH (1.0 mL), excess $TMSCHN_2$ (100 μL, 2.0 M solution) was added and stirred at room temperature for 24 h. The reacting mixture was directly subjected to HPLC (Cosmosil C_{18} MS column, 10.0×250 mm; 30–60% MeCN containing 0.05% TFA in 15 min; flow rate 2 mL/min, UV detection at 210 nm) to afford a methylester (**9**, 1.4 mg). Retention time (min): **9** (18.4). HRFAB-MS *m/z* 342.1570 $(M+H)^+$ calculated for $C_{16}H_{24}NO_7$ (Δ +1.8 mmu). ^{1}H NMR (CD_3OD), Sal, δ_H 3.98 (s, *O*Me), 7.15 (d, J=7.7 Hz, H-4), 7.50 (t, J=7.7 Hz, H-5), 7.06 (t, J=7.7 Hz, H-6), 7.98 (d, J=7.7 Hz, H-7), Atha, 3.61 (s, *O*Me), 2.43 (dd, J=15.2, 4.7 Hz, H-2a), 2.52 (dd, J=15.2, 8.1 Hz, H-2b), 4.24 (m, H-3), 1.66 (dt, J=14.1, 8.1 Hz, H-4a), 1.75 (dt, J=14.1, 5.1 Hz, H-4b), 4.21 (m, H-5), 4.12 (dt, J=1.7, 6.4 Hz, H-6), 3.70 (d, J=6.4 Hz, H-7, 2H).

4.2.7. 3,7-Bis[(*S*)-MTPA] ester of 9 (10). The methylester **9** (400 μg: 1.17 μmol) was dried in a reaction tube which was made by cutting off a NMR tube (5 mm). And the solution of DMAP in dehydrated pyridine (100 μL, 3.15 mg/mL, 2.58 μmol) was added to the reaction tube. (*R*)-MTPACl solution (0.48 mL, 2.58 μmol) was carefully added and placed for 2 h at room temperature. The reaction mixture was lyophilized and dissolved in MeOH and subjected to HPLC (Cosmosil C_{18} MS column, 10.0×250 mm; 76–100% MeCN containing 0.05% TFA in 12 min; flow rate 2 mL/min, UV detection at 210 nm) to afford a 3,7-bis[(*S*)-MTPA] ester derivative (**10**, 500 μg). Retention time (min): **10** (18.4), 5,7-bis[(*S*)-MTPA] ester (18.8), and 3,5,7-tris[(*S*)-MTPA] ester (22.4). HRFAB-MS *m/z* 774.2365 $(M+H)^+$ calculated for $C_{36}H_{38}NO_{11}$ (Δ +1.6 mmu). ^{1}H NMR (CD_3OD), Sal, δ_H 3.900 (s, *O*Me), 7.130 (d, J=7.7 Hz, H-4), 7.517 (t, J=7.7 Hz, H-5), 7.052 (t, J=7.7 Hz, H-6), 7.851 (d, J=7.7 Hz, H-7), Atha, 3.516 (s, *O*Me), 2.626 (dd, J=16.2, 9.0 Hz, H-2a), 2.715 (dd, J=16.2, 3.8 Hz, H-2b), 5.635 (m, H-3), 1.807 (m, H-4a), 1.995 (m, H-4b), 3.885 (m, H-5), 4.460 (m, H-6), 4.382 (dd, J=11.1, 5.6 Hz, H-7a), 4.614 (dd, J=11.1, 7.7 Hz, H-7b), 8.540 (br, NH).

4.2.8. 3,7-Bis[(*R*)-MTPA] ester of 9 (11). A 3,7-bis[(*R*)-MTPA] ester derivative (**11**, 500 μg) was prepared using (*S*)-MTPACl by the same procedure as described above. HRFAB-MS *m/z* 774.2360 $(M+H)^+$ calculated for $C_{36}H_{38}NO_{11}$ (Δ +1.1 mmu). ^{1}H NMR (CD_3OD), Sal, δ_H 3.923 (s, *O*Me), 7.156 (d, J=7.7 Hz, H-4), 7.525 (t, J=7.7 Hz, H-5), 7.077 (t, J=7.7 Hz, H-6), 7.894 (d, J=7.7 Hz, H-7), Atha, 3.516 (s, *O*Me), 2.687 (dd, J=16.2, 9.0 Hz, H-2a), 2.757 (dd, J=16.2, 3.8 Hz, H-2b), 5.623 (m, H-3), 1.695 (m, H-4a), 1.900 (m, H-4b), 3.685 (m, H-5), 4.388 (m, H-6), 4.223 (dd, J=11.1, 5.6 Hz, H-7a), 4.573 (dd, J=11.1, 7.7 Hz, H-7b), 8.425 (br, NH).

Acknowledgements

We thank Dr. N. Oku (National Cancer Institute at Frederick) for his advice and discussion of organic reactions. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan. Y. Ito is financially supported by Research Fellowship of Japan Society for the Promotion of Science for Young Scientists.

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Tetrahedron 60 (2004) 9081–9084
Tetrahedron

A short enantioselective synthesis of homocitric acid-γ-lactone and 4-hydroxy-homocitric acid-γ-lactones

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Received 27 May 2004; revised 12 July 2004; accepted 28 July 2004

Available online 26 August 2004

Abstract—A simple method for the synthesis of enantiopure homocitric acid γ-lactone and its 4-hydroxy analogues starting from spiro-γ-dilactone, in up to 74% isolated yield is described.

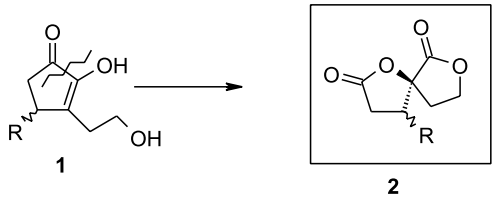
1. Introduction

(−)-*R*-Homocitrate is an intermediate in lysine biosynthesis pathway in yeast and some fungi.[1–4] This pathway is absent in plants and mammalians. That feature makes (−)-*R*-homocitrate and various citric acid derivatives promising candidates for anti-fungi therapy in human medicine, and prospective anti-fungi agents for crop protection in agriculture. The list of new antifungal citrates is far from being exhausted.[5] Additionally, chiral hydroxy acids are known as useful chiral synthons, ligands and auxiliaries in asymmetric organic synthesis.[6]

Maragoudakis and Strassmann accomplished the first synthesis of racemic homocitrate in 1966.[7] In the same year, enantioenriched *S*-homocitric acid was synthesized from (−)-quinic acid.[8] In the late nineties, interest towards homocitric acid increased again and it was synthesized from L-lactic acid and L-serine,[9] citric acid,[10] monoethyl malonate[11] and D-Na-malate.[12]

To the best of our knowledge, the 4-hydroxy derivatives of homocitric acid have not been found from natural sources yet, and have not been synthesized before. However, the corresponding isomers of hydroxycitric acids, (2*S*,3*S*)- and (2*S*,3*R*)-2-hydroxycitric acid and their derivatives are extensively distributed in nature and are present in plants.[13,14] Several reports pertaining to the pharmaceutical applications of these compounds are available.[15–17] All of the above mentioned reasons make the search for new synthetic methods of chiral citrates, their derivatives and analogues an important goal for synthetic chemists.

Asymmetric oxidation of ketones is a challenging option in the synthesis of enantioenriched compounds.[18,19] We have previously found that 3-substituted cyclopentane-1,2-diones can be oxidized with Ti(O*i*-Pr)$_4$/(+)-diethyl tartrate/*tert*-BuOOH complex (Sharpless complex),[20] resulting in enantiopure 2-alkyl-γ-lactone acids in the case of alkyl-substituted diketones[21–23] and spirodilactones **2** in the case of hydroxyethyl substituted diketones **1**.[24] These stable compounds can be used as key intermediates in many transformations. (Scheme 1).



Scheme 1.

In the present paper we demonstrate how the derivatives of hexanetriacid can be obtained starting from spirodilactone **2** according to a simple and efficient scheme (Scheme 2).

2. Results and discussion.

2.1. Preparation of homocitric acid-γ-lactone

Homocitric acid-γ-lactone was synthesized starting from

Keywords: Asymmetric oxidation; Spirodilactone; Homocitric acid; γ-Lactone; 4-Hydroxy-homocitric acid; γ-Lactone.
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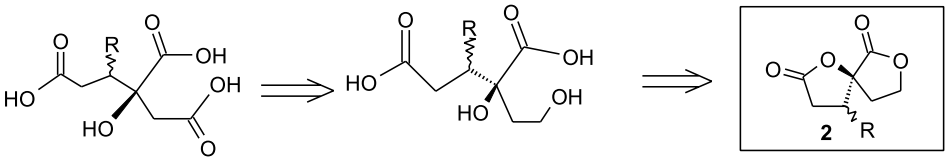
doi:10.1016/j.tet.2004.07.096



Scheme 2.

spirodilactone (*R*)-**2a** (**2a** was obtained from asymmetric oxidation of 3-hydroxyethyl-cyclopentane-1,2-dione according the described procedure[24]). We first made an attempt to convert spirodilactone **2a** into a diester **3a** (path (a), Scheme 3). However, *trans*-esterification of **2a** with methanol under basic conditions ($NaHCO_3$, K_2CO_3 or NaOMe) resulted in a 3:7 ratio of diester **3a** and lactone ester **4a** (in a 94% overall yield). The same mixture was obtained when one of the reaction products—lactone ester **4a**—was treated with methanol. Diester **3a** and lactone ester **4a** are easily separable from each other on silica gel. Jones oxidation of the separated diester **3a** followed by hydrolysis and acidification, resulted in (*R*)-homocitric acid-γ-lactone **5a** in 46% yield for two steps.

The moderate yield of **3a** from the *trans*-esterification procedure forced us to find alternatives. So, we tried a direct oxidation of spirodilactone **2a** in a form a diacid Na—or K-salt. Indeed, using simple reagents like $KMnO_4$ or $K_2S_2O_8$ (with $RuCl_3\times H_2O$ as a catalyst)[25] in basic medium afforded (*R*)-(−)-homocitric acid-γ-lactone *R*-**5a** directly from (*R*)-**2a** in 56 and 74% yield, correspondingly (path (b), Scheme 3).

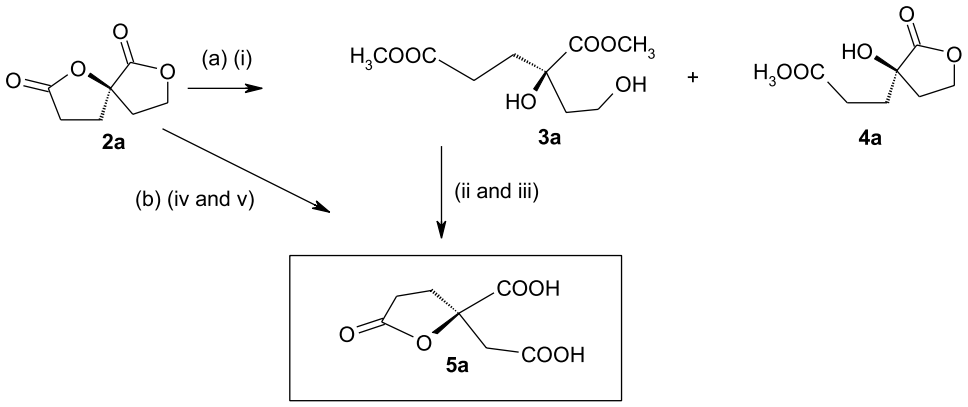
Comparison of the optical rotation of the obtained product ($[\alpha]_D=-49.8$ for **5a**) with that of the natural product[8] confirms the (*R*) absolute configuration of the homocitric acid lactone. This result is in good agreement with our earlier suggestion that the oxidation of the substrate **1a** using Ti(O*i*Pr)$_4$/(+)-diethyl tartrate/*tert*-BuOOH complex results in *R*-configuration of the newly formed stereogenic center in **2a**.[24]

2.2. Preparation of 4-hydroxyhomocitric acid-γ-lactones

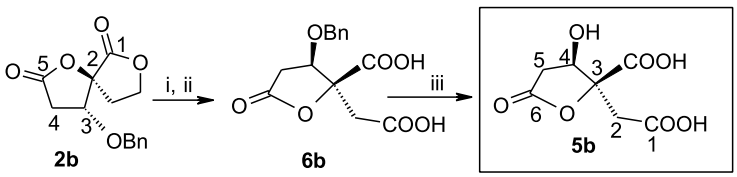
The synthesis of new homocitric acid analogs—4-hydroxy-homocitric acids was accomplished starting from benzyl-oxy-substituted spirodilactones (2*S*,3*R*)-**2b** and (2*S*,3*S*)-**2c**, respectively. Preparation of the initial diketone **1b**, its asymmetric conversion into diastereomeric spirodilactones **2b**:**2c** as a 6:1 mixture, and separation of the diastereomers has been described by us earlier.[24] The major diastereomer **2b** from this procedure (*ee* 86–88%) was recrystallized from CH_2Cl_2–ether mixture affording the necessary substrate **2b** in good yield (73%) and high enantiomeric purity (ee 98.5%). Compound (2*S*,3*R*)-**2b** was subjected to oxidation with $K_2S_2O_8$ (cat. $RuCl_3\times H_2O$) using the same procedure that is described for **2a** (Scheme 4).

Thus, (−)-4-hydroxyhomocitric acid-γ-lactone (3*S*,4*R*) **5b** was obtained from spirodilactone (2*S*,3*R*)-**2b** after oxidation, cyclization and removing the protecting benzyl group in 59% overall yield (Scheme 4).

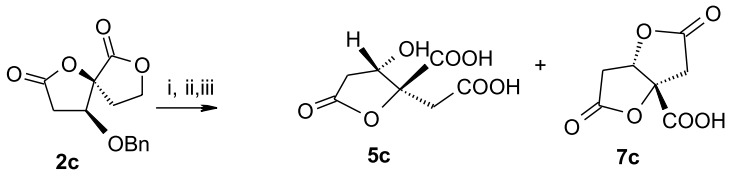
An analogous process, starting from the minor isomer (2*S*,3*S*)-**2c**, resulted in a mixture of two compounds: **5c** and **7c** (identified only by ^1H and ^{13}C NMR spectra) (Scheme 5). The *cis*-orientation of the –OH and –CH_2COOH groups in



Scheme 3. Reagents and conditions: (a) (i) $NaHCO_3$, MeOH, rt. (ii) Jones' reagent, 71%. (iii) LiOH, THF 6 h, then 1 M HCl, 65%. (b) (iv) $KMnO_4$, 1 M NaOH, 16 h, rt, (56%). (v) 1 M HCl, (74%) or (iv) $K_2S_2O_8$, $RuCl_3\times H_2O$, 0.2 N KOH. (v) 1 M HCl, (74%).



Scheme 4. Reagents and conditions: (i) $K_2S_2O_8$, $RuCl_3\times H_2O$, 0.2 M KOH. (ii) conc. HCl, CH_2Cl_2 (61% for two steps). (iii) Pd/C, H_2 (96%).



Scheme 5. Reagents and conditions: (i) $K_2S_2O_8$, $RuCl_3\times H_2O$, 0.2 M KOH. (ii) conc. HCl, CH_2Cl_2. (iii) Pd/C, H_2.

5c was also established by ^1H and ^{13}C NMR spectra confirming the structure of **7c**.

3. Conclusions

The described method affords a simple and short access to homocitric acid and its derivatives. The method enables synthesis of homocitric acid γ-lactones in both enantiomeric forms starting from 3-hydroxymethyl-1,2-cyclopentanedione via spirodilactone **2a** with the overall isolated yield of the target compounds more than 50%. The (−)-4-hydroxy-homocitric acid-γ-lactones **5b**, **5c** and bilactone acid **7c** can be obtained from 4-hydroxy-3-hydroxyethyl-cyclopentane-1,2-diones in a similar way. These are new compounds with a furanone skeleton, and biological activity is currently under study.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were determined in deuterated solvents on a Bruker AMX-500 spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from TMS. Deuterated solvent peaks were used as internal references: deutero-methanol at 3.30 and 49.00 ppm, deutero-acetone at 2.05 and 29.80 ppm. IR spectra were recorded on a Perkin–Elmer Spectrum BX FTIR spectrometer. Elemental analyses were performed on a Perkin–Elmer C,H,N,S-Analyzer 2400. Optical rotations were obtained using an A. Krüss Optronic GmbH polarimeter P 3002. TLC was performed using DC-Alufolien Kieselgel 60 F_{254} (Merck) or Silufol® UV 254 silica gel plates. Merck Silica gel 60 (0.063–0.200 mm) or Chemapol silica gel L 40/100 was used for column chromatography. All the reactions sensitive to oxygen or moisture were conducted under argon atmosphere in oven-dried glassware. Commercial reagents were generally used as received. CH_2Cl_2 was distilled from CaH_2 and stored over 3 Å molecular sieve pellets. The enantiomeric purity of the spirodilactones **2a–c** was determined on a LKB liquid, chromatograph with Uvicord UV detector, using a Daicel Chiracel ODH chiral column.

4.2. (−)-Homocitric acid lactone (5a)

Method A. To a solution of spirodilactone **2a** (64 mg, 0.41 mmol) in a mixture of 1 M NaOH/CH_2Cl_2 1:1 (4 mL), $KMnO_4$ (97 mg, 0.62 mmol) was added at 0 °C and the mixture was stirred for 16 h at room temperature. Then EtOH (4 mL) was added and the solution was filtered through Celite. EtOH was removed under reduced pressure, the remaining water was acidified to pH 1 with 6 M HCl solution and the mixture was evaporated. The residue was dissolved in acetone (10 mL) and the solid material was filtered off. Removal of the acetone, followed by flash chromatography (silica gel, petroleum ether–acetone 10:5 to 10:6) gave **5a** as white solid (43 mg, 56%); $[\alpha]_D^{20}=-49.8$ (*c* 0.36, water); ^1H NMR ($(CD_3)_2CO$): δ 3.00 and 3.20 (both d, 2H, $J=17.1$ Hz, H-2), 2.47 and 2.54 (both m, 2H, H-4), 2.60 and 2.62 (both m, 2H, H-5); ^{13}C NMR ($(CD_3)_2CO$): δ 176.33 (C-6), 172.43 (3-COOH), 170.47 (C-1), 83.42 (C-3), 41.64 (C-2), 31.83 (C-5), 28.26 (C-4); IR (KBr, cm^{-1}): 3121, 2983, 2934, 1755, 1723, 1674, 1386, 1244, 1186, 1062. Anal. calcd for $C_7H_8O_6$: C, 44.69; H, 4.29. Found: C, 44.65; H, 4.26.

Method B. To a solution of spirodilactone **2a** (29 mg, 0.19 mmol) in 0.2 M KOH (10 mL), potassium persulfate (251 mg, 0.93 mmol) followed by $RuCl_3\times H_2O$ (1 mg, 0.0044 mmol) was added with vigorous stirring. The mixture was stirred for 24 h at room temperature. Then Na_2SO_3 (94 mg, 0.74 mmol) was added at 0 °C followed by 6 M HCl (2.5 mL) after 0.5 h and stirring was continued for 1 h at room temperature. The reaction mixture was extracted with several portions of dry EtOAc. The combined extracts were dried (Na_2SO_4) and the solvents were removed. The residue was purified by flash chromatography (silica gel, petroleum ether–acetone 10:5 to 10:6) to yield **5a** as white solid (26 mg, 74%); $[\alpha]_D^{20}=-48.9$ (*c* 0.38, water). Anal. calcd for $C_7H_8O_6$: C, 44.69; H, 4.29. Found: C, 44.58; H, 4.33.

4.3. (−)-4-Benzyloxyhomocitric acid lactone (6b)

To a stirred solution of spirodilactone **2b** (48 mg, 0.18 mmol) in a mixture of 0.2 M KOH/CH_2Cl_2 8:1 (10 ml), potassium persulfate (247 mg, 0.92 mmol) and $RuCl_3\times H_2O$ (1 mg, 0.0044 mmol) were added. After stirring for 23 h at room temperature the reaction mixture was extracted with CH_2Cl_2 (10 mL), the aqueous phase was acidified to pH 1 with 1 M HCl and extracted with EtOAc (5×10 mL). The combined extracts were dried (Na_2SO_4) and the solvents were removed. To this crude triacid dry CH_2Cl_2 (10 mL) and concentrated HCl (100 μL) were added. The mixture was vigorously stirred for 2 h at room temperature. Then water (12 mL) was added and the reaction was extracted with EtOAc (3×10 mL). The combined extracts were dried (Na_2SO_4) and the solvents were removed. The residue was purified by flash chromatography (silica gel, petroleum ether–acetone 10:4 to 10:6) to yield **6b** as white solid (33 mg, 61%); $[\alpha]_D^{20}=-21$ (*c* 1.04, acetone); ^1H NMR ($CD_3OD+CDCl_3$): δ_H 7.2–7.4 (m, 5H, Ph), 4.55 and 4.58 (both d, 2H, $J=11.8$ Hz, $PhCH_2$), 4.45 (dd, 1H, $J=6.1$, 7.6 Hz, H-4), 3.24 and 2.85 (both d, 2H, $J=17.2$ Hz, H-2), 2.87 (dd, 1H, $J=7.6$, 17.8 Hz, H-5),

2.71 (dd, 1H, $J=6.1$, 17.8 Hz, H-5); ^{13}C NMR ($CD_3OD+CDCl_3$): δ_C 175.01 (C-6), 171.31 (C-1), 170.64 (C-3COOH), 137.38 (*s*-Ph), 128.96 (*m*-Ph), 128.58 (*p*-Ph), 128.27 (*o*-Ph), 87.36 (C-3), 79.11 (C-4), 73.41 (Bn CH_2), 40.29 (C-2), 35.35(C-5); IR (KBr, cm^{-1}): 2948, 1787, 1725, 1433, 1232, 1095, 1077, 741, 696. Anal. calcd for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80. Found: C, 56.81; H, 4.82.

4.4. (−)-4-Hydroxyhomocitric acid lactone (5b)

To a stirred solution of lactone **6b** (30 mg, 0.10 mmol) in MeOH (3 mL) 10% Pd/C (14 mg) was added and the mixture was stirred for 22 h at room temperature. The catalyst was removed by filtration through a pad of Silica gel and the filtrate was evaporated to give **5b** as white solid (20 mg, 96%); $[\alpha]_D^{20}=-17$ (*c* 1.20, acetone); ^{1}H NMR ($(CD_3)_2CO$): δ_H 4.73 (dd, 1H, $J=6.5$, 7.6 Hz, H-4), 3.30 and 2.92 (2H, both d, $J=17.1$ Hz, H-2), 2.97 (1H, dd, $J=7.6$, 17.6 Hz, H-5), 2.60 (1H, dd, $J=6.5$, 17.6 Hz, H-5); ^{13}C NMR ($(CD_3)_2CO$): δ_C 174.20 (C-6), 170.67 (C-3COOH), 170.04 (C-1), 87.97 (C-3), 73.07 (C-4), 39.98 (C-2), 36.72 (C-5); IR (KBr, cm^{-1}): 3416, 2944, 1789, 1737, 1408, 1202, 1176, 1068. Anal. calcd for $C_7H_8O_7$: C, 41.19; H, 3.95. Found: C, 41.55; H, 4.00.

4.5. (+)-4-Hydroxyhomocitric acid lactone (5c) and 4-hydroxyhomocitric acid dilactone (7c)

Analogously to that of **5b** from lactone **2c**, a mixture of (+)-4-hydroxyhomocitric acid lactone (**5c**), (minor component) and 4-hydroxyhomocitric acid dilactone (**7c**) (major component) were obtained. (+)-4-Hydroxyhomocitric acid lactone (**5c**). ^{1}H NMR ($(CD_3)_2CO$): δ_H 4.65 (d, 1H, $J=5.6$ Hz, H-4), 3.20 and 3.06 (2H, both d, $J=17.0$ Hz, H-2), 2.96 (1H, dd, $J=5.6$, 17.8 Hz, H-5), 2.39 (1H, d, $J=17.8$ Hz, H-5); ^{13}C NMR ($(CD_3)_2CO$): δ_C 175.20 (C-6), 168.9 (C-1 and C-3COOH), 88.40 (C-3), 72.05 (C-4), 38.32 (C-2), 37.15 (C-5). 4-Hydroxyhomocitric acid dilactone (**7c**). ^{1}H NMR ($(CD_3)_2CO$): δ_H 5.39 (d, 1H, $J=5.8$ Hz, H-4), 3.56 and 3.00 (2H, both d, $J=18.8$ Hz, H-2), 3.18 (1H, dd, $J=5.8$, 19.0 Hz, H-5), 2.86 (1H, d, $J=19.0$ Hz, H-5); ^{13}C NMR ($(CD_3)_2CO$): δ_C 173.92, 173.06 and 168.86 (C-1, C-6 and C-3COOH), 88.67 (C-3), 81.33 (C-4), 37.93 (C-2), 35.12 (C-5).

Acknowledgements

We would like to thank Mrs. Tiiu Kailas for performing FT IR spectra and elemental analysis, Estonian Science Foundation (Grants nos 4976, 5133, 5628 and Estonian Ministry of Education (Grant 0350312s01).

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Scope and limitations of montmorillonite K 10 catalysed opening of epoxide rings by amines

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Received 7 May 2004; revised 12 July 2004; accepted 28 July 2004

Available online 27 August 2004

Abstract—Montmorillonite K 10 efficiently catalyses the opening of epoxide rings by amines in high yields with excellent regio- and diastereo-selectivities under solvent-free conditions at room temperature affording an improved process for synthesis of 2-amino alcohols. Reaction of cyclohexene oxide with aryl/alkyl amines leads to the formation of *trans*-2-aryl/alkylaminocyclohexanols. For unsymmetrical epoxides, the regioselectivity is controlled by the electronic and steric factors associated with the epoxide and the amine. Selective nucleophilic attack at the benzylic carbon of styrene oxide takes place with aromatic amines, whereas, aliphatic amines exhibit preferential nucleophilic attack at the terminal carbon. Aniline reacts selectively at the less hindered carbon of other unsymmetrical epoxides. The difference in the internal strain energy of the epoxide ring in cycloalkene oxides and alkene oxides led to selective nucleophilic opening of cyclohexene oxide by aniline in the presence of styrene oxide. Due to the chelation effect, selective activation of the epoxide ring in 3-phenoxy propylene oxide takes place in the presence of styrene oxide leading to preferential cleavage of the epoxide ring in 3-phenoxy propylene oxide by aniline.

The opening of epoxide rings by amines is a frequently encountered organic reaction as the resultant 2-amino alcohols are intermediates in the synthesis of a vast range of biologically active natural and synthetic products,[1] unnatural amino acids,[2] and chiral auxiliaries.[3] The recognised method for the synthesis of 2-amino alcohols is the nucleophilic opening of the epoxide ring with amines[4] and in the classical approach,[5] involves the treatment of epoxides with amines under heating. However, the method works less well with poorly nucleophilic amines, lacks appreciable regioselectivity, poses problems in dealing with sensitive epoxides due to the potential side reactions because of high temperature, and needs an excess of amine. These shortcomings led to the development of various methodologies such as the use of alumina,[6] various metal salts (e.g. amides/triflamide,[7] perchlorates/tetrafluoroborate,[8] triflates,[9] alkoxides,[10] sulfophenyl phosphonate,[11] and halides[12]), silica under high pressure,[13] microwave irradiation,[14] hexafluoro-2-propanol (HFIP) under reflux,[15] ionic liquid,[16] $^{n}Bu_3P$,[17] Lewis acid in supercritical carbon dioxide ($scCO_2$) under high pressure at 55 °C,[18] and chromatographic silica gel (60–120 mesh).[19] However, these methodologies suffer from one or more disadvantages such as long reaction times, elevated temperatures, high pressures, use of air and/or moisture sensitive catalysts, requirement of stoichiometric amounts of catalyst, use of costly reagents/catalysts, potential rearrangement to allylic alcohols,[20] potential hazards in handling pyrophoric/moisture sensitive reagents in the preparation of the catalyst, and afford moderate yields and regioselectivities. In most of the cases, the reactions are carried out with aromatic amines only. Therefore, the development of a better catalyst for activation of epoxide rings rendering them more susceptible to nucleophilic attack under milder conditions is in high demand.

The tight legislation on the release of waste and toxic emissions, as a measure to control environmental pollution, has induced a paradigm shift in the development of new synthetic methodologies. This led us to search for a heterogeneous catalyst as it would offer several intrinsic advantages such as the ease of product separation, catalyst reuse, minimisation of the amount of salt and waste production, and prevention of corrosion by avoiding contact with hazardous acids. Therefore, we focused our attention to solid acids such as clays[21] and zeolites[22] as they have emerged as a special class of environmentally friendly catalysts because of their ease of availability/preparation and are finding industrial applications as cheap and efficient catalysts. We were attracted by a recent report on the use of montmorillonite K 10 for opening of epoxide ring by amines under microwave irradiation.[23] However, this method is limited to more nucleophilic aliphatic secondary amines,

Keywords: 2-Amino alcohol; Epoxide opening; Amines; Selectivity; Montmorillonite K 10; Catalyst.
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doi:10.1016/j.tet.2004.07.077

uses large amount of the catalyst (200% w/w), needs special apparatus, and affords moderate yields and regioselectivities. Further, the difficulty of the use of microwave in the scale-up process does not make it an attractive synthetic route. Keeping in view the prior publication dealing with the opening of oxirane ring with N-nucleophiles under microwave irradiation,[14] it is not clear whether the epoxide ring opening by amines in this method[23] was facilitated by the presence of montmorillonite K 10 or by the thermal effect of microwave irradiation. The fact that the reaction of morpholine with 3-phenoxy propylene oxide under microwave heating in neutral medium in the absence of any addendum (e.g. catalyst)[14] affords comparable yields of 1-phenoxy-3-(4-morpholinyl)propan-2-ol with that obtained by carrying out the reaction under microwave heating in the presence of montmorillonite K 10,[23] led us to believe that the opening of the epoxide rings by amines in this method[23] took place due to the thermal effect of microwave. The recent report also suggests that the aminolysis of epoxides under the treatment with microwave does not require any catalytic assistance.[24] Therefore, we took up this study to determine the scope and limitations of various clays and zeolites for use as catalysts in the opening of epoxide rings by amines. Herein we report that the use of catalytic amounts of montmorillonite K 10 facilitates the opening of epoxide rings by amines at room temperature under solvent-free conditions affording an improved synthesis of 2-amino alcohols.

In a model study, the reaction of cyclohexene oxide (**1**), a representative symmetrical epoxide, with aniline (**2**) (Scheme 1) was carried out in the presence of various clays and zeolites at room temperature under solvent-free condition (Table 1).

The montmorillonite K 10 catalysed reaction afforded 2-phenylaminocyclohexanol in 100% yields. The product was identified as the *trans* isomer **3** by comparison with the literature.[12j] The high yield and exclusive *trans* diastereoselectivity marked the catalytic efficiency of montmorillonite K 10 for the desired transformation. The recovered catalyst was used, after activation by heating at 100 °C under reduced pressure, without significant loss of catalytic activity. Montmorillonite KSF also exhibited excellent catalytic effect under similar conditions affording 92% yields but required prolonged time (24 h). However, zeolites (K/L, ZSM 100, ZSM 250, Na/Fau, and NH_4/Y) were ineffective under identical conditions.

The lack of appreciable catalytic property of the zeolites compared to that of the clays may be explained by taking into consideration the fact that the catalytic efficiency of solid acids depends upon the rate of product diffusion from the active site of the catalyst. Thus, a rapid product diffusion is desirable for better catalytic effect so as to minimise catalyst deactivation. The small pore size of zeolites (<8 Å) does not favour a rapid diffusion of the reactant/product.[22b] On the other hand, the large interlayer spacing (~10–15 Å) in clays makes them effective for the desired catalytic effect.

Table 1. Reactions of **1** with **2** in the presence of clays and zeolites[a]

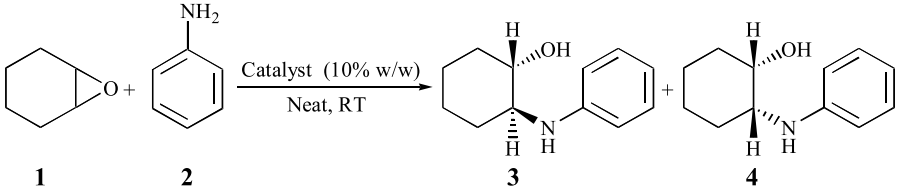
Entry	Catalyst	Time (h)	Yield (%)[b,c]
1	Montmorillonite K 10	24	98
2	Montmorillonite K 10	3	100
3	Montmorillonite KSF	24	92
4	Montmorillonite KSF	3	10[d]
5	Zeolite K/L	24	5[d]
6	Zeolite (ZSM 100)	24	15[d]
7	Zeolite (ZSM 250)	24	10[d]
8	Zeolite (Na/Fau)	24	Trace[d]
9	Zeolite (NH_4/Y)	24	Trace[d]

[a] The epoxide (3 mmol) was treated with **2** (3 mmol) in presence of the catalyst (10% w/w) at room temperature under nitrogen in the absence of solvent.
[b] The ^1H and ^{13}C NMR analyses confirmed the *trans* stereochemistry of the product.
[c] GCMS yields of *trans*-2-phenylaminocyclohexanol.
[d] The unreacted cyclohexene oxide remained intact as evidenced by the GCMS.

To establish the generality, **1** was treated with various amines (Table 2). Excellent yields were obtained with aromatic and aliphatic amines and in each occasion the resultant racemic 2-aryl/alkylaminocyclohexanol was obtained with exclusive *trans* diastereoselectivity.

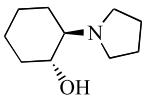
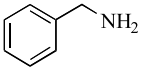
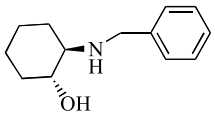
The comparison of the present method with respect to the amount of the catalyst and amine, reaction time and temperature, requirement of solvent, and product yield with those of the literature reports dealing with the reaction of **1** with **2**, reveals that this newly developed method is superior to the reported procedures. Although the $ZrCl_4$-catalysed reaction[12j] affords comparable yields at shorter time, the susceptibility of $ZrCl_4$ to hydrolytic decomposition becomes detrimental for handling and recycling of the catalyst. The high yield (98%) obtained during the reaction of **1** with pyrrolidine (**5**) (Table 2, entry 4) established that the present method is superior to the reported procedure carried out under microwave irradiation (46% yield).[23]

The results summarised in Table 2 reveal that the present method is applicable for aromatic as well as aliphatic amines. The formation of complex of metal salts having strong Lewis acid property with aliphatic amines, causes catalyst poisoining and makes the metal salts unsuitable for use as catalysts for opening of epoxide rings by aliphatic



Scheme 1. Reaction of **1** with **2** in the presence of various clays and zeolites.

Table 2. Reaction of **1** with various amines in the presence of montmorillonite K 10[a]

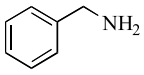
Entry	Amine	Product[b]	Yield (%)[c]
1	R=H	R=H	98
2	R=4-Me	R=4-Me	97
3	R=4-Cl	R=4-Cl	93
4			98
5			81

[a] The epoxide (3 mmol) was treated with the amine (3 mmol) in the presence of montmorillonite K 10 (30 mg, 10% w/w) at room temperature under nitrogen in the absence of solvent for 3 h.
[b] The ^{1}H and ^{13}C NMR analyses confirmed the *trans* stereochemistry of the product.
[c] Isolated yields of the corresponding amino alcohol.

amines. This is reflected by the observation that $CoCl_2$, $Cu(OTf)_2$, HFIP, zirconium sulfophenyl phosphonate, $TaCl_5$, $[Rh(CO)_2Cl]_2$, $CeCl_3$–NaI, VCl_3, and $BiCl_3$ are not effective to catalyse the reaction of epoxides with aliphatic amines. Due to the mild acidic character, montmorillonite K 10 effectively catalyses the epoxide ring opening reaction by aliphatic amines (Table 2, entries 4 and 5). Comparison of the results of the reaction of **1** with **5** and benzyl amine (**6**) obtained following the present methodology with those reported in the literature established that the present method is equal to or better than the reported procedures.

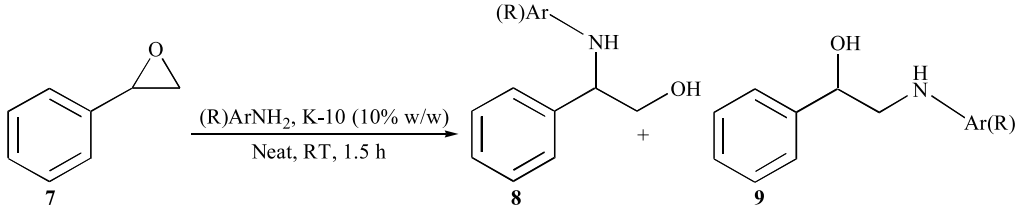
We next planned to evaluate the regioselectivity of the montmorillonite K 10 catalysed epoxide ring opening reaction with amines. Styrene oxide (**7**) was chosen as representative unsymmetrical epoxide during the reaction with amines (Scheme 2) and the results are summarised in Table 3. In each occasion, the regioselectivity was determined by GCMS analysis of the products. The product from nucleophilic attack at the benzylic carbon exhibited ion peak at m/z M^+-31 due to the loss of CH_2OH, whereas, the characteristic feature in the mass spectra of the products from the reaction at the terminal carbon of the epoxide ring was the ion peak at m/z M^+-106 due to the loss of PhCHO.[12j] The formation of the amino alcohol by nucleophilic attack at the terminal carbon of **7** was further determined by the absorption of the benzylic methine proton at $\sim\delta$ 4.70 in the ^{1}H NMR spectra.[8]

Table 3. Regioselectivity during the reaction of **7** with various amines catalysed by montmorillonite K 10[a]

Entry	Amine	Yield (%)[b]	Ratio **8**:**9**[c]
1	R=H	93	93:7[d]
2	R=4-Me	94	93:7
3	R=4-Cl	100	100:0
4		75	0:100
5		95	0:100
6		83	0:100
7		89	18:82

[a] The epoxide (3 mmol) was treated with the amine (3 mmol) in the presence of montmorillonite K 10 (30 mg, 10% w/w) at room temperature under nitrogen in the absence of solvent for 1.5 h.
[b] Isolated yields.
[c] Determined by GCMS and ^{1}H NMR.
[d] The amino alcohols **8** and **9** were obtained in 90% yields in a ratio of 93:7 in DCM.

An excellent regioselectivity of 93:7 in favour of nucleophilic attack at the benzylic carbon was observed affording 93% yield during the reaction with **2**. Other aromatic amines such as 4-methylaniline and 4-chloroaniline afforded 94 and 100% yields with 93:7 and 100:0 selectivities, respectively, in favour of nucleophilic attack at the benzylic carbon. The use of solvent such as CH_2Cl_2 did not have any influence on the product yield and regioselectivity. A preferential attack at the terminal carbon has been reported during the reaction of amines with **7** catalysed by montmorillonite K 10 under microwave irradiation.[23] However, in all of these reported examples, a secondary aliphatic amine was used. Therefore, to compare the regioselectivity of the present study with that of the reported procedure, **7** was treated with piperidine, pyrrolidine, morpholine, and benzyl amine affording 75, 95, 83, and 89% yields with 0:100, 0:100, 0:100, and 18:82 selectivities, respectively, in favour of formation of the amino alcohol from nucleophilic attack at the less hindered terminal carbon of the epoxide ring. Compared to these observations, the reaction of **7** with pyrrolidine and morpholine, following the reported procedure,[23] afforded 69 and 85% yields, respectively, with poor regioselectivities (the ratio of terminal vs. benzylic attack of 2.9 and 1.7, respectively).



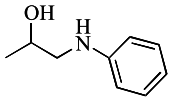
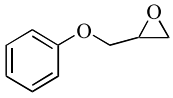
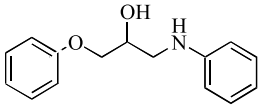
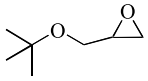
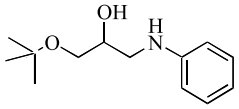
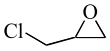
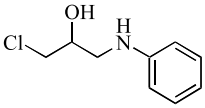
Scheme 2. Regioselectivity of the K 10 catalysed epoxide ring opening reaction of **7** with amines.

The observed preference for nucleophilic attack at the benzylic position of **7** by the aromatic amines can be rationalised taking into consideration the electronic and steric factors. Coordination of the epoxide oxygen with the Lewis acidic site of the catalyst induces a carbocationic character at the epoxide ring carbons and the resonance effect of the phenyl ring helps accumulation of the positive charge at the benzylic carbon to a greater extent compared to that at the terminal carbon.[25] An aromatic amine being less nucleophilic and having less steric factor adjacent to the amino group (compared to an aliphatic amine) reacts selectively at the benzylic carbon. In case of aliphatic amines, selective nucleophilic attack at the terminal carbon of the epoxide ring takes place due to the steric factor. The exclusive formation of the amino alcohol from nucleophilic attack at the terminal carbon in **7** by piperidine, pyrrolidine, and morpholine (entries 4–6) compared to a 18:82 regioselectivity observed with benzyl amine (entry 7) highlights the role of steric factor. The steric crowding near the nitrogen atom in the secondary amines leads to exclusive nucleophilic attack at the less hindered site of the epoxide ring. However, as the nitrogen atom in benzyl amine is relatively less crowded there is a decrease in regioselectivity.

While comparing the present methodology for the regioselective outcome during the reaction of **7** with various amines with the literature reported methodologies we observed that the preferential reaction at the benzylic position during the reaction of **7** with **2** was in conformity with other Lewis acid catalysed reactions such as DIPAT,[10b] HFIP,[15] zirconium sulfophenyl phsophonate,[11] [Bmim]BF_4,[16] $Yb(OTf)_3$–$scCO_2$,[18] $ZnCl_2$,[12h] VCl_3,[12i] $ZrCl_4$,[12j] $CrCl_3$,[12k] and silica-gel[19] affording the amino alcohols in comparable/better yields. The reverse regioselectivity observed with $CoCl_2$ is due to the radical (non-ionic) mechanism of opening of the epoxide.[12a] The selective nucleophilic attack at the terminal carbon during the $CeCl_3$–NaI catalysed reaction may be explained by the fact that the use of a 30 mol% of the catalyst in the reported procedure[12f] results in the formation of cerium anilide as the effective nucleophile favouring the less hindered carbon. The most significant advantages of the present methodologies are exemplified by the reactions with aliphatic amines leading to the amino alcohol from nucleophilic attack at the terminal carbon of the epoxide ring in **7** as the major or exclusive product. The inferior selectivity during the use of montmorillonite K 10 under microwave irradiation,[23] SmI_2,[12c] LiOTf,[9d] $ZrCl_4$,[12j] and silica-gel[19] reveals that the present methodology offers milder reaction condition so as to achieve better selectivity. The use of stronger Lewis acids such as $LiClO_4$,[8] DIPAT,[10b] SmI_2,[12c] and $ZnCl_2$[12h] leads to poor regioselectivity with marginal preference for the amino alcohol from nucleophilic attack at the benzylic carbon of the epoxide ring in **7**.

To establish the generality of the present methodology, various epoxides were treated with **2** (Table 4). In each occasion, an exclusive preference for nucleophilic attack at the terminal carbon of the epoxide ring was observed. The quantitative yields obtained (entries 1–3) in the present study clearly establish the superiority of this method over the reported procedure[23] wherein structurally similar

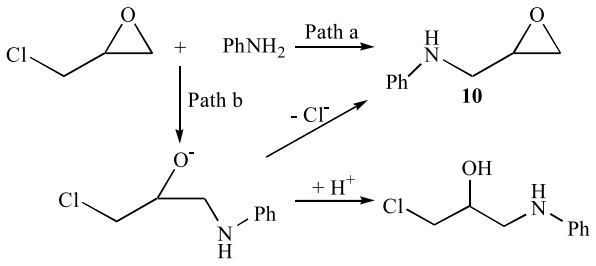
Table 4. Reaction of various epoxides with **2** in the presence of montmorillonite K 10[a]

Entry	Epoxide	Product[b]	Yield (%)[c]
1			100
2			100
3			100
4			69

[a] The epoxide (3 mmol) was treated with 2 (3 mmol) in the presence of montmorillonite K 10 (30 mg, 10% w/w) at room temperature under nitrogen in the absence of solvent for 3 h.
[b] Determined by GCMS and $^1H/^{13}C$ NMR.
[c] Isolated yields of the corresponding amino alcohol.

epoxides e.g. 1-pentene oxide, 3-phenoxy-1-propylene oxide, and 3-isopropoxy-1-propylene oxide resulted in 25, 91, and 77% yields, respectively, during the reaction with the more nucleophilic amine morpholine. The formation of the amino alcohol from attack at the terminal carbon of the epoxide ring (entries 3 and 4) as the only product further demonstrates the advantage of this method over the reported procedure[23] following which the reactions of 3-isopropoxy-1-propylene oxide and epichlorohydrin with morpholine lead to inferior regioselectivities. The comparatively poor yields obtained under microwave irradiation[23] is due to the side reactions (e.g. rearrangement, polymerisation etc.) and evaporative loss of the epoxide under the influence of unregulated thermal effect. The stringent reaction conditions under microwave irradiation and the employment of large amount of the catalyst (200% w/w) are the reasons for poor regioselectivities of the reported procedure.[23] The use of catalytic quantities (10% w/w) of montmorillonite K 10 and mild reaction condition (room temperature) overcome these problems making the present methodology better suited for epoxide opening reaction. The mild reaction conditions employed in this improved process makes recovery/recycling, wherever applicable, of the unreacted epoxide feasible.

The reaction of epichlorohydrin (entry 4) exemplified the excellent chemoselectivity leading to the formation of the amino alcohol corresponding to nucleophilic attack at the terminal carbon of the epoxide ring. No product from nucleophilic displacement of the chlorine was detected (GCMS) in the reaction mixture. As epichlorohydrine is an ambiphilic substrate its reaction with a nucleophile, in principle, may proceed via two distinct pathways: (i) direct nucleophilic displacement of chlorine (path a) or (ii) initial nucleophilic attack on the epoxide (path b) followed by protonation to form the amino alcohol or extrusion of the chlorine atom to give **10** (Scheme 2).[26] The strong



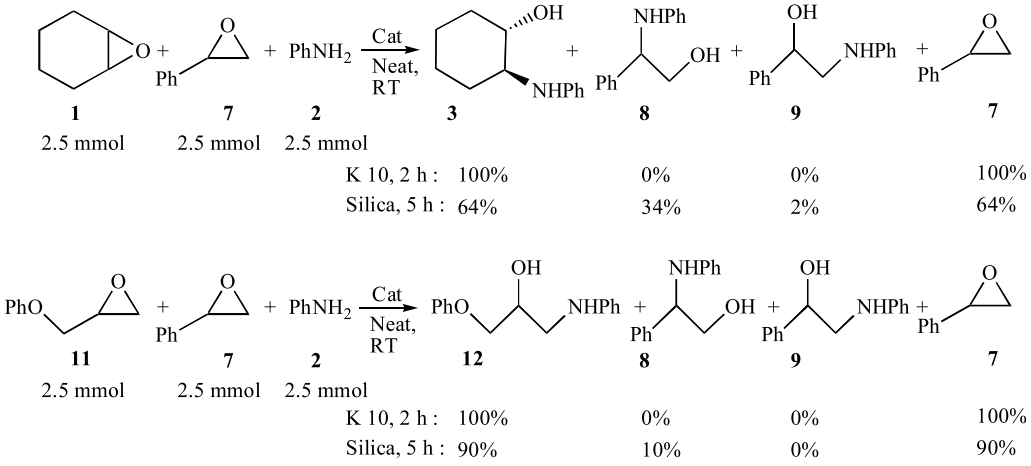
Scheme 3. Reaction of epichlorohydrine with **2**.

coordination between the catalyst and the alkoxide, generated after the nucleophilic attack on the K 10-complexed epoxide, reduces the nucleophilicity of the alkoxide anion and prohibits the concomitant elimination of the chloride anion (Scheme 3).

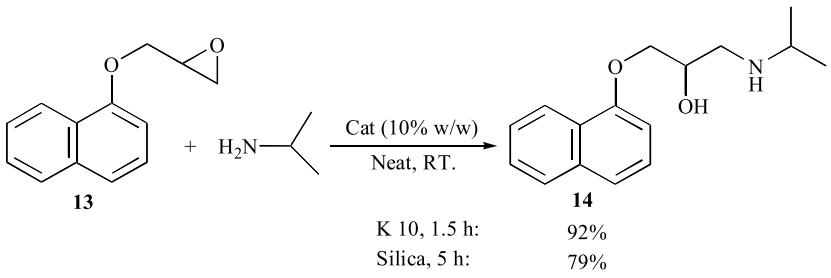
While comparing the results of Table 4 with the reported procedure dealing with a common substrate, it was revealed that the reaction of propylene oxide (entry 1) with **2** afforded a 32% yield of the desired product along with 8% yield of the regioisomeric amino alcohol in the presence of $Yb(OTf)_3$ in $scCO_2$ at 55 °C under pressure (10 MPa) for 10 h.[18] The reaction of structurally similar epoxide (e.g. *n*-dodecene-1-oxide) with **2** catalysed by zirconium sulfophenyl phosphonate resulted in the formation of a 7:1 mixture of amino alcohols in 72% yield for 21 h.[11] The $^{n}Bu_3P$ catalysed reaction of *n*-pentane-1-oxide with **2** afforded a 95:5 mixture of amino alcohols in 85% yield for 12 h.[17] In the recent report,[12k] the use of $SnCl_4 \cdot 6H_2O$ during the reaction of *n*-butene-1-oxide with **2** afforded a 64:36 mixture of amino alcohols in 46% yield at room temperature for 12 h. The superiority of the present methodology is further demonstrated by comparing the results of the reaction of 3-phenoxypropylene oxide (**11**) with **2** (entry 2) obtained in the presence of various catalysts. A 60% yield was obtained in carrying out the reaction in MeCN for 8 h in the presence of $CoCl_2$[12a] and comparable result was obtained in MeCN for 0.5 catalysed by a stoichiometric amount of $Mg(ClO_4)_2$.[8] Use of VCl_3 affords 88% yield in DCM for 4 h and 89% yield is obtained in 6 h under the catalytic influence of $[Bmim]BF_4$ (1 mL/mmol of the epoxide).[16] Recently $CrCl_3 \cdot 6H_2O$ has been used to provide 90% yield in 12 h at 50 °C.[12k]

We next planned to evaluate the efficiency of the present methodology for selective opening of epoxide rings during intermolecular competition studies. Thus, a mixture of **1** (1 equiv) and **7** (1 equiv) was treated with **2** (1 equiv) in the presence of K 10 at room temperature under solvent-free condition for 2 h (Scheme 4). Exclusive formation of the amino alcohol **3** from opening of the epoxide ring of **1** took place and no amino alcohols **8** and **9**, corresponding to epoxide ring opening of **7**, could be detected (GCMS). As the epoxide ring in **1** is more strained compared to that in **7**, selective opening of the epoxide ring of **1** takes place due to the mild Lewis acidic nature of K 10. To compare the effectiveness of K 10 with that of silica-gel,[19] this intermolecular competition for epoxide opening with **2** was carried out in the presence of silica-gel (60–120 mesh). A significant decrease in selectivity was observed and **3**, **8**, and **9** were formed in a ratio of 64:34:2 indicating that the present methodology offers milder conditions. Encouraged by these results, we planned to study the selective cleavage of epoxide ring in alkene oxides. Hence, a mixture of **7** (1 equiv) and **11** (1 equiv) was treated with **2** (1 equiv) in the presence of montmorillonite K 10 at room temperature under solvent-free conditions for 2 h (Scheme 4). Excellent selectivity was observed and the amino alcohol **12** corresponding to opening of the epoxide ring of **11** was the only product formed and **7** remained unaffected (GCMS). The presence of the phenoxyl oxygen in **11** provides a chelation effect to the Lewis acidic sites of the catalyst leading to selective activation of the epoxide ring in **11**. However, the amino alcohols **12** and **8** were obtained in a ratio of 9:1 when the reaction was catalysed by silica-gel under identical conditions demonstrating that K 10 is a better suited catalyst for selective epoxide ring opening reaction.

To demonstrate the applicability of the methodology for the synthesis of pharmaceuticals, 3-(1-napthyloxy)-1,2-epoxypropane (**13**) was treated with isopropyl amine at room temperature in the presence of montmorillonite K 10 to afford 3-(naphthalene-1-yloxy)-1-(2-propyl)amino-propane-2-ol (**14**), a β-adrenoreceptor antagonist,[27] in 92% yield (Scheme 5).[28] The amino alcohol **14** was obtained in 79% yield in 5 h under the catalytic influence of silica-gel.



Scheme 4. Selectivity of epoxide ring opening by amine during intermolecular competitions catalysed by K 10.



Scheme 5. Synthesis of propranolol.

In conclusion, the present study describes an improved and highly efficient green process for the synthesis of β-amino alcohols by montmorillonite K 10 catalysed opening of epoxide rings by amines. The advantages include high yields, excellent regio- and diastereo-selectivities, reaction under room temperature, use of cheaper and easy to handle catalyst, and environmentally benign condition. The mildness of K 10 and the reaction condition enable selective opening of epoxide ring during intermolecular competitions. The methodology has been extended for the synthesis of propanolol.

1. Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DPX 300 (300 MHz) spectrometer in $CDCl_3$ using TMS as internal standard. The IR spectra were recorded on Nicolet Impact 400 spectrometer as KBr pellets for solid and neat for liquid samples. The reactions were monitored by TLC (silica gel-G) and Shimadzu QP 5000 GCMS. Wherever, necessary, inert atmosphere for carrying out the reaction was maintained using dry nitrogen or argon using flame dried glasswares. Evaporation of solvents was performed at reduced pressure, using a Buchi rotary evaporator.

1.1. Typical procedure for reaction of epoxide with amine

Montmorillonite K 10 (30 mg, 10% w/w) was added to a magnetically stirred mixture of **1** (294 mg, 3 mmol) and **2** (279.39 mg, 3 mmol) at room temperature under nitrogen. The mixture was stirred for 3 h, diluted with Et_2O (15 mL), and filtered through a plug of cotton. The residue was washed with Et_2O (15 mL) and the combined filtrates were concentrated under vacuum to afford the product (562 mg, 98%), identical (IR, ^{1}H and ^{13}C NMR, and EIMS) to an authentic sample of *trans*-2-(phenylamino)cyclohexanol (**3**).[12j] The recovered catalyst on subsequent use, after being treated at 100 °C for 12 h under reduced pressure (5 mm Hg), afforded 90% yields during the reaction of **1** with **2**. The remaining reactions were carried out following this general procedure. In each occasion the spectral data (IR, NMR and MS) of the product were identical with those reported in the literature. New spectral data were generated for the following known compounds.

1.1.1. 2-Benzylamino-1-phenylethanol (Table 3, entry 7)[29] White solid. Mp 98–100 °C [lit.[29] 100–102 °C]. IR (KBr): 3293, 3061, 2906, 2834, 2740, 1453, 1433, 1346, 1102, 1063, 1037, 1025, 916.9, 874, 750, 694 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.25$–7.35 (m, 10H), 4.71–4.75 (dd, $J=8.86$, 3.60 Hz, 1H), 3.78–3.88 (m, 2H), 2.90–2.95 (m, 1H), 2.71–2.78 (m, 1H), 2.41 (broad s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta=142.51$, 139.72, 128.47, 128.35, 128.11, 127.47, 127.14, 125.80, 71.79, 56.49, 53.48. APCI-MS: $m/z=228$ $(M+1)^+$.

1.1.2. 3-(Naphthalene-1-yloxy)-1-(2-propyl)amino-propane-2-ol (14).[28] Montmorillonite K 10 (30 mg, 10% w/w) was added to the magnetically stirred mixture of **13** (600 mg, 3 mmol) and isopropyl amine (0.26 mL, 3 mmol) and the mixture was stirred magnetically for 1.5 h at room temperature. The mixture was diluted with Et_2O (15 mL) followed by addition of a few drops of water to settle down the catalyst and filtered through a bed of Na_2SO_4 on a plug of cotton. The residue was washed with Et_2O (2(10 mL) and the combined filtrates were concentrated under vacuum to afford the crude product which on passing through a column of silica gel (60–120, 15 g) and elution with EtOAc–hexane (1:20, 200 mL) afforded **14** as white solid (670 mg, 92%).[28] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.22$–8.26 (m, 1H), 7.78–7.81 (m, 1H), 7.42–7.51 (m, 3H), 7.35 (m, 1H), 6.81 (d, $J=7.4$ Hz, 1H), 4.26–4.31 (m, 1H), 4.11–4.23 (m, 2H), 3.06–3.11 (dd, $J=6.2$, 12.2 Hz, 1H), 2.89–3.00 (m, 2H), 1.18 (d, $J=6.2$ Hz, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta=154.26$, 134.40, 127.44, 126.34, 125.77, 125.46, 125.15, 121.79, 120.47, 104.80, 70.74, 68.69, 49.65, 48.87, 22.87. EIMS: $m/z=245$ (M^+).

The following compound is new.

1.1.3. 2-(4-Methylphenyl)amino-2-phenylethanol (Table 3, entry 2) Yellow oil. IR (neat): 3390, 3026, 2922, 2868, 1617, 1517, 1453, 1067 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.18$–7.32 (m, 5H), 6.90 (d, $J=8.1$ Hz, 2H), 6.47 (d, $J=8.1$ Hz, 2H), 4.42–4.46 (dd, $J=4.2$, 7.4 Hz, 1H), 3.85–3.90 (dd, $J=4.2$, 11.1 Hz, 1H), 3.65–3.71 (dd, $J=7.4$, 11.1 Hz, 1H), 2.18 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta=144.72$, 140.21, 129.48, 128.48, 127.23, 126.62, 119.50, 114.09, 66.88, 60.21, 20.25. EIMS: $m/z=227$ (M^+), 196 (100). CHN Anal. calcd for $C_{15}H_{17}NO$ (227.13): C, 79.26; H, 7.54; N, 6.16. Found: C, 79.23; H, 7.52; N, 6.15.

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Synthesis of potassium 2,3,4-trihydroxy-2-methylbutanoate: a leaf-closing substance of *Leucaena leucocephalam*☆

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Received 4 May 2004; revised 5 July 2004; accepted 28 July 2004

Available online 27 August 2004

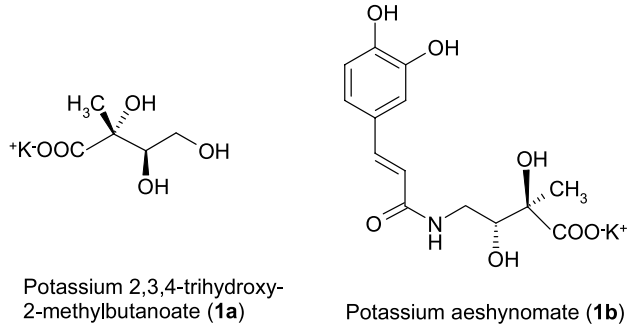
Abstract—Starting from citraconic anhydride (**2**), a six step synthesis of leaf closing substance (±)-*erythro* potassium 2,3,4-trihydroxy-2-methyl-butanoate (**1**) has been described with 29% overall yield via diesterification, OsO_4-dihydroxylation, acetonide protection, regioselective mono hydrolysis of unhindered ester moiety, borane–dimethylsulfide induced chemoselective reduction of carboxylic group and hydrolysis pathway. Surprisingly, the sodium borohydride reduction of monoester **5** and lithium borohydride reduction of **11** furnished the undesired regioisomer **7**.

1. Introduction

Most leguminosae plants close their leaves in the evening and open them in the morning.[1] This circadian rhythmic movement of the leaves is called nyctinasty and has been controlled by their biological clocks.[2] Recently, Ueda et al. have authoritatively identified several bioactive substances that regulate this leaf-movement and revealed that nyctinastic movement of the plants is dependent on the interaction between leaf-opening and leaf-closing substances. Moreover, they have demonstrated that these leaf movements are essential for the survival of legumes and they envisioned that the plant-specific leaf-movement factors could be useful as a herbicides.[3–5] Very recently, Ueda et al. have isolated potassium 2,3,4-trihydroxy-2-methyl-butanoate (**1a**) as a leaf-closing substance of *Leucaena leucocephalam*[3] and potassium aeshynomate (**1b**) as a leaf-opening substance of *Aeshynomene indica* L[5] (Fig. 1). The saccharinic acid lactone [(2*R*, 3*R*)-2,3-dihydroxy-2-methyl-γ-butyrolactone] is a potential precursor of leaf-closing substance **1** and it has also been isolated earlier as a natural product from *Astragalus lusitanicus* L.[6] and *Cicer arietinum* L.[7] To date, three syntheses of *erythro*-saccharinic acid lactone are known starting from 2-methyl-D-erythrose,[8] D-mannitol[9] and methyl pyruvate (via asymmetric aldol reaction).[10] In continuation of our on-going studies[11] on synthesis of bioactive natural products using cyclic anhydrides as potential precursors, starting from citraconic anhydride (**2**), now we herein report the synthesis of (±)-*erythro* potassium 2,3,4-trihydroxy-2-methylbutanoate (**1**) via the corresponding γ-butyrolactone **14** (Scheme 2).

2. Results and discussion

The reaction of citraconic anhydride (**2**) with methanol at 0 °C was fairly regioselective at the unhindered carbonyl[12] and furnished the mixture of regioisomers of esters **3** and **4** in 86:14 ratio (by ^{1}H NMR) in nearly 100% yield (Scheme 1). In the above reaction the major isomer **3** is probably a kinetically controlled product as the ^{1}H NMR spectrum of above mixture after one-month time revealed the presence of **3** and **4** to be 1:1 and the migration of methoxy group might be taking place via the intermediate cyclic anhydride **2**. The OsO_4-induced *cis*-dihydroxylation



Potassium 2,3,4-trihydroxy-2-methylbutanoate (**1a**)

Potassium aeshynomate (**1b**)

Figure 1. Leaf-closing and leaf-opening substances.

☆ NCL Communication No. 6667.

Keywords: Citraconic anhydride; Regioselective hydrolysis; Chemoselective reduction; Leaf-closing substance; Potassium 2,3,4-trihydroxy-2-methylbutanoate; Synthesis.
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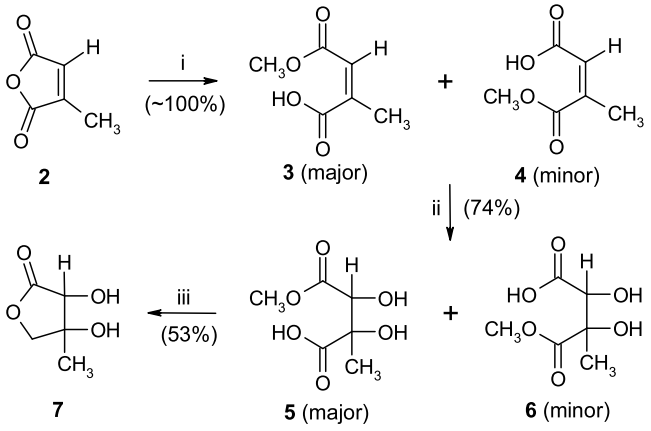
doi:10.1016/j.tet.2004.07.081



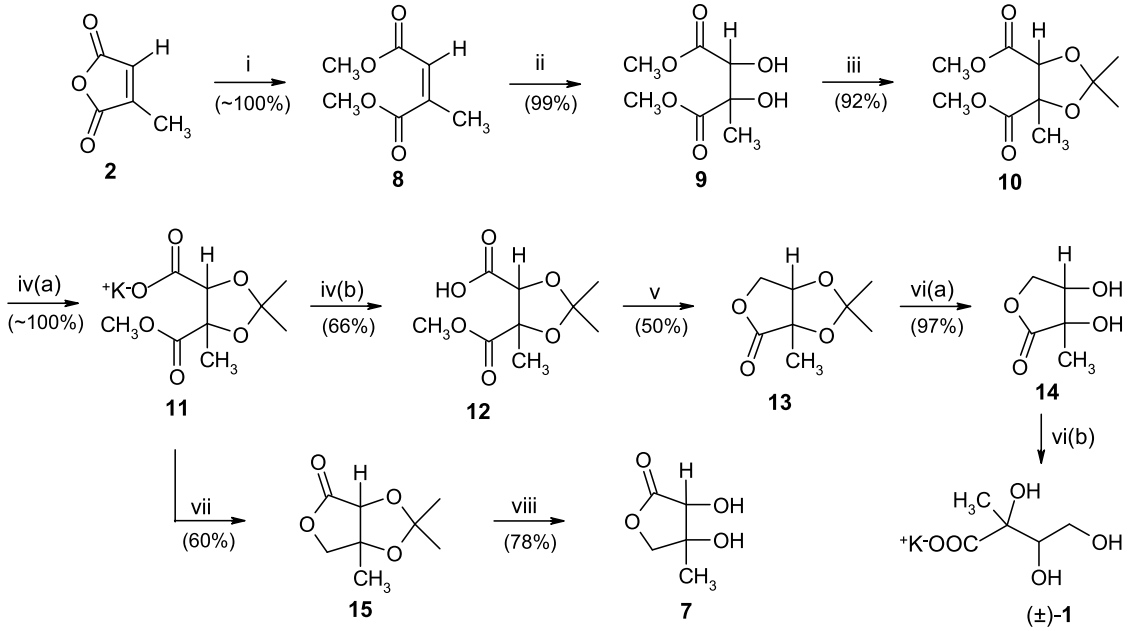
Scheme 1. Reagents, conditions and yields: (i) CH_3OH, 0 °C, 60 h (~100%, **3**:**4**=86:14); (ii) OsO_4, NMO, *t*-BuOH, CH_3COCH_3, rt, 72 h (74%, **5**:**6**=85:15), (two recrystallizations of **5** plus **6** mixture with ethyl acetate furnished pure **5** in 50% yield); (iii) $NaBH_4$, CH_3OH, reflux, 12 h, (53%).

of above **3** plus **4** mixture (86:14) again furnished the mixture of diols **5** and **6** in 85:15 ratio (by ^1H NMR) in 74% yield. Two recrystallizations of mixture of diols **5** plus **6** with ethyl acetate gave the pure diol **5** in 50% yield. Surprisingly, the $NaBH_4$-reduction of mixture of **5** plus **6** or pure **5** in methanol, exclusively furnished the undesired lactone **7** in 53% yield. The structural assignment of lactone **7** was done on the basis of three clean singlets in the ^1H NMR spectrum and ^{13}C NMR spectra. Thus our first straightforward approach to obtain **1** met with failure and then we planned for synthesis **1** using a different synthetic route as depicted in Scheme 2.

The citraconic anhydride (**2**) on treatment with methanol and catalytic amount of conc. H_2SO_4 under reflux, furnished the diester **8** in nearly 100% yield. The OsO_4-induced *cis*-dihydroxylation of **8** gave the diol **9** in 99% yield. The *cis*-diol moiety in compound **9** was protected as an acetonide using 2,2-dimethoxypropane and catalytic amount of *para*-toluenesulfonic acid (*p*-TSA) to obtain compound **10** in 92% yield. The highly regioselective hydrolysis of unhindered ester moiety in compound **10** using 1 equiv. of KOH in methanol at room temperature followed by acidification gave the desired monoacid **12** in 66% yield. The borane–dimethylsulfide complex induced chemoselective reduction of carboxylic group in compound **12** furnished the desired diol-protected lactone **13** in 50% yield.[13–15] The deprotection of the acetonide moiety using catalytic amount of TFA in water gave the desired lactone **14** in 97% yield. The treatment of lactone-diol **14** with aqueous KOH at room temperature gave the desired leaf-closing compound (±)-*erythro* potassium 2,3,4-trihydroxy-2-methylbutanoate (**1**).[16] The analytical and spectral data obtained for lactones **13** and **14** and leaf-closing compound **1** were in complete agreement with reported data.[3,8–10,17] As expected the $LiBH_4$-reduction of compound **11** gave the undesired diol-protected lactone **15** in 60% yield, which on deprotection of acetonide moiety gave the undesired lactone **7** in 78% yield.

3. Conclusion

In summary, starting from citraconic anhydride (**2**), we have demonstrated a new six-step route to leaf-closing compound **1** with 29% overall yield. In the present approach the regioselective hydrolysis of unhindered ester moiety in compound **10** and chemoselective reduction of carboxylic group in compound **12** are the key conversions. The Sharpless asymmetric dihydroxylation reactions of **8** could provide an easy access to both the enantiomers of **1**. During



Scheme 2. Reagents, conditions and yields: (i) CH_3OH, H_2SO_4, reflux, 12 h (~100%); (ii) OsO_4, NMO, *t*-BuOH, CH_3COCH_3, rt, 60 h (99%); (iii) $(CH_3)_2C(OCH_3)_2$, *p*-TSA, benzene, reflux, 3 h (92%); (iv) (a) KOH, CH_3OH, rt, 2 h (~100%); (iv) (b) 2 N HCl, (66%); (v) $BH_3(CH_3)_2S$, THF, −8 °C to rt, 36 h (50%); (vi) (a) CF_3COOH, H_2O, 0 °C to rt, 24 h (97%); (vi) (b) KOH, rt, 10 min; (vii) (a) $LiBH_4$, THF, 0 °C to rt, 6 h; (b) dil. HCl (60%); (viii) CF_3COOH, THF, H_2O, 0 °C to rt, 3 h (78%).

the $NaBH_4$-reduction of **5** the migration of –OMe group from unhindered to hindered site followed by its reduction to generate the undesired regioisomer **7** is noteworthy.

4. Experimental

4.1. General

Melting points are uncorrected Column chromatographic separations were carried out on ACME silica gel (60–120 mesh). Commercially available citraconic anhydride, osmium tetraoxide, *N*-methylmorpholine *N*-oxide, sodium borohydride, 2,2-dimethoxypropane, *p*-toluenesulfonic acid, borane–methyl sulfide complex, trifluroacetic acid were used.

4.1.1. 2-Methyl-but-2-enedioic acid 4-methyl ester and 2-methyl-but-2-enedioic acid 1-methyl ester (3 and 4). A solution of citraconic anhydride (1.00 g, 8.93 mmol) in CH_3OH (6 mL) was stirred at 0 °C for 60 h under an argon atmosphere. The reaction mixture was then concentrated and dried in vacuo to obtain compounds **3** and **4** in the ratio 86:14, respectively. The obtained compounds **3** and **4** were used for the next step without any further purification.

Compounds **3** and **4** (mixture). 1.28 g (~100% yield); colourless thick oil; ^{1}H NMR ($CDCl_3$, 500 MHz), major isomer: δ 2.09 (s, 3H), 3.82 (s, 3H), 5.90 (s, 1H), 9.43 (bs, 1H), minor isomer: δ 2.12 (s, 3H), 3.79 (s, 3H), 6.08 (s, 1H), 9.43 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz), major isomer: δ 20.8, 52.6, 121.0, 147.4, 169.1, 169.2, minor isomer: δ 21.3, 52.5, 122.6, 145.5, 166.1, 166.8; IR (neat) ν_{max} 1771, 1728, 1651, 1448 cm^{-1}.

4.1.2. 2,3-Dihydroxy-2-methyl-succinic acid 4-methyl ester and 2,3-dihydroxy-2-methyl-succinic acid 1-methyl ester (5 and 6). To a solution of olefins **3** and **4** (1.00 g, 6.94 mmol) in *t*-BuOH (12 mL) and acetone (3 mL) was added OsO_4 (0.5 mL, 0.08 mmol, 4% solution in *t*-BuOH) and NMO (7 mL, 60% aqueous solution) with constant stirring at room temperature. Reaction mixture was further stirred for 72 h and then quenched with addition of solid Na_2SO_3 (1.6 g). The reaction mixture was stirred for 1 h at room temperature and then concentrated and dried in vacuo. The crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and methanol (95:5) to furnish **5** and **6**. Analytically pure **5** was obtained in 50% yield by two recrystallizations from ethyl acetate.

Compounds **5** and **6** (mixture). 915 mg (74% yield); white solid; mp 120–125 °C; ^{1}H NMR (mixture), ($CDCl_3$+ CD_3COCD_3, 500 MHz), major isomer: δ 1.46 (s, 3H), 3.71 (s, 3H), 4.32 (s, 1H), 4.71 (bs, 2H), minor isomer: δ 1.48 (s, 3H), 3.66 (s, 3H), 4.38 (s, 1H), 4.71 (bs, 1H); IR (Nujol), mixture ν_{max} 3352, 1753, 1728, 1454 cm^{-1}.

Compound **5**. 618 mg (50% yield); white crystalline solid; mp 153–154 °C; ^{1}H NMR ($CDCl_3$ +CD_3COCD_3, 500 MHz) δ 1.45 (s, 3H), 3.71 (s, 3H), 4.33 (s, 1H); ^{13}C NMR ($CDCl_3$ +CD_3COCD_3, 125 MHz) δ 21.7, 51.4, 74.3, 75.6, 171.3, 173.7; IR (Nujol) ν_{max} 3389, 3340, 2700–2500, 1738, 1703, 1452 cm^{-1}. Anal. Calcd for $C_6H_{10}O_6$: C, 40.45; H, 5.66. Found: C, 40.51; H, 5.72.

4.1.3. 3,4-Dihydroxy-4-methyl-dihydro-furan-2-one (7). To a solution of ester **5** (100 mg, 0.56 mmol) in CH_3OH (5 mL) was added $NaBH_4$ (85 mg, 2.25 mmol) and the reaction mixture was refluxed for 12 h. The reaction mixture was then concentrated and dried in vacuo. The residue was acidified with minimum amount of dilute HCl and then extracted with ethyl acetate (15 mL×3). The organic layer was washed with brine, dried over Na_2SO_4, concentrated and dried in vacuo to obtain pure **7**.

Compound **7**. 39 mg (53% yield); faint yellow thick oil; ^{1}H NMR (D_2O, 500 MHz) δ 1.34 (s, 3H), 4.22 (s, 2H), 4.38 (s, 1H); ^{13}C NMR (D_2O, 125 MHz) δ 19.6, 73.3, 75.0, 76.0, 178.5; IR (neat) ν_{max} 3415–3360, 1778, 1117, 1007 cm^{-1}. Anal. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.63; H, 6.22.

4.1.4. Dimethyl methylmaleate (8). A solution of citraconic anhydride (4.48 g, 40 mmol) in methanol (40 mL) and H_2SO_4 (4 mL) mixture was refluxed for 12 h under nitrogen atmosphere. The reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with aqueous solution of $NaHCO_3$, brine, and dried over Na_2SO_4. Concentration of organic layer in vacuo gave pure diester **8**.

Compound **8**. 5.65 g (~100% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.04 (bs, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 5.84 (bs, 1H); IR (neat) ν_{max} 1736, 1726, 1655 cm^{-1}.

4.1.5. 2,3-Dihydroxy-2-methyl-succinic acid dimethyl ester (9). To a stirred solution of diester **8** (4.00 g, 28.17 mmol) in *t*-BuOH (16 mL) and acetone (4 mL) was added OsO_4 (1.5 mL, 0.24 mmol, 4% solution in *t*-BuOH) and NMO (14 mL, 60% aqueous solution) at room temperature. The reaction mixture was further stirred for 60 h and then quenched with solid Na_2SO_3 (3.0 g). After addition of Na_2SO_3 the reaction mixture was further stirred for 1 h at room temperature, and then concentrated and dried in vacuo. The crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:1) to furnish **9**.

Compound **9**. 5.35 g (99% yield); white crystalline solid; mp 94–96 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.54 (s, 3H), 3.24 (bs, 1H), 3.45 (bs, 1H), 3.76 (s, 3H), 3.82 (s, 3H), 4.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.4, 52.5, 52.9, 75.5, 76.5, 171.7, 174.6; IR ($CHCl_3$) ν_{max} 3491, 3348, 1735, 1726 cm^{-1}. Anal. Calcd for $C_7H_{12}O_6$: C, 43.75; H, 6.29. Found: C, 43.69; H, 6.21.

4.1.6. 2,2,4-Trimethyl-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (10). To a solution of dihydroxy compound **9** (2.00 g, 10.42 mmol) in benzene (15 mL) was added 2,2-dimethoxypropane (2.17 g, 20.84 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg, 0.01 mmol) and the reaction mixture was refluxed for 3 h using Dean and Stark apparatus containing freshly conditioned 4 Å molecular sieves (5.0 g). The reaction mixture was concentrated

and dried in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **10**.

Compound **10**. 2.22 g (92% yield); faint yellow thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 3H), 1.55 (s, 3H), 1.66 (s, 3H), 3.70 (s, 3H), 3.78 (s, 3H), 4.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.2, 26.1 (2 *gem*-methyl carbons), 51.8, 51.9, 81.5, 82.9, 111.0, 167.2, 171.1; IR ($CHCl_3$) ν_{max} 1761, 1744 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.95. Found: C, 51.66; H, 6.89.

4.1.7. Potassium 2,2,4-trimethyl-[1,3]dioxolane-4-carbmethoxy-5-carboxylate (11). To a solution of diester **10** (2.00 g, 8.62 mmol) in methanol (15 mL) was added a solution of KOH (484 mg, 8.62 mmol) in methanol (10 mL) in a drop wise fashion with constant stirring at room temperature. The reaction mixture was stirred for 1 h and concentrated in vacuo. The residue obtained was washed with $CHCl_3$ (10 mL$\times$2) to obtain pure **11**.

Compound **11**. 2.20 g ($\sim$100% yield); white solid; mp 234–236 °C; ^{1}H NMR (D_2O, 200 MHz) δ 1.33 (s, 3H), 1.46 (s, 3H), 1.55 (s, 3H), 3.59 (s, 3H), 4.33 (s, 1H); ^{13}C NMR (D_2O, 50 MHz) δ 24.9, 28.2, 28.4, 55.3, 85.7, 86.6, 113.3, 175.7, 176.5; IR (KBr) ν_{max} 1736, 1628 cm^{-1}.

4.1.8. 2,2,4-Trimethyl-[1,3]dioxolane-4,5-dicarboxylic acid 4-methyl ester (12). The salt **11** (2.00 g, 7.81 mmol) was acidified to pH 5 with minimum amount of 2 N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to obtain **12**.

Compound **12**. 1.12 g (66% yield); colourless thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.37 (s, 3H), 1.48 (s, 3H), 1.62 (s, 3H), 3.66 (s, 3H), 4.36 (s, 1H), 9.15 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.5, 26.5, 26.6, 52.3, 81.5, 83.5, 111.7, 171.3, 171.7; IR ($CHCl_3$) ν_{max} 1744, 1720 cm^{-1}. Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.39; H, 6.51.

4.1.9. 2,2,3*a*-Trimethyl-dihydro-furo[3,4-*d*][1,3]dioxol-4-one (13). To a solution of acid **12** (100 mg, 0.46 mmol) in THF (5 mL) was added borane–dimethylsulfide complex (38.3 mg, 0.50 mmol) in THF (1 mL) in a drop wise fashion with constant stirring at -8 °C. The reaction mixture was then allowed to warm up to room temperature and further stirred at room temperature for 36 h. The reaction was quenched with water (3 mL), and the reaction mixture was concentrated in vacuo. The obtained residue was stirred with diethyl ether (40 mL). The organic layer was washed with brine and dried over Na_2SO_4, concentrated and dried in vacuo. The crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **13**.

Compound **13**. 39 mg, (50% yield); colourless thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 3H), 1.47 (s, 3H), 1.57 (s, 3H), 4.32 (dd, J=4, 10 Hz, 1H), 4.44 (dd, J=0, 10 Hz, 1H), 4.49 (dd, J=0, 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.4, 26.6, 26.9, 68.9, 80.3, 81.4, 113.0, 176.7; IR ($CHCl_3$) ν_{max} 1788, 1379, 1105 cm^{-1}. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.72; H, 6.97.

4.1.10. 3,4-Dihydroxy-3-methyl-dihydro-furan-2-one (14). To a stirred solution of lactone **13** (20 mg, 0.12 mmol) in water (1 mL) was added trifluroacetic acid (0.01 mL) at 0 °C. The reaction mixture was allowed to warm up to room temperature and further stirred at room temperature for 24 h. The reaction mixture was then concentrated and dried in vacuo to obtain pure **14**.

Compound **14**. 15 mg (97% yield); faint yellow thick oil; ^{1}H NMR (CD_3OD, 200 MHz) δ 1.37 (s, 3H), 4.04 (dd, J=2, 4 Hz, 1H), 4.13 (dd, J=2, 10 Hz, 1H), 4.43 (dd, J=4, 10 Hz, 1H); ^{13}C NMR (CD_3OD, 50 MHz) δ 21.6, 73.3, 74.4, 74.6, 180.4; IR ($CHCl_3$) ν_{max} 3421, 1778, 1215, 758 cm^{-1}. Anal. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.45; H, 6.19.

4.1.11. Potassium 2,3,4-trihydroxy-2-methylbutanoate (1). To a solution of lactone **14** (10 mg, 0.08 mmol) in water (1 mL) was added KOH (4 mg, 0.08 mmol). The reaction mixture was stirred for 10 min and concentrated in vacuo to obtain **1**.[16]

Compound **1**. ^{1}H NMR (D_2O, 200 MHz) δ 1.34 (s, 3H), 3.57 (m, 2H), 3.80 (m, 1H); ^{13}C NMR (D_2O, 50 MHz) δ 25.0, 64.9, 78.5, 79.5, 183.5.

4.1.12. 2,2,6*a*-Trimethyl-dihydro-furo[3,4-*d*][1,3]dioxol-4-one (15). To the suspension of salt **11** (100 mg, 0.39 mmol) in THF (7 mL) was added $LiBH_4$ (34 mg, 1.56 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 6 h. The reaction was quenched with water and the reaction mixture was concentrated in vacuo. The aqueous layer was acidified with minimum amount of dilute HCl and extracted with ethyl acetate (15 mL$\times$3). The organic layer was washed with brine, dried over Na_2SO_4, concentrated and dried in vacuo to obtain pure **15**.

Compound **15**. 40 mg, (60% yield); white crystalline solid; mp 42–44 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 3H), 1.49 (s, 3H), 1.54 (s, 3H), 4.15 (d, J=12 Hz, 1H), 4.45 (d, J=12 Hz, 1H), 4.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.9, 27.7, 28.5, 75.7, 79.6, 83.5, 114.1, 174.5; IR ($CHCl_3$) ν_{max} 1788, 1383, 1217 cm^{-1}. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 56.01; H, 7.07.

4.1.13. 3,4-Dihydroxy-4-methyl-dihydro-furan-2-one (7). To a stirred solution of lactone **15** (20 mg, 0.12 mmol) in THF (2 mL) and water (0.5 mL) was added trifluroacetic acid (0.01 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and further stirred at room temperature for 3 h. The reaction mixture was then concentrated and dried in vacuo to obtain pure **7** in 78% yield. Analytical and spectral data matched with that of compound **7**, obtained from **5**.

Acknowledgements

S. G. thanks CSIR, New Delhi, for the award of a research

fellowship and N. P. A. thanks Department of Science and Technology, New Delhi, for financial support.

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16. The leaf-closing compound **1** is unstable around neutral or basic pH, and gradually decomposes to give lactate.[3]
17. In lactones **13** and **14**, the explanation for the low coupling constants between the methine proton and methylene protons has been given by Bacher et al.[9]

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Thermodynamics of binding between α- and β-cyclodextrins and some *p*-nitro-aniline derivatives: reconsidering the enthalpy–entropy compensation effect

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Received 23 April 2004; revised 1 July 2004; accepted 28 July 2004

Available online 26 August 2004

Abstract—The thermodynamics of binding between native α- and β-cyclodextrin towards several *p*-nitro-aniline derivatives was examined, in order to gain further insights about the occurrence of different interaction modes for the two hosts. Valuable information was achieved regarding the 'expanded hydrophobic sphere' of α-cyclodextrin. Furthermore, very interesting and unexpected aspects of the behavior of β-cyclodextrin were enlightened, such as the crucial role played by hydrogen bond interactions. Experimental data were examined under the perspective of the 'enthalpy–entropy compensation effect', and some ideas about this topic are discussed.

1. Introduction

Binding properties of both native and chemically modified cyclodextrins towards suitably sized and shaped organic molecules have been the object of extensive studies during the last decades.[1] These cyclic, bucket-shaped oligosaccharides owe their popularity to their wide range of industrial, as well as research applications, ranging from pharmaceuticals,[2] food and cosmetics technology[3] to separation[4] and chiral discrimination,[5] reaction microenvironment,[6] catalysis,[7] enzyme mimics[8] and stereoselective synthesis.[9]

A thorough understanding of the various factors affecting the host–guest inclusion phenomenon at a molecular level is needed in such a context, so considerable efforts have been devoted to this task.[10–12] There is now a general agreement that the binding equilibrium is the result of a fine balance between different stabilization sources,[11] including host desolvation and solvent reorganization, hydrophobic, dipolar and hydrogen bond interactions, conformational strain release. Their mutual interplay is classically discussed within Tabushi's scheme,[12] in terms of: (i) desolvation of the host cavity; (ii) desolvation of the guest; (iii) 'neat' inclusion of the guest into the host cavity; (iv) reorganization of the solvent pool. There is not any obvious hierarchy among the previously mentioned factors, and none of them can be assumed a priori as the ultimate driving force for the overall process. Therefore, a careful systematic investigation on the thermodynamics of binding is needed,[13] because inclusion constants alone are not able to provide us with exhaustive information.

As observed for other classes of supramolecular ligands (such as porphyrins, crown ethers, cryptands or calixarenes),[14] the existence of a specific enthalpy–entropy compensation effect for inclusion in cyclodextrins has been claimed.[14–19] This finding is interesting both as an interpretation tool and as a topic of investigation. It relies on the simple and intuitive idea that the more strongly host and guest bind together, the more the resulting host–guest complex will suffer for the loss of conformational freedom.[14,19] Its actual existence and correct interpretation have been the object of intense debate and also of severe criticism.[20] It was first empirically proposed that the slope and the intercept of the $T\Delta S^{\circ}$ versus ΔH° correlation plot might be considered respectively as a measure of the loss of degrees of freedom and of the extent of desolvation for the species involved.[14] However, more recently it has been suggested, on the basis of thermodynamic arguments,[20b,e] that the actual source of the compensation effect should be related to contributions due to solvent reorganization. Methodological objections have also been put forward, owing to the interdependence in the determination of ΔH°

Keywords: Cyclodextrins; Thermodynamics.
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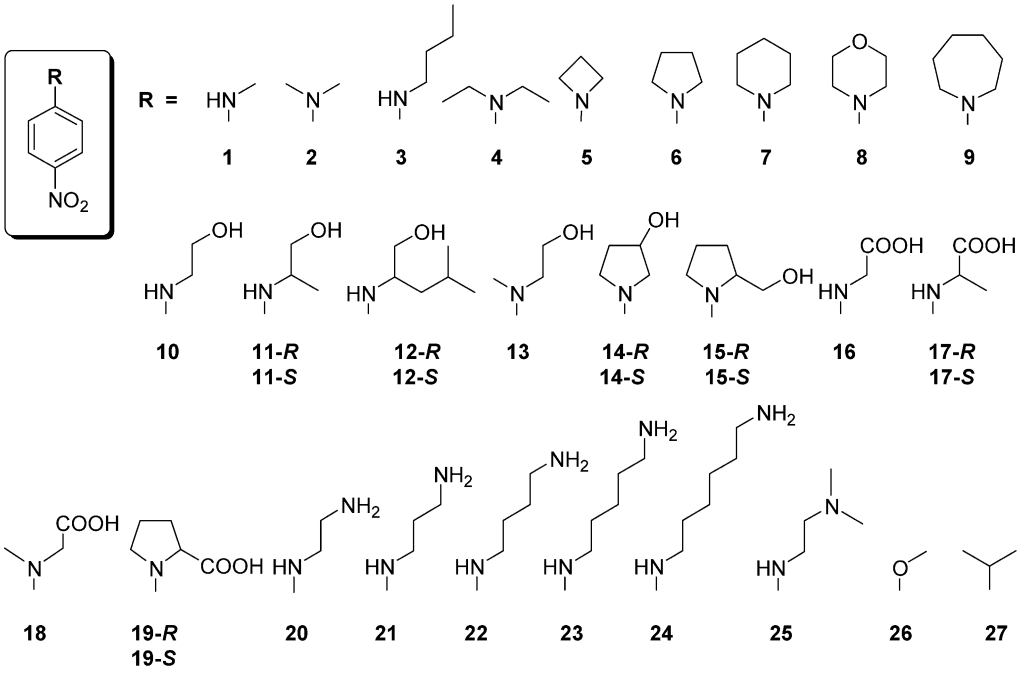
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.079

and ΔS° values, which can lead to a 'pseudo-compensation effect'.[18,20a,21]

Recently we have been interested in elucidating the inclusion properties of native and chemically modified cyclodextrins towards aromatic derivatives.[5b,11,22] In particular, we have investigated the thermodynamics of binding for α-cyclodextrin (αCD) and β-cyclodextrin (βCD) towards some *N*-substituted *p*-nitro-benzene derivatives (compounds **1**–**9**, **16**, **19**-*S*, **26** and **27** of Scheme 1).[11] These guests penetrate the cyclodextrin cavity with the nitro-group directed towards the primary rim of the host.[11,22] The two hosts showed quite different behaviors. Binding by αCD was an enthalpy-driven process, while inclusion in βCD was both enthalpy- and entropy-driven. Good ΔH° versus $T\Delta S^{\circ}$ correlations were found for both hosts, having very similar slopes (near to 0.96), although values for αCD and βCD respectively were reciprocally uncorrelated. A careful data analysis[11] led us to the conclusion that the narrow αCD cavity is able to include quite rigidly only the aromatic moiety of the guest, while its ancillary chain **R** stays exposed to the structured water molecules in the surroundings of the secondary host rim. These water molecules form a so-called 'expanded hydrophobic sphere',[13] having different properties with respect to the solvent bulk. On the other hand, the larger βCD cavity seems able to include the entire guest (with a certain flexibility), so it can interact with both its aromatic moiety and ancillary chain.

Although we were able to obtain convincing evidence about the occurrence of these different interaction modes, nonetheless several other questions arose. For example, the 'expanded hydrophobic sphere' for αCD and its interaction with the ancillary chain of the guest seemed to be an ad hoc hypothesis, which needed further experimental support. Furthermore, it seemed interesting to investigate how much the 'expanded hydrophobic sphere' of αCD, as well as the cavity and/or the secondary rim of βCD, were able to discriminate particular properties of the ancillary chain, such as its chirality or the presence of charged groups. Further doubts also came from enthalpy–entropy compensation correlations, because their similarity, despite the characteristics of the two hosts which appeared to be so different, seemed suspect. Consequently, we could also ask how reliable could be the thermodynamic data directly coming from van't Hoff plots analysis.[23] Therefore, we extended our study to *p*-nitro-aniline derivatives **10**–**25** (Scheme 1). We focused on suitable aminoalcohol, aminoacid and diamine derivatives, selected in such a way as to show appreciable differences in their properties, such as their hydrophobicity, conformational freedom, hydrogen bond ability, and the possibility to change their protonation state and charge by varying the pH value of the solvent medium, depending on their ancillary chain **R**. Among them, six enantiomeric pairs were also examined. It should be stressed that different enantiomers, as well as differenly charged forms of the same guests, will presumably experience different interactions with the host, and thus have to be formally considered as different guests. Binding constants were measured by means of UV–Vis spectrophotometry at different temperatures, ranging from 288 to 313 K in a suitable phosphate buffer solution. All guests were studied at pH = 6.0; aminoacid derivatives **16**–**19** were also studied at pH = 2.5, while diamine derivatives **20**–**25** were also studied at pH = 11.0. These pH values were chosen for consistency with our previous works,[11,22] in order to study the behavior of both the ionized and the neutral form of these guests. Experimental data, together with those for guests **1**–**9**, *p*-nitro-anisole (**26**) and *p*-nitro-isopropyl-benzene (**27**), were all subjected to a suitable statistical analysis before comparative examination.



Scheme 1. Guests **1**–**27**.

Table 1. pK_a values for aminoacid derivatives **16–19**

Guest	pK_a	pH	$\%_{HA}$	$\%_A^-$
16	3.52±0.08	2.5	91.3	8.7
		6.0	0.3	99.7
17	3.54±0.03	2.5	91.6	8.4
		6.0	0.3	99.7
18	3.18±0.01	2.5	82.7	17.3
		6.0	0.2	99.8
19	3.34±0.01	2.5	87.4	12.6
		6.0	0.2	99.8

Table 2. pK_{BH+} values for diamine derivatives **20–25**

Guest	pK_{BH+}	pH	$\%_{BH}^+$	$\%_B$
20	9.02±0.01	6.0	99.8	0.2
		11.0	0.1	99.9
21	10.05±0.05	6.0	100.0	—
		11.0	10.1	89.9
22	10.19±0.01	6.0	100.0	—
		11.0	13.4	86.6
23	10.45±0.01	6.0	100.0	—
		11.0	22.0	78.0
24	10.08±0.01	6.0	100.0	—
		11.0	10.7	89.3
25	8.43±0.01	6.0	99.6	0.4
		11.0	0.3	99.7

2. Results and discussion

2.1. Behavior of guests 16–25 in solution

As a preliminary work, the ionization equilibriums of aminoacid and diamine derivatives **16–25** in buffer solution at different pH values had to be examined. In Table 1 the pK_a values of *N*-(*p*-nitro-phenyl)-aminoacid derivatives **16–19** are reported. These guests are, in general, weaker acids than the corresponding free aminoacids[24] (relative to their first dissociation constant. The mean difference in pK_a values is ca. 1.2). This finding can probably be attributed to an unfavorable effect of the hydrophobic *p*-nitro-phenyl moiety on the solvation of the ionized carboxyl group. From these data we can immediately deduce that compounds **16–19** are fully ionized at pH=6.0. At pH=2.5 the undissociated acid form predominates, but an amount of ionized form, ranging up to 17%, is still present. Clearly, this is not strictly negligible; however, at a first approximation level we can assume guests **16–19** to be not ionized at this pH value.[25]

Data related to diamine derivatives **20–25** are reported in Table 2. In general, their pK_{BH}^+ values are comparable to those of the corresponding diamines[26] with the exception of ethylenediamine derivatives **20** and **25**, for which higher dissociation constants are found. The latter behavior can also be attributed to the effect of the *p*-nitro-phenyl moiety on the solvation of the charged ammonium group, the effect becoming weaker on increasing the diamine chain length. Also for these compounds data indicate complete ionization at pH=6.0. At pH=11.0 the free base forms fully predominate for compounds **20** and **25**. For compounds **21–24** an amount of ionized form (ranging up to 22%) is still present; however also in this case we can assume at a first approximation that its presence is not relevant.

The spectroscopic behavior of short chain derivatives **16**, **17**, **20** and **25** is quite interesting. Significant shifts of the absorption maximum in the UV–Vis spectra are observed on passing from their neutral to their ionized forms (Fig. 1). We can explain this observation considering that for all these compounds the aniline N atom is a hydrogen bond donor, which is able to interact with the functional group at the chain end. This interaction, influencing the conformational

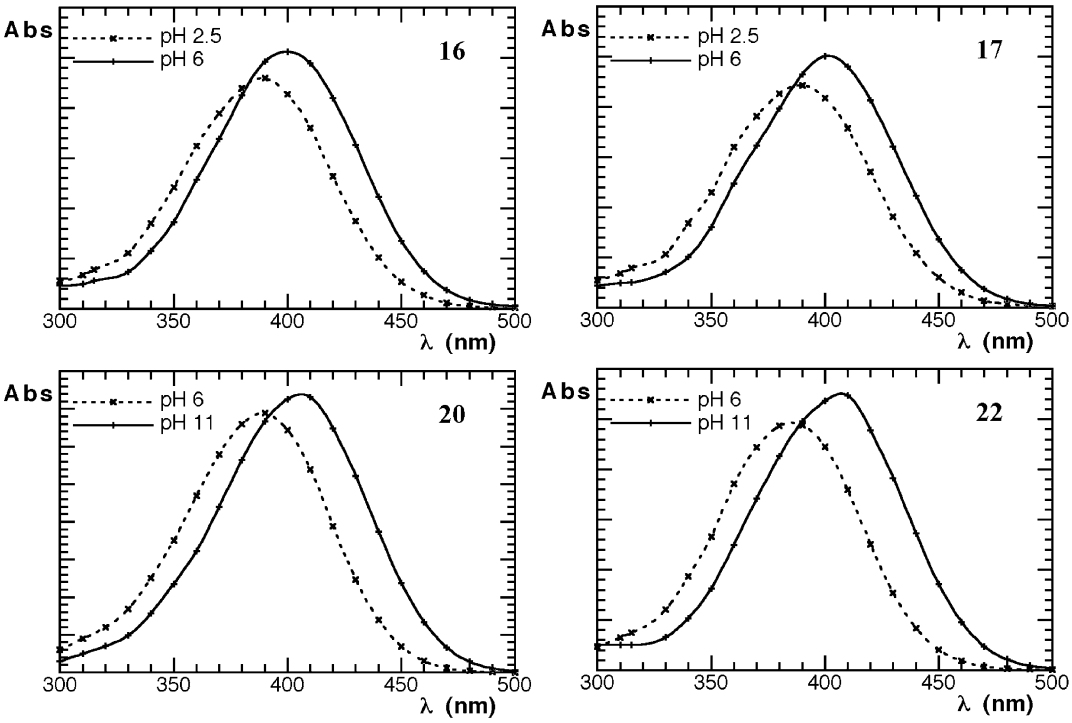


Figure 1. UV–Vis spectra of guests **16**, **17**, **20** and **22**.

Table 3. Binding constants at 298.15 K and thermodynamic parameters for inclusion of guests **1–27** in αCD

Entry	Guest	pH	K (M^{-1}, 298.15 K)	ΔG° (kJ mol^{-1})	From van't Hoff plots		Corrected (Eq. 3)	
					ΔH° (kJ mol^{-1})	$T\Delta S^\circ$ (kJ mol^{-1})	ΔH° (kJ mol^{-1})	$T\Delta S^\circ$ (kJ mol^{-1})
1	**1**	6.0	990±24[a]	−17.09±0.06[a]	−37.8±0.6[a]	−20.7±0.6[a]	−34.7±0.5	−17.6±0.5
2	**2**	6.0	1178±38[a]	−17.52±0.08[a]	−38.8±1.0[a]	−21.3±1.0[a]	−35.9±0.4	−18.4±0.4
3	**3**	6.0	1453±35[a]	−18.04±0.06[a]	−32.6±0.6[a]	−14.6±0.6[a]		
4	**4**	6.0	1118±23[a]	−17.39±0.05[a]	−34.8±1.4[a]	−17.4±1.4[a]	−35.3±0.5	−17.9±0.5
5	**5**	6.0	1197±29[a]	−17.56±0.06[a]	−38.0±0.3[a]	−20.5±0.3[a]	−36.0±0.4	−18.4±0.4
6	**6**	6.0	2123±120[a]	−18.98±0.14[a]	−36.4±0.5[a]	−17.5±0.5[a]	−39.5±0.7	−20.6±0.7
7	**7**	6.0	1346±22[a]	−17.85±0.04[a]	−38.9±1.0[a]	−20.9±1.0[a]	−36.9±0.4	−19.0±0.4
8	**8**	6.0	932±11[a]	−16.94±0.03[a]	−34.0±1.3[a]	−17.1±1.3[a]	−34.2±0.6	−17.3±0.6
9	**9**	6.0	3602±87[a]	−20.29±0.06[a]	−42.4±0.2[a]	−22.1±0.2[a]	−43.1±1.1	−22.9±1.1
10	**10**	6.0	1043±38	−17.22±0.09	−34.5±0.7	−17.3±0.7	−34.9±0.5	−17.7±0.5
11	**11**-*R*	6.0	1221±39	−17.61±0.08	−37.3±0.5	−19.7±0.5	−36.0±0.4	−18.4±0.5
12	**11**-*S*	6.0	1251±51	−17.67±0.10	−36.1±0.7	−18.5±0.7	−36.1±0.4	−18.5±0.5
13	**13**	6.0	1329±48	−17.82±0.09	−37.5±0.3	−19.7±0.4	−36.6±0.4	−18.7±0.5
14	**14**-*R*	6.0	1282±41	−17.73±0.08	−39.2±0.9	−21.5±0.9	−36.5±0.4	−18.7±0.4
15	**14**-*S*	6.0	1362±82	−17.88±0.15	−39.4±0.9	−21.5±0.9	−36.9±0.4	−19.0±0.4
16	**15**-*R*	6.0	1792±43	−18.56±0.06	−39.8±0.6	−21.2±0.6	−38.5±0.6	−19.9±0.6
17	**15**-*S*	6.0	1778±29	−18.54±0.04	−39.6±0.4	−21.1±0.4	−38.4±0.6	−19.9±0.6
18	**16**	2.5	1010±61[a]	−17.14±0.15[a]	−20.4±0.8[a]	−3.3±0.8[a]		
19	**16**	6.0	1010±37[a]	−17.14±0.09[a]	−30.6±0.9[a]	−13.5±0.9[a]	−34.7±0.5	−17.6±0.5
20	**17**-*R*	2.5	723±44	−16.31±0.15	−36.6±0.6	−20.3±0.6	−32.8±0.7	−16.5±0.7
21	**17**-*R*	6.0	1118±45	−17.39±0.10	−30.6±0.5	−13.2±0.6	−35.4±0.4	−18.0±0.4
22	**17**-*S*	2.5	891±32	−16.83±0.09	−35.2±1.0	−18.4±1.0	−33.9±0.6	−17.0±0.6
23	**17**-*S*	6.0	1006±24	−17.13±0.06	−32.7±0.5	−15.5±0.5	−34.8±0.5	−17.6±0.5
24	**18**	2.5	856±59	−16.73±0.17	−39.3±0.6	−22.5±0.7		
25	**18**	6.0	819±33	−16.62±0.10	−31.9±0.9	−15.3±0.9	−33.5±0.6	−16.8±0.6
26	**19**-*R*	2.5	943±23	−16.97±0.06	−34.5±0.3	−17.5±0.3	−34.3±0.6	−17.4±0.6
27	**19**-*R*	6.0	1226±30	−17.62±0.06	−34.6±0.4	−17.0±0.4	−36.0±0.5	−18.4±0.5
28	**19**-*S*	2.5	1039±25[a]	−17.21±0.06[a]	−30.8±0.8[a]	−17.2±0.8[a]	−34.8±0.5	−17.6±0.5
29	**19**-*S*	6.0	1187±14[a]	−17.54±0.03[a]	−35.7±1.1[a]	−17.6±1.1[a]	−35.8±0.5	−18.2±0.5
30	**20**	11.0	1197±24	−17.56±0.05	−36.4±1.0	−18.9±1.0	−35.9±0.5	−18.3±0.5
31	**20**	6.0	849±31	−16.71±0.09	−35.1±0.8	−18.4±0.8		
32	**21**	11.0	1843±60	−18.63±0.08	−39.5±0.4	−20.8±0.4	−38.8±0.6	−20.2±0.6
33	**21**	6.0	1756±43	−18.51±0.06	−37.2±0.6	−18.7±0.6	−38.5±0.5	−19.9±0.5
34	**22**	11.0	1507±55	−18.13±0.09	−37.6±0.9	−19.4±0.9	−37.4±0.5	−19.3±0.5
35	**22**	6.0	1770±36	−18.53±0.05	−37.4±0.6	−18.9±0.6	−38.5±0.5	−19.9±0.5
36	**23**	11.0	1390±79	−17.93±0.14	−35.8±0.9	−17.8±0.9	−37.0±0.4	−19.1±0.5
37	**23**	6.0	1620±65	−18.31±0.10	−37.8±0.6	−19.5±0.6	−37.8±0.5	−19.5±0.5
38	**24**	11.0	1356±66	−17.87±0.12	−36.9±0.6	−19.1±0.6	−36.7±0.4	−18.9±0.5
39	**24**	6.0	1513±37	−18.14±0.06	−34.8±0.8	−16.7±0.8	−37.3±0.5	−19.2±0.5
40	**25**	11.0	1236±35	−17.64±0.07	−36.5±0.8	−18.9±0.8	−36.1±0.4	−18.5±0.4
41	**25**	6.0	1065±26	−17.27±0.06	−34.6±0.5	−17.3±0.5	−35.2±0.5	−17.9±0.5
42	**26**	6.0	315±50[a]	−14.25±0.39[a]	−35.9±0.4[a]	−21.7±0.6[a]		
43	**27**	6.0	505±79[a]	−15.42±0.39[a]	−28.5±2.3[a]	−12.9±2.3[a]	−30.7±1.0	−15.2±1.1

[a] From Ref. 11.

equilibriums of the molecule, is favored because it involves the formation of a five-membered pseudo-cycle. A change in the protonation state of the latter group will heavily affect the occurrence of this intramolecular hydrogen bond. Its formation induces a variation in the local dipole moment of the aryl chromophore moiety, causing a bathochromic shift of the absorption maximum.

Aminoalcohol derivatives **11** and **12** presumably share the same behavior, although it is not possible to point it out in this way. The ease of forming the intramolecular hydrogen bond rapidly decreases as the chain length increases. In particular, we observed that along the series of the diamino derivatives **20**–**22**, a bathochromic shift of 17 nm is found for **20**, which decreases to 8 nm for **21** and to only 2 nm for **22**. Therefore, we can presume that the former two-carbon-chain molecule can be mostly found in its pseudo-cyclic conformation; whereas the latter four-carbon-chain derivative is almost completely in a free-chain conformation. For the intermediate three-carbon-chain compound the two conformational states are probably populated in comparable amounts.

2.2. Complexation behavior of αCD and βCD towards guests 1–27. A first overview of inclusion constants, van't Hoff parameters and chiral selection properties

Binding constants at 298.15 K and van't Hoff parameters for complexation of αCD and βCD towards substrates **1–27** are reported in Tables 3 and 4 respectively. The data indicate remarkable differences in behavior between the two examined hosts, in agreement with our previous observations.[11] Complexation with αCD is an essentially enthalpy-driven process, with ΔH° values ranging from −20.4 to −42.4 kJ mol^{-1}, while $T\Delta S^\circ$ values range from −3.3 to −22.5 kJ mol^{-1}. However, most of the ΔG° values are restricted in a narrow range of ca. 2.7 kJ mol^{-1}, which corresponds to only modest variations in binding constants. Interestingly, this indicates that we cannot gain significant information simply by consideration of the binding

Table 4. Binding constants at 298.15 K and thermodynamic parameters for inclusion of guests **1–27** in βCD

Entry	Guest	pH	K (M^{-1}, 298.15 K)	ΔG° (kJ mol^{-1})	From van't Hoff plots		Corrected (Eq. 3)		Group
					ΔH° (kJ mol^{-1})	$T\Delta S^\circ$ (kJ mol^{-1})	ΔH° (kJ mol^{-1})	$T\Delta S^\circ$ (kJ mol^{-1})	
44	**1**	6.0	1080±48[a]	−17.31±0.11[a]	−12.9±0.7[a]	4.3±0.7[a]	−13.8±0.7	3.5±0.7	A
45	**2**	6.0	710±26[a]	−16.27±0.09[a]	−10.9±0.6[a]	5.3±0.6[a]	−13.0±0.7	3.3±0.7	C
46	**3**	6.0	917±52[a]	−16.90±0.14[a]	−17.9±0.8[a]	−1.1±0.8[a]	−17.0±0.3	−0.1±0.4	B
47	**4**	6.0	588±28[a]	−15.80±0.12[a]	−14.1±0.9[a]	1.7±0.9[a]	−14.3±0.4	1.5±0.4	B
48	**5**	6.0	764±28[a]	−16.45±0.09[a]	−11.9±0.4[a]	4.5±0.4[a]	−13.0±0.7	3.5±0.7	C
49	**6**	6.0	1297±42[a]	−17.76±0.08[a]	−12.7±0.6[a]	5.0±0.6[a]	−13.0±0.7	4.7±0.7	C
50	**7**	6.0	2640±64[a]	−19.52±0.06[a]	−13.1±1.2[a]	6.4±1.2[a]	−13.0±0.7	6.5±0.7	C
51	**8**	6.0	647±26[a]	−16.04±0.10[a]	−14.7±0.6[a]	1.3±0.6[a]	−13.0±0.7	3.1±0.7	C
52	**9**	6.0	17297±349[a]	−24.18±0.05[a]	−23.2±0.4[a]	0.0±0.4[a]			
53	**10**	6.0	610±25	−15.89±0.10	−20.6±0.6	−4.7±0.6	−18.8±0.4	−2.9±0.5	A
54	**11**-*R*	6.0	641±26	−16.01±0.10	−17.6±0.4	−1.6±0.5	−18.3±0.4	−2.2±0.4	A
55	**11**-*S*	6.0	566±25	−15.70±0.11	−15.7±0.6	0.0±0.6	−19.2±0.5	−3.5±0.5	A
56	**12**-*R*	6.0	1177±57	−17.52±0.12	−14.4±0.9	3.1±0.9	−13.0±0.8	4.5±0.8	A
57	**12**-*S*	6.0	1204±44	−17.57±0.09	−11.6±0.8	6.0±0.8	−12.8±0.8	4.8±0.8	A
58	**13**	6.0	734±27	−16.35±0.09	−14.8±0.4	1.5±0.4	−15.6±0.4	0.8±0.4	B
59	**14**-*R*	6.0	954±27	−17.00±0.07	−13.3±0.6	3.6±0.6	−13.0±0.7	4.0±0.7	C
60	**14**-*S*	6.0	957±19	−17.01±0.05	−13.2±0.7	3.8±0.7	−13.0±0.7	4.0±0.7	C
61	**15**-*R*	6.0	1293±31	−17.75±0.06	−16.2±0.3	1.5±0.3	−19.2±0.5	−1.4±0.5	B
62	**15**-*S*	6.0	1182±43	−17.53±0.09	−15.4±0.2	2.1±0.3	−18.6±0.4	−1.1±0.4	B
63	**16**	6.0	348±25[a]	−14.50±0.18[a]	−22.4±1.2[a]	−8.0±1.2[a]	−24.0±1.1	−9.5±1.2	A
64	**17**-*R*	2.5	377±38	−14.70±0.25	−27.4±3.1	−12.5±3.1	−22.4±0.9	−7.7±1.0	A
65	**17**-*R*	6.0	396±27	−14.82±0.17	−25.4±0.7	−10.6±0.8	−22.2±0.9	−7.4±0.9	A
66	**17**-*S*	2.5	544±44	−15.61±0.20	−20.5±1.5	−4.8±1.5	−19.3±0.5	−3.7±0.6	A
67	**17**-*S*	6.0	540±50	−15.59±0.23	−18.4±1.8	−2.7±1.8	−19.4±0.5	−3.9±0.6	A
68	**18**	6.0	423±51	−14.98±0.30	−12.7±1.1	2.3±1.2	−12.4±0.5	2.6±0.6	B
69	**19**-*R*	2.5	858±42	−16.74±0.12	−20.4±0.4	−3.7±0.5	−16.5±0.3	0.2±0.4	B
70	**19**-*R*	6.0	594±34	−15.82±0.14	−13.1±0.4	2.7±0.6	−14.3±0.4	1.5±0.4	B
71	**19**-*S*	2.5	1018±49	−17.16±0.12	−20.8±0.2	−3.6±0.3	−17.7±0.4	−0.5±0.4	B
72	**19**-*S*	6.0	665±59[a]	−16.10±0.22[a]	−13.1±0.4[a]	3.0±0.5[a]	−15.0±0.4	1.1±0.4	B
73	**20**	11.0	684±39	−16.17±0.14	−18.4±1.0	−2.2±1.0	−17.7±0.4	−1.5±0.4	A
74	**20**	6.0	303±35	−14.16±0.29	−10.2±0.6	3.9±0.7	−9.8±0.8	4.3±0.8	B
75	**22**	11.0	1149±70	−17.46±0.15	−20.4±0.5	−3.0±0.6	−18.5±0.4	−1.0±0.5	B
76	**22**	6.0	865±35	−16.76±0.10	−17.9±0.3	−1.1±0.5	−16.7±0.3	0.1±0.4	B
77	**25**	11.0	689±28	−16.19±0.10	−16.6±1.1	−0.4±1.1	−17.5±0.4	−1.3±0.4	A
78	**25**	6.0	369±49	−14.64±0.33	−8.7±0.9	5.9±0.9	−11.2±0.6	3.5±0.7	B
79	**26**	6.0	175±25[a]	−12.80±0.35[a]	−5.8±0.2[a]	7.0±0.4[a]	−6.7±1.2	6.0±1.2	B
80	**27**	6.0	1450±88[a]	−18.04±0.15[a]	−7.9±0.3[a]	10.2±0.4[a]			

[a] From Ref. 11.

constants alone. On the other hand, complexation with βCD shows less negative ΔH° values, ranging from −5.8 to −24.2 kJ mol^{-1}, and $T\Delta S^\circ$ values correspondingly ranging from −12.5 to 10.2 kJ mol^{-1}; so only in some cases is the process both enthalpy and entropy driven. Furthermore, ΔG° values show a moderate variability, spreading over a 11.4 kJ mol^{-1} range. Lack of correlation between ΔG°, ΔH° or $T\Delta S^\circ$ values for αCD versus βCD is fully confirmed. Compensation $T\Delta S^\circ$ versus ΔH° plots show fairly good linear correlations, according to the following relationships:

for αCD: $T\Delta S^\circ = (14.8 \pm 1.9) + (0.92 \pm 0.03)\ \Delta H^\circ$ ($n = 40$, $r = 0.985$);

for βCD : $T\Delta S^\circ = (16.7 \pm 1.8) + (1.02 \pm 0.05)\ \Delta H^\circ$ ($n = 36$, $r = 0.966$).

Because both slopes are close to the critical value of 0.96 (vide infra), suspicion of a pseudo-compensation effect cannot be ruled out. In particular, the slope value for βCD should account for an almost perfect compensation between enthalpy and entropy at 298.15 K, in striking contrast with the fact that ΔG° values actually show appreciable variations.

Data regarding chiral selection properties are summarized in Table 5. αCD does not act as a chiral selector. Modest selections are indeed observed only for guest **17**. However, fair selectivities are found for βCD, in particular with alaninol and alanine derivatives **11** and **17**. It is also very interesting to notice that inversion of chiral selection is found on comparing the two aminoalcohol derivatives **11**

Table 5. Chiral selection data

Host	Guest	PH	K_R/K_S
αCD	**11**	6.0	0.98±0.05
	14	6.0	0.94±0.06
	15	6.0	1.01±0.03
	17	2.5	0.81±0.06
	17	6.0	1.11±0.05
	19	2.5	0.91±0.03
	19	6.0	1.03±0.03
βCD	**11**	6.0	1.13±0.07
	12	6.0	0.98±0.06
	14	6.0	1.00±0.03
	15	6.0	1.09±0.05
	17	2.5	0.69±0.09
	17	6.0	0.73±0.08
	19	2.5	0.84±0.06
	19	6.0	0.89±0.09

and **15** with the related aminoacid derivatives **17** and **19**. No selectivity is found for the pyrrolidinol derivatives **14**, indicating that chiral recognition depends on the distance between the chiral center and the aromatic moiety of the guest. Strangely, no selection is found for the leucinol derivatives **12**. The chiral selectivities reported here are comparable, or even better than selections reported[16,27] for aminoacids or their simple derivatives with natural or chemically modified βCDs (much better results have only been obtained in more structured systems, such as ternary complexes[5b]). These results may be easily explained on the basis of the different interaction models illustrated previously. The possibility to observe any chiral discrimination is indeed linked to the occurrence of an effective interaction between the stereogenic center and the host cavity, as happens in βCD, while the 'expanded hydrophobic sphere' of αCD is not structured enough to accomplish any recognition.

2.3. Formation of 2:1 complexes with αCD

We already observed[11] that αCD is able to form 2:1 host–guest complexes, along with the usual 1:1 complexes, with some of our guests. In particular, we had been able to measure the second partial association constant $K_{\alpha,2}$, and the related thermodynamic parameters, for guests **1**, **3**, **5**, **6** and **16**, and we were able to detect qualitatively the incipient formation of the 2:1 complexes at high (>10 mM) αCD concentration for guests **2**, **4**, **7** and **8**.[28]

We were able to qualitatively detect the incipient presence of a 2:1 complex also with ethanolamine derivative **10**. Interestingly, among substrates **11**–**15** and **17**–**19** we never had any evidence about the presence of detectable amounts of 2:1 complexes, even at high (50 mM) αCD concentration. Comparing the latter substrates with guests **6**, **10** and **16**, we can deduce that the formation of the 2:1 complex is hampered by placing either a sterically demanding or a strongly hydrophilic group on the pyrrolidine, ethanolamine or glycine frameworks of **6**, **10** or **16** respectively. For diamine derivatives **20**–**25** incipient formation of a 2:1 complex was always qualitatively detected at pH=11.0 (guests in their neutral form). In particular, we found indicative values of $K_{\alpha,2}$ at 298.15 K of $20\pm10\ M^{-1}$ and $40\pm20\ M^{-1}$ for **23** and **24** respectively, although the data did not allow us to get a reliable evaluation of the related thermodynamic parameters. However, at pH=6.0, the incipient formation of the 2:1 complex was qualitatively detected only for **23** and **24**. This finding further confirms that the presence of a hydrophilic group on the ancillary chain has a negative effect on the formation of the 2:1 complex.

2.4. Statistical analysis of binding constants and determination of corrected thermodynamic parameters

Before proceeding with a careful comparative examination of experimental data, we had to establish whether the compensation effect was real, and thus how reliable van't Hoff parameters were. As we already mentioned, regardless of the experimental procedure adopted to obtain enthalpy and entropy variations for a generic processes series (microcalorimetry or van't Hoff plot analysis) their values are determined simultaneously. Consequently, their best estimates and indeterminations are correlated.[20a] In fact, in a ΔH° versus $T\Delta S^\circ$ plot the confidence region for each experimental datum should actually be represented by a thin ellipse[29] (whose major diameter has a slope equal to 1). Under these circumstances, it can be rigorously demonstrated that the covariance between ΔH° and $T\Delta S^\circ$ is non-zero. As a consequence, good linear relationships are anyway found, having slopes depending on the mean value of the operational temperature, and irrespective of the existence of a real compensation. In particular, for a series of van't Hoff experiments carried out between 283 and 343 K, a slope of ca. 0.96 should be expected.[30] The latter result is dangerously similar to most of the slope values reported in literature for studies on cyclodextrins.[13–16]

In order to solve this problem, different approaches have been tried and reported in literature.[17,20a] In particular, Alper and Gelb developed a suitable statistical analysis method of equilibrium constant data,[18,21] which could be considered as an 'extended van't Hoff' treatment. Their method is based on a simultaneous regression analysis of all the various van't Hoff correlations for a set of experiments with n different guests, by means of Eq. 1:

$$R\ \mathrm{Ln}\ K_{ij} = -\Delta H^\circ_i/T_{ij} + \Delta S^\circ_i \quad (1)$$

where index i refers to the generic i-th experiment, and the index j individuates the generic j-th datum within the i-th experiment. If a real enthalpy–entropy compensation effect exists, according to the Eq. 2:

$$\Delta H^\circ_i = \Delta H^\circ_0 + \Theta\Delta S^\circ_i \quad (2)$$

then Eq. 1 may be re-written as:

$$R\ \mathrm{Ln}\ K_{ij} = (\Delta H^\circ_0 + \Theta\Delta S^\circ_i)/T_{ij} + \Delta S^\circ_i \quad (3)$$

In Eqs. 2 and 3 Θ is defined as the 'compensation' or 'isoequilibrium' temperature, while ΔH°_0 represents the enthalpic gain on inclusion in absence of any entropic variation. Eq. 3 corresponds to a non-linear regression problem with $n+2$ parameters, namely ΔH°_0, Θ and the n different ΔS°_i values; these parameters have in turn to be determined through the usual χ^2 minimizing condition, with χ^2 defined as:

$$\chi^2 = \sum_i \sum_j (y_{ij} - Y_{ij})^2/\sigma^2_{ij} \quad (4)$$

where y_{ij} is the calculated value of $R\ \mathrm{Ln}\ K_{ij}$, Y_{ij} is the corresponding experimental value, and σ^2_{ij} is the variance of Y_{ij}. If the minimum value of χ^2 is similar to the number of degrees of freedom for the data set, then the compensation effect is real and we directly obtain the best estimates for Θ, ΔH°_0 and the ΔS°_i values.[31] Uncertainties on these values can be subsequently obtained by means of a suitable Monte-Carlo procedure.[32] Differently, if the χ^2 value is much higher than the number of degrees of freedom, or if Θ is negative, or if the uncertainty on Θ is larger than its own value, then the compensation effect on the entire data set is false, and a deeper analysis is needed. Noticeably, if a null Θ value is found, this indicates a set of isoenthalpic reactions, for which a simpler fitting equation can be used:

$$R\ \mathrm{Ln}\ K_{ij} = -\Delta H^\circ_i/T_{ij} + \Delta S^\circ_i \quad (5)$$

Differently, if Θ tends to infinity, we have a set of isoentropic reactions, which can be treated according to Eq. 6:

$$R \ln K_{ij} = -\Delta H^\circ_i/T_{ij} + \Delta S^\circ_0 \quad (6)$$

In performing this kind of statistical data analysis, a crucial role is played by σ^2_{ij} values.[18] After the original Alper and Gelb's work,[21] σ_{ij} has been referred to as the 'experimental uncertainty' for Y_{ij}.[18,20a] In particular, analyzing a series of data from inhomogeneous sources concerning cyclodextrin complexation equilibriums, the same authors chose to fix a minimum value of 0.15 R to this 'uncertainty', in order to account for the possibility of unknown systematic errors.[18] This corresponds to a minimum 15% indetermination on K_{ij} values. In our opinion, this choice involves a 'goodness-of-fit' evaluation criterion which is not sufficiently restrictive. Our data set is indeed homogeneous in origin, and refers to strictly homogeneous substrates. Furthermore, in our case we chose to give 2σ-wide confidence intervals for our association constants, and we have found that the mean relative indetermination on our K_{ij} values is 5%. There is the general agreement that a 5–6% indetermination appears reasonable for thermodynamic as well as for kinetic constant values. Therefore, everything considered, in our opinion a minimum value for σ_{ij} of 0.03 R (0.25 J mol^{-1} K^{-1}, accounting for a 6% indetermination) seemed a more suitable choice. In other words, on the grounds of Alper's symbolism we can set:

$$\sigma_{ij} = \mathrm{MAX}\{\varepsilon_{R \ln K_{ij}}/2,\ 0.03R\} \quad (7)$$

that is, we set σ_{ij} as half the value of the 'experimental' $R \ln K_{ij}$ error ($\varepsilon_{R \ln K_{ij}}$) if this is larger than 0.03 R, otherwise as 0.03 R. It should be noticed that this value is less than 1% of the entire range of $R \ln K_{ij}$ examined. Submitting our data to this kind of analysis, we obtained very interesting results.

All data for αCD were first treated together as belonging to a single compensation model, leading to a poor result (Θ = 523 K, $\Delta H^\circ_0 = -3.8$ kJ mol^{-1}; $\chi^2 = 268.96$, 43 entries, 199 data points, 154 degrees of freedom). On the grounds of the deviations between calculated and experimental $R \ln K_{ij}$ values, a careful inspection of the entire data set led us to the conclusion that a group of five data subsets did not fit with the model and had to be excluded, namely those for guests **3**, **16** at pH = 2.5, **18** at pH 2.5, **20** at pH 6.0 and **26**. After their elimination, results were much more satisfying: $\Theta = 479 \pm 45$ K, $\Delta H^\circ_o = -6.4 \pm 2.8$ kJ mol^{-1}; $\chi^2 = 134.28$, 38 entries, 177 data points, 137 degrees of freedom.

Corrected thermodynamic parameters obtained in this way are also reported in Table 3 and are illustrated in Figure 2. These results undoubtedly account for a real compensation effect. The slope for the $T\Delta S^\circ$ versus ΔH° correlation is $\beta = 0.62 \pm 0.06$. The calculated Θ value is comparable with those reported by Alper[18] and by Linert[17] in their works for similar cases. The relatively high uncertainty on both Θ and ΔS°_0 (which are interdependent) may be due to the fact that Θ is actually quite far from the operational temperature range.[20a]

Analysis of data for βCD similarly shows that a single

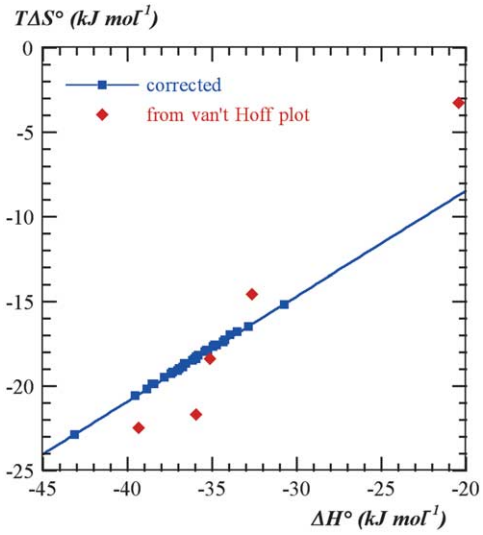


Figure 2. Corrected $T\Delta S^\circ$ versus ΔH° plot for αCD.

compensation model is absolutely unsuitable ($\Theta = -213$ K (!), $\Delta H^\circ_0 = -15.3$ kJ mol^{-1}; $\chi^2 = 428.12$, 37 entries, 173 data points, 134 degrees of freedom). So, also in this case we had to carefully inspect the data on the grounds of the deviations between calculated and experimental $R \ln K_{ij}$ values, as well as of the differences between van't Hoff and calculated thermodynamic parameters. This analysis led us to the unexpected conclusion, with very satisfactory results, that three different groups of guests may be reasonably defined:

Group A, guests **1**, **10**–**12**, **16** at pH = 6.0, **17** (both at pH = 2.5 and 6.0) **20** at pH = 11.0, **25** at pH = 11.0: $\Theta = 235 \pm 8$ K, $\Delta H^\circ_0 = -16.5 \pm 0.1$ kJ mol^{-1}; $\chi^2 = 42.12$, 13 entries, 59 data points, 44 degrees of freedom;

Group B, guests **3**, **4**, **13**, **15**, **18** at pH = 6.0, **19** (both at pH = 2.5 and 6.0), **20** at pH = 6.0, **22** (both at pH = 2.5 and

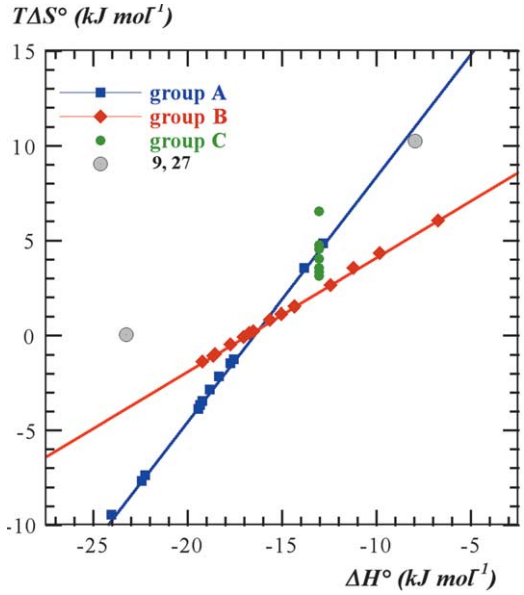


Figure 3. Corrected $T\Delta S^\circ$ versus ΔH° plot for βCD.

6.0), **25** at pH=6.0, **26**: $\Theta=494\pm38$ K, $\Delta H^{\circ}_0=-16.2\pm0.2$ kJ mol^{-1}; $\chi^2=53.48$, 15 entries, 71 data points, 54 degrees of freedom;

Group C, guests **2**, **5**–**8**, **14**. Isoenthalpic ($\Theta=0$ K), $\Delta H^{\circ}_0=-13.0\pm0.7$ kJ mol^{-1}; $\chi^2=12.80$, 7 entries, 33 data points, 24 degrees of freedom.

Guests **9** and **27** cannot be inserted in any of the preceding groups. Corrected thermodynamic parameters for βCD, also reported in Table 4, and are illustrated in Figure 3. The slopes of the $T\Delta S^{\circ}$ versus ΔH° correlations for groups A and B are $\beta_A=1.27\pm0.04$ and $\beta_B=0.60\pm0.05$ respectively.

A fair agreement is generally found between the corrected ΔH_i° or $T\Delta S_i^{\circ}$ values and those directly coming from van't Hoff plots. Differences show a standard deviation of 2.0 kJ mol^{-1}, but they are significantly large, indeed, only for guests **16** and **17** at pH=6.0 with αCD, and for guests **15** and **19** with βCD. A careful analysis of the data presented above offers us a confirmation of the two different interaction models already proposed for αCD and βCD respectively.[11] Nonetheless, data presented here provide us also with further interesting and unexpected insights.

2.5. Comparative analysis of thermodynamic data for αCD

Binding constants and $-\Delta H^{\circ}$ values with αCD for aminoalcohol guests regularly increase along the series **10**<**11**<**13**≈**14**<**15**, on increasing the hydrophobicity of the ancillary chain. The same behavior may be deduced on comparing these guests with the related aminoacid derivatives **16**–**19** (excepting **18** at pH=2.5). However, comparison between the neutral (at pH=2.5) and the ionized (at pH=6.0) forms of the latter guests is not easy to perform for several reasons. As a matter of fact, **16** and **18** go beyond the general fitting model, and further difficulties derive from the discrepancy of the calculated ΔH° values with respect to van't Hoff values for **16** and **17** at pH=6.0. Unfortunately, we do not have for the moment a satisfactory rationale for the fact that some entries have to be excluded from the general fitting model. Probably for **20** at pH=6.0 this could be related to the high solvation demand of the cationic ammonium tail group, while for **26** the problem could be the high indetermination of the association constants. Anyway, we notice that binding constants at pH=6.0 are comparable (**16**, **18**) or even higher (**17**, **19**) than at pH=2.5. Presumably, this behavior is the overall result of a balance between several contrasting factors, including the different hydrophobicity and possible conformational changes for the guest, induced on changing its protonation state. It should also be remembered that, as shown by the comparison between guests **3**, **4** and **6**, the interaction of the 'expanded hydrophobic sphere' with the ancillary chain seems to be disfavored on increasing the conformational freedom of the chain itself.

Under the latter perspective, the behavior of diamino derivatives **20**–**25** appears very interesting. For the short two-carbon-chain guests **20** and **25**, higher K and $-\Delta H^{\circ}$ values are found at pH=11.0 than at pH=6.0. This finding is in striking contrast with the usual rule that binding constants are expected to decrease on passing from a nearly neutral (pH=6.0) to an alkaline (pH=11.0) buffer,[22] due to the partial deprotonation of the host, and consequently its more difficult desolvation.[33] Also for the three-carbon-chain guest **21** the neutral form is a little more favorably included than the ionized one. Differently, longer chain derivatives **22**–**24** show higher binding constants at pH=6.0, according to the usual rule, and thus irrespective of the presence of a charged group at the end of the long ancillary chain. At both pH values, neither K nor $-\Delta H^{\circ}$ values vary monotonically along the series **20**–**24**, but pass through a maximum for **21** at pH=11.0, while at pH=6.0 the highest values are found for **21** and **22**. It is interesting to notice that the usual effects of K and $-\Delta H^{\circ}$ increase on increasing the number of methylene units, observed for different classes of linear alkyl compounds,[13] is completely overruled in this case. Furthermore, comparison between **21** and **3** shows that the replacement of the methyl group with the more hydrophilic amino or ammonium groups at the end of the ancillary chain improves the binding affinity of the guest. The binding constant for **3** may be rather compared with values found for the longest chain guest **24**.

All these considerations suggest that the dimensions of the 'expanded hydrophobic sphere' should not exceed the length of a straight three-carbon chain. The 'sphere' seems to feel unfavorably the effects of the presence of either a conformationally free or a short and charged (or even strongly solvated) ancillary chain. Strangely, a charged group just at the edge of the 'sphere' seems to have a favorable effect on its structuring (as accounted for by **21** and **22** at pH=6.0). We may hypothesize that in this case, the need to keep the charged group out of the 'sphere' has a somewhat blocking effect on the conformational freedom of the chain. On the other hand, the highly hydrophobic chains of **3**, **23** and **24** need to avoid any contact with the bulk water, and try to penetrate the 'sphere' adopting a partly folded and flexible conformation, which makes the interaction with the 'sphere' less effective.

2.6. Comparative analysis of thermodynamic data for βCD

Thermodynamic data for βCD are really interesting, because the unexpected existence of three well-defined guest groups seems to indicate that quite different situations may occur even within the same interaction model. As a matter of fact, group A collects those guests whose ancillary chain is able to give rise simultaneously to two or more hydrogen bonds, including **1** as a suitable 'anchor point', and excludes those guests whose ancillary chain either ends with a highly hydrophilic group (**20**, **22** and **25** at pH=6.0) or is so long (**22**) that the simultaneous formation of two hydrogen bonds may be entropically disfavored. On the other hand, group C collects guests whose cyclic ancillary chain has poor conformational freedom, including **2** as a suitable 'anchor point' (it should be remarked that their aniline-like N atom is unable to act as a hydrogen bond donor). All other guests are collected in group B, excluding **9** and **27**. The latter two guests go beyond the fitting models probably because their ancillary chains make them so highly hydrophobic that competition between different inclusion modes[7,11] into the βCD cavity (i.e., with the nitro group

directed towards either the primary or the secondary host rim) may occur.

Starting with group C, the occurrence of a set of isoenthalpic processes seems to suggest that the interaction between the host cavity and the ancillary chain actually involves only the two methylene groups directly linked to the aniline-like N atom, while the remaining chain is held far from the cavity and fairly exposed to the solvent shell. This hypothesis explains the lack of chiral selection for pyrrolidinol derivatives **14**. Furthermore, it agrees with the idea that an effective interaction of the ancillary chain with the host cavity may occur either if the chain is conformationally flexible (as for **3** and **4**, as compared to **6**) or if a suitable interacting group is held relatively 'near' the aniline-like N atom (as for **15** and **19**). Noticeably, inclusion entropies for the cyclic guests **5**–**9** and **14** follow the same order as their hydrophobicity. The latter finding suggests that solvent reorganization should be particularly involved in entropic contributions to the overall process, at least for these guests.

On the other hand, the behavior of the guests belonging to group A accounts for a situation in which the inclusion complex is particularly rigid, owing to the simultaneous occurrence of at least two hydrogen bonds between the guest and the host cavity or rim. Therefore, according to the low compensation temperature Θ (and the high β_A slope), variations in the entropic contributions along the group are so large that they strikingly overwhelm enthalpic variations at ordinary temperature. In fact, this leads to the uncommon situation that lower binding constants at 298.15 K are observed for those guests whose inclusion enthalpy is more favorable. By inspection of data reported in Table 4, we notice that higher $-\Delta H^\circ$ values (and lower K values) are found for **10** with respect to **12** and for **16** with respect to **17**, indicating that the presence of bulky groups on the structure of the guest causes unfavorable enthalpic contributions. These contributions may be responsible of the fairly good chiral recognitions observed for **11** and **17**, but they may also disfavor recognition if they become too heavy (as for **12**). We were not able to get a reliable estimation of the inclusion constant for **16** at pH=2.5. This may be due, in our opinion, to the fact that easier desolvation of the carboxyl group of **16** in its neutral form, rather than in its ionized form, may have the consequence of increasing the $-\Delta H^\circ$ value so much as to make the overall inclusion process too disfavored. It should also be noticed that the simultaneous formation of two (or more) hydrogen bonds requires the disruption of the guest intramolecular hydrogen bond discussed above, which is obviously an enthalpy-demanding process.

The behavior of group B guests is quite different. As Θ and β_B values account for, this time the host–guest complex does not appear to be too rigid, so enthalpic contribution variations are not completely erased by entropic variations. Inspection of thermodynamic data seems to indicate that inclusion enthalpy increases on increasing the hydrophobicity of the guest, as we can deduce on comparing aminoalcohol derivatives **13** and **15** with the corresponding aminoacid derivatives **18** and **19** in both their neutral (pH=2.5) and ionized (pH=6) forms. In agreement with this trend, inclusion enthalpy for the diamino derivative **22** decreases on passing from pH=11 to pH=6. Noticeably, also diamino derivatives **20** and **25** at pH=6 are included in this group, showing quite low $-\Delta H^\circ$ values. This confirms that their highly solvated cationic tail group is unable to interact effectively with the host cavity or rim.

2.7. Further remarks about the enthalpy–entropy compensation effect

The ability to individuate different classes of guests, unambiguously related to their structural features, is a particularly intriguing aspect of our data analysis. In fact, it allows us to achieve valuable information about the occurrence of different behaviors within the same interaction model (namely with βCD). This, in turn, can be easily related to the microscopical characteristics of the host–guest complex. Therefore, we were induced to reconsider some current ideas about the interpretation of the compensation effect.

As a matter of fact, during the last years, different attempts have been made[20b,c,e] in order to rigorously lead back compensation for a generic binding phenomenon to thermodynamics principles. Thus, theory 'demonstrated' that, at least under certain conditions, enthalpic and entropic contributions related to the reorganization of the solvent molecules, among the solvent bulk and the solvation spheres of the interacting species, 'must' exactly compensate. On the assumption that in aqueous medium, owing to the high structuring of water, solvation effects should prevail on the effects related to the so-called 'nominal process' (i.e., the neat equilibrium between solvated host, guest and complex), it has thus been inferred that solvation effects should be the actual source of the compensation effect. As a remarkable consequence, a compensation temperature Θ near to the operational temperature (and β slope value close to 1) should be always expected.[34]

Unfortunately, our data, as well as those found by other authors,[17–19] strikingly contradict these conclusions. In our opinion, such a disagreement between predictions and experimental results should indicate that, at least in our situation, solvation effects are not able to entirely conceal the 'nominal process'. In other words, our findings seem to suggest that, along a series of strictly homogeneous guests, solvation effects may be nearly constant (and thus their variations negligible). Under these conditions the occurrence of a compensation effect will actually account for information related to the 'nominal process' only. Linert[17] first warned about the opportunity to correlate only data related to series of homogeneous guests; nonetheless during the last years comprehensive correlations for very large sets of thermodynamic data have become much more popular.[13,16] However, under the perspective of our considerations, the latter choice clearly appears unsuitable. As a matter of fact, for a very large guests set the assumption of a nearly identical solvent reorganization is likely to be incorrect. Therefore, in this case the piece of information related to the actual host–guest interaction would simply be lost, being 'drowned' by solvation effects.

3. Conclusions

In conclusion, our study confirmed the occurrence different models of interaction between our hosts and guests, as previously proposed,[11] and also provided further useful insights. In particular, valuable information was deduced about the characteristics of the 'expanded hydrophobic sphere' for αCD. Furthermore, the unexpected occurrence of different compensation effects for βCD towards structurally well defined classes of guests, pointed out the mutual interplay between hydrophobic, polar and hydrogen bond interactions in determining the overall thermodynamics of the process. Nonetheless, a careful statistical data analysis is needed before proceeding with an exhaustive examination of thermodynamic parameters, because direct van't Hoff parameters are not completely reliable. Finally, some interesting critical considerations about the actual meaning of the compensation effect were presented.

4. Experimental

4.1. Materials

Commercial αCD and βCD (Fluka) were dried in a desiccator in vacuo over phosphorus pentoxide at 90 °C for at least 24 h and stored in the same apparatus at 40 °C; they were then used as such. All other commercial materials and reagents (Fluka, Aldrich) were used as such without further purification.

Compounds **1**–**9**, **16**, **19**-*S*, **26** and **27** were prepared according to literature references.[11]

Aminoalcohol derivatives **10**–**15** were prepared according to the following procedure: the appropriate aminoalcohol (10 mmol) and a slight excess of *p*-fluoro-nitrobenzene (11 mmol) were dissolved in DMSO (20 mL); after addiction of anhydrous K_2CO_3 (15 mmol), the mixture was allowed to react under gentle warming (45 °C) and stirring till completion (TLC). The mixture was then poured into water (200 mL); part of the product precipitated and was filtered off. The mother liquors were extracted with ethyl acetate; the organic extracts were dried on anhydrous Na_2SO_4 and distilled in vacuo. The crude products were joined and purified by flash chromatography on silica gel, using suitable ethyl acetate–light petrol mixtures as eluents (yield 70–85%). The purified product was finally crystallized from methanol or from ethanol–light petrol prior to use.

4.1.1. 2-*N*-(*p*-Nitro-phenyl)-amino-ethanol (10). Yellow-orange crystals, mp 108 °C. IR (nujol) ν_{max} 3439, 3271, 1599, 1549, 1502 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 3.29 (q, $J=5.6$ Hz, 2H, –NHCH_2–), 3.63 (q, $J=5.6$ Hz, 2H, –CH_2OH), 4.90 (t, $J=5.6$ Hz, 1H, –O*H*), 6.71, 8.03 (2d, $J=9.3$ Hz, 2H+2H, *p*$NO_2C_6H_4$NH–), 7.37 (t, $J=5.4$ Hz, 1H, –N*H*–). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.47; H, 5.35; N, 15.77.

4.1.2. (*R*)-2-*N*-(*p*-Nitro-phenyl)-amino-propanol (11-*R*) and (*S*)-2-*N*-(*p*-nitro-phenyl)-amino-propanol (11-*S*). Yellow crystals, mp 120–121 °C. IR (nujol) ν_{max} 3430, 3290, 1600, 1540, 1495 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 1.19 (d, $J=6.5$ Hz, 3H, –CH_3), 3.35–3.51 (m, 2H, –CH_2OH), 3.60–3.71 (m, 1H, –NH–C*H*(CH_3)–), 4.89 (1H, t, $J=5.6$ Hz, –O*H*), 6.72, 8.02 (2d, $J=9.4$ Hz, 2H+2H, *p*$NO_2C_6H_4$NH–), 7.16 (d, $J=7.9$ Hz, 1H, –N*H*–). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.98; H, 6.27; N, 14.11.

4.1.3. (*R*)-2-*N*-(*p*-Nitro-phenyl)-amino-4-methyl-pentanol (12-*R*) and (*S*)-2-*N*-(*p*-nitro-phenyl)-amino-4-methyl-pentanol (12-*S*). Yellow crystals, mp 98–99 °C. IR (nujol) ν_{max} 3467, 3304, 1603, 1545, 1506 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 0.89, 0.97 (2d, $J=6.5$ Hz, 3H+3H, –CH(CH_3)$_2$), 1.40–1.55 (m, 1H, –NH–C*H*<), 3.36–3.50, 3.54–3.66 (2m 1H+1H, –CH_2OH), 4.84 (t, $J=5.4$ Hz, 1H, –O*H*), 6.65, 8.09 (2d, $J=9.4$ Hz, 2H+2H, *p*$NO_2C_6H_4$NH–), 7.12 (d, $J=8.5$ Hz, 1H, –N*H*–). Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.28; H, 7.88; N, 11.40.

4.1.4. 2-*N*-Methyl-*N*-(*p*-nitro-phenyl)-amino-ethanol (13). Yellow crystals, mp 104–105 °C. IR (nujol) ν_{max} 3437, 1593, 1578, 1517 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 3.14 (s, 3H, >NCH_3), 3.58–3.69 (m, 4H, –CH_2–CH_2OH), 4.88 (br s, 1H, –O*H*), 6.71, 8.03 (2d, $J=9.3$ Hz, 2H+2H, *p*$NO_2C_6H_4$N<). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.37; H, 6.00; N, 14.25

4.1.5. (*R*)-*N*-(*p*-Nitro-phenyl)-3-hydroxy-pyrrolidine (14-*R*) and (*S*)-*N*-(*p*-nitro-phenyl)-3-hydroxy-pyrrolidine (14-*S*). Red-orange crystals, mp 177–178 °C. IR (nujol) ν_{max} 3468, 1599, 1556, 1518 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 1.96–2.18 (m, 2H, >NCH$_2$CH_2–), 3.25–3.45 (m, 4H, –CH_2–N–CH_2–), 4.45–4.51 (m, 1H, >C*H*–OH), 5.16 (d, $J=3.6$ Hz, 1H, –O*H*), 6.63, 8.08 (2d, $J=9.3$ Hz, 2H+2H, *p*$NO_2C_6H_4$N<). Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.82; H, 5.88; N, 13.20.

4.1.6. *N*-(*p*-Nitro-phenyl)-(*D*)-prolinol (15-*R*) and *N*-(*p*-nitro-phenyl)-(*L*)-prolinol (15-*S*). Yellow crystals, mp 114 °C. IR (nujol) ν_{max} 3456 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 1.93–2.14 (m, 4H, –CH_2CH_2–), 3.22–3.41 (m, 2H, >N–CH_2–), 3.48–3.57 (m, 2H, –CH_2–OH), 3.92–4.00 (m, 1H, >NC*H*–), 4.97 (dd, $J=6.0$, 5.6 Hz, 1H, –O*H*), 6.73, 8.09 (2d, $J=9.4$ Hz, 2H+2H, *p*$NO_2C_6H_4$N<). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.28; H, 6.59; N, 12.40.

Aminoacid derivatives **17**, **18** and **19**-*R* were prepared according to the following procedure: the appropriate aminoacid (10 mmol) was treated with an equimolar amount of 1 M tetrabutylammonium hydroxide in methanol; the solvent was removed in vacuo, and the residue was dissolved in DMSO (20 mL). A slight excess of *p*-fluoro-nitrobenzene (11 mmol) and anhydrous K_2CO_3 (11 mmol) was added and the mixture was allowed to react under gentle warming (45 °C) and stirring till completion (TLC). The mixture was then poured into cold water (200 mL) and extracted with CH_2Cl_2. The aqueous phase was collected, acidified with HCl up to pH=2.0 and extracted with ethyl acetate; the latter organic extract was dried on anhydrous Na_2SO_4, concentrated in vacuo, and the residue finally

purified by chromatography on silica gel with light petrol–ethyl acetate mixtures as eluents (yield 60–80%). In some cases it was convenient to isolate the product as the sodium salt: the product was dissolved in a minimum amount of methanol and an equimolar amount of a methanol concentrated NaOH solution was carefully added; the resulting solution was then dropped in a ten-fold volume of Et_2O, and the finely precipitated product was filtered off.

4.1.7. *N*-(*p*-Nitro-phenyl)-(*D*)-alanine sodium salt (17-*R*·Na) and *N*-(*p*-Nitro-phenyl)-(*L*)-alanine sodium salt (17-*S*·Na). Red-orange powder, 82–84 °C. IR (nujol) ν_{max} 3269, 1611, 1580, 1547, 1501 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 1.43 (d, $J=6.9$ Hz, 3H, –CH_3), 4.03–4.12 (m, 1H, –NHCH(CH_3)–), 6.69, 8.02 (2d, $J=8.8$ Hz, 2H+2H, $p$$NO_2C_6H_4$NH–), 7.42 (d, $J=7.2$ Hz, 1H, –NH–). Anal. Calcd for $C_9H_9N_2NaO_4$: C, 46.56; H, 3.91; N, 12.07. Found: C, 46.42; H, 3.88; N, 11.91.

4.1.8. *N*-(*p*-Nitro-phenyl)-sarcosine (18). Yellow solid, mp 120–140 °C (decomp.), IR (nujol) ν_{max} 1740, 1599, 1583, 1518 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 3.16 (s, 3H, >N–CH_3), 4.35 (s, 2H, –CH_2–), 6.82, 8.11 (2d, $J=9.4$ Hz, 2H+2H, $p$$NO_2C_6H_4$N<), 12.95 (br s, 1H, –COOH). Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.72; H, 4.68; N, 13.41.

4.1.9. *N*-(*p*-Nitro-phenyl)-(*D*)-proline (19-*R*). Orange-brown solid; mp >250 °C (decomp.). IR (nujol) ν_{max} 1720 cm^{-1}. ^1H NMR (250 MHz, DMSO) δ 1.96–2.40 (m, 4H, –CH_2–CH_2CH_2–CH<), 3.43–3.64 (m, 2H, >N–CH_2–), 4.47 (dd, $J=8.6$, 2.4 Hz, 1H, >CH–COOH), 6.63, 8.12 (d, $J=9.3$ Hz, 2H, $p$$NO_2C_6H_4$N<). Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.77; H, 6.45; N, 11.40.

Diamine derivatives **20–25** were prepared as follows: *p*-fluoro-nitrobenzene (10 mmol) was dissolved in DMSO (20 mL) and 5 equiv of the appropriate diamine were added. The mixture was allowed to react at 80 °C under stirring till completion (TLC). The mixture was poured into water (200 mL), acidified with HCl up to pH=4 and extracted with CH_2Cl_2. The aqueous phase was then treated with a concentrated NaOH solution up to pH=12 and extracted with ethyl acetate. The organic extracts were dried on anhydrous Na_2SO_4 and distilled in vacuo. The residue was finally purified by crystallization from methanol (yield 75–90%). Sometimes it was convenient to isolate the low-melting product as hydrochloride: the product was dissolved in a minimum amount of methanol and a slight excess of 12 M HCl was slowly added; the resulting solution was then dropped in a ten-fold amount of Et_2O and the product was finally recovered by filtration.

4.1.10. *N*-(*p*-Nitro-phenyl)-1,2-diamino-ethane (20). Yellow solid, mp 138–141 °C. IR (nujol) ν_{max} 3360, 3359, 3224, 3171, 1600, 1550, 1501 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 1.68 (br s, 2H, NH_2), 2.78 (t, $J=6.3$ Hz, 2H, –C$H_2$$NH_2$), 3.13–3.23 (m, 2H, –NHCH_2–), 6.70, 8.04 (2d, $J=9.3$ Hz, 2H+2H, $p$$NO_2C_6H_4$NH–), 7.36 (br t, 1H, –N$H$–). Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C: 52.81; H, 5.99; N, 23.31.

4.1.11. *N*-(*p*-Nitro-phenyl)-1,3-diamino-propane (21). Yellow crystals, mp 108–110 °C. IR (nujol) ν_{max} 3358, 3298, 3275, 3229, 1603, 1549, 1504 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 1.48 (br s, 2H, –NH_2), 1.68 (quint., $J=6.7$ Hz, 2H, –CH_2–CH_2–CH_2–), 2.58 (t, $J=6.7$ Hz, 2H, –CH_2–NH_2), 3.25 (br t, $J=6.7$ Hz, 2H, –NHCH_2–), 6.68, 8.05 (2d, $J=9.2$ Hz, 2H+2H, $p$$NO_2C_6$-$H_4$NH–), 7.39 (br s, 1H, –N$H$–). Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.40; H, 6.90; N, 21.29.

4.1.12. *N*-(*p*-Nitro-phenyl)-1,4-diamino-butane (22). Yellow-orange crystals, mp 100 °C. IR (nujol) ν_{max} 3352, 3294, 3216, 3167, 1600, 1550, 1500 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 1.36 (br s, 2H, –NH_2), 1.40–1.52, 1.57–1.69 (2m, 2H+2H, –CH_2–CH_2–), 2.55–2.64 (m, 2H, –C$H_2$$NH_2$), 3.15–3.22 (m, 2H, –NHCH_2–), 6.68, 8.03 (2d, $J=9.2$ Hz, 2H+2H, $p$$NO_2C_6H_4$NH–), 7.39 (bt, 1H, –N$H$–). Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.70; H, 7.49; N, 20.21.

4.1.13. *N*-(*p*-Nitro-phenyl)-1,5-diamino-pentane hydrochloride (23·HCl). Yellow-orange powder, mp 161–163 °C. IR (nujol) ν_{max} 3321, 1603, 1528, 1501 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 1.40–1.52 (m, 2H, –CH_2–CH_2–CH_2–CH_2–CH_2–), 1.57–1.73 (m, 2H+2H, –CH_2–CH_2–CH_2–CH_2–CH_2–), 2.77–2.86 (quint., $J=6.4$ Hz, 2H, –NHCH_2–), 3.14 (br t, $J=6.4$ Hz, 2H, –C$H_2$$NH_3^+$), 3.50 (br s, 3H, –N$H_3^+$), 6.71, 8.03 (2d, $J=9.3$ Hz, 2H+2H, $p$$NO_2$-$C_6H_4$NH–), 7.53 (br s, 1H, –N$H$–). Anal. Calcd for $C_{11}H_{18}ClN_3O_2$: C, 50.87; H, 6.99; N, 16.18. Found: C, 50.69; H, 7.08; N, 15.98.

4.1.14. *N*-(*p*-Nitro-phenyl)-1,6-diamino-exane (24). Yellow-orange crystals, mp 89–90 °C. IR (nujol) ν_{max} 3225, 3178 1607, 1551, 1504 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6) δ 1.36–1.45, 1.55–1.64 (2m, 6H+2H, –CH_2–CH_2–CH_2–CH_2–), 1.87 (br s, 2H, –NH_2), 2.54–2.57 (m, 2H, –C$H_2$$NH_2$), 3.15–3.22 (m, 2H, –NHCH_2–), 6.68, 8.03 (2d, $J=9.3$ Hz, 2H+2H, $p$$NO_2C_6H_4$NH–), 7.36 (br t, 1H, –N$H$–). Anal. Calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H 8.07; N 17.71. Found: C, 60.57; H, 7.94; N, 17.81.

4.1.15. *N*,*N*-Dimethyl-*N′*-(*p*-nitro-phenyl)-1,2-diamino-ethane hydrochloride (25·HCl). Yellow powder, mp 178–180 °C. IR (nujol) ν_{max} 3244, 2611, 2469, 1594, 1539, 11498 cm^{-1}. ^1H NMR (250 MHz, DMSO) δ 2.85 (s, 6H, –NH(CH_3)$_2^+$), 3.31 (2H, t, $J=6.6$ Hz, –CH_2-NH^+<), 3.62–3.70 (m, 2H, –NHCH_2–), 6.81, 8.08 (2d, $J=9.2$ Hz, 2H+2H, $p$$NO_2C_6H_4$NH–), 7.39 (br t, 1H, –N$H$–), 10.86 (br s, 1H, –N$H$($CH_3$)$_2^+$). Anal. Calcd for $C_{10}H_{16}ClN_3O_2$: C, 48.88; H, 6.56; N, 17.10. Found: C, 48.69; H, 6.67; N, 16.95.

Stock phosphate buffer solutions were prepared according to literature reports and used within a few days, after checking the actual pH value. Freshly double-distilled water was used for the preparation of the buffers, which were in turn used as solvents for the preparation of the measurement solutions.

4.2. Measurement of pK_a or pK_{BH}^+ of 17–18 and 20–25

(i) A weighed amount (ca. 40 μmol) of the sodium salts of

17 or **18** was introduced in a water-jacketed vessel thermostated at 298.1±0.3 K and was dissolved with double-distilled water (20 mL) under magnetic stirring. A stream of fine Argon bubbles was passed for 15 min through the solution, which was then titrated with a 0.1 M standardized HCl solution introduced into the vessel by a microsyringe. (ii) A weighed amount (ca. 40 μmol) of the diamine derivatives **20**, **21**, **22** or **24** was introduced in a water-jacketed vessel thermostated at 298.1±0.3 K and was dissolved with a 0.0025 M standardized HCl solution (20 mL) under magnetic stirring. A stream of fine Argon bubbles was passed for 15 min through the solution, which was then titrated with a 0.1 M standardized NaOH solution introduced into the vessel by a microsyringe. (iii) A weighed amount (about 40 μmol) of the hydrochlorides of derivatives **23** or **25** was introduced in a water-jacketed vessel thermostated at 298.1±0.3 K and was dissolved with double-distilled water (20 mL) under magnetic stirring. A stream of fine Argon bubbles was passed for 15 min through the solution, which was then titrated with a 0.1 M standardized NaOH solution introduced into the vessel by a microsyringe.

In each case, the titration experiment was performed by following the pH value variations. Data were finally processed fitting the pH versus added base curve by means of the proper equation obtained analytically.

4.3. UV–Vis spectra and binding constants measurement

Solutions for UV–Vis spectra and binding constants measurements were prepared at a fixed concentration of guest (usually about 30 mM) and at a concentration of host ranging up to 0.05 M for α-CD, or up to 0.008 M for β-CD (according to the maximum solubility of the two cyclodextrins). UV–Vis spectra were recorded at different temperatures ranging from 288.15 to 318.15 K on a Beckmann DU-7 spectrophotometer equipped with a Peltier temperature controller, able to keep the temperature within a ±0.1 K indetermination. Suitable work wavelengths for each guest were chosen after recording some 'difference spectra' by comparison of the samples without cyclodextrin and in the presence of given amounts of cyclodextrin. The absorbances of the different solutions at the work wavelength were processed by direct non-linear regression analysis.[11,35]

Acknowledgements

Financial support from the University of Palermo (funds for selected research topics) and Italian MIUR within the National Research Project 'Non-aromatic heterocycles in stereo-controlled processes' is gratefully acknowledged.

Supplementary Data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2004.07.079.

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25. Data of Table 1 also allow us to rule out the occurrence of a zwitterionic form for aminoacid derivatives **16–19** at pH 2.5. As a matter of fact, the behaviour of a hypothetical zwitterionic form should be comparable to that of a *p*-nitro-anilinium ion, for which a pK_a value of 1 or lower should be expected.
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28. The incipient formation of a 2:1 complex is easily deduced by the deviations, in the absorbance versus αCD concentration plots, from the trend expected under the hypothesis of the existence of a 1:1 complex only.
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30. More precisely, a 'compensation temperature' of 310 K is expected, see Ref. 21
31. More often the compensation relationship is written as:

$$T\Delta S^{\circ}_i = T\Delta S^{\circ}_0 + \beta\Delta H^{\circ}_i \quad (8)$$

with $\beta = T/\Theta$. By comparison of Eqs. 2 and 8 we easily obtain that $\Delta H^{\circ}_0 = -\Theta\Delta S^{\circ}_0$. Inserting Eq. 8 in Eq. 3, two further relationships can be easily deduced:

$$R \text{ Ln } K_{ij} = \Theta\Delta S^{\circ}_0/T_{ij} + (1 - \Theta/T_{ij})\Delta S^{\circ}_i \quad (9)$$

$$R \text{ Ln } K_{ij} = (1/1 - \Theta/T_{ij})\Delta H^{\circ}_i + \Delta S^{\circ}_0 \quad (10)$$

Eq. 9 is equivalent to the original Eq. 3, differently, Eq. 10 allows us to obtain directly ΔH°_i rather than ΔS°_i values. The actual use of either relationship may somewhat appear as a matter of taste. We tried to use both, obtaining the same results; however in our opinion Eq. 10 is the most convenient to handle.
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33. A similar effect could also be caused by partial protonation in the presence of an acidic buffer. This fact should be taken into account, when discussing the behaviour of aminoacid guests **16–19**.
34. It is strange to observe that in some occasions (see Ref. 20b) this thesis has been supported with experimental data for which there is the concrete danger of dealing with a pseudo-compensation effect. In fact, it should be considered that, under these circumstances, a real compensation would be indistinguishable from a false one.
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Tetrahedron 60 (2004) 9113–9119

Easy, inexpensive and effective oxidative iodination of deactivated arenes in sulfuric acid

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Received 2 April 2004; revised 5 July 2004; accepted 28 July 2004

Available online 28 August 2004

Abstract—Two 'model' deactivated arenes, benzoic acid and nitrobenzene, were effectively monoiodinated within 1 h at 25–30 °C, with strongly electrophilic I^+ reagents, prior prepared from diiodine and various oxidants (CrO_3, $KMnO_4$, active MnO_2, HIO_3, $NaIO_3$, or $NaIO_4$) in 90% (v/v) concd sulfuric acid (ca. 75 mol% H_2SO_4). Next, an $I_2/NaIO_3$/90% (v/v) concd H_2SO_4 exemplary system was used to effectively mono- or diiodinate a number of deactivated arenes. All former papers dealing with the direct iodination of deactivated arenes are briefly reviewed.

1. Introduction

Aromatic iodides are widely used in organic synthesis; hence many different synthetic methods (direct and indirect), or their improvements, have been reported for their effective preparation.[1] Moreover, they are able to form a large variety of stable aromatic iodine(III or V) compounds, which have found increasing applications in modern organic synthesis.[2] Our two latest reviews[3,4] relate and explain a variety of aromatic iodination methods suitable for both activated and deactivated aromatics, devised in our laboratory since 1990, as well as our novel methods for preparing several classes of aromatic hypervalent iodine compounds, easily attainable from aromatic iodides.

There is a large number of synthetic methods for the direct iodination of activated aromatics, but those suitable for the deactivated ones are less numerous. Initially, diiodine in hot 50–65% oleum, in which the electrophile is probably I_2^+, has been used to polyiodinate strongly deactivated molecules, but it is difficult to use such systems for partial iodination under controlled conditions.[1] Masson[5] remarked that I_3^+ in concentrated sulfuric acid would monoiodinate nitrobenzene and triiodinate chlorobenzene, but his observations were not exploited. Barker and Waters[6] showed that diiodine and silver sulfate in ca. 90% concd sulfuric acid (in which the iodinating agent is believed to be AgI_2^+) monoiodinated e.g. nitrobenzene in 55% yield at 100 °C and within ca. 1 h. Arotsky and co-workers[7] used diiodine in 20% oleum for the iodination of a range of aromatic nitrocompounds. The iodination of nitrobenzene for 19.5 h at room temperature gave 3-iodonitrobenzene in 52% crude yield; at 100 °C with 3 equiv of iodinating agent, 1,3,5-triiodobenzene was obtained in 26% crude yield, similar reaction at 180 °C gave hexaiodobenzene in only 3% crude yield—these were the first examples of iodo-denitration. They also monoiodinated 1,3-dinitrobenzene in 89% crude yield, and diiodinated 1,2-dinitrobenzene in 57% crude yield, at 170–180 °C during 105 min, but they failed to likewise iodinate 1,4-dinitrobenzene. Olah and co-workers[8] iodinated several deactivated aromatics with *N*-iodosuccinimide (NIS) in trifluoromethanesulfonic acid (triflic acid); it is believed that the active agent is 'superelectrophilic' protosolvated iodine(I) triflate, which is generated in situ. For example, at room temperature and within 2 h, 3-iodonitrobenzene was formed from nitrobenzene in 86% yield. Kobayashi and co-workers[9] reacted various aromatics with diiodine in the presence of silver triflate; it gave e.g. 3-iodonitrobenzene in 45% yield based on the silver salt, when an excess of nitrobenzene was reacted at 150 °C for 1.5 h. Chambers and co-workers[10] passed F_2/N_2 mixtures through the systems containing diiodine and various deactivated arenes suspended in concd H_2SO_4 mixed with various inert co-solvents, at room temperature. In this way, e.g. nitrobenzene afforded 3-iodonitrobenzene in 58–82% crude yields, while 1,3- and 1,4-dinitrobenzenes were unaffected; the details of the said process are still uncertain. Chaikovski, Filimonov and co-workers[11–13] reported on the

Keywords: Iodoarenes; Deactivated arenes; Iodine; Direct oxidative iodination; Oxidation.
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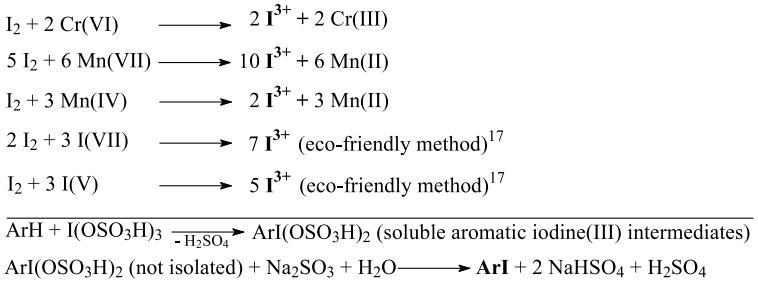
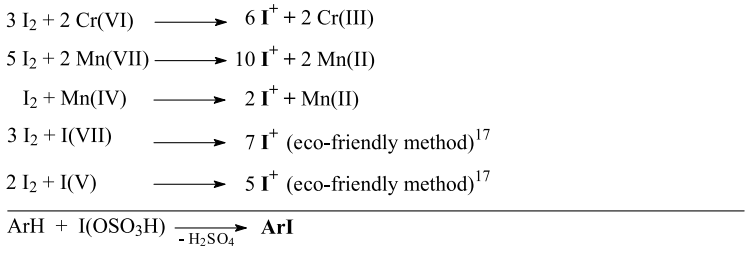
doi:10.1016/j.tet.2004.07.095



Scheme 1.



Scheme 2.

effective iodination of numerous deactivated arenes with some very active I^+ species. The superelectrophilic iodinating reagent (reagent 'I^+') was primarily prepared[11] in the reaction of iodine(I) chloride with silver sulfate in 90% (v/v) concd H_2SO_4; mononitroarenes were easily iodinated at 0–20 °C within 15–150 min, while dinitroarenes required heating to 100–170 °C and longer reaction times. Along with the iodination, a side chlorination process also took place to a certain extent. Later, the same Russian chemists[12] effectively iodinated various deactivated arenes, also in 90% (v/v) concd H_2SO_4, with a new powerful reagent, 2,4,6,8-tetraiodo-2,4,6,8-tetraazabicyclo[3.3.0]-octane-3,7-dione (2,4,6,8-tetraiodoglycoluril, TIG) at 0 °C and within 30–90 min, to obtain 40–82% yields of the purified mono- or diiodinated products. Finally,[13] they monoiodinated only nitrobenzene (in 79% yield) with NIS in 90% (v/v) concd H_2SO_4, at room temperature for 20 min. It is known,[8,14] that *N*-iodoimides can be a useful source of a positive iodine, I^+, when their reactions proceed in strongly polar and/or acidic media. Lulinski et al.[15] monoiodinated several deactivated arenes, however not nitrobenzene, with sodium periodate used alone as the iodinating reagent. They failed to isolate the expected (and still hypothetical) periodyl intermediates, $ArIO_3$. After completing the reactions, carried out in the $NaIO_4$/AcOH/Ac_2O/concd H_2SO_4 system, they were quenched with aq Na_2SO_3 solutions to give the expected iodoarenes in 45–78% yields.

Previously, we reported (see Ref. 3, pp 1332–1345) on the oxidative iodination of a number of deactivated arenes, including nitrobenzene, always in anhydrous solvent mixtures, AcOH/Ac_2O/concd H_2SO_4 (a catalyst and reagent; other inorganic acids were less effective), by using the following oxidants for this purpose: CrO_3, $KMnO_4$, active MnO_2, $NaIO_3$, $NaIO_4$, and quite recently a urea-hydrogen peroxide adduct (UHP).[16] In order to generate in the iodinating mixtures some strongly electrophilic I^{3+} intermediates to afford the effective iodination of some halobenzenes and deactivated arenes, the appropriate combinations of the reactants were used (see Scheme 1).[†] The reactions took place in warm iodinating mixtures containing iodine(III) sulfate or more reactive iodine(III) hydrogensulfate.[3] The cooled reaction mixtures were quenched with excess aq Na_2SO_3 solutions to destroy unreacted diiodine and any oxidized species (Scheme 1). After simple workups (see experimental sections in our former papers),[3,16] the purified iodoarenes were obtained in 18–95% yields. On the other hand, our oxidative iodinations of benzene, some halobenzenes and activated arenes were the most effective by generating in anhydrous solvent mixtures, AcOH/Ac_2O/concd H_2SO_4, some less electrophilic I^+ intermediates. The appropriate combinations of the reactants were used (see Scheme 2).[18] The reactions took place in warm iodinating mixtures containing iodine(I) sulfate or more reactive iodine(I) hydrogensulfate[3] (Scheme 2). The reactions were quenched with excess aq Na_2SO_3 solutions. After simple workups, the purified iodoarenes were obtained in 22–92% yields.

Taking into account all the aforesaid literature reports, we have tried to achieve the effective oxidative iodination of deactivated arenes, including nitrobenzene, with some strongly electrophilic I^+ intermediates, simply generated from diiodine and various oxidants according to Scheme 2, but in 90% (v/v) concd H_2SO_4. In our opinion, water present there in a deficit, ca. 25 mol% H_2O, acts as a stronger base, considerably increasing the general polarity of so prepared

[†] See the following review in which such stable, though strongly hygroscopic, compounds as $I_2(SO_4)_3$, $I(OSO_3H)_3$, $ArISO_4$, and $ArI(OSO_3H)_2$ are discussed and referred to the literature: Kasumov, T. M.; Koz'min, A. S.; Zefirov, N. S. *Usp. Khim.* **1997**, *66*, 936–952; *Russ. Chem. Rev.* **1997**, *66*, 843–857.

iodinating systems: H_2O (a base) + H_2SO_4 (in excess) → $(H_3O)^+(HSO_4)^-$. This favors the full ionization of the iodinating intermediates, $IOSO_3H$, to form more reactive solvated species, I^+ and HSO_4^-. We have expected that such iodinating solutions would react as the superelectrophilic iodinating reagents, I^+, capable to iodinate various deactivated arenes. Our expectations have indeed been fulfilled to a great extent (vide infra).

2. Results and discussion

At first, we carried out the preliminary oxidative iodination reactions as follows: finely powdered diiodine was suspended in 90% (v/v) concd H_2SO_4, followed by an oxidant added portionwise with stirring and keeping the temperature below 30 °C; altogether, seven various inorganic oxidants (Table 1) were checked out by us experimentally. The stirring was continued for 30 min at 25–30 °C to afford dark brown solutions having very strong iodinating properties—which remained virtually unchanged, even after their storing for several days in the dark at room temperature. We have found that for the most effective monoiodination of benzoic acid (a 'model' moderately deactivated arene), the I^+ intermediates generated in the previously prepared iodinating solution should be used in ca. 10% excess, whereas for the most effective monoiodination of nitrobenzene (a 'model' strongly deactivated arene) they should be used in ca. 100% excess; see Table 1 for the definite amounts of diiodine and particular oxidants, as well as for the volumes of 90% (v/v) concd H_2SO_4, used by us in each of the preliminary iodination reactions. Next, using a 'direct' method of aromatic iodination, either benzoic acid or nitrobenzene (10 mmol; 0% excess) was added to the appropriate iodinating solution, and the stirring was continued for 1 h at 25–30 °C. The final reaction mixtures were poured into ice-water, the crude products were collected by filtration, washed with cold water, air-dried in the dark, and recrystallized from appropriate organic solvents (Table 1). These experiments confirmed our former expectations (vide supra). We extended the said 'direct' iodination method onto a number of deactivated arenes; for more details see the experimental section, and the yields given in Table 2 (in brackets).

Table 1. Monoiodination of benzoic acid or nitrobenzene: reaction conditions and final yields of pure products, using the 'direct' method of aromatic iodination

90% concd H_2SO_4 (mL)	Diiodine (g; mmol)	Oxidant (g; mmol)	Yield[a] (%)
(a) Oxidative iodination of PhCOOH (1.22 g; 10 mmol; 0% excess) to give pure 3-iodobenzoic acid, mp 187–188 °C (from CCl_4)[b]; lit.[12] mp 185–186 °C (from 50% aq *i*-PrOH)			
37.5	1.40; 5.5	CrO_3: 0.37; 3.7	78
37.5	1.40; 5.5	$KMnO_4$: 0.35; 2.2	80
37.5	1.40; 5.5	MnO_2 (85%): 0.56; 5.5	68
37.5	1.40; 5.5	MnO_2 (90%): 0.53; 5.5	85
30.0	1.12; 4.4	HIO_3: 0.39; 2.2	80
30.0	1.12; 4.4	$NaIO_3$: 0.44; 2.2	80
32.0	1.20; 4.7	$NaIO_4$: 0.34; 1.6	80
(b) Oxidative iodination of $PhNO_2$ (1.23 g; 10 mmol; 0% excess) to give pure 3-iodonitrobenzene, mp 37–38 °C (from petroleum ether); lit.[13] mp 35–36 °C (from EtOH)			
68.0	2.54; 10.0	CrO_3: 0.67; 6.7	77
68.0	2.54; 10.0	$KMnO_4$: 0.63; 4.0	61
68.0	2.54; 10.0	MnO_2 (85%): 1.0; 10.0	69
68.0	2.54; 10.0	MnO_2 (90%): 0.96; 10.0	76
55.0	2.03; 8.0	HIO_3: 0.70; 4.0	75
55.0	2.03; 8.0	$NaIO_3$: 0.79; 4.0	85
58.0	2.18; 8.6	$NaIO_4$: 0.61; 2.8	70

[a] The given yields were optimized.

[b] From our repeated crystallization experiments with crude 3-IC_6H_4-COOH we have established that CCl_4 was a most effective and selective solvent as compared with 50% aq *i*-PrOH[12] or $CHCl_3$; the respective crystallization losses were as follows: 17, 25, and 22%, and the product recrystallized once from CCl_4 showed a higher purity (mp, TLC).

Furthermore we selected, just for example, only one of the above iodinating systems, viz. $I_2/NaIO_3$/90% (v/v) concd H_2SO_4 (Table 1), to effectively mono- or diiodinate a number of more or less deactivated arenes (Table 2). However, we have established experimentally that more uniform crude products were obtained from mildly deactivated arenes, forming readily the hardly separable mixtures of mono- and diiodinated products, when an 'inverse' method of aromatic iodination was applied; see Section 4.2.6. in the experimental section. Next, this method was consequently used for all substrates shown in Table 2. In this case, the appropriate iodinating solutions were very slowly added dropwise to the stirred suspensions of iodinated arenes in given volumes of 90% (v/v) concd H_2SO_4. After completing the reactions within 1 h, mostly at 25–30 °C, the reaction mixtures were poured into ice-water, and the precipitated monoiodinated products were worked up as above. When some arenes were purposely diiodinated (Table 2), we used only half of their amounts, i.e. 5 mmol, with respect to those used for their monoiodination, i.e. 10 mmol, and the diiodination reaction times were prolonged to 2 h. Generally, all the iodinated arenes, taken in strictly stoichiometric amounts (0% excess), were always reacted with the iodinating solutions used in the excesses: 10, 50, or 100%. For more details see the Section 4.

It is possible to put forward some plausible reaction paths for the oxidative iodination of deactivated arenes with the applied $I_2/NaIO_3$/90% (v/v) concd H_2SO_4 liquid system, as well as to derive the resulting stoichiometries (Scheme 3). For the other iodinating systems shown in Table 1, a similar reasoning is applicable; see Ref. 3, pp 1332–1345.

In Scheme 3 we suggest that the apparently less reactive I_2SO_4 intermediates (in our opinion, $2I^+$ and SO_4^{2-} are there more tightly bound together that I^+ and HSO_4^- in iodine(I) hydrogensulfate)[3] would react with excess H_2SO_4 to give the more reactive $IOSO_3H$ intermediates, which are fully ionized in very strongly polar iodinating solutions. This is why all the iodinating solutions applied in this work do represent, in fact, the superelectrophilic iodinating reagents, I^+, capable to iodinate various deactivated arenes, including nitrobenzene, under relatively mild conditions, in good yields, and within short times; see our results shown in Tables 1 and 2, as well as the reaction conditions reported in the experimental section.

Table 2. Final yields and melting points (uncorrected) of pure monoiodinated or diiodinated products, with using the $I_2/NaIO_3$/90% (v/v) concd H_2SO_4 iodinating systems. These results were obtained by the 'inverse' method of aromatic iodination. For comparison, also the yields obtained by the 'direct' iodination method are given below (in brackets), while the corresponding melting points were practically the same

Substrate	Product	Yield[a] (%)	Mp (°C)/S[b]	Lit. mp (°C)
(a) Oxidative monoiodination of some deactivated arenas				
$C_6H_5NO_2$[c]	$3\text{-}IC_6H_4NO_2$	83 (85)	37–38/P	35–36[13]
$4\text{-}CH_3C_6H_4NO_2$	$3\text{-I-}4\text{-}CH_3C_6H_3NO_2$	74	55–56/E	54–56[11a]
$2\text{-}CH_3OC_6H_4NO_2$	$5\text{-I-}2\text{-}CH_3OC_6H_3NO_2$	76	97–99/E	97[20]
$4\text{-}CH_3OC_6H_4NO_2$	$3\text{-I-}4\text{-}CH_3OC_6H_3NO_2$	84	93–96/E	97[20]
$4\text{-}IC_6H_4NO_2$[d]	$3,4\text{-}I_2C_6H_3NO_2$	56 (58)	108–110/E	109–111[11b]
C_6H_5COOH	$3\text{-}IC_6H_4COOH$	78 (80)	187–188/C	185–186[12]
$4\text{-}ClC_6H_4COOH$	$4\text{-Cl-}3\text{-}IC_6H_3COOH$	82 (83)	215–216/B	216–217[20]
$4\text{-}IC_6H_4COOH$	$3,4\text{-}I_2C_6H_3COOH$	46 (46)	265–266/E	258–259[20]
$4\text{-}CH_3C_6H_4COOH$	$3\text{-I-}4\text{-}CH_3C_6H_3COOH$	77[e]	208–210/E	210–212[20]
$4\text{-}CH_3OC_6H_4COOH$	$3\text{-I-}4\text{-}CH_3OC_6H_3COOH$	80[e]	242–243/E	233–234[20]
$C_6H_5COOCH_3$	$3\text{-}IC_6H_4COOCH_3$	76 (78)	50–51/P	50–52[17]
$4\text{-}CH_3OC_6H_4COOCH_3$	$3\text{-I-}4\text{-}CH_3OC_6H_3COOCH_3$	67	97–98/E	95–97[20]
$C_6H_5CONH_2$[d]	$3\text{-}IC_6H_4CONH_2$	74 (74)	185–187/E	186.5[20]
$C_6H_5SO_2NH_2$[d]	$3\text{-}IC_6H_4SO_2NH_2$	77 (79)	151–152/W	152–153[21]
C_6H_5CHO[d]	$3\text{-}IC_6H_4CHO$	57 (56)	53–54/E	54–56[12]
$4\text{-}ClC_6H_4CHO$	$4\text{-Cl-}3\text{-}IC_6H_3CHO$	73 (73)	114–116/E	117[20]
C_6H_5I	$1,4\text{-}I_2C_6H_4$	50[e]	125–126/E	128–129[12]
(b) Oxidative diiodination of some deactivated arenes				
$4\text{-}CH_3C_6H_4NO_2$[d]	$3,5\text{-}I_2\text{-}4\text{-}CH_3C_6H_2NO_2$	77 (77)	111–113/E	115–116[11b]
$4\text{-}CH_3OC_6H_4NO_2$[d]	$3,5\text{-}I_2\text{-}4\text{-}CH_3OC_6H_2NO_2$	78 (78)	130–132/E	133–135[20]
$4\text{-}ClC_6H_4COOH$[d]	$4\text{-Cl-}3,5\text{-}I_2C_6H_2COOH$	73 (74)	288–290/E	303–304[22]
$4\text{-}IC_6H_4COOH$[d]	$3,4,5\text{-}I_3C_6H_2COOH$	54[f] (57)	300–302/E	289–290[20]
$4\text{-}CH_3C_6H_4COOH$[d]	$3,5\text{-}I_2\text{-}4\text{-}CH_3C_6H_2COOH$	68 (71)	330–332/D	334–335[23]
$4\text{-}CH_3OC_6H_4COOH$[d]	$3,5\text{-}I_2\text{-}4\text{-}CH_3OC_6H_2COOH$	66 (66)	253–255/E	255–256[20]
$C_6H_5COC_6H_5$	$3\text{-}IC_6H_4COC_6H_4I\text{-}3'$	33[e]	151–153/A	152–153[20]
$C_6H_5SO_2C_6H_5$[d]	$3\text{-}IC_6H_4SO_2C_6H_4I\text{-}3'$	61 (61)	122–123/E	122–123[24]
$C_6H_5COCOC_6H_5$	$3\text{-}IC_6H_4COCOC_6H_4I\text{-}3'$	54	124–126/E	127–128[11a]

[a] The given yields were optimized. Satisfactory microanalyses obtained for the purified products: I±0.3%; their purities and homogeneities were checked by TLC and ^1H NMR spectra (not shown here).[19]

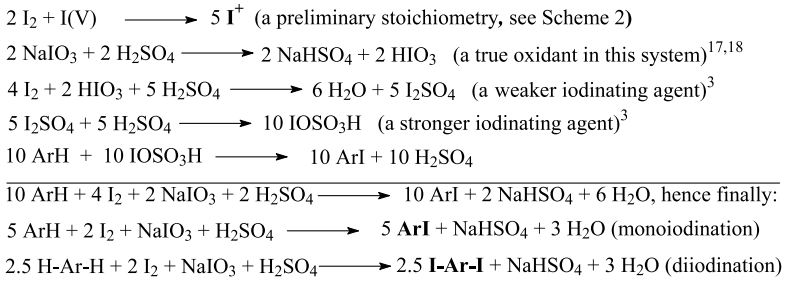
[b] Solvent (S) used for crystallization: A—Me_2CO; B—aq AcOH; C—CCl_4; D—extracted with boiling EtOH and hot-filtered; E—EtOH; P—petroleum ether, bp 35–60 °C; W—water.

[c] Nitrobenzene was monoiodinated with the previously prepared iodinating solution containing the I^+ intermediates in ca. 100% excess.

[d] The respective deactivated arenes were iodinated with the previously prepared iodinating solutions containing the I^+ intermediates in ca. 50% excess. Except of nitrobenzene, the remaining ones were iodinated with the previously prepared iodinating solutions containing the I^+ intermediates in ca. 10% excess.

[e] The respective iodination reactions were carried out at 0–5 °C, whereas the remaining ones were carried out at 25–30 °C.

[f] When we increased the preparative scale 10-fold, the same purified product was obtained in 55% yield, mp 302–303 °C. It can be used as the substrate for preparing X-ray contrasts.



Scheme 3.

3. Conclusions

The good yields, mild and easy experimental conditions, and low prices of the commercial inorganic reagents used for preparing the fairly stable iodinating solutions are attractive features of this novel oxidative iodination method. In our work, we excluded the use of costly *N*-iodoimides, silver salts, and triflic acid, formerly applied (vide supra) for the effective iodination of deactivated arenes. We also excluded the hazardous uses of F_2/N_2 gaseous mixtures, fuming sulfuric acid (oleum), or toxic iodine(I) chloride. Organic solvents are used only for purification of the crude iodinated products. The strongly acidic wastes left after some of the iodination reactions, i.e. after those with using HIO_3, $NaIO_3$ or $NaIO_4$ as the oxidants, can be neutralized, diluted with water, and disposed of without problem—hence, such iodination reactions are environmentally benign,[17] and in our opinion can be safely scaled up.

4. Experimental

4.1. General

The structures of the purified mono- or diiodinated products (their purities and homogeneities were prior checked with TLC), all reported in the literature, were supported by their melting points (uncorrected) compared with the literature data (Tables 1 and 2). The structures were also supported by correct elemental analyses (%I) and ^{1}H NMR solution spectra (not shown here) compared with the respective spectra of authentic samples.[19] Elemental analyses were carried out at the Institute of Organic Chemistry, The Polish Academy of Sciences, Warsaw. ^{1}H NMR spectra were run at the Department of Physical Chemistry, Medical University of Warsaw. The commercial reagents and solvents (Aldrich) were used without further purification. Molecular iodine should be finely powdered in order to facilitate its dissolution in the reaction mixtures.

4.2. General procedures, with using the $I_2/NaIO_3$/90% (v/v) concd H_2SO_4 system

4.2.1. Preparations of three various iodinating solutions. Definite amounts of finely powdered diiodine and next $NaIO_3$ were suspended in given volumes of 90% (v/v) concd H_2SO_4 (Table 1). The mixtures were stirred for 30 min at 25–30 °C to give the dark brown iodinating solutions, containing either ca. 11 mmol (10% excess) of the I^+ intermediates [used for the iodination of benzoic acid and several substrates shown in Table 2] or ca. 20 mmol (100% excess) of the I^+ intermediates [used only for the monoiodination of nitrobenzene, Tables 1 and 2]. For the mono- or diiodination of the remaining substrates (Table 2), the iodinating solution containing ca. 15 mmol (50% excess) of the I^+ intermediates was prepared, as above, from diiodine (1.52 g, 6.0 mmol) and $NaIO_3$ (0.60 g, 3.0 mmol) suspended in 90% (v/v) concd H_2SO_4 (41 mL).

4.2.2. 'Direct' monoiodination of benzoic acid; cf. Table 1. Benzoic acid (1.22 g, 10 mmol, 0% excess) was added to the iodinating solution containing the I^+ intermediates in ca. 10% excess, and the stirring was continued for 1 h at 25–30 °C. The final reaction mixture was poured, with stirring, into ice-water (300 g). The crude solid product was collected by filtration, washed with cold water until the filtrates were neutral, air-dried in the dark, and recrystallized from CCl_4 (60 mL) to give pure 3-iodobenzoic acid in 80% yield; 1.98 g.

Quite similarly, also 4-chlorobenzoic acid, 4-iodobenzoic acid, methyl benzoate, and 4-chlorobenzaldehyde (10 mmol, 0% excess) were monoiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (in brackets).

4.2.3. 'Direct' monoiodination of benzamide. Benzamide (1.21 g, 10 mmol; 0% excess) was added to the iodinating solution containing the I^+ intermediates in ca. 50% excess, and the stirring was continued for 1 h at 25–30 °C. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from ethanol (15 mL) to give pure 3-iodobenzamide in 74% yield; 1.83 g.

Quite similarly, also benzenesulfonamide, benzaldehyde, and 4-iodonitrobenzene (10 mmol, 0% excess) were monoiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (in brackets).

4.2.4. 'Direct' monoiodination of nitrobenzene; cf. Table 1. Nitrobenzene (1.23 g, 10 mmol; 0% excess) was added to the iodinating solution containing the I^+ intermediates in ca. 100% excess, and the stirring was continued for 1 h at 25–30 °C. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from petroleum ether, bp 35–60 °C (30 mL) to give pure 3-iodonitrobenzene in 85% yield; 2.12 g.

4.2.5. 'Direct' diiodination of anisic acid. Anisic acid (0.76 g, 5 mmol, 0% excess) was added to the iodinating solution containing the I^+ intermediates in ca. 50% excess, and the stirring was continued for 2 h at 25–30 °C. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from ethanol (16 mL) to give pure 3,5-diiodoanisic acid in 66% yield; 1.34 g.

Quite similarly, also 4-nitrotoluene, 4-nitroanisole, 4-chlorobenzoic acid, 4-iodobenzoic acid, 4-toluic acid, and diphenyl sulfone (5 mmol, 0% excess) were diiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (in brackets).

4.2.6. 'Inverse' monoiodination of benzoic acid. Benzoic acid (1.22 g, 10 mmol, 0% excess) was suspended in 90% (v/v) concd H_2SO_4 (20 mL) at 25–30 °C. While keeping the same temperature, we slowly added dropwise, with stirring and within 45 min, the iodinating solution containing the I^+ intermediates in ca. 10% excess, and the stirring was continued at 25–30 °C for a further 15 min. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from CCl_4 (60 mL) to give pure 3-iodobenzoic acid in 78% yield; 1.94 g.

Quite similarly, also 4-nitrotoluene, 2- and 4-nitroanisole, 4-chlorobenzoic acid, 4-iodobenzoic acid, methyl benzoate, methyl anisate, and 4-chlorobenzaldehyde (10 mmol, 0% excess) were monoiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (without brackets).

Note. 4-Toluic acid, anisic acid, and iodobenzene (10 mmol, 0% excess) were similarly monoiodinated, but their iodination reactions were carried out at 0–5 °C to give more uniform crude products as compared with those obtained at 25–30 °C (TLC).

Some mildly deactivated arenes, viz. 4-nitrotoluene, 2- and

4-nitroanisole, 4-toluic acid, anisic acid, and its methyl ester, and iodobenzene were effectively monoiodinated only by the 'inverse' method (Table 2). When the same substrates were monoiodinated by the 'direct' method, then the corresponding crude products were heavily contaminated by undesirable diiodinated side products (TLC); though their repeated recrystallizations gave the same pure monoiodinated products (mp, %I), but the inavoidable crystallization losses lowered the yields by ca. 20–50%.

4.2.7. 'Inverse' monoiodination of benzamide. Benzamide (1.21 g, 10 mmol, 0% excess) was suspended in 90% (v/v) concd H_2SO_4 (20 mL) at 25–30 °C. While keeping the same temperature, we slowly added dropwise, with stirring and within 45 min, the iodinating solution containing the I^+ intermediates in ca. 50% excess, and the stirring was continued at 25–30 °C for a further 15 min. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from ethanol (15 mL) to give pure 3-iodobenzamide in 74% yield; 1.83 g.

Quite similarly, also 4-iodonitrobenzene, benzenesulfonamide, and benzaldehyde (10 mmol, 0% excess) were monoiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (without brackets).

4.2.8. 'Inverse' monoiodination of nitrobenzene. The best result was attained as follows: nitrobenzene (1.23 g, 10 mmol, 0% excess) was suspended in 90% (v/v) concd H_2SO_4 (20 mL) at 25–30 °C. While keeping the same temperature, the iodinating solution containing the I^+ intermediates in ca. 100% excess was added at once, in one portion, and the stirring was continued at 25–30 °C for 1 h. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from petroleum ether, bp 35–50 °C (30 mL) to give pure 3-iodonitrobenzene in 83% yield; 2.07 g.

4.2.9. 'Inverse' diiodination of benzil. Benzil, diphenylethanedione (1.05 g, 5 mmol, 0% excess) was suspended in 90% (v/v) concd H_2SO_4 (10 mL) at 25–30 °C. While keeping the same temperature, the iodinating solution containing the I^+ intermediates in ca. 10% excess was slowly added dropwise, with stirring and within 45 min. The stirring was continued at 25–30 °C for a further 75 min. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from ethanol (15 mL) to give pure 3,3′-diiodobenzil in 54% yield; 1.25 g. cf. Ref. 25.[‡]

Note. Benzophenone (0.91 g, 5 mmol, 0% excess) was similarly diiodinated, but its iodination reaction was carried out at 0–5 °C to give a fairly uniform crude product, which was recrystallized from acetone to give pure 3,3′-diiodobenzophenone in only 33% yield; 0.72 g. At 25–30 °C, the final crude product was notably contaminated with hardly separable isomeric admixtures, and with a trace of a triiodinated benzophenone (TLC, %I).

4.2.10. 'Inverse' diiodination of 4-nitrotoluene. 4-nitrotoluene (0.68 g, 5 mmol, 0% excess) was suspended in 90% (v/v) concd H_2SO_4 (10 mL) at 25–30 °C. While keeping the same temperature, the iodinating solution containing the I^+ intermediates in ca. 50% excess was slowly added dropwise, with stirring and within 45 min. The stirring was continued at 25–30 °C for a further 75 min. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from ethanol (27 mL) to give pure 2,6-diiodo-4-nitrotoluene in 77% yield; 1.50 g.

Quite similarly, also 4-nitroanisole, 4-chlorobenzoic acid, 4-iodobenzoic acid, 4-toluic acid, anisic acid, and diphenyl sulfone (5 mmol, 0% excess) were diiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (without brackets).

These results were partly presented at the XLVIth Annual Meeting of the Polish Chemical Society, Lublin, 15–18 September, 2003.

[‡] The diiodination of benzil, at 90 °C for 2 h, with an $I_2/Ag_2SO_4/90\%$ H_2SO_4 system, gave the crude product (84%) containing 85.1% 3,3′-, 14.7% 2,2′-, and only 0.2% 4,4′-diiodobenzil. It shows that on increasing the iodination temperatures, the undesirable admixtures of isomeric side products are enlarged.

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Gas-phase thermolysis of thieno[3,2-*e*][1,2,4]triazines. Interesting routes towards heterocyclic ring systems

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Received 19 January 2004; revised 5 July 2004; accepted 28 July 2004

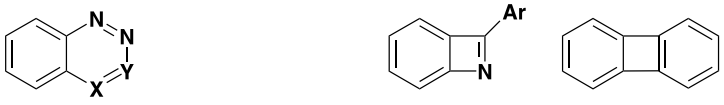
Available online 28 August 2004

Abstract—Gas-phase thermolysis of thieno[3,2-*e*][1,2,4]triazines gave benzonitrile, isothiazole, pyrimidine, [1]benzothieno[2,3-*d*]-pyrimidine and thieno[3,2-*d*]thiazole derivatives. A mechanism of these pyrolytic transformation was proposed. Two new and efficient syntheses of the starting thieno[3,2-*e*][1,2,4]triazines were reported.

1. Introduction

Flash vacuum pyrolysis (FVP) of cinnolines[1,2] **A**, 1,2,4-benzotriazines[3] **B** and 1,2,3-benzotriazines[3] **C** has been studied and was shown to give a direct and easy access to many interesting compounds some of which are otherwise difficult to obtain. The primary step in the pyrolysis of these compounds involves mainly N_2 elimination, yielding the corresponding diradical intermediates which subsequently combines intramolecularly into the corresponding condensed cyclobutenes or benzazetes, or undergo further rearrangement or fragmentation before yielding the final products. Thus, flash vacuum pyrolysis of cinnoline derivatives **A** has been shown to lead to initial loss of nitrogen to give diradicals which then cyclize to give biphenylene derivatives when X, Y are condensed benzo derivatives. Recently, we have also found that FVP of 3-acylcinnolines (X=CH and Y=CCOAr) initially gave diradicals which undergo several rearrangements yielding mainly polycondensed aromatic and heteroaromatic compounds.[1] Rees, Storr and co-workers have thoroughly studied the flash vacuum pyrolysis of 1,2,4-benzotriazines **B** and 1,2,3-benzotriazines **C**, as possible routes to benzazetes.[3,4] With the exception of 4-aryl-1,2,3-benzotriazine **C** (R=Ph, *p*-$MeOC_6H_4$) which could be converted pyrolytically into 2-aryl-benzazetes **D**, other 1,2,3-benzotriazine and 1,2,4-benzotriazine derivatives initially lose N_2 followed by RCN (i.e. the heterocyclic ring) and gave biphenylene **E** (Scheme 1).[3]

In the present investigation we studied the pyrolysis products of thieno[3,2-*e*][1,2,4]triazines **1a–d** in order to study the pyrolytic behavior of this ring system in comparison with their benzo analogs **B** as well as their synthetic potentialities.



A X = Y = C-R (Cinnolines)
B X = N, Y = CR (Benzo-1,2,4-triazines)
C X = CR, Y = N (Benzo-1,2,3-triazines)

D **E**

Scheme 1.

Keywords: FVP; Triazines; Heterocycles.
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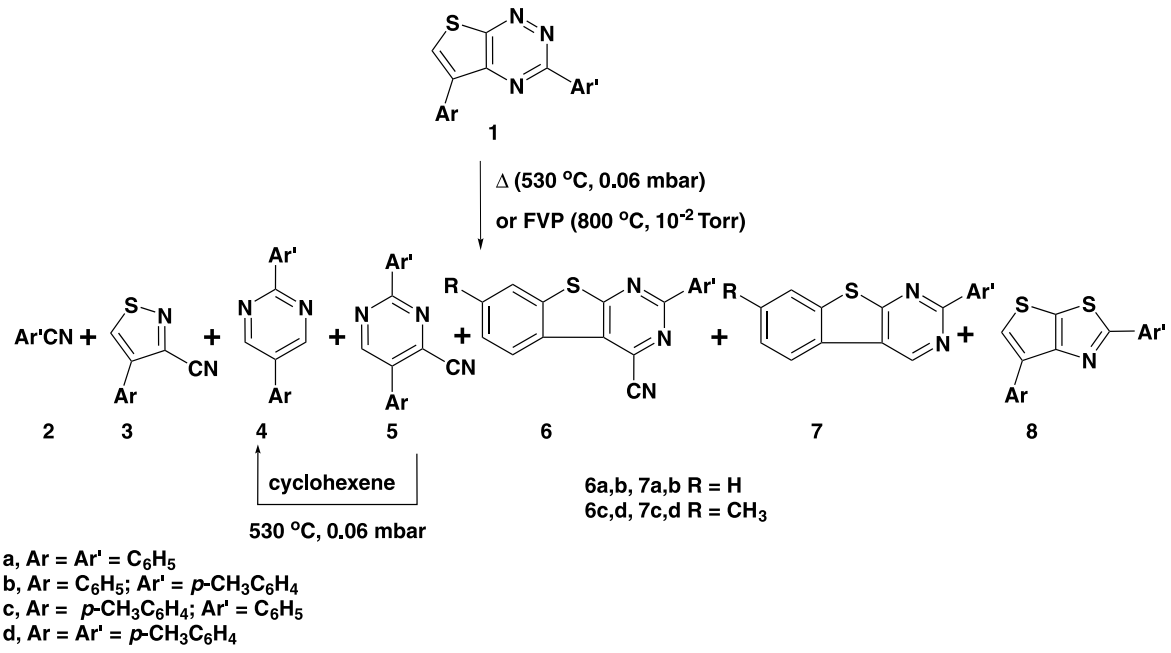
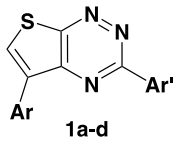
doi:10.1016/j.tet.2004.07.076



Scheme 2.



a, Ar = Ar' = C_6H_5
b, Ar = C_6H_5; Ar' = *p*-$CH_3C_6H_4$
c, Ar = *p*-$CH_3C_6H_4$; Ar' = C_6H_5
d, Ar = Ar' = *p*-$CH_3C_6H_4$

2. Results and discussion

Reaction products from complete gas-phase pyrolysis of thieno[3,2-*e*][1,2,4]triazines **1a–d** (Scheme 2) were obtained at optimal reactor conditions of temperature, pressure (0.06 mbar) and substrate residence time compatible with >98% reaction established for completed pyrolysis as evident from HPLC analysis. The products of pyrolysis of **1a** were separated by preparative HPLC and by column chromatography. These products were characterized using GCMS, LCMS, ^{1}H, ^{13}C NMR and 2D NMR spectroscopy. Thus, compound **1a** upon pyrolysis gave benzonitrile **2a**, 3-cyano-4-phenylisothiazole **3a**, 2,5-diphenylpyrimidine **4a**, 3-cyano-2,5-diphenylpyrimidine **5a**, 4-cyano-2-phenyl[1]benzothieno[2,3-*d*]pyrimidine **6a**, 2-phenyl[1]benzothieno[2,3-*d*]pyrimidine **7a** and 3,5-diphenylthieno[3,2-*d*]thiazole **8a** in the percentage yields indicated in Table 1. On the other hand, compounds **2a**, **3a**, **5a** and **6a** could only be detected upon FVP of **1a** at 800 °C and 0.02 Torr.

Similar pyrolysis (static and FVP) of **1b–d** gave the corresponding benzonitriles **2**, 4-aryl-3-cyanothiazoles **3**, 2,5-diarylpyrimidines **4**, 2,5-diaryl-4-cyanopyrimidines **5**,

Table 1. Pyrolysis products of **1a–d** (% yields[a] from Static, FVP) and characteristic ^{1}H NMR signal[b] of the heterocyclic ring

Substrate	Pyrolysis products (% yields)						
	2	**3**	**4**	**5**	**6**	**7**	**8**
1a	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**
Static	34	19	4	13	12	4	12
FVP	51	18	0	5	3	0	0
^{1}H NMR		8.80	9.05	9.08		9.47	7.60
1b	**2b**	**3a**	**4b**	**5b**	**6b**	**7b**	**8b**
Static	25	17	10	10	10	5	10
FVP	49	14	0	10	4	0	0
^{1}H NMR		8.80	9.03	9.05		9.42	
1c	**2b**	**3c**	**4c**	**5c**	**6c**	**7c**	**8c**
Static	23	17	6	6	9	4	9
FVP	55	12	0	4	4	0	0
^{1}H NMR		8.75	9.04	9.06		9.42	
1d	**2b**	**3c**	**4d**	**5d**	**6d**	**7d**	**8d**
Static	23	17	6	6	9	4	9
FVP	54	13	0	5	2	0	0
^{1}H NMR		8.75	9.00	9.03		9.43	

[a] Yields measured by HPLC and ^{1}H NMR spectroscopy.
[b] Measured in $CDCl_3$, singlet (1H) for compounds **3a**,**c**, **5a–d**, **7a–d**, **8a** and singlet (2H) for compounds **4a–d**.

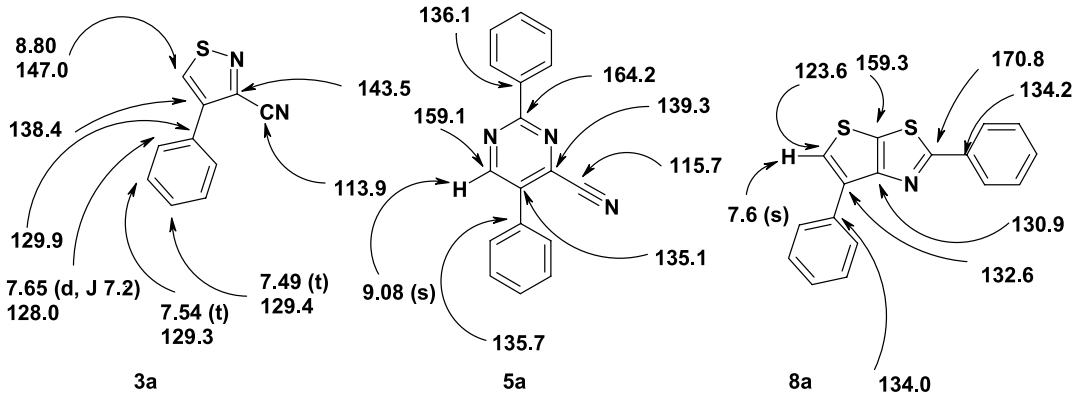


Figure 1. ^{1}H and ^{13}C NMR spectroscopy assignments of **3a**, **5a** and **8a**.

2-aryl-4-cyano[1]benzothieno[2,3-*d*]pyrimidines **6**, 2-aryl-[1]benzothieno[2,3-*d*]pyrimidines **7** and 2,4-diaryl-thieno[3,2-*d*]thiazoles **8**.

The pyrolysates were qualitatively and quantitatively determined by HPLC (Table 1) and by ^{1}H NMR. The structure of these pyrolysis products was also established by LCMS, GCMS, ^{1}H, ^{13}C and 2D NMR.

Assignments of heterocyclic ring protons and carbons of compounds **3a**, **5a** and **8a** are shown in Figure 1. These assignments were made based on H,H-COSY, HMQC and HMBC experiments.

Figure 2 shows the numbering used in the following NMR correlations. For compound **3a**, the HMBC correlation showed the following proton carbon cross peaks: H^5 at δ 8.80 correlates with C^3, C^4, C^7, H^8 at δ 7.65 correlates with C^4, C^{10}, H^9 at δ 7.54 correlates with C^7 and H^{10} at δ 7.49 correlates with C^8. For compound **5a**, the HMBC correlation showed the following proton carbon cross peaks: H^6 at δ 9.08 correlates with C^2, C^4, C^5, C^7, C^{12}, H^9 at δ 8.53 correlates with C^2, C^{11} and H^{13} at δ 7.66 correlates with C^5. Other correlations could not be clearly assigned due to interference in the ^{1}H NMR. For compound **8a**, the HMBC correlation showed the following proton carbon cross peaks: H^5 at δ 7.60 correlates with C^{3a}, C^{6a}, C^{11}, H^8 at δ 8.08 correlates with carbons C^2 and H^{12} at δ 8.18 correlates with C^4. Other correlations could not be clearly assigned due to overlapping signals in the ^{1}H NMR spectra.

The structure of compound **7a** was confirmed by preparing an authentic sample following the reported procedure described for the parent ring system and its 2-methyl derivative.[5] The details of this synthesis will be published later.

From Table 1 it is clear that FVP gave similar products to those obtained from static pyrolysis except those (**4**, **7**) in which the cyano group has been lost (i.e. replaced by H) or a sulfur atom is captured by the intermediates to produce the corresponding thieno[3,2-*d*]thiazoles **8**. This could be explained by further fragmentation during the long residence time during static pyrolysis (15 m at 530 °C) compared to FVP (10 ms at 800 °C).

Scheme 3 illustrates possible mechanistic routes explaining the formation of **2**–**8** obtained in the present pyrolytic studies of compounds **1**. The first route starts by extrusion of N_2 to give the diradicals **9** which then capture sulfur from the decomposition products to give compounds **8**. The second route which explains the formation of the rest of the reaction products takes place by initial N–N bond cleavage to give the diradicals **10** which rearrange to the cyano diradicals **11** which fragments further to give the nitriles **2** and the

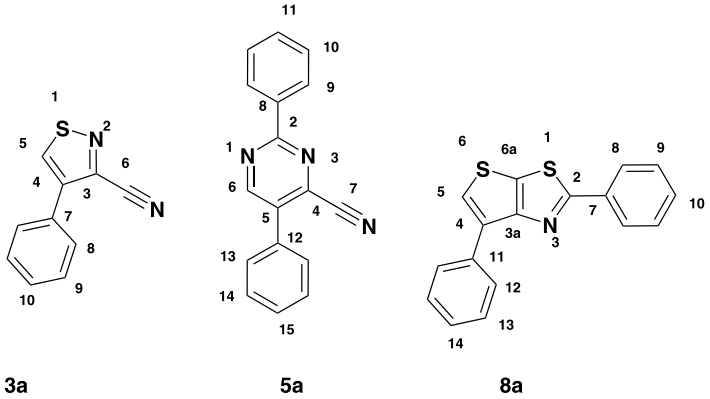
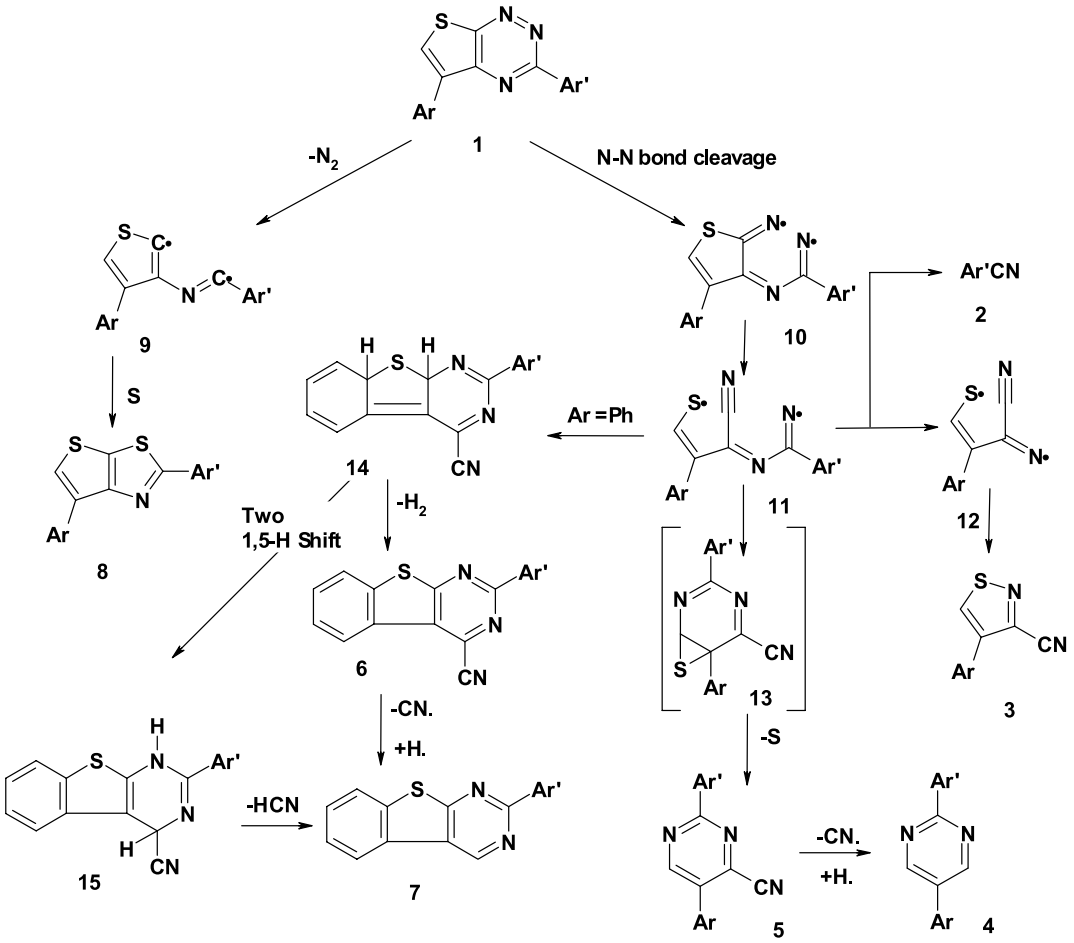
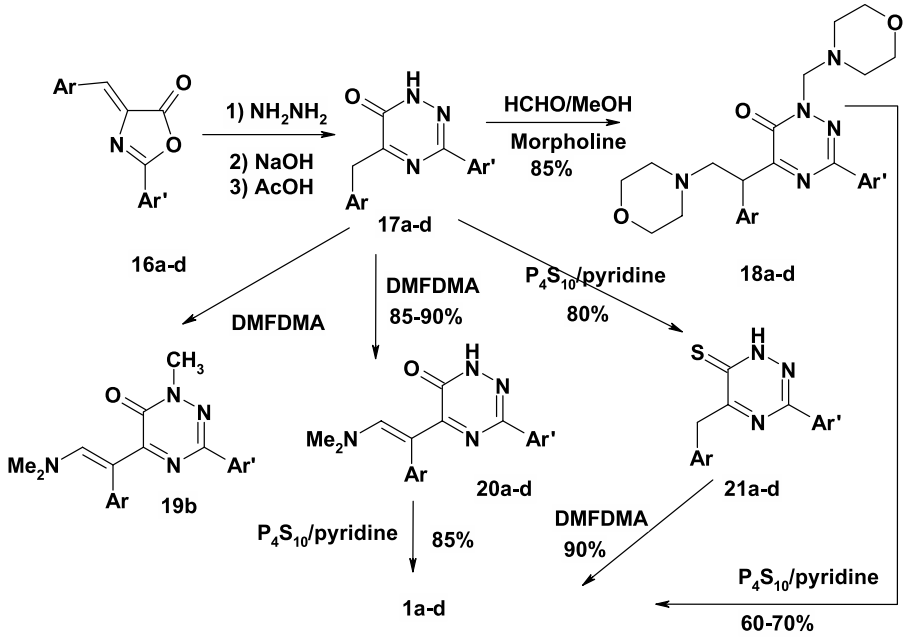


Figure 2. ^{1}H and ^{13}C NMR signal assignments of **3a**, **5a** and **8a**.



Scheme 3.



Scheme 4.

diradicals **12**. The latter cyclize intramolecularly via diradicals bonding to give **3**.

Alternatively the diradicals **11** via two intramolecular radical cyclizations give the intermediates **14** followed by loss of H_2 to form **6**. The formation of **7** might result either from **6** via thermal loss of CN and replacement with H radicals or from **14** via two successive 1,5-H-shift to give **15** followed by elimination of HCN.

The diradicals **11** also, combine to give the intermediate **13** which aromatizes via loss of S to give **5**. The latter presumably, via thermal loss of CN and replacement with H radicals give the corresponding 2,5-diarylpyrimidines **4**. This presumption was substantiated by the fact that pyrolysis of each of **5a**,**b** in the presence of cyclohexene (as a hydrogen source) at 530 °C gave the corresponding 2,5-diarylpyrimidines **4a**,**b** respectively.

The starting thienotriazines **1a–d** were prepared as shown in Scheme 4 starting from the corresponding oxazolone **16a–d** using our described method[6] for the synthesis of **1a** via the Mannich bases **18a–d**. Thus, the appropriate oxazolones **16a–d** were converted into the corresponding 5-arylmethyl-1,2,4-triazin-6(5H)-ones **17a–d** upon treatment with hydrazine hydrate followed by aqueous NaOH. The latter were then converted into their corresponding bis-Mannich basses **18a–d** upon treatment with HCHO and morpholine in methanol. Thiation of **18a–d** with phosphorus pentasulfide in pyridine gave the corresponding thieno[3,2-*e*][1,2,4]tiazines **1a–d** in ca. 55% overall yields from **17a–d** to **1a–d**.[6] In the present study also, two new more efficient methods are described for the synthesis of **1a–d**. Thus, heating **17a–d** at 100 °C with DMFDMA for 5 min gave ca. 80% of the corresponding dimethylenamines **20a–d**. Longer reaction time led to further methylation with the formation of 1-methyl derivatives **19b**. Heating **20a–d** with phosphorus pentasulfide in pyridine under reflux gave the corresponding thieno[3,2-*e*][1,2,4]triazines **1a–d** in ca. 85%. Alternatively, thiation of **17a–d** gave the corresponding 1,2,4-triazine-6(1*H*)-thiones **21a–d**. Heating the latter at 100 °C with DMFDMA for 30 min gave ca. 90% of the corresponding thienotriazines **1a–d**.

3. Conclusions

The present study offers interesting new routes towards heterocyclic compounds some of which are new derivatives. The present study also shows that the thienotriazines behaves differently from the corresponding benzo analogs. This can be explained as due to the effect of the more electron rich five-membered condensed thiophene ring and its further pyrolysis affected by the cleavage of the S–C bond. Also, comparison between FVP and static pyrolysis demonstrates the potential synthetic applications of these pyrolytic techniques in organic synthesis.

4. Experimental

All melting points are uncorrected IR spectra were recorded in KBr disks using Perkin Elmer System 2000 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400, 400 MHz super-conducting NMR spectrometer. Mass spectra were measured on VG Autospec-Q (high resolution, high performance, tri-sector GC/MS/MS) and with LCMS using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Microanalyses were performed on LECO CH NS-932 Elemental Analyzer. Separation of reaction products was performed using preparative HPLC WATER PREP 4000 series with PDA detector WATER 2996.

4.1. Pyrolysis of 1a–d: general procedures

(A) Static pyrolysis **1a–d**. Each substrates (0.2 g) was introduced in the reaction tube (1.5×12 cm Pyrex), cooled in liquid nitrogen, sealed under vacuum (0.06 mbar) and put in the pyrolyser for 15 min at 530 °C, a temperature that is required for complete pyrolysis of the substrate as indicated by preliminary HPLC study The pyrolysate was then separated by preparative HPLC using ABZ+column with a solvent mixture of acetonitrile and water (50:50 in case for products of pyrolysis of **1a** and 60:40 in case for products of pyrolysis of **1b–d**) and collected components were evaporated and subjected to ^{1}H NMR and GCMS and LCMS studies. Also, the products were separated on column chromatography using Merck Al-silica gel $60F_{254}$, with EtOAC/petroleum ether (40–60) (1–15% of EtOAc) to give successively **8** followed by **3**, **5**, **6**, **4**, **7**.

(B) Flash vacuum pyrolysis of **1a–d**. The apparatus used was similar to the one which has been described in our recent publications.[1,7] The sample was volatilized from a tube in a Büchi Kugelrohr oven through a 30×2.5 cm horizontal fused quartz tube. This was heated externally by a Carbolite Eurotherm tube furnace MTF-12/38A to a temperature of 800 °C, the temperature being monitored by a Pt/Pt-13%Rh thermocouple situated at the center of the furnace. The products were collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2} Torr by an Edwards Model E2M5 high capacity rotary oil pump, the pressure being measured by a Pirani gauge situated between the cold trap and the pump. Under these conditions the contact time in the hot zone was estimated to be ≅10 ms. The different zones of the products collected in the U-shaped trap were analyzed by ^{1}H, ^{13}C NMR, IR and GC-MS. Relative and percent yields were determined from ^{1}H NMR. Identity of compounds obtained were confirmed by comparison of their ^{1}H, ^{13}C NMR, IR with data of products separated from preparative HPLC and column chromatography.

4.2. Pyrolysis products

4.2.1. Arylnitriles 2. *Benzonitrile* **2a**. LCMS: $m/z=104$ (M+1, 100%) ^{1}H NMR spectroscopic data identical to that reported in the literature.[8]

p-Tolunitrile **2b**. LCMS: $m/z=118$ (M+1, 100%). ^{1}H NMR spectroscopic data identical to that reported in the literature.[9]

4.2.2. 3-Cyano-4-arylisothiazoles 3. *3-Cyano-4-phenylisothiazole* **3a**. Isolated yield 17% (colorless crystals from

EtOH); [TLC, R_f=0.65, EtOAc/petroleum ether (40–60), 5:95] mp 96–98 °C. MS: *m/z*=186 (M^+, 100%). IR (KBr): 3079, 2235, 1652, 1577, 1480, 1447, 1379, 1326, 1307, 1173, 1076, 978, 862, 849, 827, 759, 744, 711, 696. ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H), 7.65 (d, 2H, *J*=7.2 Hz), 7.54 (t, 1H, *J*=7.2 Hz), 7.49 (t, 2H, *J*=7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 147.0, 143.5, 138.4, 129.9, 129.4, 129.3, 128.0, 113.9. Anal. calcd for $C_{10}H_6N_2S$ (186.2): C 64.49; H 3.25; N 15.04; S; 17.22. Found C 64.77; H 3.35; N 15.05; S; 17.50.

3-Cyano-4-p-tolylisothiazole **3c**. Isolated yield 15% (colorless crystals from MtOH); mp 128–130 °C. LCMS: *m/z*=201 (M+1). IR (KBr): 3095, 2235, 1531, 1484, 1457, 1427, 1377, 1326, 1307, 1163, 977, 796, 695. ^{1}H NMR ($CDCl_3$): δ 8.75 (s, 1H), 7.55 (d, 2H, *J*=7.8 Hz), 7.33 (d, dH, *J*=7.8 Hz), 2.48 (s, 3H). Anal. calcd for $C_{11}H_8N_2S$ (200.3): C 65.97; H 4.03; N 13.99; S 16.01. Found C 66.05; H 3.98; N 14.02; S 15.99.

4.2.3. 2,5-Diarylpyrimidines 4. *2,5-Diphenylpyrimidine* **4a**. Isolated yield 4% (colorless crystals from EtOH), [TLC, R_f=0.50, EtOAc/petroleum ether (40–60), 5:95]; mp 180–182 °C (lit.[10] mp 180–182 °C). MS: *m/z*=232 (M^+, 100%); LCMS: *m/z*=233 (M+1). ^{1}H NMR ($CDCl_3$): δ 9.05 (s, 2H, H-4,6), 8.51 (dd, 2H, *J*=8, 2 Hz), 7.66 (d, 2H, *J*=7.6 Hz), 7.58–7.45 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 163.4 (C-2), 155.2 (2CH-4,6), 137.2 (C-5), 134.5 (C), 131.7 (C), 130.8 (CH), 139.4 (2CH), 128.8 (CH), 128.5 (2CH), 128.1 (2CH), 126.8 (2CH). Anal. calcd for $C_{16}H_{12}N_2$ (232.3): C 82.73; H 5.21; N 12.06. Found C 82.68; H 5.16; N 12.00.

5-Phenyl-2-p-tolylpyrimidine **4b**. Isolated yield 4% (colorless crystals from EtOH), [TLC, R_f=0.43, $CHCl_3$/petroleum ether (40–60), 1:1]; mp 205–207 °C. MS: *m/z*=246 (M^+, 100%); LCMS: *m/z*=247 (M+1). ^{1}H NMR ($CDCl_3$): δ 9.03 (s, 2H, H-4,6), 8.39 (d, 2H, *J*=8 Hz), 7.65 (d, 2H, *J*=7.6 Hz), 7.55 (t, 2H, *J*=7.6 Hz), 7.48 (t, 1H, *J*=7.6 Hz), 7.35 (d, 2H, *J*=8 Hz), 2.46 (s, 3H). Anal. calcd for $C_{17}H_{14}N_2$ (246.3): C 82.90; H 5.73; N 11.37. Found C 82.75; H 5.56; N 11.50.

2-Phenyl-5-p-tolylpyrimidine **4c**. Isolated yield 5% (colorless crystals from EtOH). [TLC, R_f=0.48, $CHCl_3$/petroleum ether (40–60), 1:1)]; mp 218–220 °C. MS: *m/z*=246 (M^+, 100%); LCMS: *m/z*=247 (M+1). ^{1}H NMR ($CDCl_3$): δ 9.04 (s, 2H, H-4,6), 8.50 (d, 2H, *J*=7.8 Hz), 7.54 (m, 5H), 7.36 (d, 2H, *J*=7.8 Hz), 2.46 (s, 3H). Anal. calcd for $C_{17}H_{14}N_2$ (246.3): C 82.90; H 5.73; N 11.37. Found C 82.81; H 5.62; N 11.43.

2,5-Di-p-tolylpyrimidine **4d**. Isolated yield 4% (colorless crystals from EtOH), [TLC, R_f=0.54, EtOAc/petroleum ether (40–60), 1:9]; mp 213–215 °C. LCMS: *m/z*=261 (M+1). IR: 3030, 2954, 2916, 2851, 1578, 1529, 1431, 1377, 1107, 1044, 813, 786, 755. ^{1}H NMR ($CDCl_3$): δ 9.01 (s, 2H, H-4,6), 8.38 (d, 2H, *J*=8 Hz), 7.54 (d, 2H, *J*=8 Hz), 7.36 (d, 2H, *J*=8 Hz), 7.34 (d, 2H, *J*=8 Hz), 2.47, (s, 3H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 21.6, 21.5, 126.6, 128.0, 128.7, 129.7, 130.1, 131.3, 134.4, 138.8, 141.1, 154.9, 158.8. Anal. calcd for $C_{18}H_{16}N_2$ (260.3): C 83.05; H 6.19; N 10.76. Found C 82.95; H 6.08; N 10.59.

4.2.4. 4-Cyano-2,5-diarylpyrimidines 5. *4-Cyano-2,5-diphenylpyrimidine* **5a**. Isolated yield 8% (colorless crystals from EtOH), [TLC, R_f=0.65, EtOAc/petroleum ether (40–60), 3:97]; mp 142–143 °C. MS: *m/z*=257 (M^+, 100%); LCMS: *m/z*=258 (M+1). IR (KBr): 3062, 3025, 1564, 1513, 1453, 1426, 1369, 1264, 1151, 1069, 1002, 918, 873, 817, 763, 692. ^{1}H NMR ($CDCl_3$): δ 9.08 (s, 1H), 8.53 (dd, 2H, *J*=1.5, 7.2 Hz), 7.66 (dd, 2H, *J*=1.5, 8 Hz), 7.64–7.53 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 164.2 (pyrimidine C-2), 159.1 (pyrimidine CH), 139.3 (C), 136.1 (C), 135.7 (C), 135.1 (C), 132.1 (CH), 130.3 (CH), 129.6 (2CH), 129.1 (2CH), 128.8 (2CH), 128.7 (2CH), 115.7 (CN). Anal. calcd for $C_{17}H_{11}N_3$ (257.3): C 79.36; H 4.31; N 16.33. Found C 79.06; H 4.42; N 16.25.

4-Cyano-5-phenyl-2-p-tolylpyrimidine **5b**. Isolated yield 8% (colorless crystals from EtOH), [TLC, R_f=0.38, $CHCl_3$/petroleum ether (40–60), 30:70]; mp 190–192 °C. MS: *m/z*=271 (M^+, 100%); LCMS: *m/z*=272 (M+1). ^{1}H NMR ($CDCl_3$): δ 9.05 (s, 1H), 8.42 (d, 2H, *J*=8 Hz), 7.65 (dd, 2H, *J*=2, 7.6 Hz), 7.60 (m, 3H), 7.36 (d, 2H, *J*=8 Hz), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 164.1 (pyrimidine C-2), 158.9 (pyrimidine CH), 142.4 (C), 139.1 (C), 134.7 (C), 132.9 (C), 132.0 (C), 130.0 (CH), 129.8 (2CH), 129.4 (2CH), 128.8 (2CH), 128.7 (2CH), 115.6 (CN), 21.6 (CH_3). Anal. calcd for $C_{18}H_{13}N_3$ (271.3): C 79.68; H 4.83; N 15.49. Found C 79.58; H 4.63; N 15.25.

4-Cyano-2-phenyl-5-p-tolylpyrimidine **5c**. Isolated yield 6% (colorless crystals from EtOH), [TLC, R_f=0.43, $CHCl_3$/petroleum ether (40–60), 30:70]; mp 195–197 °C. MS: *m/z*=271 (M^+, 100%); LCMS: *m/z*=272 (M+1). ^{1}H NMR ($CDCl_3$): δ 9.06 (s, 1H), 8.52 (dd, 2H, *J*=1.6, 8 Hz), 7.56 (m, 5H), 7.41 (d, 2H, *J*=8 Hz), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 164.1 (pyrimidine C-2), 158.9 (pyrimidine CH), 142.4 (C), 139.1 (C), 134.7 (C), 132.9 (C), 132.0 (C), 130.0 (CH), 129.8 (2CH), 129.4 (2CH), 128.8 (2CH), 128.7 (2CH), 115.6 (CN), 21.6 (CH_3). Anal. calcd for $C_{18}H_{13}N_3$ (271.3): C 79.68; H 4.83; N 15.49. Found C 79.70; H 4.65; N 15.35.

4-Cyano-2,5-di-p-tolylpyrimidine **5d**. Isolated yield 4% (colorless crystals from EtOH), [TLC, R_f=0.49, EtOAc/petroleum ether (40–60), 1:9]; mp 160–162 °C. LCMS: *m/z*=286 (M+1). ^{1}H NMR ($CDCl_3$): δ 9.03 (s, 1H), 8.41 (d, 2H, *J*=8 Hz), 8.52 (d, 2H, *J*=8 Hz), 7.40 (d, 2H, *J*=7.8 Hz), 7.33 (d, 2H, *J*=7.8 Hz), 2.46 (s, 6H).). Anal. calcd for $C_{19}H_{15}N_3$ (285.3): C 79.98; H 5.30; N 14.73. Found C 79.70; H 5.40; N 14.95.

4.2.5. 4-Cyano-2-aryl[1]benzothieno[2,3-*d*]pyrimidines 6. *4-Cyano-2-phenyl[1]benzothieno[2,3-d]pyrimidine* **6a**. Isolated yield 8% (pale yellow crystals from EtOH), [TLC, R_f=0.42, AcOEt/petroleum ether (40–60), 4:96]; mp 210–211 °C. MS: *m/z*=287 (M^+, 100%); LCMS *m/z*=288 (M+1). ^{1}H NMR ($CDCl_3$): δ 8.81 (dd, 1H, *J*=2, 6.8 Hz), 8.62 (dd, 2H, *J*=1.6, 7.6 Hz), 8.00 (dd, 1H, *J*=2, 7.6 Hz), 7.70 (m, 2H), 7.58 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 172.7, 161.6, 137.9, 135.7, 132.7, 131.8, 130.0, 128.9, 128.8, 128.5, 126.6, 125.7, 124.3, 123.3, 115.6. Anal. calcd for $C_{17}H_9N_3S$ (287.4): C 71.06; H 3.16; N 14.62, S 11.16. Found: C 71.08; H 3.10; N 14.63; S 11.25.

4-Cyano-2-p-tolyl[1]benzothieno[2,3-d]pyrimidine **6b**. Isolated yield 8% (pale yellow crystals from EtOH), mp 234–236 °C. MS: $m/z=301$ (M^+, 80%); LCMS $m/z=302$ (M+1). ^{1}H NMR ($CDCl_3$): δ 8.50 (dd, 1H, $J=1.6$, 8 Hz), 8.41 (d, 2H, $J=8$ Hz), 8.23 (dd, 2H, $J=1.6$, 8 Hz), 7.91 (dd, 1H, $J=1.6$, 8 Hz), 7.36 (d, 2H, $J=8$ Hz), 2.47 (s, 3H). Anal. calcd for $C_{18}H_{11}N_3S$ (301.4): C 71.74; H 3.68; N 13.94; S 10.64. Found: C 71.88; H 3.57; N 14.03; S 10.75.

4-Cyano-7-methyl-2-phenyl[1]benzothieno[2,3-d]pyrimidine **6c**. Isolated yield 7% (pale yellow crystals from EtOH), mp 246–248 °C. LCMS $m/z=302$ (M+1). ^{1}H NMR ($CDCl_3$): δ 8.67 (s, 1H), 8.46 (dd, 2H, $J=1.6$, 7.9 Hz), 7.95 (m, 5H), 2.48 (s, 3H). Anal. calcd for $C_{18}H_{11}N_3S$ (301.4): C 71.74; H 3.68; N 13.94; S 10.64. Found: C 71.69; H 3.75; N 14.10; S 10.61.

4-Cyano-7-methyl-2-p-tolyl[1]benzothieno[2,3-d]pyrimidine **6d**. LCMS $m/z=302$ (M+1).

4.2.6. 2-Aryl[1]benzothieno[2,3-*d*]pyrimidines 7. *2-Phenyl[1]benzothieno[2,3-d]pyrimidine* **7a**. Isolated yield 4% (colorless crystals from EtOH), [TLC, $R_f=0.38$, AcOEt/petroleum ether (40–60), 4:96]; mp 196–198 °C. MS: $m/z=262$ (M^+, 60%); LCMS $m/z=263$ (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 9.47 (s, 1H), 8.59 (dd, 2H, $J=1.7$, 7.5 Hz), 8.24 (dd, 1H, $J=2$, 7.5 Hz), 7.90 (dd, 1H, $J=1.8$, 7.6 Hz), 7.59–7.54 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 170.8, 161.9, 149.3, 137.4, 137.3, 131.1, 130.9, 128.7, 128.5, 128.3, 125.7, 125.4, 123.3, 122.0. Anal. calcd for $C_{16}H_{10}N_2S$ (262.3): C 73.26; H 3.84; N 10.68; S 12.22. Found: C 73.58; H 3.65; N 10.41; S 12.32.

2-p-Tolyl[1]benzothieno[2,3-d]pyrimidine **7b**. Isolated yield 4% (colorless crystals from EtOH), mp 222–224 °C. LCMS $m/z=277$ (M+1). ^{1}H NMR ($CDCl_3$): δ 9.45 (s, 1H), 8.49 (d, 2H, $J=8$ Hz), 8.23 (dd, 1H, $J=2$, 7.8 Hz), 7.95 (dd, 1H, $J=1.8$, 7.8 Hz), 7.57 (m, 2H), 7.36 (d, 2H, $J=7.8$ Hz), 2.47 (s, 3H). Anal. calcd for $C_{17}H_{12}N_2S$ (276.4): C 73.88; H 4.38; N 10.14; S 11.60. Found: C 73.76; H 4.53; N 10.15; S 11.48.

7-Methyl-2-phenyl[1]benzothieno[2,3-d]pyrimidine **7c**. Isolated yield 4% (colorless crystals from EtOH), mp 230–232 °C. LCMS $m/z=277$ (M+1). ^{1}H NMR ($CDCl_3$): δ 9.40 (s, 1H), 8.57 (dd, 2H, $J=1.6$, 8 Hz), 8.11 (d, 1H, $J=8$ Hz), 7.75 (s, 1H), 7.51 (m, 3H), 8.10 (d, 1H, $J=8.4$ Hz), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.6, 162.3, 149.4, 137.3, 137.2, 131.1, 130.8, 129.1, 128.7, 128.4, 127.2, 125.7, 123.3, 121.8, 21.9. Anal. calcd for $C_{17}H_{12}N_2S$ (276.4): C 73.88; H 4.38; N 10.14; S 11.60. Found: C 73.80; H 4.45; N 10.21; S 11.38.

7-Methyl-2-p-tolyl[1]benzothieno[2,3-d]pyrimidine **7d**. LCMS $m/z=291$ (M+1).

4.2.7. 2,6-Diarylthieno[3,2-*d*]thiazoles: 8. *2,6-Diphenylthieno[3,2-d]thiazole* **8a**. Isolated yield 9% (colorless crystals from EtOH), [TLC, $R_f=0.85$, AcOEt/petroleum ether (40–60), 3:97]; mp 160–162 °C. MS: $m/z=293$ (M^+, 100%); LCMS $m/z=294$ (M+1). ^{1}H NMR ($CDCl_3$): δ 8.18 (d, 2H, $J=7.6$ Hz), 8.08 (dd, 2H, $J=1.6$, 7.6 Hz), 7.60 (s, 1H), 7.54–7.46 (m, 5H), 7.40 (t, 1H, $J=7.6$ Hz). ^{13}C NMR ($CDCl_3$): δ 170.8, 159.3, 134.2, 134.0, 132.6, 130.9, 130.5, 129.0, 128.7, 127.8, 127.2, 126.7, 123.6. Anal. calcd for $C_{17}H_{11}NS_2$ (293.4): C 69.59; H 3.78; N 4.77; S 21.86. Found: C 69.81; H 4.02; N 4.45; S 21.88.

2-p-Tolyl-6-phenylthieno[3,2-d]thiazole **8b**. LCMS $m/z=$ 308 (M+1).

3.6-p-Tolyl-2-phenylthieno[3,2-d]thiazole **8c**. LCMS $m/z=$ 308 (M+1).

2,6-Di-p-Tolylthieno[3,2-d]thiazole **8d**. LCMS $m/z=322$ (M+1).

4.3. Pyrolysis of 5a,b with cyclohexene

A mixture each of **5a**,**b** (30 mg) and cyclohexene (0.1 ml), cooled in liquid nitrogen, sealed and pyrolysed as described for compounds **1** for 15 min at 530 °C. The products showed by HPLC, ^{1}H NMR, LCMS the formation of the corresponding compounds **4a**,**b**, respectively, in approximately 80%.

4.4. 3-Aryl-5-arylmethyl-1,2,4-triazin-6(1*H*)-ones 17a–d: general procedure

To a stirred suspension of each of **16a–d**[11] (10 mmol) in methanol (20 ml) was added at room temperature hydrazine hydrate (80%, 1 ml). The mixture was kept stirring for 2 h (the yellow starting compounds **16a–d** completely dissolved after that time and white crystals precipitated). Aqueous NaOH solution (4%, 50 ml) was added and the mixture was heated under reflux for 5 min. After cooling the mixture was acidified with acetic acid and the precipitate was collected and recrystallized from ethanol to give the corresponding products **17a–d**.

4.4.1. Compound 17a. Yield 85%. Pale yellow crystals, mp 178–180 °C (lit.[12,13] 180 °C).

4.4.2. Compound 17b. Yield 85%. Pale yellow crystals, mp 197–198 °C. MS: $m/z=277$ (M^+, 100%). IR: 3314, 3203, 3133, 3065, 3013, 2865, 1654, 1588, 1564, 1273, 1179, 1129, 925, 828, 737, 697, 668. ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H), 4.29 (s, 2H), 7.23–7.30 (m, 3H), 7.35 (t, 2H, $J=$ 7.6 Hz), 7.47 (d, 2H, $J=7.6$ Hz), 8.03 (d, 2H, $J=8$ Hz), 11.28 (br, 1H). Anal. calcd for $C_{17}H_{15}N_3O$ (277.3): C 73.63; H 5.45; N 15.15. Found: C 73.57; H 5.49; N 15.35.

4.4.3. Compound 17c. Yield 90%. Pale yellow crystals, mp 208–210 °C. MS: $m/z=277$ (M^+, 100%), LCMS $m/z=278$ (M+1). IR: 3311, 3201, 3128, 3019, 2968, 2865, 1657, 1591, 1568, 1465, 1272, 1125, 923, 793, 696. ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H), 4.26 (s, 2H), 7.16 (d, 2H, $J=$ 7.6 Hz), 7.36 (d, 2H, $J=8$ Hz), 7.38–7.48 (m, 3H), 8.16 (d, 2H, $J=7.6$ Hz), 11.46 (br, 1H). Anal. calcd for $C_{17}H_{15}N_3O$ (277.3): C 73.63; H 5.45; N 15.15. Found: C 73.60; H 5.50; N 15.21.

4.4.4. Compound 17d. Yield 85%. Pale yellow crystals, mp 220–222 °C. MS: $m/z=291$. IR: 3204, 3134, 3016, 2895, 1657, 1589, 1564, 1514, 1273, 1179, 922, 829, 669. ^{1}H NMR ($CDCl_3$): δ 2.34, 2.42 (2s, 6H), 4.25 (s, 2H), 7.15 (d,

2H, $J=8$ Hz), 7.27 (d, 2H, $J=7.6$ Hz), 7.37 (d, 2H, $J=7.6$ Hz), 8.04 (d, 2H, $J=8$ Hz), 11.53 (br, 1H). Anal. calcd for $C_{18}H_{17}N_3O$ (291.4): C 74.21; H 5.88; N 14.42. Found: C 74.37; H 6.08; N 14.67.

4.5. 3-Aryl-5-[(1-aryl-2-morpholino)ethyl]-1-morpholinomethyl-1,2,4-triazin-6(1*H*)-ones (Mannich bases) 18a–d. General procedure

To a stirred cold (5 °C) solution of each of **17a–d** (2 mmol) in methanol (20 ml) was added formaldehyde (2 ml) and morpholine (2 ml). Stirring was continued at 5 °C for 2 h and then at room temperature overnight. The solid precipitated was collected and recrystallized from ethanol to give the corresponding Mannich products **18a–d**.

4.5.1. Compound 18a. Yield 85%. Canary yellow crystals mp 148 °C (lit.[6] 148 °C).

4.5.2. Compound 18b. Yield 85%. Canary yellow crystals mp 165–167 °C. MS: $m/z=475$ (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, ArMe), 2.48 (m, 2H), 2.65 (m, 2H), 2.78 (t, 4H, $J=4.5$ Hz), 2.84 (dd, 1H, $J=12.5$, 4.5 Hz), 3.57 (m, 5H), 3.68 (t, 4H, $J=4.5$ Hz), 4.93 (d, 1H, $J=12.8$ Hz), 5.05 (m, 1H), 5.11 (d, 1H, $J=12.8$ Hz), 7.24–7.34 (m, 5H), 7.47 (d, 2H, $J=7.8$ Hz), 8.09 (d, 2H, $J=8$ Hz). ^{13}C NMR ($CDCl_3$): δ 21.5, 44.0, 50.6, 53.9, 62.5, 66.9 ($2CH_2$), 72.2, 126.4, 127.4, 128.7, 128.8, 129.8, 131.4, 138.3, 140.4, 146.7, 154.6, 171.1. Anal. calcd for $C_{27}H_{33}N_5O_3$ (475.6): C 68.19; H 6.99; N 14.73. Found: C 68.11; H 7.06; N 14.78.

4.5.3. Compound 18c. Yield 85%. Canary yellow crystals mp 160–162 °C. MS: $m/z=475$ (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, ArMe), 2.48 (m, 2H), 2.65 (m, 2H), 2.78 (t, 4H, $J=4.5$ Hz), 2.84 (dd, 1H, $J=12.5$, 4.5 Hz), 3.59 (m, 5H), 3.70 (t, 4H, $J=4.5$ Hz), 4.93 (d, 1H, $J=12.8$ Hz), 5.01 (m, 1H), 5.12 (d, 1H, $J=12.8$ Hz), 7.14 (d, 2H, $J=7.6$ Hz), 7.36 (d, 2H, $J=8$ Hz), 7.50 (m, 3H), 8.20 (dd, 2H, $J=8$, 1.6 Hz). ^{13}C NMR ($CDCl_3$): δ 21.1, 43.6, 50.6, 53.9, 62.4, 66.9 ($2CH_2$), 72.3, 126.7, 128.5, 128.7, 129.4, 130.1, 134.2, 135.2, 137.3, 146.5, 154.6, 171.4. Anal. calcd for $C_{27}H_{33}N_5O_3$ (475.6): C 68.19; H 6.99; N 14.73. Found: C 68.00; H 6.98; N 14.73.

4.5.4. Compound 18d. Yield 85%. Canary yellow crystals mp 140–142 °C. MS: $m/z=489$ (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 2.32, 2.45 (2s, 6H, ArMe), 2.45 (m, 2H), 2.65 (m, 2H), 2.78 (m, 5H), 3.61 (m, 9H), 4.91 (d, 1H, $J=12.8$ Hz), 5.00 (m, 1H), 5.11 (d, 1H, $J=12.8$ Hz), 7.13 (d, 2H, $J=7.6$ Hz), 7.30 (d, 2H, $J=7.6$ Hz), 7.36 (d, 2H, $J=7.6$ Hz), 8.09 (d, 2H, $J=7.6$ Hz). ^{13}C NMR (and DEPT) ($CDCl_3$): δ 21.0 (CH_3), 21.5 (CH_3), 43.6 (CH), 50.6 (CH_2), 53.9 (CH_2), 62.4 (CH), 66.9 ($2CH_2$), 72.2 (CH_2), 126.7 (2CH), 128.6 (2CH), 129.3 (2CH), 129.4 (2CH), 131.7 (C), 135.3 (C), 137.1 (C), 140.1 (C), 146.7 (C), 154.6 (C), 171.2 (C). Anal. calcd for $C_{28}H_{35}N_5O_3$ (489.6): C 68.69; H 7.21; N 14.30. Found: C 68.57; H 7.34; N 14.11.

4.6. 5-(2-Dimethylamino-1-arylvinyl)-3-aryl-1,2,4-triazin-6(1*H*)-ones 20a–d. General procedure

A mixture of each of **17a–d** (1 mmol) and DMFDMA (1 ml) was heated at 100 °C (steam bath) for 5 min. After cooling and adding EtOH (5 ml), the precipitate was collected and recrystallized to give the corresponding products **20a–d**.

4.6.1. Compound 20a. Yield 85%. Yellow crystals (DMF), mp 250–252 °C. IR: 3184, 3138, 3023, 2918, 1643, 1588, 1466, 1417, 1383, 1274, 1190, 1169, 942, 875, 776, 701. MS: $m/z=318$ (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 2.83 (br, 6H, NMe_2), 7.28–7.35 (m, 5H), 7.36 (m, 3H), 7.84 (d, 2H, $J=7.6$ Hz), 9.53 (s, 1H), 10.99 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 34.7 (NCH_3), 125.6 (C), 126.5 (CH), 126.7 (2CH), 127.7 (2CH), 128.1 (2CH), 129.2 (CH), 135.5 (C), 137.8 (C), 149.6 (C), 153.2 (CH), 155.4 (C), 159.2 (C). Anal. calcd for $C_{19}H_{18}N_4O$ (318.4): C 71.68; H 5.70; N 17.60. Found: C 71.54; H 5.65; N 17.56.

4.6.2. Compound 20b. Yield 85%. Yellow crystals (DMF), mp 260–262 °C. IR: 3184, 3142, 2921, 1642, 1591, 1465, 1383, 1174, 1113, 940, 872, 828. ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H, Ar*Me*), 2.84 (br, 6H, NMe_2), 7.09 (d, 2H, $J=8$ Hz), 7.29 (m, 3H), 7.41 (d, 2H, $J=7.8$ Hz), 7.68 (d, 2H, $J=7.6$ Hz), 9.48 (s, 1H), 10.18 (br, 1H, NH). Anal. calcd for $C_{20}H_{20}N_4O$ (332.4): C 72.27; H 6.06; N 16.85. Found: C 72.03; H 6.10; N 16.80.

4.6.3. Compound 20c. Yield 85%. Yellow crystals (DMF), mp 280–282 °C. MS: $m/z=332$ (M^+, 100%). IR: 3184, 3140, 3025, 2965, 1645, 1589, 1465, 1383, 1280, 1188, 1110, 937, 875, 792, 700. ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H, Ar*Me*), 2.79 (br, 6H, NMe_2), 7.09 (m, 4H), 7.30 (m, 3H), 7.83 (d, 2H, $J=8$ Hz), 9.51 (s, 1H), 10.23 (br, 1H, NH). Anal. calcd for $C_{20}H_{20}N_4O$ (332.4): C 72.27; H 6.06; N 16.85. Found: C 72.22; H 6.08; N 16.86.

4.6.4. Compound 20d. Yield 85%. Yellow crystals (MeCN/ETOH), mp 286–288 °C. IR: 3182, 3024, 2967, 1648, 1591, 1465, 1419, 1329, 1280, 1189, 1110, 875, 791, 702. ^{1}H NMR ($CDCl_3$): δ 2.33, 2.43 (2s, 6H, 2Ar*Me*), 2.86 (br, 6H, NMe_2), 7.11 (d, 2H, $J=7.6$ Hz), 7.17 (m, 4H), 7.69 (d, 2H, $J=7.6$ Hz), 9.47 (s, 1H), 10.19 (br, 1H, NH). Anal. calcd for $C_{21}H_{22}N_4O$ (346.4): C 72.81; H 6.40; N 16.17. Found: C 72.65; H 6.35; N 16.18.

4.7. 5-(2-Dimethylamino-1-arylvinyl)-3-*p*-tolyl-1-methyl-1,2,4-triazin-6(1*H*)-ones 19b

A mixture of **17b** (1 mmol) and DMFDMA (1 ml) was heated at 100 °C (steam bath) for 1 h. After cooling and adding EtOH (5 ml), the precipitate was collected and recrystallized from EtOH to give yellow crystals of **19b**, yield 86%, mp 168–170 °C. IR: 3055, 3029, 2920, 1637, 1586, 1479, 1456, 1379, 1255, 1174, 952, 827, 707. ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H), 2.82 (br, 6H, Me_2N), 3.78 (s, 3H), 7.09 (d, 2H, $J=7.8$ Hz), 7.28 (m, 3H), 7.38 (t, 2H, $J=7.8$ Hz), 7.71 (d, 2H, $J=7.8$ Hz) 9.45 (s, 1H). Anal. calcd for $C_{21}H_{22}N_4O$ (346.4): C 72.81; H 6.40; N 16.17. Found: C 72.73; H 6.50; N 16.16.

4.8. 3-Aryl-5-arylmethyl-1,2,4-triazine-6(1*H*)-thiones 21a–d. General procedure

A solution of each of **17a–d** (2 mmol) and phosphorus pentasulfide (0.7 g, 3 mmol) in anhydrous pyridine (15 ml) was heated under reflux for 3 h. After cooling the precipitate

was collected and recrystallized from ethanol to give the corresponding 1,2,4-triazine-6(1H)-thiones **21a–c**.

4.8.1. Compound 21a. Mp 190 °C (lit.[14] 190 °C).

4.8.2. Compound 21b. Yield 85%. Yellow crystals, mp 208–210 °C. MS: $m/z=293$ (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H), 4.55 (s, 2H), 7.27–7.37 (m, 5H), 7.49 (d, 2H, $J=7.2$ Hz), 8.03 (d, 2H, $J=7.6$ Hz), 12.00 (br, 1H). Anal. calcd for $C_{17}H_{15}N_3S$ (293.4): C 69.60; H 5.15; N 14.32, S 10.93. Found: C 69.59; H 5.15; N 14.55; S 11.04.

4.8.3. Compound 21c. Yield 80%. Yellow crystals, mp 218–220 °C. MS: $m/z=293$ (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 4.51 (s, 2H), 7.16 (d, 2H, $J=$ 7.2 Hz), 7.39 (d, 2H, $J=7.2$ Hz), 7.48 (m, 3H), 8.16 (d, 2H, $J=7$ Hz), 12.00 (br, 1H). Anal. calcd for $C_{17}H_{15}N_3S$ (293.4): C 69.60; H 5.15; N 14.32; S 10.93. Found: C 69.61; H 5.08; N 14.50; S 10.75.

4.8.4. Compound 21d. Yield 80%. Yellow crystals, mp 230–232 °C. MS: $m/z=307$ (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 2.35, 2.43 (2s, 6H), 4.50 (s, 2H), 7.15 (d, 2H, $J=7.6$ Hz), 7.28 (d, 2H, $J=7.6$ Hz), 7.38 (d, 2H, $J=$ 7.6 Hz), 8.05 (d, 2H, $J=7.6$ Hz), 12.23 (br, 1H). Anal. calcd for $C_{18}H_{17}N_3S$ (307.4): C 70.33; H 5.57; N 13.67; S 10.43. Found: C 70.30; H 5.55; N 13.93; S 10.43.

4.9. Thieno[3,2-*e*][1,2,4]triazines 1a–d. General procedure

Method A. A solution of each of **18a–d** (2 mmol) and phosphorus pentasulfide (0.7 g, 3 mmol) in pyridine (10 ml) was heated under reflux for 3 h. After cooling the precipitate was collected and recrystallized from the proper solvent to give the corresponding products **1a–d** in 60–70% yields.

Method B. A solution of each of **20a–d** (1 mmol) and phosphorus pentasulfide (0.34 g, 1.5 mmol) in pyridine (10 ml) was heated under reflux for 2 h. After cooling the precipitate was collected and recrystallized from the proper solvent to give the corresponding products **1a–d** in ca. 85% yields.

Method C. A mixture of each of **21a–d** (1 mmol) and DMFDMA (1 ml) was heated under reflux for 0.5 h. After cooling and triturating with ethanol the precipitate was collected and recrystallized from the proper solvent to give the corresponding products **1a–d** in ca. 90% yields.

4.9.1. Compound 1a. Yellowish green crystals (EtOH), mp 198–200 °C (lit.[6] mp 198 °C).

4.9.2. Compound 1b. Yellowish green crystals (EtOH), mp 203–205 °C LCMS $m/z=304$ (M+1). IR: 3067, 2909, 2851, 1609, 1531, 1497, 1444, 1331, 1177, 1119, 799, 724, 690. ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H), 7.39 (d, 2H, $J=$ 8 Hz), 7.50 (t, 1H, $J=7.7$ Hz), 7.59 (t, 2H, $J=7.7$ Hz), 8.11 (d, 2H, $J=7.7$ Hz), 8.33 (s, 1H), 8.59 (d, 2H, $J=8$ Hz). ^{13}C NMR ($CDCl_3$): δ 21.6, 128.0 (2CH), 128.4 (2CH), 128.7 (CH), 128.9 (2CH), 129.7 (2CH), 132.3 (C), 132.4 (C), 134.2 (C), 134.8 (C), 141.7 (C), 150.3 (C), 160.4 (C), 160.6 (C). Anal. calcd for $C_{18}H_{13}N_3S$ (303.4): C 71.26; H 4.32; N 13.85; S 10.57. Found: C 71.00; H 4.43; N 14.01; S 10.54.

4.9.3. Compound 1c. Yellowish green crystals (DMF), mp 198–200 °C LCMS $m/z=304$ (M+1). IR: 3072, 2916, 2859, 1627, 1503, 1467, 1335, 1173, 821, 696. ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H), 7.40 (d, 2H, $J=7.8$ Hz), 7.58 (m, 3H), 8.01 (d, 2H, $J=8$ Hz), 8.30 (s, 1H) 8.69 (dd, 2H, $J=2$, 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 21.4 (CH_3), 127.8 (2CH), 128.4 (2CH), 128.9 (2CH), 129.4 (C), 129.8 (2CH), 131.3 (CH), 134.1 (CH), 134.3 (C), 135.4 (C), 138.8 (C), 149.6 (C), 160.1 (C), 160.7 (C). Anal. calcd for $C_{18}H_{13}N_3S$ (303.4): C 71.26; H 4.32; N 13.85; S 10.57. Found: C 71.30; H 4.34; N 13.71; S 10.80.

4.9.4. Compound 1d. Yellowish green crystals (MeCN), mp 202–204 °C MS: $m/z=317$ (M^+, 100%); LCMS $m/z=$ 318 (M+1). ^{1}H NMR ($CDCl_3$): δ 2.48, 2.49 (2s, 6H, Ar*Me*), 7.38 (d, 2H, $J=8$ Hz), 7.39 (d, 2H, $J=8$ Hz), 7.99 (d, 2H, $J=8$ Hz), 8.27 (s, 1H) 8.58 (d, 2H, $J=8$ Hz). ^{13}C NMR ($CDCl_3$): δ 21.4, 21.6 ($2CH_3$), 127.8 (2CH), 128.4 (2CH), 129.3 (C), 129.4 (2CH), 129.7 (2CH), 132.5 (C), 134.3 (CH), 138.8 (C), 141.8 (C), 149.8 (C), 153.2 (C), 160.2 (C), 160.4 (C). Anal. calcd for $C_{19}H_{15}N_3S$ (317.4): C 71.90; H 4.76; N 13.24; S 10.10. Found: C 71.69; H 4.91; N 13.30; S 10.08.

Acknowledgements

The support of the University of Kuwait received through research grant no. SC06/01 and the facilities of ANALAB and SAF (grants no. GS01/01, GS02/01, GS03/01) are gratefully acknowledged.

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Tetrahedron 60 (2004) 9131–9137
Tetrahedron

Efficient microwave-assisted synthesis of new sulfonylbenzimidazole-4,7-diones: heterocyclic quinones with potential antitumor activity

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Received 24 May 2004; revised 19 July 2004; accepted 27 July 2004

Available online 28 August 2004

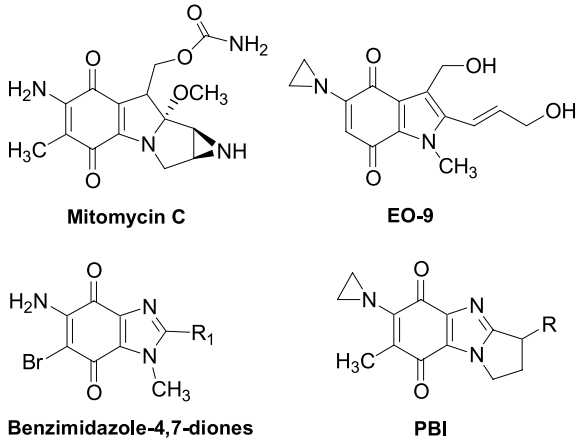
Abstract—New benzimidazoloquinones substituted at 2-position by a sulfonyl group have been synthesized via a final microwave assisted step using 2-chloromethyl-1,5,6-trimethylbenzimidazole-4,7-dione **7** as starting material.

1. Introduction

A great number of heterocyclic quinones have been extensively investigated for their biological activity and especially for their noticeable antitumor activity. Mitomycins[1–4] and the corresponding mitosenes (such as EO9[5] and many indole analogues[6]) are well-known examples of reductive alkylating quinones (Scheme 1). The reductive alkylation process involves the formation of an alkylating quinone methide species upon reduction of the quinone and elimination of the leaving group.[7] Pyrrolo[1,2-*a*]benzimidazoles (PBI) represent a new class of antitumor agent exhibiting cytotoxic activity against a variety of cancer cell lines. Significant biological properties also appear in some benzimidazolediones.[8,9] 5-Amino-6-bromobenzimidazole-4,7-dione shows good antitumor activity in vivo on P388 leukemia.[10] Furthermore, arylsulfone derivatives are well known for their biological properties such as antiviral[11] and antitumor[12–15] effects.

On the other hand, microwave irradiation is extensively used for the rapid synthesis of a variety of heterocyclic compounds.[16–21] The beneficial effects of microwave irradiation are finding an increased role in process chemistry, especially when conventional methods require forcing conditions or prolonged reaction times.[22–25]

Microwaves have also shown an advantage where processes involve sensitive reagents or when products may decompose under prolonged reaction conditions. The possibilities offered by this technology are particularly attractive for multi-step synthesis[26–28] and drug discovery process where high yielding protocols and avoidance or ease of purification are highly desirable.



Scheme 1.

In the light of the above reports and our continued interest in the preparation of new biologically active compounds,[29–32] we decided to synthesize a series of variously substituted benzimidazole-4,7-diones in order to evaluate their antiproliferative activity. The aim is to develop original and environmentally friendly procedures partially under microwave irradiation, and to investigate the influence of the

Keywords: Benzimidazole-4,7-diones; Microwave irradiation; *S*-Alkylation; Sulfones.
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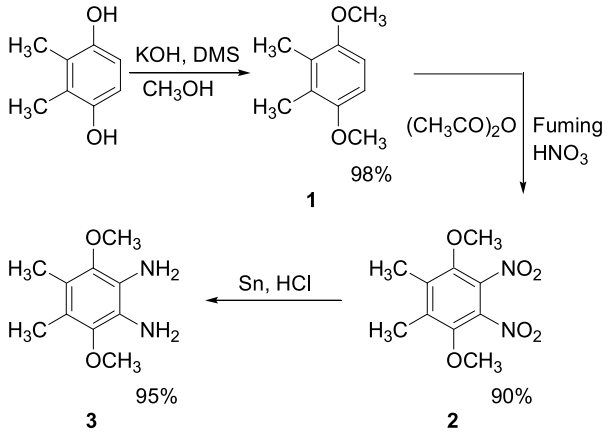
doi:10.1016/j.tet.2004.07.070

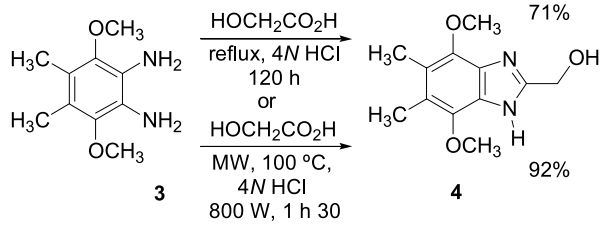


Scheme 2.

Table 1. Synthesis of (4,7-dimethoxy-5,6-dimethyl-1*H*-benzimidazol-2-yl)-methanol **4**

Entry	Conditions	Yield[a] (%)
1	Reflux toluene, 120 h	49
2	Reflux PPA, 120 h	55
3	Reflux 4*N* HCl, 24 h	14
4	Reflux 4*N* HCl, 48 h	32
5	Reflux 4*N* HCl, 120 h	71
6	800 W, 100 °C, 4*N* HCl, 30 min	34
7	800 W, 100 °C, 4*N* HCl, 1 h	70
8	800 W, 100 °C, 4*N* HCl, 1 h 30	92

[a] Yield of isolated and purified product.



Scheme 3.

sulfonyl group at the 2-position of the benzimidazole-4,7-dione nucleus.

2. Results and discussion

Some benzimidazole-4,7-dione derivatives have been previously reported in the literature.[33–35] Their synthesis was based on Day's method.[36] The (4,7-dimethoxy-5,6-dimethyl-1*H*-benzimidazol-2-yl)-methanol **4** was synthesized according to this procedure with significant modifications.

The hydroxyl functions of the commercially available 2,3-dimethyl-1,4-hydroquinone were protected by methylation using dimethylsulfate in alkaline medium to give compound **1** (98% yield).[37] The 1,4-dimethoxy-2,3-dimethyl-5,6-dinitrobenzene **2** was carried out by nitration of 1,4-dimethoxy-2,3-dimethylbenzene **1** with fuming nitric acid in acetic anhydride, with a 90% yield compared to 18.5% by using acetic acid (Scheme 2).[38]

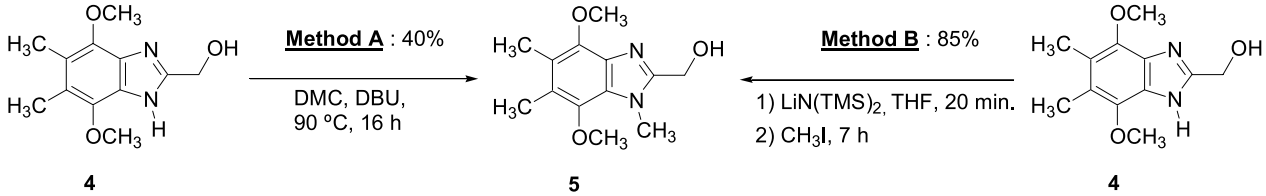
The reduction of **2** has been described in the literature with catalytic hydrogenation (83%),[38] using Pd/C, CH_3OH/HCl. In order to simplify the procedure, several trials were attempted to reduce the nitro groups of the 1,4-dimethoxy-2,3-dimethyl-5,6-dinitrobenzene **2** using Zn in acetic acid (34%), $FeCl_3$ in hydrazine (monoreduction), $NaBH_4$ or $TiCl_3$ in water-acetone (43%), but the yields obtained were rather poor and the reduction was sometimes incomplete. However, when the reduction was carried out using tin in concentrated hydrochloric acid the yield of the resulting diamine **3** was as high as 95%, and the process simplified.

The hydroxymethylbenzimidazole **4** could be obtained via the reaction of the *o*-diamine **3** with glycolic acid. In order to optimize the reaction yield, several experiments were attempted in refluxing toluene or in refluxing PPA (Table 1). After 120 h of reaction, a portion of starting material remained unchanged. When the cyclocondensation of **3** with glycolic acid was performed in refluxing 4*N* HCl solution, during 120 h, **4** was obtained in 71% yield (Scheme 3). Microwave irradiation is another potential strategy to realize this cycloaddition. The hydroxymethyl compound **4** was prepared in 92% yield from the condensation of the *o*-diamine **3** with glycolic acid in typical procedure (800 W, 100 °C, 4*N* HCl, 1 h 30). The reaction rate was accelerated from 120 to 1 h 30, which represents a rate increase of up to 80 times, with a simplified procedure and a higher yield (Table 1).

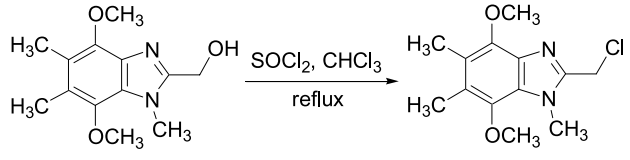
Two methods were tested to carry out a selective methylation of the NH group of **4**. Comparison of reaction times for *N*-methylation clearly shows the advantage of the protocol using lithium bis(trimethylsilyl)amide.[39,40] Indeed, we discovered that a more efficient conversion (85%) can be achieved in a shorter time at a lower temperature when method B is used (Scheme 4).

The (4,7-dimethoxy-1,5,6-trimethyl-1*H*-benzimidazol-2-yl)-methanol **5** was treated with thionyl chloride to give the corresponding chloromethyl derivative **6** in good yield (Scheme 5).

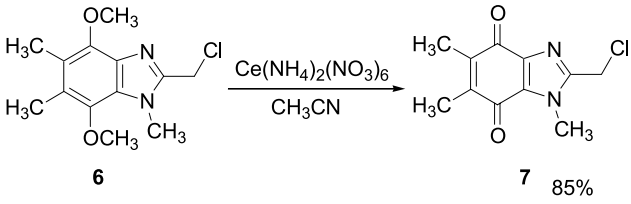
In the last step, an oxidative demethylation of **6** by treatment



Scheme 4.



Scheme 5.

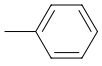
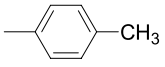
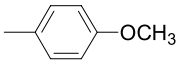
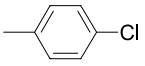
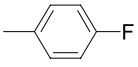
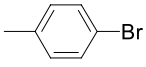
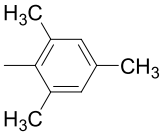
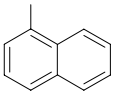
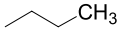


Scheme 6.

with cerium ammonium nitrate (CAN) gave the target quinone **7** in good yield (Scheme 6).[10]

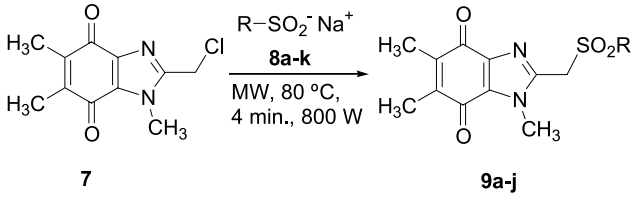
The 2-chloromethyl-1,5,6-trimethylbenzimidazole-4,7-dione **7** served as a point of departure for the synthesis of several new sulfonyl derivatives in benzimidazole-4,7-dione series.

Table 2. Benzimidazole-4,7-diones derivatives **9a–j** produced via Scheme 7[a]

Entry	R	Product	Yield[b] (%)
1		**9a**	87 (70)
2		**9b**	82 (68)
3		**9c**	85 (70)
4		**9d**	81 (65)
5		**9e**	89 (73)
6		**9f**	90 (75)
7		**9g**	80 (65)
8		**9h**	92 (78)
9		**9i**	80 (65)
10		**9j**	88 (71)

[a] All the reactions are performed using 3 equiv. of **8**.
[b] Yield of isolated and purified product, under microwave irradiation (800 W, 4 min, 80 °C). Parentheses show yield obtained using oil-bath heating (80 °C, 2 h).

Treating with the sodium salts of sulfinic acid derivatives **8a–j** in aqueous solution gave the corresponding *S*-alkylation products **9a–j** in 65–78% yields. Under conventional heating, a temperature of 80 °C was selected for 2 h. To evaluate the purely non-thermal microwave effects, the same temperature was applied under microwave irradiation, in water, during 4 min (Scheme 7). The results are summarized in Table 2. The use of microwave irradiation led to the same products, with higher yields (80–92%) in a shorter time (2 h to 4 min). It is evident that the effect lies in the enhancement by microwave radiation of nucleophilic attack by the sulfur atom on the chloromethyl group. This effect can be easily understood by considering the possible microwave activation affects by dipole–dipole interactions and by an increase in the polarity of the system during the reaction.



Scheme 7.

All the products obtained are to be screened for their antitumor activity and results will subsequently be published.

3. Conclusion

We describe here an efficient route to new benzimidazole-4,7-diones, from the intermediate 2-chloromethyl-1,5,6-trimethylbenzimidazole-4,7-dione **7** prepared in high yield (50%) in 7 steps. The microwave-assisted process, in contrast to conventional heating, gives the desired compounds in higher overall yield with shorter reaction times and products that are more easily purified. The specific non-thermal microwave effects are attributed to enhancements in microwave-materials interaction due to polarity increase during the reaction. This work confirms that reaction mixtures exposed to microwaves allow an easy and rapid access to original heterocyclic quinones with potential antitumor activities.

4. Experimental

4.1. General experimental

Melting points were determined on Büchi B-540 and are uncorrected. Elemental analyses were performed by the Microanalyses center of the University of Aix-Marseille 3 and of the INP-ENSCT (Toulouse, France). Both ^{1}H and ^{13}C NMR spectra were determined on a Bruker ARX 200 spectrometer. The ^{1}H chemical shifts are reported as ppm downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvent peak: $CDCl_3$ (76.9 ppm). Solvents were dried by conventional methods. The following adsorbent was used for column

chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC were performed on 5 cm×10 cm aluminium plates coated with silica gel 60F-254 (Merck) in an appropriate solvent.

4.2. Microwave instrumentation

Multimode reactor: ETHOS Synth Lab station (Ethos start, Milestone Inc). The multimode microwave has a twin magnetron (2×800 W, 2.45 GHz) with a maximum delivered power of 1000 W in 10 W increments (pulsed irradiation). Built-in magnetic stirring (Teflon-coated stirring bar) was used in all operations. During experiments, time, temperature and power were measured with the 'easy WAVE' software package. The temperature was measured throughout the reaction and evaluated by an infrared detector, which indicated the surface temperature.

In order to compare microwave irradiation with conventional heating, the reactions were performed under similar experimental conditions (weight of reactants and temperature) using a thermostated oil bath. The temperature was measured by the insertion of a Quick digital thermometer into the reaction mixture and the rate of the temperature rise was adjusted to be the same as measured under microwave irradiation.

4.3. Experimental procedure

4.3.1. 1,4-Dimethoxy-2,3-dimethylbenzene (1). 2,3-Dimethyl-1,4-hydroquinone (9.5 g, 70 mmol) was dissolved in methanol (75 mL) containing dimethyl sulfate (75 mL). The solution was heated and stirred vigorously, then a solution of potassium methoxide (95 g of KOH in 475 mL of methanol) was added quickly. The mixture was refluxed for 1 h. The precipitate was filtered, washed with water and dried in air. Recrystallization from methanol gave **1** (98%) as a white solid; mp 78 °C (Lit., 76–77 °C);[37] δ_H (200 MHz; $CDCl_3$) 2.16 (6H, s, 2 CH_3), 3.78 (6H, s, 2 OCH_3), 6.66 (2H, s, H Ar).

4.3.2. 1,4-Dimethoxy-2,3-dimethyl-5,6-dinitrobenzene (2). To a solution of 1,4-dimethoxy-2,3-dimethylbenzene **1** (10 g, 60.2 mmol) in acetic anhydride (80 mL) was added dropwise at 0 °C fuming nitric acid (15 mL). The reaction mixture was then heated at 90 °C for 1 h, poured into crushed ice (100 mL). The precipitate was filtered, washed with water and dried in air. Recrystallization from ethanol gave **2** (90%) as a yellow solid; mp 155 °C (Lit., 147–150 °C);[38] δ_H (200 MHz; $CDCl_3$) 2.30 (6H, s, 2 CH_3), 3.87 (6H, s, 2 OCH_3); δ_C NMR ($CDCl_3$) 13.53 (2 CH_3), 63.10 (2 OCH_3), 137.90 (2 C), 146.60 (2 C).

4.3.3. 3,6-Dimethoxy-4,5-dimethylbenzene-1,2-diamine (3). To a solution of tin (37 g, 312 mmol) in concentrated HCl (100 mL), was added 1,4-dimethoxy-2,3-dimethyl-5,6-dinitrobenzene **2** (10 g, 39 mmol). The reaction mixture was stirred vigorously until the excess of tin disappeared. The solution was then filtered, the precipitate was dissolved in water (100 mL), basified with 20% ammonia and extracted three times with chloroform (50 mL). The organic layers were dried over magnesium sulfate and concentrated under vacuum. Recrystallization of the residue from petroleum ether–chloroform (5/5) gave **3** (95%) as a white solid; mp 112 °C (Lit., 107–110 °C);[38] δ_H (200 MHz; $CDCl_3$) 2.11 (6H, s, CH_3), 3.43 (4H, s, NH_2), 3.68 (6H, s, OCH_3); δ_C NMR (50 MHz; $CDCl_3$) 11.91 (2 CH_3), 59.80 (2 OCH_3), 119.94 (2 C), 126.20 (2 C), 143.17 (2 C).

4.3.4. (4,7-Dimethoxy-5,6-dimethyl-1*H*-benzimidazol-2-yl)methanol (4). *Conventional conditions.* To a solution of 3,6-dimethoxy-4,5-dimethylbenzene-1,2-diamine **3** (10 g, 51 mmol) in 4*N* HCl (100 mL) was added glycolic acid (5.8 g, 76.3 mmol) in 4*N* HCl (50 mL). The reaction mixture was refluxed for 120 h. After cooling, the mixture was basified with 20% ammonia. The precipitate was filtered, washed with water and dried in air. Recrystallization from chloroform–ethanol (9/1) gave **4** (71%) as a white solid.

Microwave irradiation conditions. To a solution of 3,6-dimethoxy-4,5-dimethylbenzene-1,2-diamine **3** (10 g, 51 mmol) in 4*N* HCl (100 mL) was added glycolic acid (5.8 g, 76.3 mmol) in 4*N* HCl (50 mL). The reaction mixture was irradiated in a microwave oven (Ethos start) for 1 h 30 at a power of 800 W. After cooling, the mixture was basified with 20% ammonia. The precipitate was filtered, washed with water and dried in air. Recrystallization from chloroform–ethanol (9/1) gave **4** (92%) as a white solid; mp 163–164 °C; δ_H (200 MHz; $CDCl_3$) 2.23 (6H, s, CH_3), 3.88 (6H, s, OCH_3), 4.92 (2H, s, CH_2); δ_C (50 MHz; $CDCl_3$) 12.33 (2 CH_3), 58.00 (CH_2), 61.12 (2 OCH_3), 123.45 (2 C), 130.68 (2 C), 141.83 (2 C), 153.62 (C); Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86; found: C, 60.52; H, 6.79; N, 11.71.

4.3.5. (4,7-Dimethoxy-1,5,6-trimethyl-1*H*-benzimidazol-2-yl)methanol (5). *Method A.* To a solution of (4,7-dimethoxy-5,6-dimethyl-1*H*-benzimidazol-2-yl)methanol **4** (10 g, 42.3 mmol) in dimethyl carbonate (100 mL) was added dropwise DBU (1,8-diazabicyclo[5,4,0]undec-7-ene) (6.4 g, 42.03 mmol). The reaction mixture was heated to 90 °C and stirred during 16 h. After evaporation, the residue was dissolved in chloroform and washed with water (3× 30 mL). The organic layer was dried over magnesium sulfate and the solvent was removed under vacuum. The residue was dissolved in chloroform and washed with water. Purification on silica gel eluting with ethyl acetate and recrystallization from chloroform–ethanol (9/1) gave **5** (40%) as a white solid.

Method B. To a solution of (4,7-dimethoxy-5,6-dimethyl-1*H*-benzimidazol-2-yl)methanol **4** (10 g, 42.3 mmol) in THF (150 mL) was added dropwise at 0 °C under nitrogen lithium bis(trimethyl)silyl amide (14 g, 83.66 mmol). The reaction mixture was warmed to room temperature and stirred for 20 min. A solution of methyl iodide (6.63 g, 46.72 mmol) in THF (10 mL) was added dropwise via a syringe. The solution was stirred for 7 h. Water (200 mL) was added and the mixture was extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over magnesium sulfate and the solvent was removed under vacuum. Purification on silica gel eluting with ethyl acetate and recrystallization from chloroform–ethanol (9/1) gave **5** (85%) as a white solid; mp 192–193 °C; δ_H (200 MHz; $CDCl_3$) 2.16 (6H, s, CH_3), 3.12 (3H, s, NCH_3), 3.98 (6H, s,

OCH_3), 4.85 (2H, s, CH_2); δ_C (50 MHz; $CDCl_3$) 12.12 (CH_3), 12.35 (CH_3), 31.29 (NCH_3), 56.92 (CH_2), 61.04 (OCH_3), 62.12 (OCH_3), 122.13 (C), 124.80 (C), 127.92 (C), 134.08 (C), 139.83 (C), 145.05 (C), 152.51 (C). Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19; found: C, 62.31; H, 7.26; N, 11.22.

4.3.6. 2-Chloromethyl-4,7-dimethoxy-1,5,6-trimethyl-1*H*-benzimidazole (6). To a solution of (4,7-dimethoxy-1,5,6-trimethyl-1*H*-benzimidazol-2-yl)methanol **5** (10 g, 40 mmol) in chloroform (125 mL) was added dropwise thionyl chloride (10.5 mL). The mixture was refluxed for 4 h. The excess of thionyl chloride was then evaporated under vacuum. The residue was dissolved in chloroform and washed with water (3×50 mL). The organic layer was dried over magnesium sulfate. Purification of the crude product on silica gel eluting with chloroform and recrystallization from petroleum ether–chloroform (5/5) gave **6** (80%) as a white solid; mp 98–99 °C; δ_H (200 MHz; $CDCl_3$) 2.24 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.78 (3H, s, NCH_3), 4.03 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 4.80 (2H, s, CH_2); δ_C (50 MHz; $CDCl_3$) 12.22 (CH_3), 12.44 (CH_3), 31.54 (NCH_3), 36.96 (CH_2), 61.12 (OCH_3), 62.21 (OCH_3), 122.24 (C), 125.74 (C), 128.22 (C), 134.72 (C), 139.64 (C), 145.51 (C), 147.43 (C); Anal. Calcd for $C_{13}H_{17}ClN_2O_2$: C, 58.10; H, 6.38; N, 10.42; found: C, 58.13; H, 6.50; N, 10.40.

4.3.7. 2-Chloromethyl-1,5,6-trimethyl-1*H*-benzimidazole-4,7-dione (7). To a solution of 2-chloromethyl-4,7-dimethoxy-1,5,6-trimethyl-1*H*-benzimidazole **6** (5 g, 18.6 mmol) in acetonitrile (100 mL) was added dropwise a mixture of CAN (25.5 g, 46.5 mmol) in water (30 mL). The reaction mixture was stirred for 3 h and the solvent was evaporated under vacuum. The residue was dissolved in chloroform and washed with water (3×30 mL). The organic layer was dried over magnesium sulfate and the solvent was removed under vacuum. Recrystallization from 2-propanol gave **7** (85%) as a yellow solid; mp 168–169 °C; δ_H (200 MHz; $CDCl_3$) 2.06 (3H, s, CH_3), 2.09 (3H, s, CH_3), 4.03 (3H, s, NCH_3), 4.72 (2H, s, CH_2); δ_C (50 MHz; $CDCl_3$) 12.53 (CH_3), 12.89 (CH_3), 32.97 (NCH_3), 35.98 (CH_2), 131.92 (C), 140.63 (C), 141.02 (C), 141.54 (C), 149.55 (C), 179.30 (C), 181.12 (C); Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74; found: C, 55.30; H, 4.61; N, 11.75.

4.4. General procedure for the synthesis of the sulfone derivatives (9a–j)

The sodium salts were commercially available or prepared as previously described.[41]

Conventional conditions. To a solution of sodium salt of substituted sulfinic acid (2.52 mmol) in water (50 mL) at 80 °C, was added 2-chloromethyl-1,5,6-trimethyl-1*H*-benzimidazole-4,7-dione **7** (0.2 g, 0.84 mmol). The reaction mixture was heated at 80 °C for 2 h and filtered. The precipitate was dried in air, recrystallized from 2-propanol/chloroform (8:2).

Microwave irradiation conditions. To a solution of sodium salt of substituted sulfinic acid (2.52 mmol) in water (50 mL) was added 2-chloromethyl-1,5,6-trimethyl-1*H*-benzimidazole-4,7-dione **7** (0.2 g, 0.84 mmol). The reaction mixture was irradiated in a microwave oven (Ethos start) for 4 min at a power of 800 W. The aqueous solution was extracted with toluene (3×20 mL). The organic extracts were dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The product required was recrystallized from 2-propanol/chloroform (8:2).

4.4.1. 2-Benzenesulfonylmethyl-1,5,6-trimethyl-1*H*-benzimidazole-4,7-dione (9a). Yellow solid; 87% yield; mp 256–258 °C; δ_H (200 MHz; $CDCl_3$) 2.07 (6H, s, CH_3), 4.12 (3H, s, NCH_3), 4.65 (2H, s, CH_2); 7.51–7.73 (5H, m, H Ar); δ_C (50 MHz; $CDCl_3$) 12.17 (CH_3), 12.45 (CH_3), 33.30 (NCH_3), 54.68 (CH_2), 128.46 (2 CH), 129.40 (2 CH), 131.90 (C), 134.66 (CH), 137.65 (C), 140.31 (C), 141.04 (C), 141.90 (C), 143.19 (C), 178.66 (C), 180.47 (C). Anal. Calcd for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13; found: C, 59.29; H, 4.70; N, 8.13.

4.4.2. 1,5,6-Trimethyl-2-(toluene-4-sulfonylmethyl)-1*H*-benzimidazole-4,7-dione (9b). Yellow solid; 82% yield; mp 274–276 °C; δ_H (200 MHz; $CDCl_3$) 2.00 (6H, s, CH_3), 2.43 (3H, s, CH_3), 4.13 (3H, s, NCH_3), 4.62 (2H, s, CH_2), 7.29–7.32 (2H, d, $J=7.9$ Hz, H Ar), 7.56–7.60 (2H, d, $J=7.9$ Hz, H Ar); δ_C (50 MHz; $CDCl_3$) 12.05 (CH_3), 12.24 (CH_3), 21.27 (CH_3), 32.82 (NCH_3), 53.33 (CH_2), 128.32 (2 CH), 129.98 (2 CH), 131.65 (C), 135.73 (C), 139.85 (C), 140.01 (C), 140.55 (C), 143.76 (C), 145.19 (C), 178.25 (C), 180.44 (C). Anal. Calcd for $C_{18}H_{18}N_2O_4S$: C, 60.32; H, 5.06; N, 7.82; found: C, 60.34; H, 5.08; N, 7.80.

4.4.3. 2-(4-Methoxybenzenesulfonylmethyl)-1,5,6-trimethyl-1*H*-benzimidazole-4,7-dione (9c). Yellow solid, 85% yield; mp 264–265 °C; δ_H (200 MHz; $CDCl_3$) 2.00 (6H, s, CH_3), 3.87 (6H, s, NCH_3 and OCH_3), 5.08 (2H, s, CH_2), 7.12–7.16 (2H, d, $J=8.9$ Hz, H Ar), 7.69–7.73 (2H, d, $J=8.9$ Hz, H Ar); δ_C (50 MHz; $CDCl_3$) 12.39 (CH_3), 12.57 (CH_3), 33.14 (NCH_3), 53.82 (CH_2), 56.36 (OCH_3), 115.05 (2 CH), 130.38 (C), 130.98 (2 CH), 131.95 (C), 140.18 (C), 140.65 (C), 142.40 (C), 144.27 (C), 164.18 (C), 178.58 (C), 180.78 (C). Anal. Calcd for $C_{18}H_{18}N_2O_5S$: C, 57.74; H, 4.85; N, 7.48; found: C, 57.90; H, 4.80; N, 7.45.

4.4.4. 2-(4-Chlorobenzenesulfonylmethyl)-1,5,6-trimethyl-1*H*-benzimidazole-4,7-dione (9d). Yellow solid, 81% yield; mp 294–295 °C; δ_H (200 MHz; $CDCl_3$) 1.98 (6H, s, CH_3), 3.91 (3H, s, NCH_3), 5.23 (2H, s, CH_2), 7.71 (2H, d, $J=8.9$ Hz, H Ar), 7.80 (2H, d, $J=8.9$ Hz, H Ar); δ_C (50 MHz; $CDCl_3$) 12.25 (2 CH_3), 33.93 (NCH_3), 55.05 (CH_2), 129.04 (2 CH), 130.42 (2 CH), 137.23 (C), 139.65 (C), 140.05 (C), 143.47 (C), 150.20 (C),153.40 (C), 154.35 (C), 178.60 (C), 180.30 (C). Anal. Calcd for $C_{17}H_{15}ClN_2O_4S$: C, 53.90; H, 3.99; N, 7.39; found: C, 53.76; H, 4.02; N, 7.35.

4.4.5. 2-(4-Fluorobenzenesulfonylmethyl)-1,5,6-trimethyl-1*H*-benzimidazole-4,7-dione (9e). Yellow solid, 89% yield; mp 288–290 °C; δ_H (200 MHz; $CDCl_3$) 1.97 (6H, s, CH_3), 3.90 (3H, s, NCH_3), 5.21 (2H, s, CH_2), 7.43–7.50 (2H, m, H Ar), 7.82–7.89 (2H, m, H Ar); δ_C (50 MHz; $CDCl_3$) 12.03 (CH_3), 12.21 (CH_3), 33.23 (NCH_3), 53.50 (CH_2), 116.85 (CH), 117.31 (CH), 131.98 (CH), 132.19 (CH), 134.71 (C), 140.20 (C), 140.42 (C), 140.95 (C), 143.97 (C), 144.10 (C), 156.05 (C), 178.40 (C), 181.90 (C).

Anal. Calcd for $C_{17}H_{15}FN_2O_4S$: C, 56.35; H, 4.17; N, 5.24; found: C, 56.20; H, 4.13; N, 5.30.

4.4.6. 2-(4-Bromobenzenesulfonylmethyl)-1,5,6-trimethyl-1*H*-benzimidazole-4,7-dione (9f). Yellow solid, 90% yield; mp 295–296 °C; δ_H (200 MHz; $CDCl_3$) 1.99 (6H, s, CH_3), 3.91 (3H, s, NCH_3), 5.22 (2H, s, CH_2), 7.71 (2H, d, $J=8.9$ Hz, H Ar), 7.86 (2H, d, $J=8.9$ Hz, H Ar); δ_C (50 MHz; $CDCl_3$) 12.39 (CH_3), 12.57 (CH_3), 33.23 (NCH_3), 53.50 (CH_2), 130.10 (2 CH), 131.20 (2 CH), 136.50 (C), 138.90 (C), 139.95 (C), 144.20 (C), 151.10 (C),153.80 (C), 154.68 (C), 178.50 (C), 180.75 (C). Anal. Calcd for $C_{17}H_{15}BrN_2O_4S$: C, 48.24; H, 3.57; N, 6.62; found: C, 48.39; H, 3.63; N, 6.56.

4.4.7. 1,5,6-Trimethyl-2-(2,4,6-trimethylbenzene-sulfonylmethyl)-1*H*-benzimidazole-4,7-dione (9g). Yellow solid, 80% yield; mp 260–261 °C; δ_H (200 MHz; $CDCl_3$) 2.08 (6H, s, CH_3), 2.29 (3H, s, CH_3), 2.43 (6H, s, CH_3), 4.14 (3H, s, NCH_3), 4.61 (2H, s, CH_2), 6.93 (2H, s, H Ar); δ_C (50 MHz; $CDCl_3$) 12.17 (CH_3), 12.49 (CH_3), 21.09 (CH_3), 22.84 (2 CH_3), 33.35 (NCH_3), 53.67 (CH_2), 131.93 (C), 132.48 (2 CH), 140.27 (C), 140.52 (C), 141.02 (C), 142.50 (C), 143.64 (C), 143.80 (C), 144.40 (C), 145.80 (C), 179.38 (C), 180.45 (C). Anal. Calcd for $C_{20}H_{22}N_2O_4S$: C, 62.16; H, 5.74; N, 7.25; found: C, 62.29; H, 5.68; N, 7.17.

4.4.8. 1,5,6-trimethyl-2-(naphthalene-1-sulfonylmethyl)-1*H*-benzimidazole-4,7-dione (9h). Yellow solid, 92% yield; mp 285–287 °C; δ_H (200 MHz; $CDCl_3$): 1.94 (s, 6H, CH_3), 3.77 (s, 3H, NCH_3), 5.24 (s, 2H, CH_2), 7.68 (m, 3H, H Ar), 8.20 (m, 4H, H Ar); δ_C (50 MHz; $CDCl_3$): 12.38 (CH_3), 12.56 (CH_3), 33.14 (NCH_3), 54.01 (CH_2), 123.85 (CH), 125.28 (CH), 127.54 (CH), 128.77 (C), 129.19 (CH), 129.84 (CH), 131.58 (CH), 131.93 (C), 133.74 (C), 134.17 (C), 136.45 (CH), 140.14 (C), 140.31 (C), 140.82 (C), 143.84 (C), 178.47 (C), 180.61 (C). Anal. Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.94; H, 4.60; N, 7.10; found: C, 63.65; H, 4.67; N, 7.12.

4.4.9. 1,5,6-Trimethyl-2-(thiophene-2-sulfonylmethyl)-1*H*-benzimidazole-4,7-dione (9i). Yellow solid, 80% yield; mp 285–286 °C; δ_H (200 MHz; $CDCl_3$) 1.99 (6H, s, CH_3), 3.84 (3H, s, NCH_3), 5.26 (s, 2H, CH_2), 7.27 (1H, dd, $J=3.8$, 4.9 Hz, H Het), 7.70 (1H, dd, $J=1.3$, 3.8 Hz, H Het), 8.14 (1H, dd, $J=1.3$, 4.9 Hz, H Het); δ_C (50 MHz; $CDCl_3$) 12.40 (CH_3), 12.59 (CH_3), 33.11 (NCH_3), 54.93 (CH_2), 129.09 (CH), 131.97 (C), 136.06 (CH), 137.01 (CH), 138.98 (C), 140.22 (C), 140.39 (C), 140.92 (C), 142.50 (C), 178.58 (C), 180.75 (C). Anal. Calcd for $C_{15}H_{14}N_2O_4S_2$: C, 51.41; H, 4.03; N, 7.99; found: C, 51.34; H, 4.11; N, 7.85.

4.4.10. 2-(Butane-1-sulfonylmethyl)-1,5,6-trimethyl-1*H*-benzimidazole-4,7-dione (9j). Yellow solid, 88% yield; mp 152–153 °C; δ_H (200 MHz; $CDCl_3$) 0.93 (3H, t, $J=8.1$ Hz, CH_3), 1.45 (2H, m, CH_2), 1.81 (2H, m, CH_2), 2.08 (3H, s, CH_3), 2.10 (3H, s, CH_3), 3.13 (2H, t, $J=7.9$ Hz, CH_2), 4.09 (3H, s, NCH_3), 4.48 (s, 2H, CH_2); δ_C (50 MHz; $CDCl_3$) 12.15 (CH_3), 12.45 (CH_3), 13.47 (CH_3), 21.55 (CH_2), 23.30 (CH_2), 33.14 (NCH_3), 51.35 (CH_2), 51.91 (CH_2), 131.72 (C), 140.45 (C), 141.05 (C), 143.70 (C), 159.30 (C), 178.58 (C), 180.72 (C). Anal. Calcd for $C_{15}H_{20}N_2O_4S$: C, 55.54; H, 6.21; N, 8.64; found: C, 55.37; H, 6.31; N, 8.72.

Acknowledgements

This work was supported by the Centre National de la Recherche Scientifique and the Universities of Aix-Marseille. We express our thanks to Professor H. El-Kashef for stimulating discussions, and G. Lanzada for technical collaboration.

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Ring transformation of cyclohepta[*b*]pyrimido[5,4-*d*]furan-8(7*H*),10(9*H*)-dionylium ion to the corresponding pyrrole derivatives via troponeimine intermediates: photo-induced autorecycling oxidizing reactions of some amines

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Received 7 July 2004; revised 26 July 2004; accepted 26 July 2004

Available online 26 August 2004

Abstract—Ring transformation of 7,9-dimethylcyclohepta[*b*]pyrimido[5,4-*d*]furan- 8(7*H*),10(9*H*)-dionylium tetrafluoroborate $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ to 7,9-dimethylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrrole-8(7*H*),10(9*H*)-dionylium tetrafluoroborate $\mathbf{6a–d}^+\cdot\mathbf{BF}_4^-$ consists of the reaction of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ with amines and subsequent exchange of the counter-ion using aq. HBF_4. Reactions of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ with aniline and 4-substituted anilines afforded the corresponding pyrrole derivatives $\mathbf{6a–c}^+\cdot\mathbf{BF}_4^-$ directly in good yields. On the other hand, reaction of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ with benzylamine gave the troponeimine intermediate **9**, which was not converted to $\mathbf{6d}^+\cdot\mathbf{BF}_4^-$ and reverted to $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ by adding HBF_4; however, it was converted to $\mathbf{6d}^+\cdot\mathbf{BF}_4^-$ upon treatment with $(COCl)_2$ or $SOCl_2$, followed by exchange of the counter-ion. In a search for the characteristics of **9**, inspection and comparison of the X-ray crystal analyses, NMR and UV–vis spectra, and CV measurement of **9** and N,N-disubstituted troponeimine derivatives **12** were carried out to suggest the remarkable structure of **12** having ionic C–O bonding between the imine–carbon atom and the oxygen atom of the barbituric acid moiety in the solid state. Thus, characteristics of **9** were ascribed to the sterically hindered and favorable conformation of N-protonated troponeimine intermediates. Furthermore, novel photo-induced oxidation reactions of a series of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ towards some amines under aerobic conditions were carried out to give the corresponding imines in 455–8362% yields [based on compounds $\mathbf{4}^+$, $\mathbf{5}^+$, and $\mathbf{6a,e}^+$], suggesting the oxidation reaction occurs in an autorecycling process. Mechanistic aspects of the amine-oxidation reaction are also postulated.

1. Introduction

Flavins are known to play an important role as cofactors in a wide variety of biological redox reactions.[1] Dehydrogenation reactions represent a major category of processes mediated by a subclass of flavoenzymes known as oxidases. Included in this group are the oxidative transformations of alcohols to carbonyl compounds, of amines to imines, and of fatty acid esters to their α,β-unsaturated analogs.[2] The flavin-redox systems have been investigated extensively through synthetic model systems and theoretical calculations.[3] Among these, 5-deazaflavin **1a** (Fig. 1) has been studied extensively in both enzymatic[4] and model systems,[5,6] in the hope of gaining mechanistic insight into flavin-catalyzed reactions. In this relation, 5-deaza-10-oxaflavin **1b** (2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione),[7] in

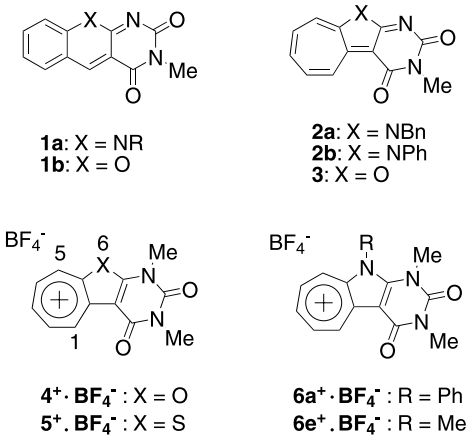

Figure 1.

Keywords: 7,9-Dimethylcyclohepta[*b*]pyrimido[5,4-*d*]furan-8(7*H*),10(9*H*)-dionylium tetrafluoroborate; 7,9-Dimethylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrol-8(7*H*),10(9*H*)-dionylium tetrafluoroborate; Ring-transformation; Photo-induced oxidation reaction.

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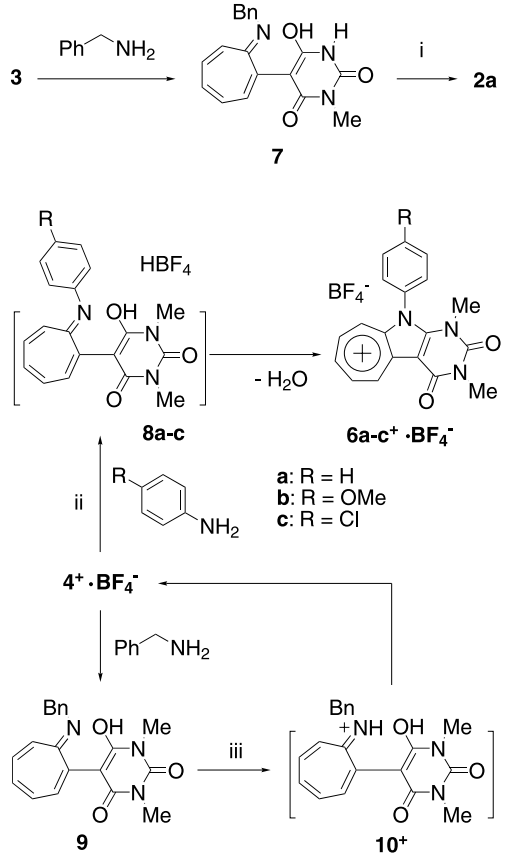
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.063

which the nitrogen atom is replaced by an oxygen, has also been synthesized and found to possess a strong function to oxidize alcohols to the corresponding carbonyl compounds. On the basis of the above observations, we have previously studied the preparation of 6-substituted 9-methylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(6*H*),10(9*H*)-diones (**2a**,**b**)[8] and 9-methylcyclohepta[*b*]pyrimido[5,4-*d*]furan-8,10(9*H*)-diones (**3**),[9] which are structural isomers of 5-deazaflavin **1a** and 5-deaza-10-oxaflavin **1b**. Furthermore, we have recently reported the synthesis, properties, and reactivity of 7,9-dimethylcyclohepta[*b*]pyrimido[5,4-*d*]furan-8(7*H*),10(9*H*)-dionylium tetrafluoroborate ($\mathbf{4}^+\cdot\mathbf{BF}_4^-$)[11,12] and its sulfur and nitrogen analogues $\mathbf{5}^+\cdot\mathbf{BF}_4^-$ and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$.[13,14] In addition, novel photo-induced autorecycling oxidizing reactions of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ toward some alcohols are studied as well.[12–14] Thus, the uracil-annulated heteroazulenes such as $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ are very interesting from the viewpoint of exploration of novel functions. Through these studies, we have accomplished a ring-transformation of **3** to **2a**,**b**,[10] which are clarified to have oxidizing ability toward some amines: the reaction of **3** with some amines undergoes ring-opening reaction of furan to give troponimine intermediates which undergo thermal ring-closure to give **2**.

From this viewpoint, we studied the ring transformation of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ to the corresponding pyrrole derivatives **6a**–$\mathbf{d}^+\cdot\mathbf{BF}_4^-$. In order to clarify the reactivity of the troponeimine intermediate, the detailed structural features



Scheme 1. Reagents and conditions: (i) 1,4-dioxane, reflux, 5 h; (ii) (a) CH_3CN, reflux, 3 h, (b) 42% aq HBF_4, Ac_2O, 0 °C, 1 h; (iii) 42% aq. HBF_4, Ac_2O, 0 °C, 1 h.

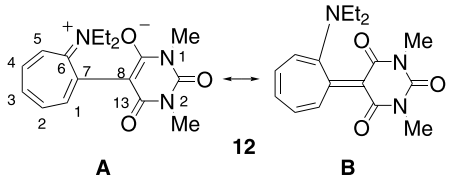


Figure 2. Numbering is shown according to the ORTEP drawing of **12**.

of isolated troponeimine intermediate **9** (Scheme 1) and N,N-disubstituted troponeimine **12** (Fig. 2) were investigated by inspection of their X-ray crystal analyses and spectral data including CV measurements. The remarkable structure of **12** having ionic C–O bonding between the imine-carbon atom and the oxygen atom of the barbituric acid moiety in the solid state was clarified. Thus, characteristics of **9** are rationalized by postulating sterically hindered and favorable conformation of the N-protonated troponeimine intermediates. Furthermore, the oxidizing ability of a series of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ toward some amines was studied as well. Furthermore, mechanistic aspects of the amine-oxidation reaction are also postulated. We report herein the results in detail.

2. Results and discussion

2.1. Ring-transformation

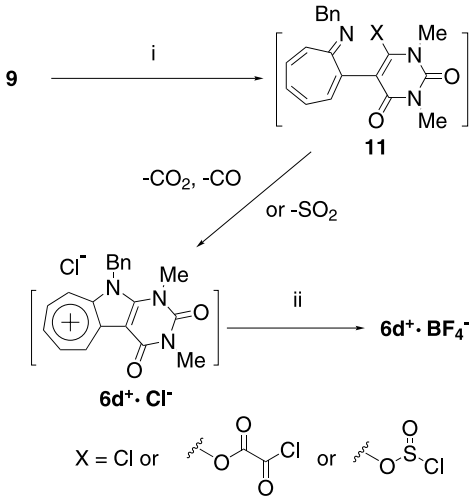
As the ring transformation of **3a** to **2a**,**b**, we have reported that the thermal reaction of troponeimine **7**, obtained by the reaction of **3** with benzylamine, gives neutral pyrrole derivative **2a** (Scheme 1).[10] Thus, a reaction of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ with $PhNH_2$ was carried out to give the corresponding troponeimine **8a**, which is labile and easily cyclizes at room temperature to give $\mathbf{6a}^+$. Thus, a thermal reaction of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ with $PhNH_2$ was carried out to give $\mathbf{6a}^+\cdot\mathbf{BF}_4^-$ quantitatively (Scheme 1, Table 1, entry 1). In order to elucidate the generality of this method, reactions of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ with 4-substituted anilines were carried out (Table 1). The reactions of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ with 4-$MeOC_6H_4NH_2$ and 4-$ClC_6H_4NH_2$ afforded the corresponding $\mathbf{6b,c}^+\cdot\mathbf{BF}_4^-$ in quantitative yields, respectively (entries 2 and 3). On the reaction of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ with 4-$NCC_6H_4NH_2$, which has a strong electron-withdrawing substituent, addition reaction was not observed in the ^1H NMR monitoring during prolonged reaction time, and the starting materials were recovered quantitatively (cf. entry 4).

On the other hand, we have recently reported that the reaction of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ with benzylamine gives troponeimine **9** (Scheme 1).[12] While the reaction of **9** with HBF_4 regenerates $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ (Scheme 1), thermal reaction of **9** resulted in the formation of a complicated mixture, and the expected compound $\mathbf{6d}^+\cdot\mathbf{BF}_4^-$ was not obtained.[12] Regarding the X-ray analysis of compounds $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$, large steric hindrance between the N6-substituent and N7Me has been suggested.[14] Thus, the possible steric hindrance between the large benzyl group and the NMe group in **9** seems to inhibit the cyclization. Thus, in order to accomplish the ring-transformation of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ to $\mathbf{6d}^+\cdot\mathbf{BF}_4^-$, inhibition of the nucleophilic attack of oxygen of the barbituric acid moiety as well as acceleration of the

Table 1. Results for the reaction of $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$ with aniline and 4-substituted anilines

Entry	$\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$	Aniline	Time[a]/h	Product	Yield[b]/%
1	$\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$	$PhNH_2$	3	$\mathbf{6a}^{+}\cdot\mathbf{BF}_4^{-}$	100
2	$\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$	$4\text{-}MeOC_6H_4NH_2$	3	$\mathbf{6b}^{+}\cdot\mathbf{BF}_4^{-}$	100
3	$\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$	$4\text{-}ClC_6H_4NH_2$	3	$\mathbf{6c}^{+}\cdot\mathbf{BF}_4^{-}$	100
4	$\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$	$4\text{-}NCC_6H_4NH_2$	24	None[c]	—

[a] Reaction was carried out in CH_3CN solution under reflux.
[b] Isolated yield.
[c] Reaction did not proceed and the starting materials were recovered quantitatively.



Scheme 2. Reagents and conditions: (i) $(COCl)_2$ or $SOCl_2$, conditions described in Table 2; (ii) 42% aq. HBF_4, Ac_2O, 0 °C, 1 h.

nucleophilic attack of nitrogen of the troponeimine moiety is necessary (vide infra). Thus, upon treatment with $(COCl)_2$ and $SOCl_2$, the hydroxyl group of **9** was expected to convert to a leaving group X, which can not attack the troponeimine moiety (Scheme 2). Under both conditions, the reaction of **9** with $(COCl)_2$ afforded a mixture of $\mathbf{6d}^{+}\cdot\mathbf{BF}_4^{-}$ and $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$ (Table 2, entries 1–3). In contrast, the reaction of **9** with $SOCl_2$ proceeded at room temperature to give $\mathbf{6d}^{+}\cdot\mathbf{BF}_4^{-}$ quantitatively (Table 2, entry 4).

Compound $\mathbf{6a}^{+}\cdot\mathbf{BF}_4^{-}$ was identified on the basis of a comparison of the physical data with those of the authentic specimen.[14] In addition, new compounds $\mathbf{6b–d}^{+}\cdot\mathbf{BF}_4^{-}$ were fully characterized on the basis of the ^1H and ^{13}C NMR, IR, and mass spectral data as well as elemental analysis. Furthermore, the CV measurement of $\mathbf{6b–d}^{+}\cdot\mathbf{BF}_4^{-}$ in CH_3CN exhibited irreversible reduction waves ($E1_{red}$), which are summarized in Table 3, together with those of the reference compounds. The irreversible nature is probably due to the formation of a radical species and its dimerization, as reported to be a typical property of uracil-annulated heteroazulenylium ions $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$,[12] $\mathbf{5}^{+}\cdot\mathbf{BF}_4^{-}$,[13] and $\mathbf{6a,e}^{+}\cdot\mathbf{BF}_4^{-}$.[14] While the $E1_{red}$ of $\mathbf{6d}^{+}\cdot\mathbf{BF}_4^{-}$ is similar to that of $\mathbf{6a}^{+}\cdot\mathbf{BF}_4^{-}$ (−0.84 V),[14] the $E1_{red}$ of $\mathbf{6b,c}^{+}\cdot\mathbf{BF}_4^{-}$ are less negative than that of $\mathbf{6a}^{+}\cdot\mathbf{BF}_4^{-}$. This feature is rationalized on the basis of the electron-withdrawing property of MeO- and Cl-substituted phenyl groups in $\mathbf{6b,c}^{+}\cdot\mathbf{BF}_4^{-}$, in which the substituted phenyl groups experience steric hindrance with the N7Me group and would twist against the plane of the heteroazulene unit.

2.2. Structural properties of troponeimines

We have recently reported that the reaction of $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$ with diethylamine gives the troponeimine **12** (Fig. 2).[12] Thus, the detailed characteristics of **9** and **12** are interesting

Table 2. Results for the reaction of imine **9** with $(COCl)_2$ and $SOCl_2$

Run	Additive	Solvent	Conditions	Product (yield[a]/%)
1	$(COCl)_2$	$(CH_2Cl)_2$	Room temperature, 1 h	$\mathbf{6d}^{+}\cdot\mathbf{BF}_4^{-}$ (26), $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$ (74)[b]
2	$(COCl)_2$	$(CH_2Cl)_2$	70 °C, 1 h	$\mathbf{6d}^{+}\cdot\mathbf{BF}_4^{-}$ (25), $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$ (75)[b]
3	$(COCl)_2$	None	Reflux, 3 h	$\mathbf{6d}^{+}\cdot\mathbf{BF}_4^{-}$ (78), $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$ (22)[b]
4	$SOCl_2$	None	Room temperature, 10 min	$\mathbf{6d}^{+}\cdot\mathbf{BF}_4^{-}$ (100)

[a] Isolated yield.
[b] Product ratio was calculated by ^1H NMR spectroscopy.

Table 3. Redox potentials of $\mathbf{6b–d}^{+}\cdot\mathbf{BF}_4^{-}$, **9**, and **12** and reference compounds $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$, $\mathbf{5}^{+}\cdot\mathbf{BF}_4^{-}$, and $\mathbf{6a,e}^{+}\cdot\mathbf{BF}_4^{-}$

Compound	Redox potential[a]		Compound	Redox potential[a]	
	$E1_{red}$	$E1_{ox}$		$E1_{red}$	$E1_{ox}$
$\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$[b]	−0.58	—	$\mathbf{6d}^{+}\cdot\mathbf{BF}_4^{-}$	−0.84	—
$\mathbf{5}^{+}\cdot\mathbf{BF}_4^{-}$[b]	−0.53	—	$\mathbf{6e}^{+}\cdot\mathbf{BF}_4^{-}$[c]	−0.87	—
$\mathbf{6a}^{+}\cdot\mathbf{BF}_4^{-}$[d]	−0.84	—			
$\mathbf{6b}^{+}\cdot\mathbf{BF}_4^{-}$	−0.80	—	**9**	−1.40	+0.63
$\mathbf{6c}^{+}\cdot\mathbf{BF}_4^{-}$	−0.76	—	**12**	−1.85	+0.41

[a] V vs. $Ag/AgNO_3$; cathodic and anodic peak potentials.
[b] Ref. 10.
[c] Ref. 15.
[d] Ref. 13.

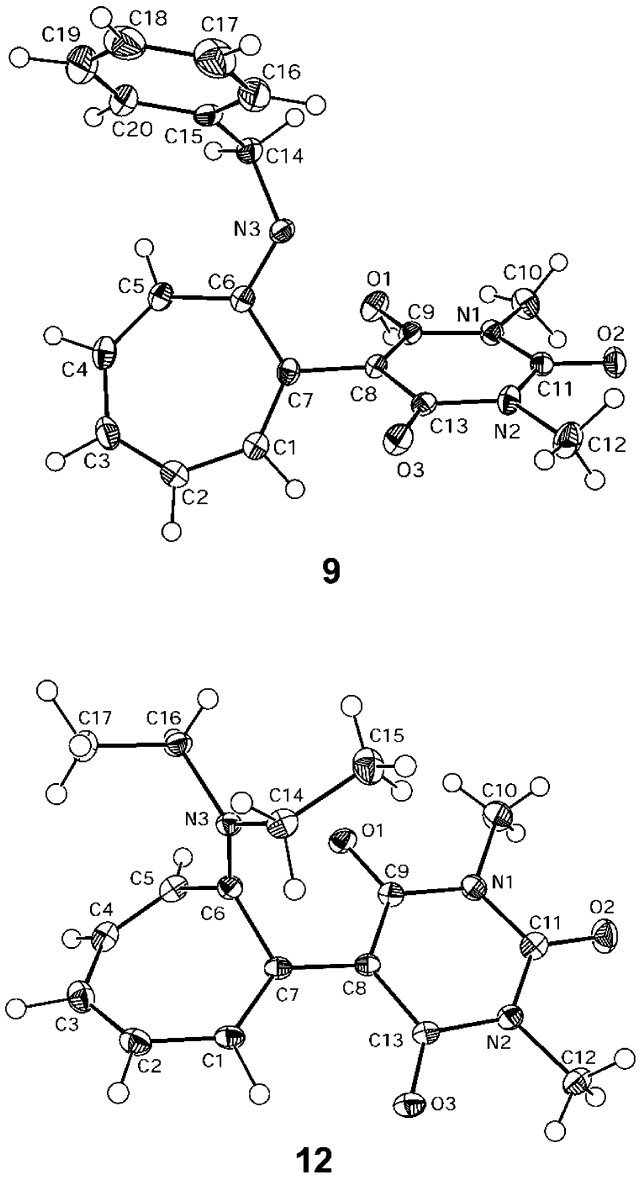


Figure 3. ORTEP drawing of **9** and **12** with thermal ellipsoid plot (50% probability).

in the view of clarifying the unreactive nature of **9** in the present ring transformation. Single crystals of **9** and **12** were obtained by recrystallization from $CHCl_3$ and AcOEt, respectively, and their ORTEP drawings are shown in Figure 3. The barbituric acid moiety of **9** has a nearly planar structure, while the troponeimine moiety has a boat shape, but the deformation from planarity is small. Furthermore, the troponeimine moiety of **9** shows a large bond alternation. In addition, the atomic distances of O1–C6 and N3–C9 are 3.039 and 3.023 Å, respectively (Table 4), and the dihedral angle of C6–C7–C8–C9 is 57.3°. On the other hand, the troponeimine moiety of **12** shows a large bond alternation as shown in the canonical structure **12-A** (Fig. 2, Table 4), which is supported by the ^1H and ^{13}C NMR study.[12] While the barbituric acid moiety of **12** has a nearly planar structure, the troponeimine moiety is highly distorted to a boat shape. A remarkable feature is the short atomic distance of O1–C6 (2.362 Å), which is larger than a typical O–C covalent bond (1.43 Å),[16] but it is considerably shorter than the sum of the van der Waals radii (3.25 Å).[16] This is probably due to the interaction between the O1 and the C6; however, the sum of the bond angles of N3–C6–C5, N3–C6–C7, and C5–C6–C7 is 359.1°, and thus, the C6 carbon atom exists as sp^2 hybridization. Furthermore, the short bond length of the N3–C6 (1.304 Å) suggests its double bond character, and the bond length of the O1–C9 is similar to that of the O3–C13. These features support that the interaction of the O1–C6 is an ionic bonding, and not a covalent bonding in the solid state. The remarkable structure of **12** seems close to the transition state of the intramolecular nucleophilic addition of the O1 atom reverting to the furan-ring of $\mathbf{4}^+$: intermediate $\mathbf{10}^+$, generated by protonation of **9**, may have a structure similar to that of **12**, and thus, the acidic reaction of **9** using aq. HBF_4 easily regenerate $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ (Scheme 1). Thus, in order to accomplish the ring transformation of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ to $\mathbf{6d}^+\cdot\mathbf{BF}_4^-$, $(COCl)_2$ or $SOCl_2$ is required for cyclization of **9** to $\mathbf{6d}^+\cdot\mathbf{BF}_4^-$ (vide supra).

On the other hand, in the ^1H NMR spectrum of **12**, the signals of N1Me and N3Me appear equivalent (δ 3.34) at room temperature.[12] They appear as two sharp singlets at low temperature (−90 °C), while the signals of the seven-membered ring show no appreciable change. Thus, rapid rotation around the C7–C8 bond of **12** (Fig. 2) clearly occurs on the NMR time scale at room temperature in solution. Through variable temperature ^1H NMR measurement of **12**, the coalescence temperature was determined to be 261 K, and the chemical shift difference between N1Me and N3Me was 50.6 Hz. Consequently, rotational barrier ($\Delta G^{\ddagger}$) around the C7–C8 bond was determined to be 12.75 kcal mol^{-1}. In the ^{13}C NMR spectrum of **12** at −90 °C, the signals of two carbonyl-carbons C9 and C13 appear as two sharp signals (δ_C 160.3 and 161.5), which is not changed from the

Table 4. Bond lengths and atomic distance of **9** and **12** obtained by X-ray structure analysis

Bond[a]	Bond length/Å		Bond[a]	Bond length/Å	
	9	**12**		**9**	**12**
O1–C6[b]	3.039(3)	2.362(3)	C1–C7	1.372(4)	1.375(3)
N3–C9[b]	3.023(3)	3.300(3)	N3–C6	1.331(4)	1.305(3)
C1–C2	1.429(4)	1.444(3)	C7–C8	1.479(4)	1.448(3)
C2–C3	1.348(4)	1.369(4)	C8–C9	1.408(4)	1.414(3)
C3–C4	1.419(4)	1.429(4)	C8–C13	1.421(4)	1.425(3)
C4–C5	1.354(4)	1.359(4)	O1–C9	1.242(3)	1.243(3)
C5–C6	1.436(3)	1.457(3)	O3–C13	1.243(3)	1.239(3)
C6–C7	1.459(4)	1.486(3)			

[a] The numbering is shown in Figure 3.
[b] Atomic distance.

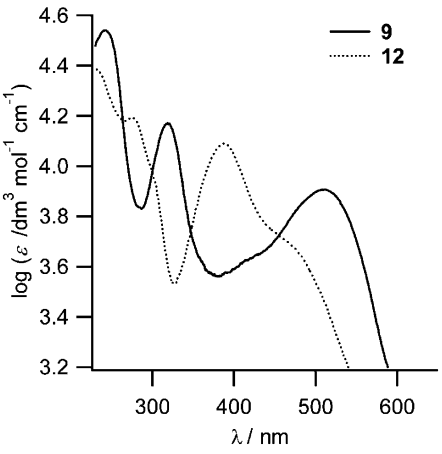
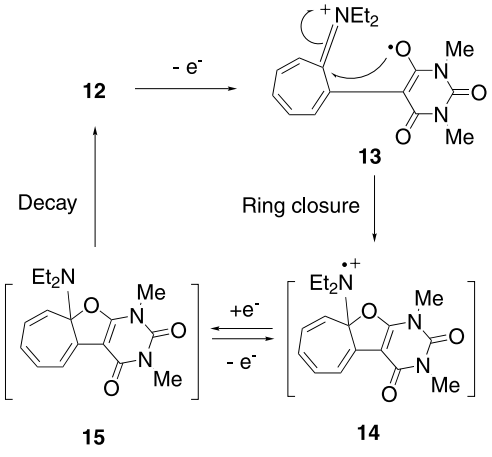


Figure 4. UV–vis spectra of **9** and **12** in CH_3CN.

equivalent signal at room temperature (δ_C 162.1).[12] In addition, the chemical shift of the iminium-carbon C6 at −90 °C (δ_C 172.6) is similar to the corresponding signal at room temperature (δ_C 174.4),[12] thus, the interaction between the carbonyl oxygen atom O1 and the C6 would not be large in solution.

The UV–vis spectral data of **9** and **12** in CH_3CN are summarized in Figure 4. The spectra of **9** and **12** show remarkable difference, and the longest wavelength absorption maximum of **12** shows a blue-shift by 122 nm, as compared with that of **9**. Furthermore, the reduction and oxidation potentials of **9** and **12** in CH_3CN were determined by cyclic voltammetry (CV), and each reduction wave and oxidation wave are irreversible. While the reduction potentials ($E1_{red}$) of **9** and **12** are −1.40 and −1.85 V, respectively, their oxidation potentials ($E1_{ox}$) are +0.63 and +0.41 V, respectively. Thus, the values ($E1_{red}$ and $E1_{ox}$) of **12** are more negative than those of **9**. After the first cycle of CV measurement of **12**, another reversible reduction wave was recorded at +0.10 V, which is probably the reduction wave of **14**, generated by cyclization of **13** under CV measurement (Scheme 3). After generation of **14** and subsequent measurement in the limited range of −0.20 and +0.40 V, decay of this wave was observed due to the slow ring-opening reaction of **15** giving **12**. In contrast, neutral imine **9** does not exhibit behavior similar to that of **12**.

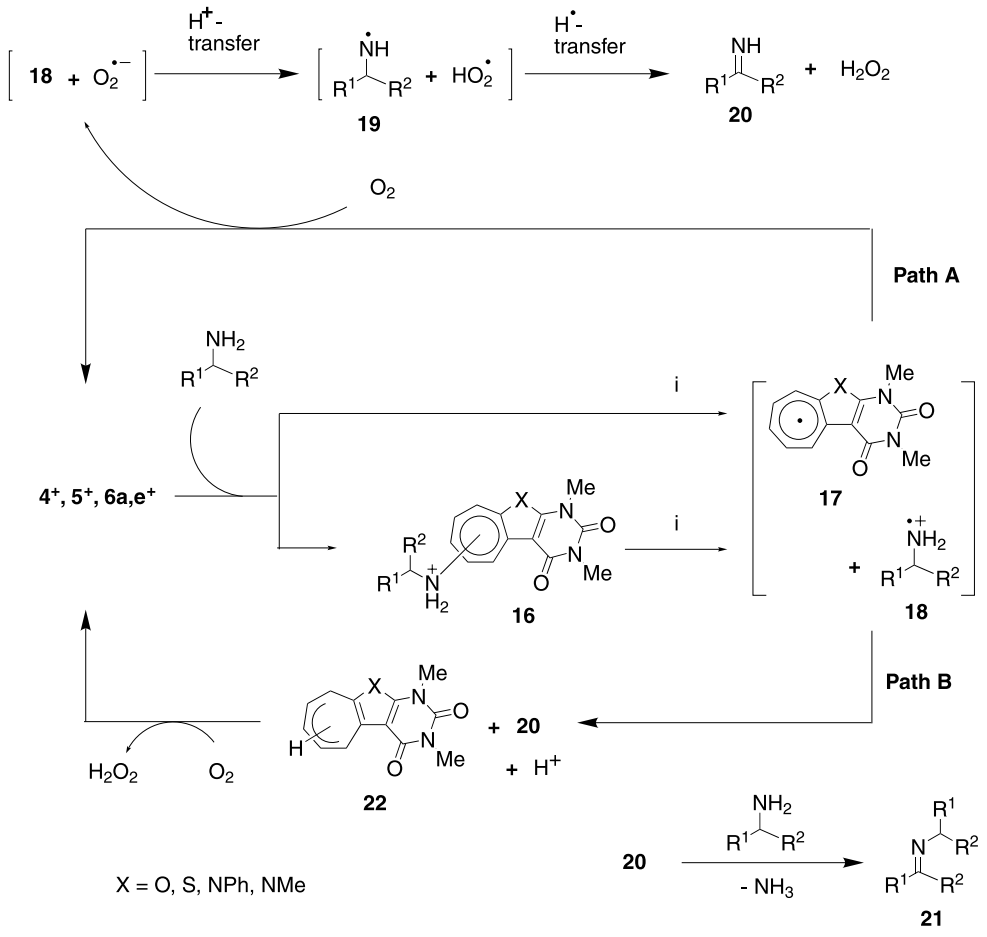


Scheme 3.

2.3. Autorecycling oxidation

We have previously reported that compounds $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ undergo autorecycling oxidation of some alcohols to give the corresponding carbonyl compounds under photo-irradiation.[12–14] In this context and in a search for other functions, we examined the oxidation of some amines by using $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ as well as sulfur analogue $\mathbf{5}^+\cdot\mathbf{BF}_4^-$ under aerobic and photo-irradiation conditions (RPR-100, 350 nm lamps). We found that a series of compounds $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ have an oxidizing ability toward some amines to give the corresponding imines. Imines **20** are produced at first; and they react with other amines to result in the formation of $R^1R^2C{=}N{-}CHR^1R^2$ (**21**) (Scheme 4). The results are summarized in Table 5. Direct irradiation of the amines in the absence of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ (named 'blank') gives the imines in low to modest yields. Thus, the yields of imines are calculated by subtraction of the 'blank' yield from the yields obtained in the presence of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$. More than 100% yields are obtained [based on compounds $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$] (Table 5), and thus, autorecycling oxidation clearly proceeds; however, cyclohexylamine was not oxidized (Table 5, entries 26–29). In order to clarify the details of the oxidizing reaction, time dependency of the yields of the imines was investigated as summarized in Table 5 (entries 1–16) and Figure 5. Concerning the oxidizing reaction using $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, the yield of benzaldimine was increased simply as the irradiation time was prolonged to 8 h. After irradiation for 12 and 16 h, the yield of benzaldimine is not so increased, suggesting plausible decomposition of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$. A Similar feature is observed in the oxidizing reaction by using $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$. The photo-irradiation of CD_3CN solution of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ in the absence of amine under aerobic conditions, decomposition of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ was not observed as monitored by their ^1H NMR spectra. Thus, the decomposition of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ would occur in their oxidation cycle.

Furthermore, in the oxidation of benzylamine by using $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$, the yield of the imine became higher in the order $\mathbf{6e}^+\cdot\mathbf{BF}_4^- < \mathbf{6a}^+\cdot\mathbf{BF}_4^- < \mathbf{5}^+\cdot\mathbf{BF}_4^-$ (Table 5, entries 5–16). This fact is probably ascribed to the $E1_{red}$ values in the order $\mathbf{6e}^+\cdot\mathbf{BF}_4^-$ (−0.87 V)[14] > $\mathbf{6a}^+\cdot\mathbf{BF}_4^-$ (−0.84 V)[14] > $\mathbf{5}^+\cdot\mathbf{BF}_4^-$ (−0.53 V).[13] [The reduction potentials of $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ in the ground state would be correlated with their LUMO's, and thus, the LUMO's of these compounds would be lower in the order $\mathbf{6e}^+\cdot\mathbf{BF}_4^- > \mathbf{6a}^+\cdot\mathbf{BF}_4^- > \mathbf{5}^+\cdot\mathbf{BF}_4^-$. In the excited state of these compounds, the electron-accepting orbital would be the singly occupied HOMO's. In as much as the UV–vis spectra of these compounds are similar, and thus, the energy level of HOMO's of the compounds is expected to be lower in the order $\mathbf{6e}^+\cdot\mathbf{BF}_4^- > \mathbf{6a}^+\cdot\mathbf{BF}_4^- > \mathbf{5}^+\cdot\mathbf{BF}_4^-$.] A similar tendency was observed in the cases of the oxidation of 1-phenylethylamine and hexylamine (Table 5, entries 19–21 and 23–25). Benzylamine and hexylamine are oxidized more effectively by using $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ (Table 5, entries 4 and 22), which has a lower



Scheme 4. Reagents and conditions: (i) hν, aerobic, CH_3CN, room temperature.

oxidizing ability toward 1-phenylethylamine as compared to $\mathbf{5}^+\cdot\mathbf{BF}_4^-$ (cf. entries 18 and 19). The feature is probably due to the ring-opening reaction of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ with some amines. However, in the oxidation of benzylamine by using isolated **9**, the yield of the imine (643%) is lower than that by using $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ (8161%) (Table 5, entries 17 and 4). Thus, the presence of HBF_4 is necessary for the effective oxidizing cycle, suggesting that the reaction of **9** with HBF_4 would regenerate $\mathbf{4}^+\cdot\mathbf{BF}_4^-$ in the oxidizing cycle.

In a search for the substituent effect of benzylamine toward oxidation, the oxidation reactions of 4-substituted

Table 5. Autorecycling oxidation of some amines by $\mathbf{4}^+\cdot\mathbf{BF}_4^-$–$\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ under photo-irradiation[a]

Entry	Compound	Amine	Time/h	Yield[b]/%	Entry	Compound	Amine	Time/h	Yield[b]/%
1	$\mathbf{4}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	4	4601	18	$\mathbf{4}^+\cdot\mathbf{BF}_4^-$	$PhCH(Me)NH_2$	16	3947
2	$\mathbf{4}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	8	7559	19	$\mathbf{5}^+\cdot\mathbf{BF}_4^-$	$PhCH(Me)NH_2$	16	7040
3	$\mathbf{4}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	12	7951	20	$\mathbf{6a}^+\cdot\mathbf{BF}_4^-$	$PhCH(Me)NH_2$	16	3533
4	$\mathbf{4}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	16	8161	21	$\mathbf{6e}^+\cdot\mathbf{BF}_4^-$	$PhCH(Me)NH_2$	16	2367
5	$\mathbf{5}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	4	3552	22	$\mathbf{4}^+\cdot\mathbf{BF}_4^-$	Hexylamine	16	7464
6	$\mathbf{5}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	8	5076	23	$\mathbf{5}^+\cdot\mathbf{BF}_4^-$	Hexylamine	16	4457
7	$\mathbf{5}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	12	6846	24	$\mathbf{6a}^+\cdot\mathbf{BF}_4^-$	Hexylamine	16	2557
8	$\mathbf{5}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	16	6993	25	$\mathbf{6e}^+\cdot\mathbf{BF}_4^-$	Hexylamine	16	1564
9	$\mathbf{6a}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	4	1476	26	$\mathbf{4}^+\cdot\mathbf{BF}_4^-$	Cyclohexylamine	16	0[c]
10	$\mathbf{6a}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	8	2552	27	$\mathbf{5}^+\cdot\mathbf{BF}_4^-$	Cyclohexylamine	16	0[c]
11	$\mathbf{6a}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	12	4133	28	$\mathbf{6a}^+\cdot\mathbf{BF}_4^-$	Cyclohexylamine	16	0[c]
12	$\mathbf{6a}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	16	4175	29	$\mathbf{6e}^+\cdot\mathbf{BF}_4^-$	Cyclohexylamine	16	0[c]
13	$\mathbf{6e}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	4	455	30	$\mathbf{4}^+\cdot\mathbf{BF}_4^-$	$4\text{-}MeOC_6H_4CH_2NH_2$	16	6278
14	$\mathbf{6e}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	8	1385	31	$\mathbf{4}^+\cdot\mathbf{BF}_4^-$	$4\text{-}MeC_6H_4CH_2NH_2$	16	7967
15	$\mathbf{6e}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	12	2993	32	$\mathbf{4}^+\cdot\mathbf{BF}_4^-$	$4\text{-}ClC_6H_4CH_2NH_2$	16	8362
16	$\mathbf{6e}^+\cdot\mathbf{BF}_4^-$	$PhCH_2NH_2$	16	3000	33	$\mathbf{4}^+\cdot\mathbf{BF}_4^-$	$4\text{-}PyCH_2NH_2$	16	6789
17	**9**	$PhCH_2NH_2$	16	643					

Isolated by converting to the corresponding 2,4-dinitrophenylhydrazone.

[a] CH_3CN solution was irradiated by RPR-100, 350 nm lamps under aerobic conditions.

[b] Based on $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$ used; the yield is calculated by subtraction of the 'blank' yield from the total yield of carbonyl compound in the presence of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$.

[c] The blank yield was higher than the yield in the presence of $\mathbf{4}^+\cdot\mathbf{BF}_4^-$, $\mathbf{5}^+\cdot\mathbf{BF}_4^-$, and $\mathbf{6a,e}^+\cdot\mathbf{BF}_4^-$.

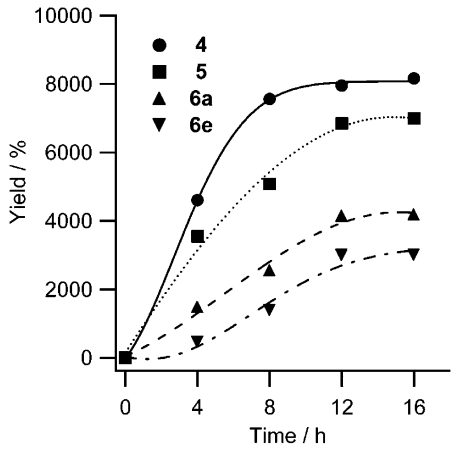


Figure 5. Time dependency of autorecycling oxidation of benzylamine by using $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$, $\mathbf{5}^{+}\cdot\mathbf{BF}_4^{-}$, and $\mathbf{6a,e}^{+}\cdot\mathbf{BF}_4^{-}$.

benzylamines and picolylamine were carried out by using $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$ under aerobic and photo-irradiation conditions (Table 5, entries 30–33). The yields of imines are plotted against the Hammet constants σ_p[17] of the substituents on the phenyl group and 4-picolylamine in Figure 6. The plots seem to show a maximum value, and the yield of photo-induced oxidation of the benzylamines becomes low at either the high value (σ_p 0.23, 4-$ClC_6H_4CH_2NH_2$) or the low value (σ_p −0.27, 4-$MeOC_6H_4CH_2NH_2$). The yields of the imine derived from 4-picolylamine, which corresponds to the benzylamine having a strong electron-withdrawing substituent, becomes low and may be close to the yield expected from 4-nitrobenzylamine. Thus, the oxidizing reaction by using $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$ becomes less effective for the amines, which have both lower and higher oxidation potential. This feature is similar to the cases of the photo-induced oxidizing reaction of benzy alcohol by using a flavin analogue[18] and the case of photo-induced oxidizing reaction of benzylamine by using **2a**,**b**,[10] and thus, it is rationalized by the pathways via a tropyl radical intermediate (vide infra).

The mechanistic pathways for the present oxidation of amines are depicted in Scheme 4 by using general structures.[18] The electron-transfer from amine to the excited state of $\mathbf{4}^{+}$, $\mathbf{5}^{+}$, and $\mathbf{6a,b}^{+}$ would occur to produce radicals **17** and a cation radical **18**. On the other hand, the amine-adducts obtained by the reaction of $\mathbf{4}^{+}$, $\mathbf{5}^{+}$, and $\mathbf{6a,e}^{+}\cdot\mathbf{BF}_4^{-}$ with amines, are stable in solution in the dark.[12–14] Thus, there is also a possibility that the homolysis of **16** by photo irradiation would afford **17** and **18** directly. An electron transfer from radical species **17** to a molecular oxygen would regenerate $\mathbf{4}^{+}$, $\mathbf{5}^{+}$, and $\mathbf{6a,e}^{+}$, and the superoxide anion radical, since tropyl radical derivatives are known to be readily oxidized by molecular oxygen.[19] Then, a proton-transfer from cation radical **18** to a superoxide anion radical occurs to result in the formation of the products **20** and H_2O_2 (Path A). Compound **20** reacts with excess amine to give imine **21**. Substituted benzylamine having a more negative oxidation potential seems to favor the electron transfer process from amine to the excited state of $\mathbf{4}^{+}$, $\mathbf{5}^{+}$, and $\mathbf{6a,e}^{+}$, but disfavors the proton transfer process from the cation radical **18** to the superoxide anion radical. On the contrary, substituted benzylamine having a more positive oxidation potential disfavors the electron transfer process from amine to the excited state of $\mathbf{4}^{+}$, $\mathbf{5}^{+}$, and $\mathbf{6a,e}^{+}$, while the proton transfer process from cation radical **18** to the superoxide anion radical becomes more favorable. As such, a sensitive balance between the electron donor ability of amine and the proton donor ability of cation radical **18** is required to achieve the efficient photo-induced oxidation reaction of amines. There may be an alternative mechanistic pathway (Path B), in which compound **22** and the imine **20** are generated directly from **17** and **18**; the former compound is oxidized under aerobic and photo-irradiation conditions to regenerate $\mathbf{4}^{+}$, $\mathbf{5}^{+}$, and $\mathbf{6a,e}^{+}$. Under aerobic and photo-irradiation conditions, the CD_3CN solution of **22** was easily oxidized to regenerate $\mathbf{4}^{+}$, $\mathbf{5}^{+}$, and $\mathbf{6a,e}^{+}$ quantitatively. Thus, autorecycling oxidation would also be possible in this Path B. However, attempted detection of compound **17** or its dimers or compound **22** was unsuccessful in the oxidation reaction of benzylamine under degassed and photo-irradiation conditions (degassed by freeze–pump–thaw cycles). Thus, we prefer the former pathway (Path A).

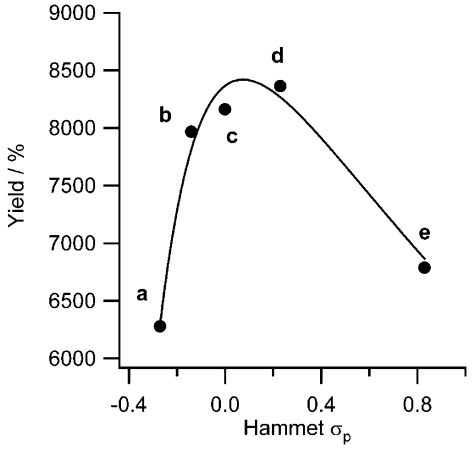


Figure 6. The Hammet plot of autorecycling oxidation of 4-substituted benzylamine by $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$. (a: 4-$MeOC_6H_4CH_2NH_2$, b: 4-$MeC_6H_4CH_2NH_2$, c: $PhCH_2NH_2$, d: 4-$ClC_6H_4CH_2NH_2$, e: 4-$PyCH_2NH_2$).

3. Conclusion

The ring transformation of $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$ to the corresponding pyrrole derivatives $\mathbf{6a–d}^{+}\cdot\mathbf{BF}_4^{-}$ was accomplished. Furthermore, the detailed characteristics of troponeimine intermediates **9** and **12** were clarified by the inspection of their X-ray crystal analyses, NMR, UV–vis spectra, and CV measurements. Novel photo-induced oxidation reaction of $\mathbf{4}^{+}\cdot\mathbf{BF}_4^{-}$, $\mathbf{5}^{+}\cdot\mathbf{BF}_4^{-}$, and $\mathbf{6a,e}^{+}\cdot\mathbf{BF}_4^{-}$ toward some amines under aerobic conditions was clarified to give the corresponding imines in more than 100% yield [based on compounds $\mathbf{4}^{+}$, $\mathbf{5}^{+}$, and $\mathbf{6a,e}^{+}$], suggesting the oxidation reaction occurs in an autorecycling process. Mechanistic aspects of the amine-oxidation are also postulated.

4. Experimental

4.1. General

IR spectra were recorded on a HORIBA FT-710

spectrometer. Mass spectra and high-resolution mass spectra were run on JMS-AUTOMASS 150 and JMS-SX102A spectrometers. Unless otherwise specified, ^{1}H and ^{13}C NMR spectra were recorded on JNM-lambda500 and AVANCE600 spectrometers using CD_3CN as a solvent, and the chemical shifts are given relative to internal $SiMe_4$ standard; *J*-values are given in Hz. Mps were recorded on a Yamato MP-21 apparatus and were uncorrected.

4.2. Ring transformation of $4^+ \cdot BF_4^-$ to $6a–c^+ \cdot BF_4^-$

To a solution of $\mathbf{4}^+ \cdot \mathbf{BF_4^-}$ (99 mg, 0.3 mmol) in CH_3CN (10 mL) was added aniline or 4-substituted aniline (1.2 mmol), and the mixture was heated under reflux until the reaction was completed (Table 1). The mixture was concentrate in vacuo, the resulting residue was dissolved in a mixture of acetic anhydride (5 mL) and 42% aq HBF_4 (1 mL) at 0 °C, and it was stirred for another 1 h. To the mixture was added Et_2O (50 mL) and the precipitates were collected by filtration to give products $\mathbf{6a–c}^+ \cdot \mathbf{BF_4^-}$ (Table 1). Compound $\mathbf{6a}^+ \cdot \mathbf{BF_4^-}$ was identical with the authentic specimen.[14]

4.2.1. 7,9-Dimethyl-6-(4′-methoxyphenyl)cyclohepta[*b*]-pyrimido[5,4-*d*]pyrrole-8(7*H*), 10(9*H*)-dionylium tetrafluoroborate ($\mathbf{6b}^+ \cdot \mathbf{BF_4^-}$). Orange prisms; mp 227–230 °C dec (from CH_3CN/Et_2O); ^{1}H NMR (500 MHz, CD_3CN) δ 3.17 (3H, s, 7-Me), 3.46 (3H, s, 9-Me), 3.95 3H, s, OMe), 7.27 (2H, d, J=9.0 Hz, Ph-3′, 5′), 7.59 (2H, d, J=9.0 Hz, Ph-2′, 6′), 8.31 (1H, d, J=10.2 Hz, H-5), 8.37 (1H, dd, J=10.2, 9.7 Hz, H-4), 8.56 (1H, dd, J=9.7, 9.5 Hz, H-3), 8.63 (1H, dd, J=10.3, 9.5 Hz, H-2), 9.94 (1H, d, J=10.3 Hz, H-1); ^{13}C NMR (150.9 MHz, CD_3CN) δ 29.1, 33.5, 56.9, 99.8, 116.9, 126.3, 131.8, 134.1, 139.8, 141.2, 143.4, 143.6, 145.8, 151.1, 152.2, 153.5, 159.0, 163.5; IR (KBr) ν 1717, 1675, 1084 cm^{-1}; MS (FAB) *m/z* 348 (M^+-BF_4); HRMS calcd for $C_{20}H_{18}BF_4N_3O_3$: 348.1347 ($M-BF_4$). Found: 348.1391 (M^+-BF_4). Anal. calcd for $C_{20}H_{18}BF_4N_3O_3$: C, 55.20; H, 4.17; N, 9.66. Found: C, 54.95; H, 4.08; N, 9.43.

4.2.2. 6-(4′-Chlorophenyl)-7,9-dimethylcyclohepta[*b*]-pyrimido[5,4-*d*]pyrrole-8(7*H*), 10(9*H*)-dionylium tetrafluoroborate ($\mathbf{6c}^+ \cdot \mathbf{BF_4^-}$). Greenish prisms; mp 266–269 °C dec (from CH_3CN/Et_2O); ^{1}H NMR (500 MHz, CD_3CN) δ 3.17 (3H, s, 7-Me), 3.46 (3H, s, 9-Me), 7.70 (2H, d, J=8.8 Hz, Ph-2′, 6′), 7.80 (2H, d, J=8.8 Hz, Ph-3′, 5′), 8.29 (1H, d, J=10.2 Hz, H-5), 8.37 (1H, dd, J=10.2, 9.8 Hz, H-4), 8.58 (1H, dd, J=9.8, 9.7 Hz, H-3), 8.65 (1H, dd, J=10.2, 9.7 Hz, H-2), 9.95 (1H, d, J=10.2 Hz, H-1); ^{13}C NMR (150.9 MHz, CD_3CN) δ 29.2, 33.8, 100.0, 132.1, 132.3, 133.1, 134.2, 139.2, 139.9, 141.4, 143.7, 143.9, 146.1, 150.6, 152.0, 153.4, 159.0; IR (KBr) ν 1722, 1675, 1084 cm^{-1}; MS (FAB) *m/z* 352 (M^+-BF_4); HRMS calcd for $C_{19}H_{15}BClF_4N_3O_2$: 352.0853 ($M-BF_4$). Found: 352.0858 (M^+-BF_4). Anal. calcd for $C_{19}H_{15}BClF_4N_3O_2$: C, 51.91; H, 3.44; N, 9.56. Found: C, 51.80; H, 3.38; N, 9.46.

4.3. Reaction of 9 with $(COCl)_2$ in $(CH_2CCl)_2$

To a solution of **9** (35 mg, 0.1 mmol) in $(CH_2Cl)_2$ (2 mL) was added $(COCl)_2$ (65 mg, 0.5 mmol), and the mixture was stirred at room temperature or 70 °C for 1 h. After the reaction was completed, the mixture was concentrated in vacuo. The resulting residue was dissolved in a mixture of acetic anhydride (1 mL) and 42% aq HBF_4 (0.2 mL) at 0 °C, and the mixture was stirred for another 1 h. To the mixture was added Et_2O (10 mL) and the precipitates were collected by filtration to give a mixture of $\mathbf{6d}^+ \cdot \mathbf{BF_4^-}$ and $\mathbf{4}^+ \cdot \mathbf{BF_4^-}$ (Table 2, runs 1 and 2).

4.4. Reaction of 9 with $(COCl)_2$ without solvent

A solution of **9** (35 mg, 0.1 mmol) in $(COCl)_2$ (2 mL) was heated under reflux for 3 h. After the reaction was completed, the mixture was concentrate in vacuo. The resulting residue was dissolved in a mixture of acetic anhydride (1 mL) and 42% aq HBF_4 (0.2 mL) at 0 °C, and the mixture was stirred for another 1 h. To the mixture was added Et_2O (10 mL) and the precipitates were collected by filtration to give a mixture of $\mathbf{6d}^+ \cdot \mathbf{BF_4^-}$ and $\mathbf{4}^+ \cdot \mathbf{BF_4^-}$ (Table 2, run 3).

4.5. Reaction of 9 with $SOCl_2$

A solution of **9** (35 mg, 0.1 mmol) in $SOCl_2$ (2 mL) was heated under reflux for 3 h. After the reaction was completed, the mixture was concentrate in vacuo. The resulting residue was dissolved in a mixture of acetic anhydride (1 mL) and 42% aq HBF_4 (0.2 mL) at 0 °C, and the mixture was stirred for another 1 h. To the mixture was added Et_2O (10 mL) and the precipitates were collected by filtration to give a single product $\mathbf{6d}^+ \cdot \mathbf{BF_4^-}$ (Table 2, run 5).

4.5.1. 7,9-Dimethyl-6-benzylcyclohepta[*b*]pyrimido [5,4-*d*]pyrrole-8(7*H*),10(9*H*)-dionylium tetrafluoroborate ($\mathbf{6d}^+ \cdot \mathbf{BF_4^-}$). Orange prisms; mp 210–211 °C (from CH_3CN/Et_2O); ^{1}H NMR (600 MHz, CD_3CN) δ 3.45 (3H, s, 9-Me), 3.75 (3H, s, 7-Me), 6.12 (2H, s, CH_2), 7.19–7.21 (2H, m, *m*-Ph), 7.40–7.44 (3H, m, *o*,*p*-Ph), 8.44 (1H, dd, J=10.2, 10.0 Hz, H-2), 8.57 (1H, dd, J=10.0, 9.5 Hz, H-4), 8.62 (1H, dd, J=10.2, 9.5 Hz, H-3), 8.76 (1H, d, J=10.2 Hz, H-5), 9.97 (1H, d, J=10.2 Hz, H-1); ^{13}C NMR (150.9 MHz, CD_3CN) δ 29.0, 33.8, 51.2, 100.5, 126.4, 129.6, 130.3, 133.0, 134.9, 139.6, 141.1, 143.6, 143.9, 145.8, 149.4, 152.1, 154.2, 158.8; IR (KBr) ν 1717, 1675, 1084 cm^{-1}; MS (FAB) *m/z* 332 (M^+-BF_4); HRMS calcd for $C_{20}H_{18}BF_4N_3O_2$: 332.1399 ($M-BF_4$). Found: 332.1379 (M^+-BF_4). Anal. calcd for $C_{20}H_{18}BF_4N_3O_2+1/5H_2O$: C, 56.82; H, 4.39; N, 9.94. Found: C, 56.75; H, 4.42; N, 9.96.

4.6. X-ray structure determination of 9[†]

Reddish plate, $C_{20}H_{19}N_3O_3+2CHCl_3$, M=588.14, monoclinic, space group $P2_1/c$, a=11.1393(4) Å, b=19.5525(8) Å, c=11.6973(6) Å, β=94.569(2) °, V=2539.6(2) Å^3, Z=4, D_c=1.538 g mL^{-1}, crystal dimensions 0.50×0.40×0.10 mm^3. Data were measured on a Rigaku RAXIS-RAPID radiation diffractomater with graphite monochromated Mo Kα radiation. Total 24288 reflections were collected, using the ω–2θ scan technique to a maximum 2θ value of 55.0°. The structure was solved by direct methods and refined by a full-matrix least-squares method using SIR92 structure analysis software,[20] with 357

[†] CCDC reference number 243861.

variables and 3617 observed reflections [$I>3.00\sigma(I)$]. The non-hydrogen atoms were refined anisotropically. The weighting scheme $w=4F_o^2[0.500\sigma_c^2(F_o)0.002F_o^2]^{-1}$ gave satisfactory agreement analysis. The final R and Rw values were 0.0410 and 0.1220. The maximum peak and minimum peak in the final difference map were 0.61 and -0.77 e$^-$/Å^3, respectively.

4.7. X-ray structure determination of 12[‡]

Orange prism, $C_{17}H_{21}N_3O_3$, $M=315.37$, orthorhombic, space group $Pna21$, $a=7.1520(2)$ Å, $b=18.7731(5)$ Å, $c=11.4415(3)$ Å, $V=1536.20(7)$ Å^3, $Z=4$, $D_c=1.363$ g mL^{-1}, crystal dimensions $0.80\times0.50\times0.10$ mm^3. Data were measured on a Rigaku RAXIS-RAPID radiation diffractomater with graphite monochromated Mo Kα radiation. Total 13,877 reflections were collected, using the ω–2θ scan technique to a maximum 2θ value of 55.0°. The structure was solved by direct methods and refined by a full-matrix least-squares method using SIR92 structure analysis software,[20] with 230 variables and 1671 observed reflections [$I>3.00\sigma(I)$]. The non-hydrogen atoms were refined anisotropically. The weighting scheme $w=4F_o^2[0.500\sigma_c^2(F_o)+0.0030F_o^2]^{-1}$ gave satisfactory agreement analysis. The final R and R_w values were 0.0440 and 0.1230. The maximum peak and minimum peak in the final difference map were 0.26 and -0.32 e$^-$/Å^3, respectively.

4.7.1. Variable temperature NMR data of 12. Temperature: -90 °C (CD_2Cl_2): ^{1}H NMR (500 MHz) δ 1.02 (3H, t, $J=7.2$ Hz, CH_3), 1.34 (3H, t, $J=7.2$ Hz, CH_3), 3.22 (3H, s, NMe), 3.33 (3H, s, NMe), 3.44–3.53 (2H, m, CH_2), 3.58–3.65 (1H, m, CH_2), 3.71–3.78 (1H, m, CH_2), 6.76 (1H, dd, $J=10.6$, 7.2 Hz, H-3), 6.83 (1H, d, $J=11.6$ Hz, H-5), 7.09 (1H, dd, $J=11.6$, 7.2 Hz, H-4), 7.12 (1H, dd, $J=10.6$, 8.4 Hz, H-2), 8.64 (1H, d, $J=8.4$ Hz, H-1); ^{13}C NMR (125.7 MHz) δ 10.7 (CH_3), 11.3 (CH_3), 26.9 (NCH_3), 27.3 (NCH_3), 44.0 (CH_2), 46.0 (CH_2), 86.2 (C-5), 113.1 (C-7′), 122.7 (C-3′), 124.4 (C-5′), 126.0 (C-2′), 129.8 (C-6′), 133.4 (C-4′), 151.9 (C-2), 160.3 (C-4 or 6), 161.5 (C-4 or 6), 172.6 (C-1′).

4.8. Cyclic voltammetry of 9, 12, and 6b–d$^+\cdot$BF$_4^-$

The reduction potential of **9**, **12**, and **6b–d**$^+\cdot$**BF**$_4^-$ was determined by means of CV-27 voltammetry controller (BAS Co). A three-electrode cell was used, consisting of Pt working and counter electrodes and a reference Ag/$AgNO_3$ electrode. Nitrogen was bubbled through an acetonitrile solution (4 mL) of **9**, **12**, and **6b–d**$^+\cdot$**BF**$_4^-$ (0.5 mmol dm^{-3}) and Bu_4NClO_4 (0.1 mol dm^{-3}) to deaerate it. The measurements were made at a scan rate of 0.1 V s^{-1} and the voltammograms were recorded on a WX-1000-UM-019 (Graphtec Co) X-Y recorder. Immediately after the measurements, ferrocene (0.1 mmol) ($E_{1/2}=+0.083$) was added as the internal standard, and the observed peak potential was corrected with reference to this standard. Compounds **9** and **12** exhibited one irreversible oxidation wave and one irreversible reduction wave. Compounds **6b–d**$^+\cdot$**BF**$_4^-$ exhibited one irreversible reduction wave.

[‡] CCDC reference number 243862.

4.9. General procedure for the autorecycling oxidation of amines catalyzed by 4$^+\cdot$BF$_4^-$, 5$^+\cdot$BF$_4^-$, and 6a,e$^+\cdot$BF$_4^-$ under photo-irradiation

A CH_3CN (16 mL) solution of compounds **4**$^+\cdot$**BF**$_4^-$, **5**$^+\cdot$**BF**$_4^-$, and **6a**,**e**$^+\cdot$**BF**$_4^-$ (0.005 mmol) and amines (2.5 mmol, 500 equiv.) in a Pyrex tube was irradiated by RPR-100, 350 nm lamps under aerobic conditions for the period indicated in Table 5. The reaction mixture was concentrated in vacuo and diluted with Et_2O and filtered. The ^{1}H NMR spectra of the filtrates revealed the formation of the imines (Table 5). The filtrate was treated with a saturated solution of 2,4-dinitrophenylhydrazine in 6% HCl to give 2,4-dinitrophenylhydrazone. The results are summarized in Table 5.

Acknowledgements

Financial support from a Waseda University Grant for Special Research Project and 21COE ‘Practical Nanochemistry’ from MEXT, Japan, is gratefully acknowledged. We thank the Materials Characterization Central Laboratory, Waseda University, for technical assistance with the spectral data, elemental analyses and X-ray analyses.

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Short and stereoselective synthesis of polysubstituted cyclohexanones

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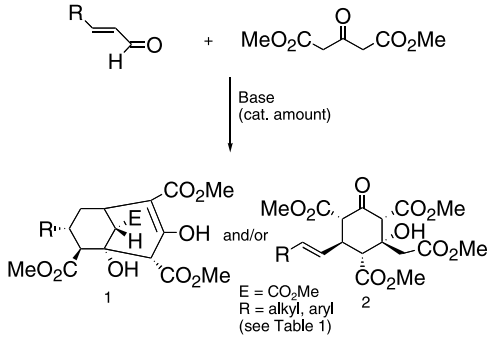
Received 28 May 2004; revised 29 June 2004; accepted 23 July 2004

Available online 26 August 2004

Abstract—Two equivalents of dimethyl 1,3-acetonedicarboxylate reacted with α,β-unsaturated aldehydes to form novel polysubstituted cyclohexanones **2** in an efficient one-step procedure. The reactions proceeded at room temperature in the presence of catalytic amount of sodium methoxide, affording the products in high yields in a remarkably stereoselective manner. The products are of possible biological interest.

1. Introduction

Polysubstituted cyclohexanones and cyclohexanols are widespread structural subunits in biologically active compounds, and related molecules have been used as starting materials in the synthesis of pharmaceuticals[1,2] and in natural product syntheses.[3–6] As part of a research programme aimed at exploring the chemical and biological properties of bicyclo[3.3.1]nonan-3-ones **1**,[7,8] we observed that the base-catalyzed reaction between an α,β-unsaturated aldehyde and dimethyl 1,3-acetonedicarboxylate to yield **1**, suffered from the concomitant formation of the polysubstituted cyclohexanones **2** (Scheme 1). In particular, the formation of **2** was a persisting problem when the reaction was scaled up (e.g. from 0.5 to 5–10 g). In occasional instances **2** was the only product isolated.



Scheme 1. The preparation of **1** and **2**.

The simplicity and the stereoselectivity of the reaction prompted us to search for reaction conditions that would maximize the yields of the cyclohexanones **2**. Similar stereoselectivity has recently been observed in the condensation of dimethyl 1,3-acetonedicarboxylate with pentane-2,3-dione.[9] A probable pathway for the formation of **2** is outlined in Scheme 2, proposing the intermediate formation of the conjugated derivative **3** as a result of an 1,2-addition of dimethyl 1,3-acetonedicarboxylate to the α,β-unsaturated aldehyde. The intermediate **3** undergoes an 1,4-addition with a second molecule of the keto diester with an ensuing ring closure of the symmetrical intermediate **4**. The proposed formation of the bicyclo[3.3.1]nonan-3-ones **1** has been incorporated in Scheme 2 for comparative purposes.[10] Accordingly, products **1** are probably formed by an initial 1,4-addition of the keto diester to the unsaturated aldehyde to form a cyclohexenone derivative as an intermediate.

2. Results and discussion

In accordance with the rationalizations set forth in Scheme 2 we were searching for reaction conditions that would favor an initial 1,2-addition of the keto diester to the α,β-unsaturated aldehyde. In short, the best results with respect to the formation of **2** were obtained by stirring a methanol solution of the reactants for 24 h at ambient temperature in the presence of 4–5% of sodium methoxide. Using 2% NaOMe resulted in a slower reaction without improvement of yield and using 8–10% NaOMe resulted in decreased

Keywords: 1,3-Acetonedicarboxylate; Polysubstituted cyclohexanones; Stereoselective reaction; Claisen condensation.
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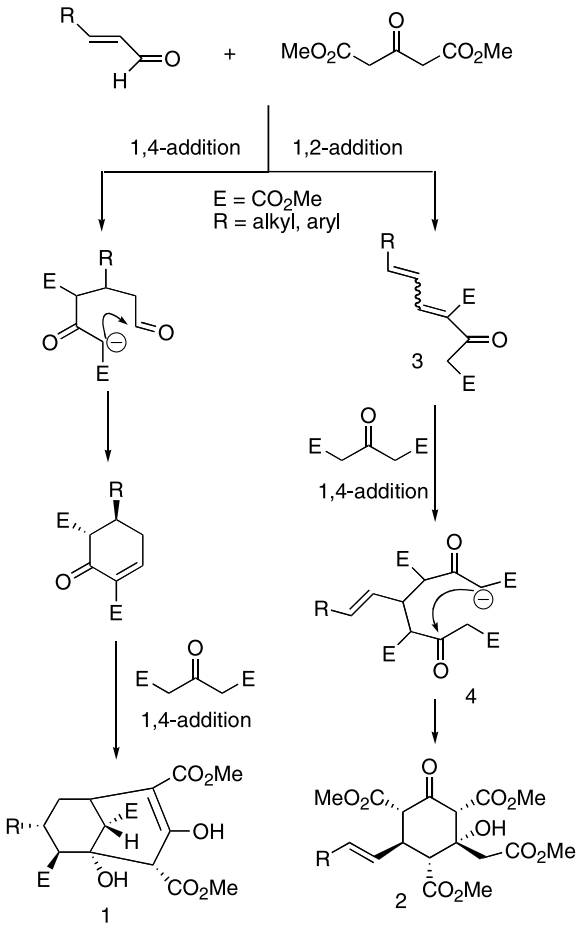
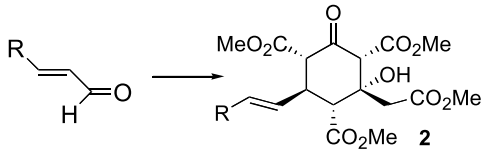
doi:10.1016/j.tet.2004.07.061

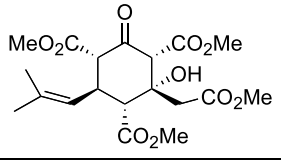


Scheme 2. Proposed pathways for the formation of **1** and **2**.

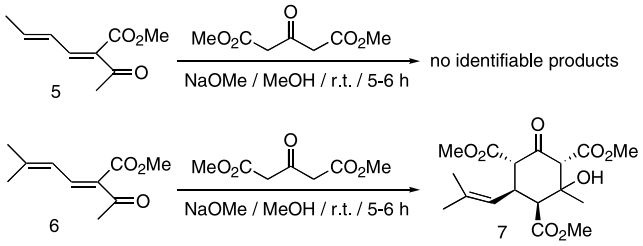
yields. The results are summarized in Table 1. The products **2** were only sparingly soluble in methanol at ambient temperature, which simplified the purification procedure in case of a concomitant formation of **1**. Methanol was used as the recrystallization solvent in order to obtain samples for analytical and spectroscopic purposes. The formation of **2** could be largely suppressed by refluxing the methanol solution of dimethyl 1,3-acetonedicarboxylate and an α,β-unsaturated aldehyde in the presence of 20 mol% of lithium methoxide. This afforded the bicyclo[3.3.1]nonan-3-ones **1** in 50–70% yield. It has been reported recently that the yields of **1** can be substantially increased by stirring the reactants in THF for 5–6 days at room temperature in the presence of TBAF or piperidine.[10]

Table 1. Preparation of cyclohexanones **2**



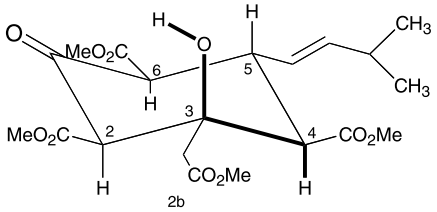
Compound	R	Yield (%)
2a	Ethyl	68
2b	Isopropyl	62
2c	Phenyl	80
2d	4-Methoxyphenyl	46
2e	2-Methoxyphenyl	39
2f	4-Chlorophenyl	73
2g	2-Chlorophenyl	76
2h	4-Nitrophenyl	73
2i	2-Nitrophenyl	79
2j		96

The intermediate formation of **3** was not detected at any time during the reaction. In order to corroborate the proposed mechanism displayed in Scheme 2, the conjugated model compounds **5** and **6**, depicted in Scheme 3, were synthesized according to the procedure described by Moorhoff.[11] Both compounds, **5** and **6**, were subjected to the reaction conditions that had been optimized for the formation of **2** (4% sodium methoxide in methanol, ambient temperature). The reactions were monitored with TLC and the conjugated starting materials had disappeared after 5–6 h of stirring. In case of **5** no identifiable products could be isolated, and that concurs with our findings that the reaction between dimethyl 1,3-acetonedicarboxylate and crotonaldehyde did not yield **2**. Compound **6** yielded the cyclohexanone derivative **7** which corresponds to **2**.



Scheme 3. The reaction of **5** and **6** with dimethyl 1,3-acetonedicarboxylate.

The stereochemistry proposed for **2a–j** is displayed in Scheme 4 using **2b** as an example. It is based on the observation that the signal assigned to H-6 appeared as doublet with $J=12.0$ Hz, and the signal for H-4 appeared as dd with $J=12.0$, 1.5 Hz. A third signal at δ 3.96 was assigned to H-5 and exhibited a td with $J=12.0$, 8.8 Hz. This led to the assignment of axial dispositions for all three protons. As noted above, the signal for H-4 appeared as dd with the smaller coupling constant of $J=1.5$ Hz being due to a long range coupling between H-4 and the hydroxyl proton of the C-3 hydroxyl. This indicated that both the hydroxyl group and the H-4 are in axial dispositions, supporting the proposed relative configuration at C-3 depicted in Scheme 4. The hydroxyl group is probably hydrogen bonded to an oxygen atom of the ester group at



Scheme 4. Proposed stereochemistry of **2b** with the largest groups in equatorial dispositions.

C-2, which might provide the conformational homogeneity to allow detectable long range coupling. An analogous argument was used to define the stereochemistry of **2a**–**j**. A long range coupling between the hydroxyl proton of the C-3 hydroxyl and H-4 was observed in all cases. Such long range coupling involving a hydroxyl proton, although presumably rare, has been described in the literature.[12,13] It is worth mentioning that the hydroxyl proton of the cyclohexanone **7** did not display a long range coupling, and for that reason the relative configuration at C-3 could not be determined with NMR. Moreover, a signal at δ 2.85, assigned to H-4, appeared as d with $J=5.1$ Hz, suggesting an equatorial disposition for that proton.

The structures of **2a**–**j** were determined by their spectroscopic and analytical data, and furthermore the structure of **2b** was confirmed unambiguously by single crystal X-ray analysis (see ORTEP drawing, Fig. 1).[14] The hydroxyl group at the C-3 carbon took axial orientation, and the distance between the hydroxyl (O-2) proton and the ester oxygen (O-7) of the ester group at the C-4 carbon was 2.49 Å, that can be attributed as a weak hydrogen bonding. Moreover, it is noteworthy that the crystal structure of **2b** does not have the hydroxyl proton in an orientation favorable for a long range coupling with H-4.

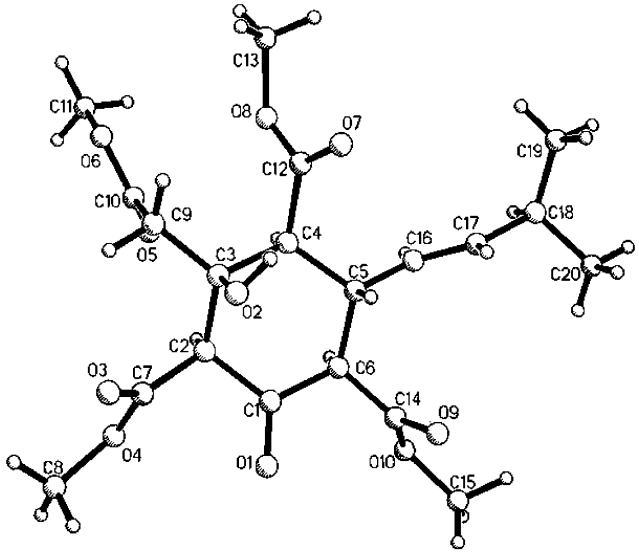


Figure 1. X-ray crystal structure of **2b**.

The exclusive formation of **2a**–**j** with the hydroxyl group at C-3 in an axial disposition is of interest. In spite of the absence of the rigorous data, it might be assumed that the stereodifferentiation occurs in the ring-closure step, i.e. in the transformation of **4** to **2** in Scheme 2. This transformation takes place, arguably, in a chair-like transition state with the participating carbonyl oxygen occupying a pseudoaxial disposition leaving the pseudoequatorial position for the larger $-CH_2CO_2Me$ group.

In summary, a short and efficient procedure is described for the synthesis of polysubstituted cyclohexanones from dimethyl 1.3-acetonedicarboxylate and α,β-unsaturated aldehydes in a remarkably stereoselective reaction. The protocol appears to be of general validity, representing an expedient access to moderately complex molecules from simple starting materials. Work is currently being undertaken in our laboratory to further explore the chemistry of these compounds.

3. Experimental

3.1. General information

The ^1H and ^{13}C NMR spectra were recorded in $CHCl_3$ at 250 and 62.9 MHz respectively, unless otherwise cited. Chemical shifts are reported in ppm with respect to residual $CHCl_3$ at 7.26 downfield from tetramethylsilane, and coupling constants are given in hertz. When appropriate, 2D COSY (H/H and C/H) and DEPT experiments were employed to delineate the stereostructures. Elemental analyses were carried out at the University of Iceland, and at the University of London. Melting points were determined in open capillaries and are uncorrected. Analytical TLC was performed by using 0.25 mm coated silica gel plates with F-254 indicator. Visualization was accomplished by UV light.

3.2. General procedure

To a stirred solution of sodium (0.04 mmol) and dimethyl 1,3-acetonedicarboxylate (2.2 mmol) in methanol (10 mL) was added slowly an α,β-unsaturated aldehyde (1.0 mmol in methanol, 2 mL). The mixture was stirred at room temperature until the aldehyde had disappeared, as monitored by TLC (dichloromethane–ethyl acetate = 10:1). The crystals were filtered off, washed with methanol and dried under vacuum. If necessary, the crystals could be recrystalized from methanol. The yields in Table 1 always refer to the recrystallized products. If the filtrate was concentrated and refrigerated over night, an additional small amount of crystals could often be obtained, sometimes contaminated by the bicyclo[3.3.1]nonan-3-one **1**. All new compounds reported here were characterized on the basis of complementary spectral data (^1H and ^{13}C NMR, elemental analysis). The structure of **2b** was confirmed unambiguously by X-ray analysis.

3.2.1. 5-(1-Butenyl)-3-hydroxy-2,4,6-tris(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]cyclohexanone (2a). Prepared from 2-pentenal as a white solid in 68% yield: mp 140–141 °C; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=7.5$ Hz, 3H), 1.92 (qdd, $J=7.5$, 6.5, 1.2 Hz, 2H), 2.71 (AB system, $\nu_A=2.63$ ppm, $\nu_B=2.79$ ppm, $J_{AB}=17.6$ Hz, 2H), 3.17 (dd, $J=12.0$, 1.5 Hz, 1H), 3.34 (dd, $J=12.0$, 0.6 Hz, 1H), 3.59 (dt, $J=8.7$, 12.0 Hz, 1H), 3.67 (s, 3H), 3.699 (s, 3H), 3.701 (s, 3H), 3.78 (s, 3H), 4.33 (d, $J=0.6$ Hz, 1H), 4.47 (d, $J=1.5$ Hz, 1H (D_2O-exchangeable)), 5.16 (ddt, $J=15.3$, 8.7, 1.2 Hz, 1H), 5.67 (dt, $J=15.3$, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6 (q), 25.4 (t), 41.2 (d), 42.4 (t), 51.8 (q), 51.9 (q), 52.1 (q), 52.6 (q), 52.9 (d), 61.5 (d), 61.8 (d), 74.7 (s), 126.1 (d), 137.6 (d), 167.6 (s), 169.8 (s), 170.5 (s, 2C), 197.7 (s). Anal. calcd for $C_{19}H_{26}O_{10}$: C, 55.07; H, 6.32. Found: C, 55.10; H, 6.35.

3.2.2. 3-Hydroxy-2,4,6-tris(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-5-(3-methyl-1-butenyl)cyclohexanone (2b). Prepared from 4-methyl-2-pentenal as a white solid in 62% yield: mp 137–138 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J=6.7 Hz, 6H), 2.12–2.25 (m, 1H), 2.74 (AB system, ν_A=2.67 ppm, ν_B=2.81 ppm, J_{AB}=17.6 Hz, 2H), 3.18 (dd, J=11.9, 1.5 Hz, 1H), 3.34 (dd, J=11.5, 0.6 Hz, 1H), 3.61 (td, J=11.9, 8.8 Hz, 1H), 3.69 (s, 3H), 3.717 (s, 3H), 3.722 (s, 3H), 3.80 (s, 3H), 4.35 (d, J=0.6 Hz, 1H), 4.52 (d, J=1.5 Hz, 1H (D_2O-exchangeable)), 5.13 (ddd, J=15.2, 8.8, 1.1 Hz, 1H), 5.61 (dd, J=15.2, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6 (2C), 31.4, 41.7, 42.8, 52.3, 52.4, 52.6, 53.1, 53.4, 62.0, 62.2, 75.2, 124.3, 143.7, 168.0, 170.2, 170.9, 171.0, 196.2. Anal. calcd for $C_{20}H_{28}O_{10}$: C, 56.07; H, 6.59. Found: C, 56.36; H, 6.51.

3.2.3. 3-Hydroxy-2,4,6-tris(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-5-(2-phenyl-1-ethenyl)cyclohexanone (2c). Prepared from cinnamaldehyde as a white solid in 80% yield: mp 179–180 °C; ^{1}H NMR ($CDCl_3$) δ 2.77 (AB system, ν_A=2.70 ppm, ν_B=2.84 ppm, J_{AB}=17.8 Hz, 2H), 3.33 (dd, J=11.9, 1.8 Hz, 1H), 3.49 (dd, J=12.5, 0.4 Hz, 1H), 3.66 (s, 3H), 3.71 (s, 3H), 3.73 (s, 3H), 3.82 (s, 3H), 3.88 (ddd, J=12.5, 11.9, 9.0 Hz, 1H), 4.44 (d, J=0.4 Hz, 1H), 4.56 (d, J=1.8 Hz, 1H (D_2O-exchangeable)), 5.92 (dd, J=15.8, 9.0 Hz, 1H), 6.57 (d, J=15.8 Hz, 1H), 7.24–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 41.5, 42.3, 52.0, 52.1, 52.4, 52.7, 52.9, 61.1, 61.9, 74.9, 126.3, 126.5 (2C), 128.0, 128.5 (2C), 134.5, 136.2, 167.4, 169.8, 170.2, 170.6, 197.5. Anal. calcd for $C_{23}H_{26}O_{10}$: C, 59.74; H, 5.67. Found: C, 59.78; H, 5.68.

3.2.4. 3-Hydroxy-2,4,6-tris(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-5-[2-(*p*-methoxy)phenyl-1-ethenyl]cyclohexanone (2d). Prepared from *p*-methoxycinnamaldehyde as a white solid in 46% yield: mp 142–143 °C; ^{1}H NMR ($CDCl_3$) δ 2.76 (AB system, ν_A=2.68 ppm, ν_B=2.84 ppm, J_{AB}=17.7 Hz, 2H), 3.31 (dd, J=12.0, 1.6 Hz, 1H), 3.47 (d, J=12.0 Hz, 1H), 3.65 (s, 3H), 3.70 (s, 3H), 3.73 (s, 3H), 3.75–3.90 (partly obscured signal, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 4.42 (s, 1H), 4.54 (d, J=1.6 Hz, 1H (D_2O-exchangeable)), 5.77 (dd, J=15.7, 9.0 Hz, 1H), 6.50 (d, J=15.7 Hz, 1H), 6.82 (apparent d, J=8.7 Hz, 2H), 7.23 (apparent d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 41.6, 42.3, 51.96, 52.04, 52.3, 52.79, 52.83, 55.3, 61.3, 61.9, 74.8, 113.9 (2C), 124.0, 127.7 (2C), 129.0, 133.8, 159.5, 167.4, 169.8, 170.3, 170.6, 197.6. Anal. calcd for $C_{24}H_{28}O_{11}$: C, 58.53; H, 5.73. Found: C, 58.72; H, 5.70.

3.2.5. 3-Hydroxy-2,4,6-tris(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-5-[2-(*o*-methoxyphenyl)-1-ethenyl]cyclohexanone (2e). Prepared from *o*-methoxycinnamaldehyde as a white solid in 39% yield: mp 146–147 °C; ^{1}H NMR ($CDCl_3$) δ 2.77 (AB system, ν_A=2.70 ppm, ν_B=2.84 ppm, J_{AB}=17.7 Hz, 2H), 3.32 (dd, J=12.0, 1.5 Hz, 1H), 3.49 (d, J=12.0 Hz, 1H), 3.68 (s, 3H), 3.72 (s, 3H), 3.73 (s, 3H), 3.87 (td, J=12.0, 8.9 Hz, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 4.42 (s, 1H), 4.55 (d, J=1.5 Hz, 1H (D_2O-exchangeable)), 5.93 (dd, J=15.8, 8.9 Hz, 1H), 6.85 (d, J=15.8 Hz, 1H), 6.83 (d, J=8.1 Hz, 1H), 6.89 (d, J=8.0 Hz, 1H) 7.17–7.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 41.9, 42.4, 52.0, 52.1, 52.3, 52.8, 53.0, 55.4, 61.4, 61.9, 74.8, 110.8, 120.4, 125.5, 126.96, 127.05, 129.0, 129.6, 156.8, 167.4, 169.8, 170.4, 170.6, 197.7. Anal. calcd for $C_{24}H_{28}O_{11}$: C, 58.53; H, 5.73. Found: C, 58.64; H, 5.62.

3.2.6. 5-[2-(*p*-Chlorophenyl)-1-ethenyl]-3-hydroxy-2,4,6 tris(methoxycarbonyl)-3 [(methoxycarbonyl)methyl]-cyclohexanone (2f). Prepared from *p*-chlorocinnamaldehyde as a white solid in 73% yield: mp 153–154 °C; ^{1}H NMR (acetone-d_6) δ 2.60 (d, J=17.3 Hz, 1H), 2.94 (d, J=17.3 Hz, 1H), 3.34 (dd, J=11.9, 1.4 Hz, 1H), 3.59 (s, 3H), 3.62 (s, 3H), 3.65 (s, 3H), 3.73 (s, 3H), 3.79 (td, J=11.9, 8.9 Hz, 1H), 4.02 (dd, J=11.9, 0.6 Hz, 1H), 4.52 (d, J=0.6 Hz, 1H), 4.61 (d, J=1.4 Hz, 1H (D_2O-exchangeable)), 6.19 (dd, J=15.9, 8.9 Hz, 1H), 6.51 (d, J=15.9 Hz, 1H), 7.32 (apparent d, J=8.7 Hz, 2H), 7.40 (apparent d, J=8.7 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 41.3, 41.7, 50.8 (2C), 51.00, 51.4, 52.0, 59.7, 61.8, 74.2, 127.4 (2C), 128.0, 128.1 (2C), 131.9, 135.0, 156.5, 167.3, 168.9, 169.5, 169.7, 197.7. Anal. calcd for $C_{23}H_{25}ClO_{10}$: C, 55.59; H, 5.07. Found: C, 55.58; H, 5.20.

3.2.7. 5-[2-(*o*-Chlorophenyl)-1-ethenyl]-3-hydroxy-2,4,6-tris(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-cyclohexanone (2g). Prepared from *o*-chlorocinnamaldehyde as a white solid in 76% yield: mp 157–158 °C; ^{1}H NMR ($CDCl_3$) δ 2.77 (AB system, ν_A=2.71 ppm, ν_B=2.83 ppm, J_{AB}=17.8 Hz, 2H), 3.34 (dd, J=12.0, 1.7 Hz, 1H), 3.50 (dd, J=12.1, 0.5 Hz, 1H), 3.71 (s, 3H), 3.73 (s, 3H), 3.75 (s, 3H), 3.82 (s, 3H), 3.93 (ddd, J=12.1, 12.0, 9.0 Hz, 1H), 4.44 (d, J=0.5 Hz, 1H), 4.59 (d, J=1.7 Hz, 1H (D_2O-exchangeable)), 5.89 (dd, J=15.6, 9.0 Hz, 1H), 6.94 (d, J=15.6 Hz, 1H), 7.14–7.21 (m, 2H), 7.28–7.36 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 41.6, 42.3, 52.0, 52.2, 52.5, 52.7, 52.8, 61.1, 61.9, 74.9, 126.8, 127.1, 129.0, 129.5, 129.6, 131.1, 133.1, 134.7, 167.3, 169.8, 170.2, 170.6, 197.3. Anal. calcd for $C_{23}H_{25}ClO_{10}$: C, 55.59; H, 5.07. Found: C, 55.64; H, 5.34.

3.2.8. 3-Hydroxy-2,4,6-tris(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-5-[2-(*p*-nitrophenyl)-1-ethenyl]-cyclohexanone (2h). Prepared from *p*-nitrocinnamaldehyde as a white solid in 73% yield: mp 161–162 °C; ^{1}H NMR ($CDCl_3$) δ 2.77 (AB system, ν_A=2.70 ppm, ν_B=2.84 ppm, J_{AB}=17.8 Hz, 2H), 3.38 (dd, J=12.0, 1.7 Hz, 1H), 3.51 (d, J=12.2 Hz, 1H), 3.67 (s, 3H), 3.72 (s, 3H), 3.74 (s, 3H), 3.83 (s, 3H), 3.95 (ddd, J=12.2, 12.0, 9.0 Hz, 1H), 4.46 (s, 1H), 4.59 (d, J=1.7 Hz, 1H (D_2O-exchangeable)), 6.11 (dd, J=15.8, 9.0 Hz, 1H), 6.64 (d, J=15.8 Hz, 1H), 7.43 (apparent d, J=8.8 Hz, 2H), 8.16 (apparent d, J=8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 36.2, 37.2, 46.9, 47.0, 47.1, 47.4, 47.8, 55.4, 56.8, 69.8, 116.9 (2C), 121.9 (2C), 126.1, 127.5, 137.3, 142.1, 162.1, 164.69, 164.71, 165.4, 191.9. Anal. calcd for $C_{23}H_{25}NO_{12}$: C, 54.44; H, 4.97; N, 2.76. Found: C, 54.18; H, 5.30; N, 2.60.

3.2.9. 3-Hydroxy-2,4,6-tris(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-5-[2-(*o*-nitrophenyl)-1-ethenyl]-cyclohexanone (2i). Prepared from *o*-nitrocinnamaldehyde as a white solid in 79% yield: mp 155–156 °C; ^{1}H NMR ($CDCl_3$) δ 2.78 (AB system, ν_A=2.72 ppm, ν_B=2.83 ppm, J_{AB}=17.8 Hz, 2H), 3.37 (dd, J=12.0, 1.8 Hz, 1H), 3.50 (dd, J=12.5, 0.6 Hz, 1H), 3.74 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 3.97 (ddd, J=12.5, 12.0, 8.9 Hz, 1H), 4.44 (d, J=0.6 Hz, 1H), 4.60 (d, J=1.8 Hz, 1H

(D_2O-exchangeable)), 5.88 (dd, $J=15.5$, 8.9 Hz, 1H), 7.03 (d, $J=15.5$ Hz, 1H), 7.35–7.45 (m, 2H), 7.55 (td, $J=7.7$, 1.2 Hz, 1H), 7.96 (dd, $J=8.1$, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 41.7, 42.7, 52.4, 52.8, 52.9, 53.1, 53.3, 61.4, 62.3, 75.3, 125.0, 129.0, 129.6, 131.0, 132.2, 132.9, 133.7, 148.0, 167.7, 170.3, 170.5, 171.0, 197.6. Anal. calcd for $C_{23}H_{25}NO_{12}$: C, 54.44; H, 4.97; N, 2.76. Found: C, 54.28; H, 5.24; N, 2.78.

3.2.10. 3-Hydroxy-2,4,6-tris(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-5-(2-methyl-1-propenyl)-cyclohexanone (2j). Prepared from 3-methyl-2-butenal as a white solid in 96% yield: mp 149–150 °C; ^1H NMR ($CDCl_3$) δ 1.63 (d, $J=1.2$ Hz, 3H), 1.66 (d, $J=1.2$ Hz, 3H), 2.70 (AB system, $\nu_A=2.62$ ppm, $\nu_B=2.79$ ppm, $J_{AB}=17.6$ Hz, 2H), 3.11 (dd, $J=11.8$, 1.6 Hz, 1H), 3.28 (dd, $J=11.8$, 0.6 Hz, 1H), 3.65 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 3.78 (s, 3H), 3.94 (td, $J=11.8$, 10.3 Hz, 1H), 4.36 (d, $J=0.6$ Hz, 1H), 4.53 (d, $J=1.6$ Hz, 1H (D_2O-exchangeable)), 4.82 (dm, $J=$ 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1 (q), 25.8 (q), 37.5 (d), 42.4 (t), 51.8 (q), 51.9 (q), 52.1 (q), 52.7 (q), 53.1 (d), 61.6 (d), 61.8 (d), 74.8 (s), 122.0 (d), 138.1 (s), 167.7 (s), 170.0 (s), 170.5 (s), 170.6 (s), 197.9 (s). Anal. calcd for $C_{19}H_{26}O_{10}$: C, 55.07; H, 6.32. Found: C, 54.92; H, 6.18.

3.2.11. 3-Hydroxy-2,4,6-tris(methoxycarbonyl)-3-methyl-5-(2-methyl-1-propenyl)cyclohexanone (7). White crystals; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.67 (d, $J=1.3$ Hz, 3H), 1.69 (d, $J=1.3$ Hz, 3H), 2.85 (d, $J=$ 5.1 Hz, 1H), 3.70 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 3.85 (ddd, $J=12.2$, 9.8, 5.1 Hz, 1H), 4.01 (dd, $J=12.2$, 0.6 Hz, 1H), 4.24 (d, $J=0.6$ Hz, 1H), 4.57–4.64 (br s, 1H (D_2O-exchangeable)), 4.76 (dm, $J=9.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 25.9, 26.6, 36.9, 51.9, 52.0, 52.5, 54.7, 58.3, 61.0 75.1, 120.8, 137.6, 168.7, 171.0, 172.8, 199.8. Analytically pure sample was not obtained.

Acknowledgements

Financial support from the Icelandic Science Foundation is gratefully acknowledged. The authors thank Dr. A. Mishnev for the X-ray crystallographic determination.

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Tetrahedron 60 (2004) 9155–9162

Strapped porphyrin rosettes based on the melamine–cyanuric acid motif. Self-assembly and supramolecular recognition

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Received 27 May 2004; revised 16 July 2004; accepted 23 July 2004

Available online 27 August 2004

Abstract—This paper describes studies on the synthesis, self-assembly behavior, and complexing properties of several strapped porphyrin-incorporated melamine–cyanuric or melamine-barbiturate-based rosette supramolecules in chloroform-*d*. Strapped porpyrin cyanuric acid $\mathbf{H_2}$**1** and its Zn (II) complex **Zn1** were designed and synthesized. Both $\mathbf{H_2}$**1** and **Zn1** could combine melamine derivatives **11** or **12** to afford porphyrin rosettes, which are more stable than the model rosette initially reported by Whitesides due to the larger size of the porphyrin unit. The new porphyrin rosettes could efficiently complex tripyridyl derivative **13** through intermolecular, cooperative coordination between Zn (II) and pyridine. Two new pyridine-bearing barbiturates **18a** and **18b** were also synthesized. Mixing the identical amount of **18a** or **18b** with **11** or **12** in chloroform-*d* led to the formation of new isomeric rosettes as a result of different orientation of the pyridine unit of **18a** or **18b** in the rosettes. ^{1}H NMR study also revealed that porpyrin-bearing rosette $\mathbf{Zn1}_3\cdot\mathbf{11}_3$ could complex pyridine-bearing rosette $\mathbf{11}_3\cdot\mathbf{18a}_3$, leading to the formation of new two-layer-typed supramolecular architectures.

1. Introduction

In recent years, the self-assembly of small molecular units into larger, ordered architectures has been intensively investigated for the design of artificial receptors and novel materials.[1–16] Because of its unique feature of directionality, specificity, and stability, hydrogen bonding has been one of the most versatile non-covalent forces for the self-assembly of well-defined supramolecular systems.[17–21] Over the years, a number of efficient triple and quadruple hydrogen bonding modes have been developed.[17–19] The triply hydrogen bonded melamine–cyanuric acid motif has been extensively studied for the formation of the so-called 'rosette' supramolecuar structures.[22] Especially, a number of elegant double rosettes have been assembled based on calix[4]arene scaffolds bearing two melamine moieties.[23] In principle, introduction of additional binding or recognizing units into this relatively stable and highly symmetric supramolecular architectures might produce new generation of artificial multi-component receptors or assemblies of higher order. However, examples of this kind of rosette receptors are very limited.[24–26]

We have recently developed an efficient method to synthesize strapped tetraphenylporphyrin derivatives.[27] The additional aliphatic strap, which connects two oppositely located phenyl groups, not only completely prevents the atropisomerization of the corresponding porphyrins,[28,29] but also ensures that any ligand can approach the porphyrin metal ion only from the strap-free side, and consequently can improves the selectivity of multi-component recognition.[30] In search for new generation of multi-component porphyrin receptors, we had introduced a cyanuric acid moiety to the strapped porphyrin skeleton. In this paper, we report the self-assembly of a new series of hydrogen bonded rosettes based on this strapped porphyrin-connected cyanuric acid and its recognition for tripyridyl and rosette guests.

2. Results and discussion

Compounds $\mathbf{H_2}$**1** and **Zn1** have been used for the self-assembly of the new porphyrin rosettes. The syntheses of $\mathbf{H_2}$**1** and **Zn1** are provided in Scheme 1. Thus, compound **2** was first treated with excessive dibromide **3** in hot DMF in the presence of potassium carbonate to produce **4** in 65% yield. Bromide **4** then reacted with phenol **5** under similar conditions to afford compound **6** in 72% yield. A Mitsunobu reaction of **6** with cyanuric acid in DMF gave precursor **7** in 36% yield. Compound **9** was then prepared in 90% yield from the reaction of **8** and iso-pentyl bromide under the conditions for preparation of **4**. Treatment of **9** with pyrrole in refluxing toluene under the catalysis of tosyl acid produced **10** in 76% yield. Dipyrrole **10** was then reacted with **7** in trifluoroacetic acid, followed by oxidation with

Keywords: Hydrogen bonding; Molecular recognition; Self-assembly; Porphyrin; Heterocyclic compounds.
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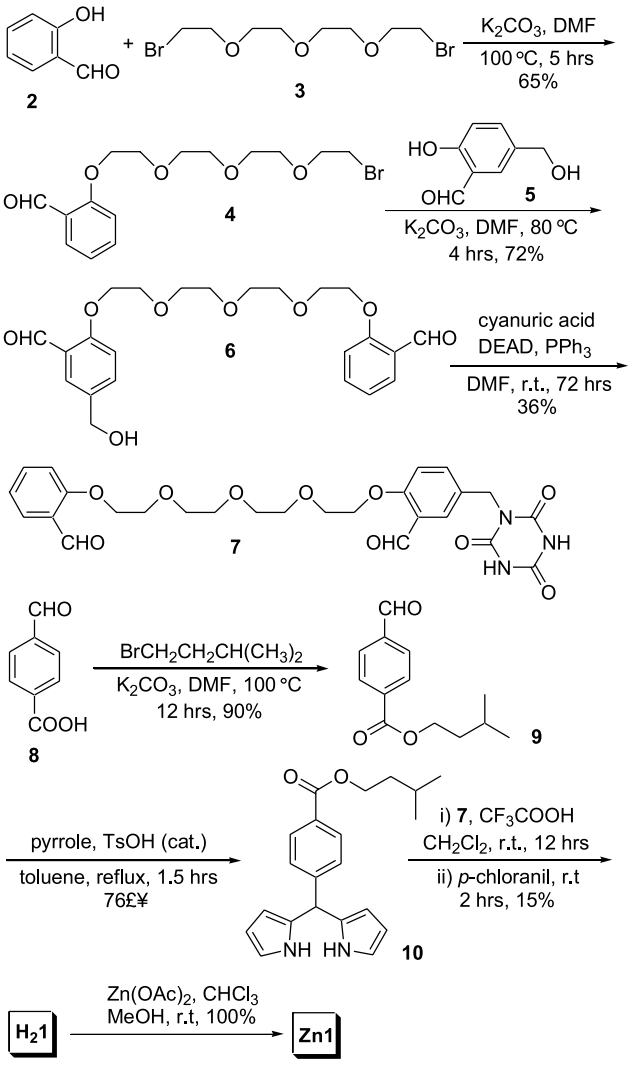
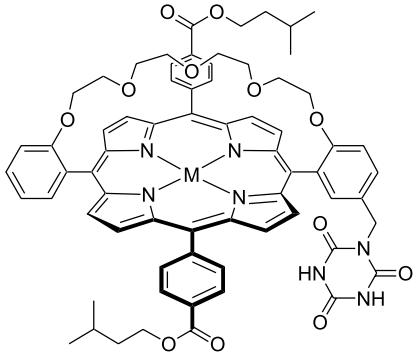
doi:10.1016/j.tet.2004.07.072



Scheme 1.

p-chloranil, to produce **1** in 15% yield. Treatment of porphyrin **1** with zinc acetate in mixture of chloroform and methanol afford **Zn1** quantitatively. Compounds $\mathbf{H_21}$ and **Zn1** are highly soluble in common organic solvents such as chloroform and dichloromethane. With porphyrins $\mathbf{H_21}$ and **Zn1** in hand, melamine derivatives **11** and **12** were prepared according to the reported method.[31]



Although both **11** and **12** are insoluble in chloroform, adding 1 equiv of **1** to the suspension of **11** or **12** in chloroform-*d* led to the melamines to dissolve completely. ^{1}H NMR spectrum displayed a singlet at $\delta=14.86$ and 14.79 ppm, respectively, for the H-1 of $\mathbf{H_21}$ (Fig. 1, the numbering of the signals are shown in Fig. 2), clearly showing that rosette structures $(\mathbf{H_21})_3\cdot\mathbf{11}_3$ and $(\mathbf{H_21})_3\cdot\mathbf{12}_3$ (Fig. 2), were generated.[31,32] It had been reported that melamines with substituents of smaller size, like **12**, and simple alkylated cyanuric acids could only generate infinite tapes but not cyclic rosette motif.[31] The formation of rosette $(\mathbf{H_21})_3\cdot\mathbf{12}_3$ might be ascribed to the introduction of the large porphyrin unit in $\mathbf{H_21}$, which prevents the formation of tape structures due to enlarged steric hindrance.

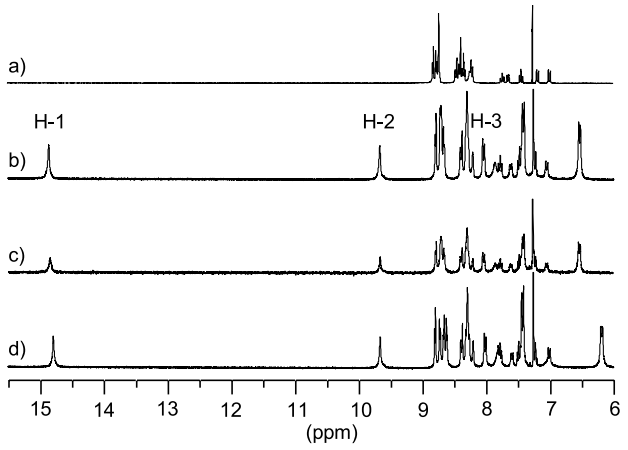


Figure 1. Partial ^{1}H NMR spectrum (400 MHz) in chloroform-*d* at 25 °C: (a) $\mathbf{H_21}$ (10 mM), (b) $\mathbf{H_21}+\mathbf{11}$ (1:1, 10 mM), (c) $\mathbf{H_21}+\mathbf{11}$ (1:1, 1 mM), and (d) $\mathbf{H_21}+\mathbf{12}$ (1:1, 10 mM).

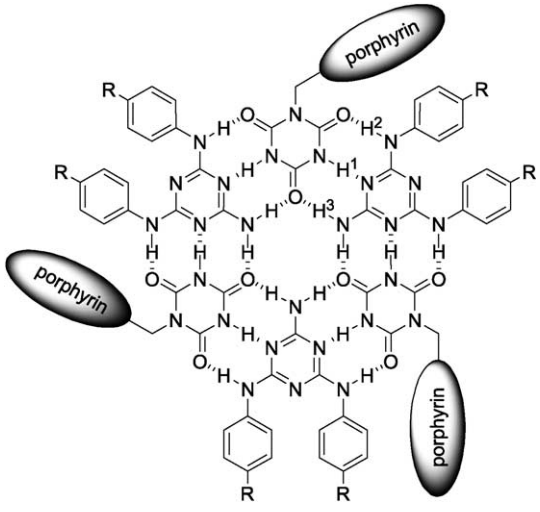


Figure 2. Porphyrin rosettes $(\mathbf{H_21})_3\cdot\mathbf{11}_3$ (R=*t*-Bu) and $(\mathbf{H_21})_3\cdot\mathbf{12}_3$ (R=*n*-Bu) formed in chloroform-*d*.

Upon reducing the concentration to 1.0 mM, the signals of the H-1 and H-2 of the 1:1 mixture of $\mathbf{H_21}$ with **11** or **12** in chloroform-*d* showed very small upfield shifts ($\leq$0.031 ppm) (Fig. 3), indicating that the rosette structures were stable within the concentration range studied. Previous study by Whitesides et al. had shown that the model rosette motif formed from **11** and alkylated cyanuric acid became unstable at the concentration of less than 4.0 mM in chloroform.[31] The present dilution experiments revealed that the new rosettes assembled from $\mathbf{H_21}$ and **11** or **12** are

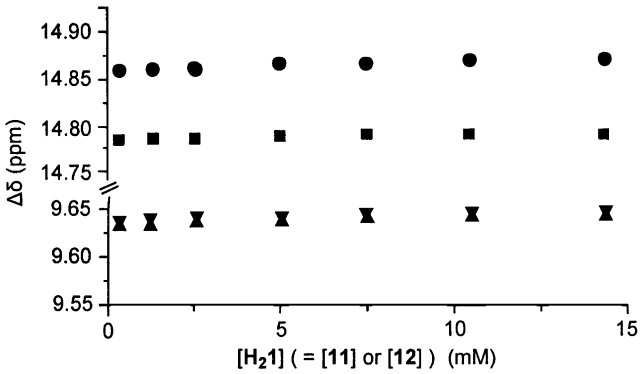
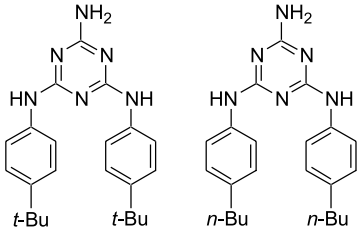


Figure 3. Concentration-dependent changes of the chemical shifts of H-1 (●) and H-2 (▼) of rosette $(\mathbf{H_2 1})_3 \cdot \mathbf{11}_3$ and H-1 (■) and H-2 (▲) of rosette $(\mathbf{H_2 1})_3 \cdot \mathbf{12}_3$ in chloroform-*d* at 25 °C.

obviously more stable than the model systems and indicated that the large porphyrin moiety in $\mathbf{H_2 1}$ facilitated the formation of the rosette motif. ^{1}H NMR experiments revealed that similar rosettes $(\mathbf{Zn1})_3 \cdot \mathbf{11}_3$ and $(\mathbf{Zn1})_3 \cdot \mathbf{12}_3$ were also formed when the identical amount of **Zn1** and **11** or **12** were mixed in chloroform-*d*. The H-1 signals of both rosettes moved upfield slightly (−0.040 and −0.058 ppm) compared with the corresponding Zn (II)-free rosettes. Lowering the concentration of the 1:1 mixtures in chloroform-*d* to 1.0 ppm did not cause the H-1 signal to shift pronouncedly (≤ -0.033 ppm). The results showed that these two rosettes are also very stable and there is no important coordination between the zinc ion of **Zn1** and the amino groups of **11** or **12**.



The complexation of rosette $(\mathbf{Zn1})_3 \cdot \mathbf{11}_3$ towards **13** was then investigated in chloroform-*d*. Compound **13** was prepared in 73% yield from **14** and cyanuric acid, as shown in Scheme 2. Addition of 1 equiv of **13** to the solution of rosette $(\mathbf{Zn1})_3 \cdot \mathbf{11}_3$ in chloroform-*d* caused the purplish red color of the rosette solution to change to dark purple. ^{1}H NMR spectrum revealed remarkable upfield shifts for all the signals of **13** (−6.73, −1.96, and ca. −1.3 ppm for the α-H, β-H, and CH_2, respectively) (Fig. 4). These results clearly indicated that the supramolecular complex $(\mathbf{Zn1}_3 \cdot \mathbf{11}_3) \cdot \mathbf{13}$ was formed.[33] The signals of **13** in the mixture solution had been assigned by changing the ratio of **13** and the rosette. The H-1 and H-2 signals of the rosette was also shifted upfield slightly upon complexation with **13**. Reducing the concentration of the 1:1 mixture of $(\mathbf{Zn1})_3 \cdot \mathbf{11}_3$ with **13** in chloroform-*d* from 10 to 0.8 mM did not cause notable change of the chemical shifts of the signals of **13**, indicating that no important dissociation occurred. Attempt to quantitatively study the binding stability of tri-component complex $[(\mathbf{Zn1})_3 \cdot \mathbf{11}_3] \cdot \mathbf{13}$ with the UV–vis titration method did not succeed since such titration needs the concentration of the porphyrin receptor to be on the scale of ca. 10^{-5}–10^{-6} M. At such low concentration, rosette $\mathbf{Zn1}_3 \cdot \mathbf{11}_3$ would dissociate partially and could not be treated as a single species. As expected, similar supramolecular complex $(\mathbf{Zn1}_3 \cdot \mathbf{12}_3) \cdot \mathbf{13}$ was also formed when the identical molar amount of rosette $(\mathbf{Zn1}_3 \cdot \mathbf{11}_3)$ and **13** was mixed in chloroform-*d*, which had also been supported by the ^{1}H NMR results.

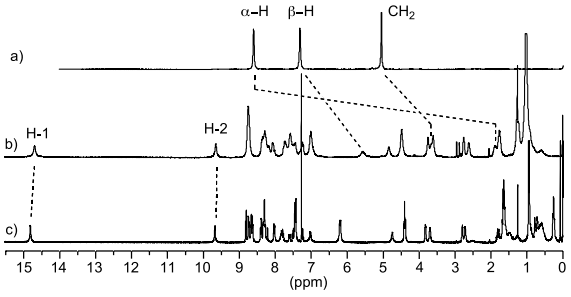
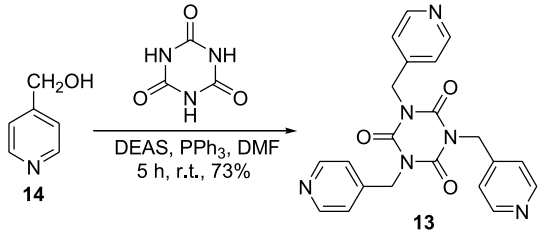
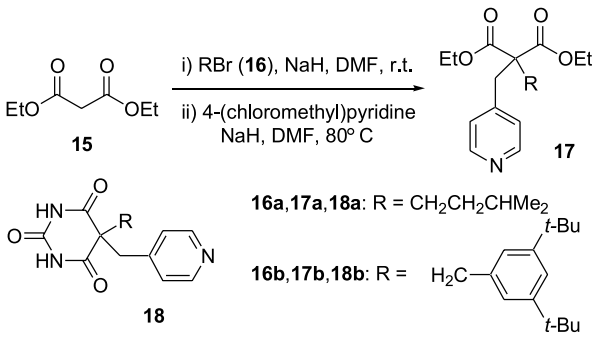


Figure 4. Partial ^{1}H NMR spectrum (400 MHz) of: (a) **13** (3.3 mM), (b) **13** (3.3 mM) + $(\mathbf{Zn1})_3 \cdot \mathbf{11}_3$ (3.3 mM) and (c) $(\mathbf{Zn1})_3 \cdot \mathbf{11}_3$ (3.3 mM) in chloroform-*d* at 25 °C.

The binding between different rosettes were also investigated. Initially, we tried to prepare mono-(4-pyridyl)methylated cyanuric acid as our precursor to assemble pyridine-bearing rosette guest. Unfortunately, the product was insoluble in chloroform even in the presence of **11** or **12**. We then prepared compounds **18a** and **18b** as our assembling building blocks, as shown in Scheme 3.



Scheme 2.



Scheme 3.

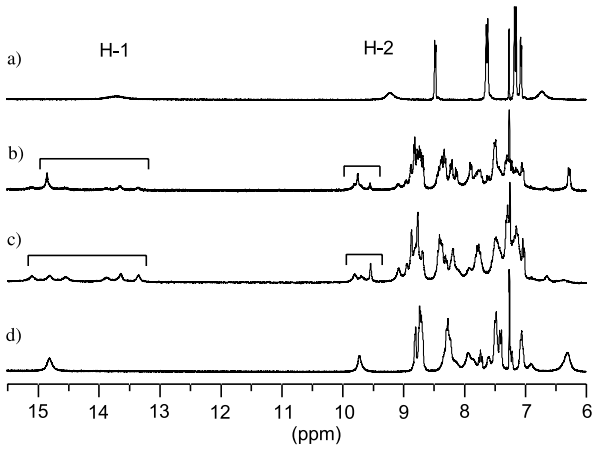
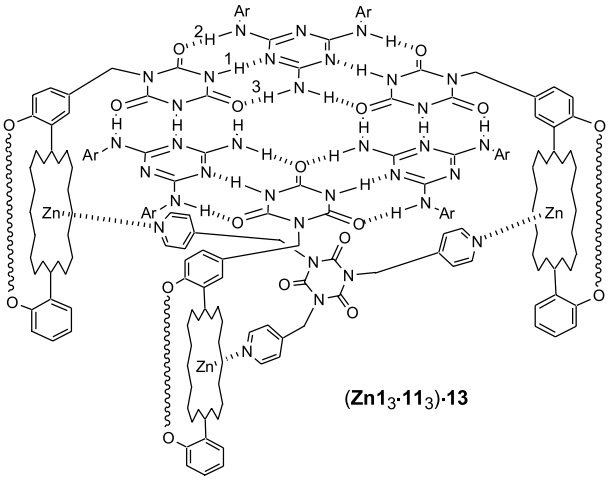
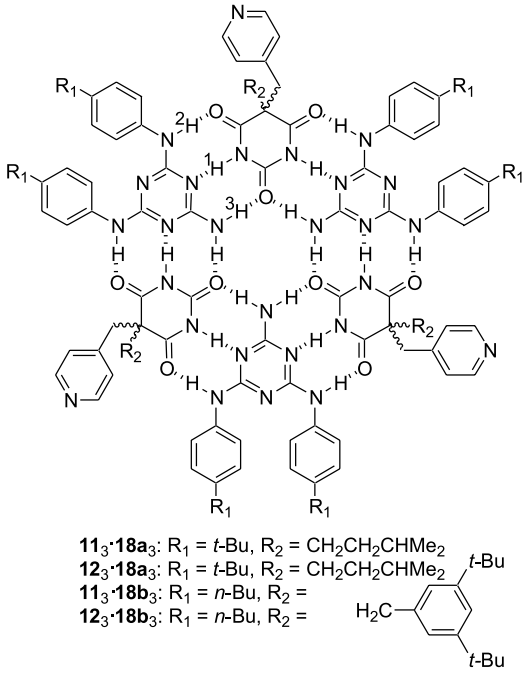


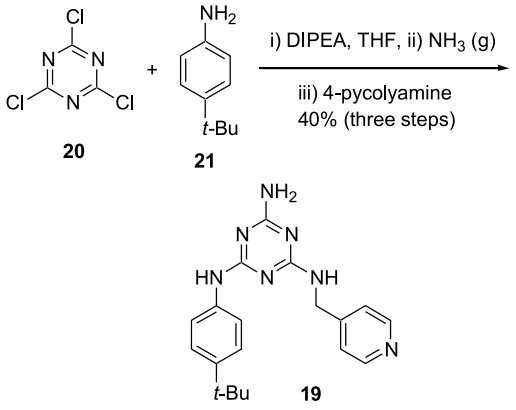
Figure 5. ^{1}H NMR spectrum (400 MHz) in chloroform-*d* at 25 °C. (a) $\mathbf{11}_3\cdot\mathbf{18a}_3$ (1:1, 3.4 mM), (b) $(\mathbf{Zn1}_3\cdot\mathbf{11}_3)$ (1.7 mM)+$\mathbf{11}_3\cdot\mathbf{18a}_3$ (1:1, 3.4 mM), (c) $(\mathbf{Zn1}_3\cdot\mathbf{11}_3)$ (3.4 mM)+$\mathbf{11}_3\cdot\mathbf{18a}_3$ (1:1, 3.4 mM), and (d) $(\mathbf{Zn1}_3\cdot\mathbf{11}_3)$ (3.4 mM).

^{1}H NMR spectrum in chloroform-*d* revealed that rosette $\mathbf{11}_3\cdot\mathbf{18a}_3$ was also formed when the identical molar amount of **11** and **18a** was mixed (Fig. 5a). In principle, there were two possible isomers depending on the relative orientation of **18a** in the rosette structure. The fact that the NH of **18a** displayed a broadened signal indicates that the two isomers exchange slowly on the ^{1}H NMR time scale. Similar results were also observed when mixing **11** with **18b** or **12** with **18a** or **18b** in chloroform-*d*, suggesting that isomeric rosettes were also formed in these mixtures. Mixing a solution of $\mathbf{11}_3\cdot\mathbf{18a}_3$ with a solution of $\mathbf{Zn1}_3\cdot\mathbf{11}_3$ caused the NH signals of both supramolecules to split into three sets of signals of comparable integrated strength in the ^{1}H NMR spectrum in chloroform-*d* (Fig. 5b and c). The prunosus color of the solution of rosette $(\mathbf{Zn1})_3\cdot\mathbf{11}_3$ also turned to dark purple after addition of $\mathbf{11}_3\cdot\mathbf{18a}_3$. These results clearly indicated that the two rosettes bound each other to afford the new supramolecular complex $[(\mathbf{Zn1})_3\cdot\mathbf{11}_3]\cdot[\mathbf{11}_3\cdot\mathbf{18a}_3]$. The splitting in the ^{1}H NMR spectrum can be attributed to different orientation of **18a** in the two-layer supramolecular complex. In principle, there were at most four isomeric complexes formed between the rosettes because the pyridine units of the three **18a** molecules could have four different patterns of arrangement in the supramolecular complex: all-up, up–up–down, up–down–down, and all-down. Unfortunately, at the present stage, we could establish the relative yields of the isomers. Similar result was also obtained when rosettes $\mathbf{11}_3\cdot\mathbf{18b}_3$ and $\mathbf{Zn1}_3\cdot\mathbf{11}_3$ was mixed, which afforded three sets of signals of the hydrogen bonded NHs. This observation indicated that the larger 3,5-di-*tert*-butylphenyl group did not function to improve the selectivity of the self-assembly of supramolecular complex $[\mathbf{11}_3\cdot\mathbf{18b}_3]\cdot[\mathbf{Zn1}_3\cdot\mathbf{11}_3]$. The fact that stable complex $[\mathbf{11}_3\cdot\mathbf{18b}_3]\cdot[\mathbf{Zn1}_3\cdot\mathbf{11}_3]$ could be formed between two giant rosette assemblies indicates that the complexation is a dynamic process and both assemblies can adapt their conformation to produce a supramolecular complex as stable as possible.

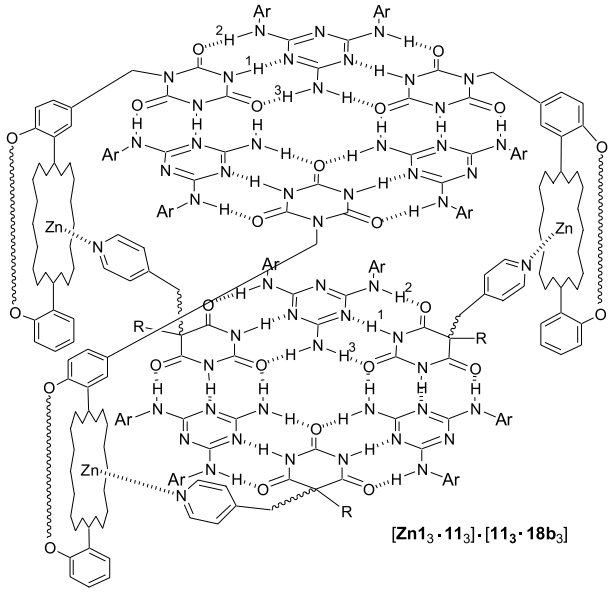




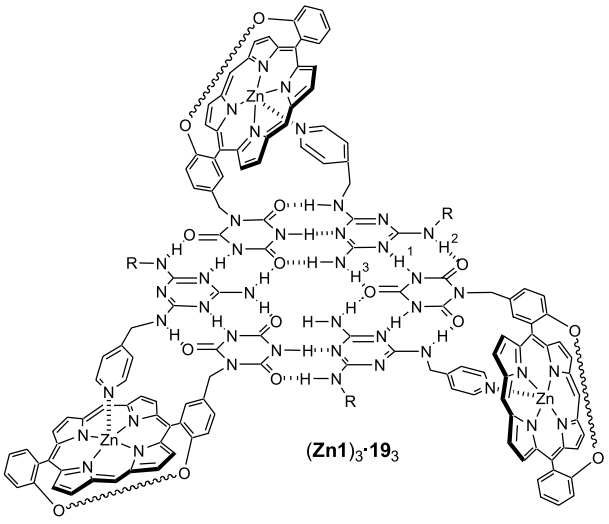
In principle, introducing pyridine unit to melamine might lead to its corresponding rosette with **Zn1** to be more stable as a result of additional intermolecular coordination. To detect this possibility, compound **19** was prepared from the reaction of compound **20** and **21**, followed by treatment of the intermediates with ammonia gas and 4-pycolyl amine, consecutively, as shown in Scheme 4. As expected, mixing the identical molar amount of **Zn1** and **19** in chloroform-*d* generated rosette $(\mathbf{Zn1})_3\cdot\mathbf{19}_3$, as indicated by the ^{1}H NMR spectrum (Fig. 6), which displayed the characteristic hydrogen bonded NH signals in the downfield area. Due to the unsymmetrical feature of the melamine skeleton, the ^{1}H NMR spectrum displayed multiple sets of signals for the hydrogen bonded NH of the rosette. This result indicated that the rosette, in which the three **19** molecules were arranged completely in one-direction pattern, was not generated exclusively, although such an arrangement should facilitate the formation of three intermolecular coordinations between the Zn (II) of **Zn1** and the pyridine of **19** and in principle the corresponding rosette should be more stable than other rosette isomers.[34,35]



Scheme 4.



Adding **19** to the solution of rosette $(\mathbf{Zn1})_3\cdot\mathbf{11}_3$ in chloroform-*d* forced **11** to release from the rosette, obviously due to the formation of more stable complexes between **Zn1** and **19**. The release of **11** as insoluble solid was completed when 1 equiv of **19** was added, as evidenced by the ^{1}H NMR spectrum (Fig. 6c), which was actually very close to that of the 1:1 mixture of **Zn1** and **19** (Fig. 6d) of the identical concentration. This observation showed that rosette $(\mathbf{Zn1})_3\cdot\mathbf{19}_3$ was remarkably more stable than $(\mathbf{Zn1})_3\cdot\mathbf{11}_3$ as a result of the additional inter-component coordination in the former assembly.



3. Conclusion

We have demonstrated that, by introducing additional strapped porphyrin unit to the cyanuric acid moiety, the hydrogen bonded melamine–cyanuric acid-motif-based rosette assemblies could be utilized as new generation of supramolecular receptors for binding relatively larger

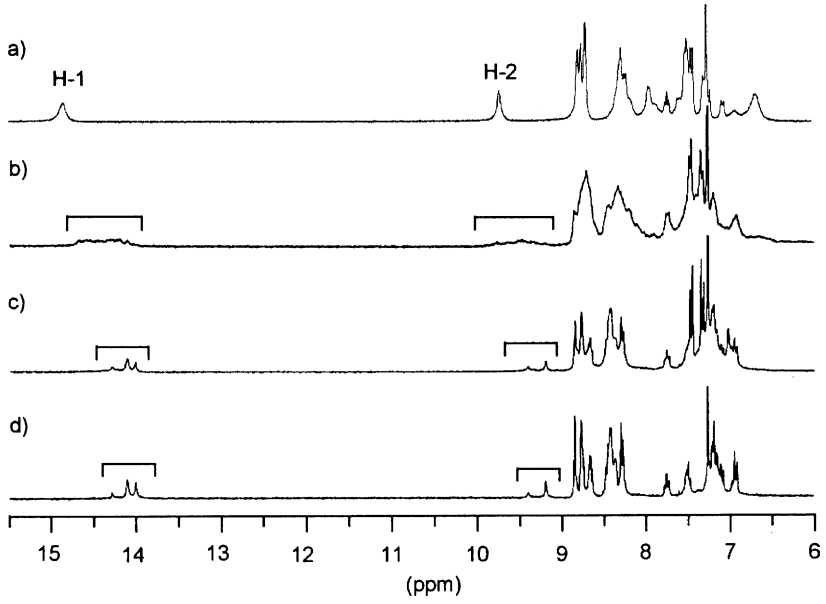


Figure 6. Partial ^{1}H NMR spectrum (400 MHz) in chloroform-*d* at 25 °C: (a) $\mathbf{Zn1}_3\cdot\mathbf{11}_3$ (1:1, 3.3 mM), (b) **Zn1** (10 mM)+**11** (10 mM)+**19** (5 mM), (c) **Zn1** (10 mM)+**11** (10 mM)+**19** (10 mM), and (d) $\mathbf{Zn1}_3\cdot\mathbf{19}_3$ (3.3 mM).

molecular or supramolecular guests. Although the binding selectivity needs to be improved further, the interaction between two discrete rosettes represents a new approach to the construction of new two-layer-typed supramolecular architectures. The next step will be introducing two cyanuric acid units to the opposite phenyl groups of the porphyrin moiety, which would produce new building block for assembling two-layer-typed porphyrin boxes for new molecular or supramolecular encapsulation.

4. Experimental

4.1. General methods

The ^{1}H NMR spectra were recorded on 400 or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards. Chloroform (δ 7.26 ppm) was used as an internal standard for chloroform-*d*. Elemental analysis was carried out at the SIOC Analytical Center. Unless otherwise indicated, all commercially available materials were used as received. All solvents were dried before use following standard procedures. All reactions were carried out under an atmosphere of nitrogen.

4.1.1. 2-(2-[2-[2-(2-Bromeothoxy)-ethoxy]-ethoxy]-ethoxy)-benzaldehyde (4). To a mixture of salicaldehyde **2** (8.50 mL, 80.0 mmol) and potassium carbonate (20.0 g, 0.15 mol) in DMF (100 mL) was added dibromide **3** (60.0 g, 0.19 mol). The mixture was stirred at 100 °C for 5 h and then concentrated under reduced pressure. The resulting residue was triturated with ether (500 mL) and the organic layer washed with diluted sodium hydroxide solution, water, brine, and dried over sodium sulfate. After evaporation of the solution in vacuo, the crude product was purified by column chromatography (petroleum ether/EtOAc, 2.5:1) to afford the title compound as colorless oil (18.8 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47 (5, J=6.3 Hz, 2H), 3.68–3.76 (m, 8H), 3.81 (t, J=6.3 Hz, 2H), 3.93 (t, J=5.0 Hz, 2H), 4.26 (t, J=4.7 Hz, 2H), 6.89–7.06 (m, 2H), 7.54 (d, d, J_1=1.8 Hz, J_2=8.0 Hz, 1H), 7.84 (d, d, J_1=1.8 Hz, J_2=7.7 Hz, 1H), 10.49 (s, 1H). MS (EI): m/z 281 $[M-Br]^+$. Anal. Calcd for $C_{15}H_{21}Bro_5$: C, 49.88; Br, 22.12; H, 5.86. Found: C, 49.71; Br, 22.29; H, 5.86.

4.1.2. 2-[2-(2-[2-[2-(2-Formyl-phenoxy)-ethoxy]-ethoxy)-ethoxy]-5-hydroxymethyl-benzaldehyde (6). A mixture of **3** (7.60 g, 50.0 mmol), **4** (15.6 g, 43.4 mmol), potassium carbonate (13.0 g, 94.0 mmol) and tetrabutylammonium iodide (0.74 g, 2.00 mmol) in DMF (100 mL) was stirred at 80 °C for 4 h. The solvent was removed under reduced pressure and the resulting residue was triturated with dichloromethane (300 mL). The organic phase was washed with diluted sodium hydroxide solution, water, brine, and dried over sodium sulfate. After evaporation under reduced pressure, the residue was subjected to column chromatography (CH_2Cl_2/EtOAc, 80:1) to afford **6** as oily solid (13.6 g, 72). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.68–3.75 (m, 8H), 3.91–3.94 (m, 4H), 4.23–4.27 (m, 4H), 4.65 (s, 2H), 6.97–7.05 (m, 3H), 7.51–7.59 (m, 2H), 7.79–7.84 (m, 2H), 10.49 (s, 1H), 10.50 (s, 1H). MS (EI): m/z 432 $[M]^+$. Anal. Calcd for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53. Found: C, 64.07; H, 6.57.

4.1.3. 2-[2-(2-{2-[2-(2-Formyl-phenoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-5-(2,4,6-trioxo-[1,3,5]triazinan-1-ylmethyl)-benzaldehyde (7). To a stirred solution of **6** (2.16 g, 5.00 mmol), triphenylphosphine (1.97 g, 7.50 mmol), and cyanuric acid (1.94 g, 15.0 mmol) in DMF (80 mL) was added dropwise a solution of DEAD (1.5 equiv, 40% in toluene) in DMF (10 mL) at room temperature. The solution was stirred for 60 h and the solvent was evaporated in vacuo. The resulting residue was washed with water thoroughly and dried to give a crude product, which was purified by column chromatography (CH_2Cl_2/EtOAc/MeOH, 3:3:0.3) to afford **7** as a white solid (1.02 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67–3.73 (m, 8H), 3.89 (t, J=4.5 Hz, 4H), 4.20 (q, J=4.7 Hz, 4H), 4.80 (s, 2H), 6.85–6.99 (m, 3H), 7.49–7.55 (m, 2H), 7.77–7.83 (m, 2H), 9.69 (br, 2H), 10.38 (s, 1H), 10.46 (s, 1H). MS (EI): m/z 427 $[M-C_3H_4N_2O_3]^+$. Anal. Calcd for $C_{26}H_{29}N_3O_{10}$: C, 57.45; H, 5.38; N, 7.73. Found: C, 57.29; H, 5.21; N, 7.52.

4.1.4. 4-Formyl-benzoic acid 3-methyl-butyl ester (9). This compound was synthesized in 90% yield as colorless oil by using the procedure described for preparation of compound **4**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (d, d, J_1=1.8 Hz, J_2=6.1 Hz, 6H), 1.66–1.86 (m, 3H), 4.40 (t, J=6.6 Hz, 2H), 7.96 (d, J=7.8 Hz, 2H), 8.20 (d, J=7.8 Hz, 2H), 10.11 (s, 1H). MS (EI): m/z 220 $[M]^+$. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.92; H, 7.51.

4.1.5. 4-[Bis-(1*H*-pyrrol-2-yl)-methyl]-benzoic acid 3-methyl-butyl ester (10). A solution of **9** (14.1 g, 64.0 mmol) and pyrrole (43.0 g, 0.64 mol) in toluene (250 mL) was degassed by a stream of nitrogen for 30 min. Then, hot saturated tosyl acid solution in toluene (1 mL) was added in one portion. The solution was heated under reflux for 1.5 h and then cooled to room temperature. The solution was washed with potassium carbonate solution (2 N, 50 mL), water (50 mL), brine (50 mL), and dried over potassium carbonate. After the solvent was evaporated under reduced pressure, the resulting oily residue was purified by column chromatography (chloroform) to afford compound **10** as a white solid (16.5 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, J=6.6 Hz, 6H), 1.64–1.83 (m, 3H), 4.34 (t, J=6.5 Hz, 3H), 5.52 (s, 1H), 5.89 (s, 2H), 6.16 (q, J=3.0 Hz, 2H), 6.71 (s, 2H), 7.28 (d, J=8.1 Hz, 2H), 7.97 (d, J=8.1 Hz, 4H). MS (EI): m/z 336 $[M]^+$. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.76; H, 7.32; N, 8.08.

4.1.6. Porphyrin $H_2$1. Compounds **7** (2.17 g, 4.00 mmol) and **10** (2.69 g, 8.00 mmol) were dissolved in dichloromethane (850 mL). The solution was degassed with nitrogen for 30 min and then trifluoroacetic acid (1 mL) was added in one portion. The solution was stirred at room temperature for 12 h and a solution of 4-chloranil (2.00 g) in THF (50 mL) was added. The mixture was stirred at room temperature for another 2 h and then concentrated in vacuo to afford a solid residue, which was purified by column chromatography (CH_2Cl_2/AcOEt/MeOH, 15:10:1). The desired compound was obtained as a purple solid (0.68 g, 15%). Mp 182–182.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ

−2.79 (s, 2H), −0.47- −0.42 (m, 4H), 0.78–0.83 (m, 4H), 1.05 (d, J=6.3 Hz, 12H), 1.80 (q, J=6.7 Hz, 4H), 1.88–1.97 (m, 2H), 2.73–2.79 (m, 2H), 3.71 (t, J=3.5 Hz, 2H), 3.78 (t, J=3.5 Hz, 2H), 4.53 (t, J=6.7 Hz, 4H), 4.95 (s, 2H), 6.99 (d, J=8.0 Hz, 1H), 7.18 (d, J=7.5 Hz, 1H), 7.45 (t, J=7.5 Hz, 1H), 7.64 (d, d J_1=8.0 Hz, J_2=1.5 Hz, 1H), 7.73 (d, d, J_1=8.0 Hz, J_2=1.5 Hz, 1H), 8.19–8.47 (m, 12H), 8.73–8.93 (m, 8H). MS (ESI): m/z 1174 $[M+H_2O]^+$. Anal. Calcd for $C_{68}H_{67}N_7O_{12}\cdot H_2O$: C, 68.50; H, 5.84; N, 8.23. Found: C, 68.67; H, 5.84; N, 8.05.

4.1.7. Porphyrin Zn1. This compound was prepared quantitatively form $\mathbf{H_2 1}$ after stirring with zinc acetate (2 equiv) in chloroform and THF at room temperature for 12 h. Mp >200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.47 to −0.42 (m, 4H), 0.78–0.83 (m, 4H), 1.05 (d, J=6.3 Hz, 12H), 1.80 (q, J=6.7 Hz, 4H), 1.88–1.97 (m, 2H), 2.73–2.79 (m, 2H), 3.71 (t, J=3.5 Hz, 2H), 3.78 (t, J=3.5 Hz, 2H), 4.53 (t, J=6.7 Hz, 4H), 4.95 (s, 2H), 6.99 (d, J=8.0 Hz, 1H), 7.18 (d, J=7.5 Hz, 1H), 7.44 (t, J=7.5 Hz, 1H), 7.64 (d, d, J_1=8.0 Hz, J_2=1.5 Hz, 1H), 7.73 (d, d, J_1=8.0 Hz, J_2=1.5 Hz, 1H), 8.19–8.47 (m, 12H), 8.73–8.93 (m, 8H). MS (ESI): m/z 1237 $[M+H]^+$. Anal. Calcd for $C_{68}H_{65}N_7O_{12}Zn$: C, 65.99;, 5.29; N, 7.92. Found: C, 65.69; H, 5.14; N, 7.81.

4.1.8. 1,3,5-Tris-pyridin-4-ylmethyl-[1,3,5]triazinane-2,4,6-trione (13). To a stirred solution of cyanuric acid (0.13 g, 1.00 mmol), triphenylphosphine (1.30 g, 5.00 mmol) and **14** (0.55 g, 5.00 mmol) in DMF was added DEAD (5.00 mmol, 40% in toluene) at room temperature. Stirring was continued at room temperature for another 5 h, and then the solvent was removed under reduced pressure. The resulting residue was triturated with chloroform (100 mL), and the organic phase was washed with water, brine, and dried over sodium sulfate. After evaporation of the solvent in vacuo, the residue was purified by column chromatography to afford **13** as a white solid (0.29 g, 73%). Mp 198–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05 (s, 6H), 7.31 (s, 6H), 8.60 (s, 6H). MS (EI): m/z 402 $[M]^+$. Anal. Calcd for $C_{21}H_{18}N_6O_3\cdot 0.5H_2O$: C, 61.30; H, 4.66; N, 20.43. Found: C, 61.44; H, 4.51; N, 20.58.

4.1.9. 5-(3-Methyl-butyl)-5-pyridin-4-ylmethyl-pyrimidine-2,4,6-trione (18a). To a stirred solution of diethyl malonate (8.00 g. 50.0 mmol) in dry DMF (200 mL) was added sodium hydride (60%, 1.60 g, 40.0 mmol). After stirring for 30 min, iso-pentyl bromide (5.65 g, 40.0 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated in vacuo to afford a oily residue which was triturated with ether (200 mL). The organic phase was washed with diluted hydrochloric acid, water, brine, and dried with sodium sulfate. After evaporation of the solvent, the residue was purified by column chromatography ($CHCl_3$/MeOH, 20:1) to give the desired intermediate in ca. 80% yield. To a solution of this product (ca. 33 mmol) in dry DMF (100 mL) was added sodium hydride (60%, 2.80 g, 70.0 mmol) in portions. After stirring at room temperature for 30 min, 4-(chloromethyl)pyridine (4.17 g, 35.0 mmol) in DMF (50 mL) was added. The mixture was stirred at 80 °C for 3 h and then concentrated in vacuo. The residue was triturated with ether (300 mL) and the organic phase was washed with water, brine, and dried over sodium sulfate. After evaporation of the solvent and column chromatography (CH_2Cl_2/EtOAc, 15:1), the crude product **17a** was obtained as oil (3.71 g, 35%). To a solution of sodium ethoxide (3.40 g, 50.0 mmol) in ethanol (50 mL) was added urea (0.63 g, 10.5 mmol). Then, the above **17a** was added one portion. The reaction mixture was heated under reflux for 12 h and then concentrated in vacuo. The resulting residue was subjected to column chromatography (CH_2Cl_2/MeOH, 15:1) to give a crude product. After recrystallization from ethanol, pure **18a** was obtained as a white solid (1.03 g, 33%). Mp 244–246 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.83 (d, J=6.5 Hz, 6H), 0.96–1.03 (m, 2H), 1.44–1.48 (m, 1H), 1.94–1.20 (m, 2H), 3.14 (s, 2H), 6.70 (d, J=5.4 Hz, 2H), 8.47 (d, J=5.4 Hz, 2H), 11.50 (s, 1H). MS (EI): m/z 289 $[M]^+$. Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.20; H, 6.54; N, 14.56.

4.1.10. 5-(3,5-Di-*tert*-butyl-benzyl)-5-pyridin-4-ylmethyl-pyrimidine-2,4,6-trione (18b). This compound was prepared as a white solid following the procedures described for **18a**. Mp 266 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22 (s, 9H), 3.27–3.33 (m, 4H), 6.86 (d, J=1.8 Hz, 2H), 7.03 (d, J=5.9 Hz, 2H), 7.23 (s, 1H), 8.47 (d, J=5.9 Hz, 2H). MS (EI): m/z 421 $[M]^+$. Anal. Calcd for $C_{25}H_{31}N_3O_3$: C, 71.23; H, 7.41; N, 9.97. Found: C, 71.35; H, 7.54; N, 9.65.

4.1.11. *N*-(4-Butyl-phenyl)-*N′*-pyridin-4-ylmethyl-[1,3,5]triazine-2,4,6-triamineA (19). A solution of 4-*tert*-butylaniline **21** (0.50 g, 3.30 mmol) in THF (5 mL) was added dropwise over 5 min to an ice-cooled solution of cyanuric chloride (0.62 g, 3.30 mmol) and DIPEA (2 mL) in THF (10 mL). The reaction mixture was stirred for 2 h, and then allowed to warm to room temperature. Ammonia gas was then bubbled to the solution for 3 h and then hexane (40 mL) was added. The precipitate resulted was filtered and washed with hexane to yield a crude product which was used for next step directly: A suspension of this precipitate, DIPEA (3 mL) and 4-picolyamine (2 mL) in chloroform and THF (10 mL, 1:1) was refluxed for 15 h and then concentrated in vacuo. The resulting residue was triturated with chloroform (50 mL) and the organic phase washed with water, brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by column chromatography ($CHCl_2$/MeOH 20:1) to give **19** as a yellow solid (0.46 g, 40%). Mp 113–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 9H), 4.61 (d, J=6.0 Hz, 2H), 4.95 (s, 2H), 5.59 (br, 1H), 7.02 (s, 1H), 7.23–7.41 (br, m, 8H), 8.56 (d, J=6.0 Hz, 2H). MS (EI): m/z 349 $[M]^+$. Anal. Calcd for $C_{19}H_{23}N_7$: C, 65.31; H, 6.63; N, 28.06. Found: C, 65.19; H, 6.69; N, 28.14.

Acknowledgements

We thank the Ministry of Science and Technology (No. G2000078101), the National Natural Science Foundation, and the State Laboratory of Bioorganic and Natural Products Chemistry of China for financial support. We also thank Prof. Min Shi for helpful discussion.

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Tetrahedron 60 (2004) 9163–9170
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α-Hydroxy carboxylic acids as ligands for enantioselective diethylzinc additions to aromatic and aliphatic aldehydes

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Received 27 May 2004; revised 1 July 2004; accepted 23 July 2004

Available online 25 August 2004

Abstract—The first examples of the enantioselective titanium-mediated diethylzinc additions to aromatic and aliphatic aldehydes catalyzed by optically active α-hydroxy acids are presented. The reactions proceed with very good yield and good asymmetric induction. Enantioselectivities up to 90% are obtained depending on ligand and aldehyde used. A stereochemical model for the reaction is proposed.

1. Introduction

The enantioselective organometallic addition to aldehydes is a valuable method for the synthesis of optically active secondary alcohols and several efficient catalysts have been developed, various types of chiral ligands can be used for such additions. Since 1986, when DAIB was introduced by Noyori,[1] the amount of very useful and efficient dialkylamino alcohols has grown dramatically,[2] and now includes not only dialkylamino alcohols but also amino thiols,[3] oxazolines[4–6] and even diols such as TADDOLs[7,8] and BINOLs.[9–11] Further progress in enantioselective additions to aldehydes was achieved, when Ohno and co-workers reported diethylzinc additions in the presence of titanium tetraisopropoxide and a chiral bissulfonamide.[12] Since then, extensive synthetic studies were conducted and α-hydroxy sulfonamides and bissulfonamides were proven to be very efficient ligands for additions of dialkylzincs.[13–17] Although the exact mechanism of the process is not known, recent structural and mechanistic investigations showed that the active catalytic intermediates could be an ethyltitanium species derived from the transfer of an ethyl group from zinc to titanium or a bimetallic species containing an ethylzinc compound.[15] Both ligand accelerated diethylzinc additions and alkyltitanium additions to carbonyl compounds exhibit excellent chemoselectivity.[18] For mixtures of aldehydes and ketones, only addition to the aldehyde carbonyl group is observed whilst ketones remain intact. This led us to the conclusion that carboxylic acids could serve as ligands in $Ti(O^iPr)_4$ catalyzed additions of diethylzinc to aldehydes. For the second coordination site, we chose the hydroxy group so that our ligands belong to the readily accessible family of α-hydroxy acids **1**. Recently we have presented a preliminary communication[19] on the addition of diethylzinc to benzaldehyde (**2**) catalyzed by α-hydroxy acids **1** and the purpose of this paper is to give a full account on the enantioselective diethylzinc addition to aromatic and aliphatic aldehydes (Scheme 1).

Keywords: Diethylzinc; Titanium tetraisopropoxide; α-Hydroxy acids; Aldehydes; Enantioselective.

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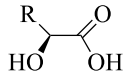
doi:10.1016/j.tet.2004.07.060

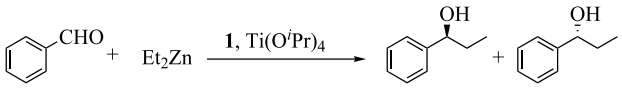
2. Results and discussion

2.1. Synthesis of α-hydroxy acids

2.1.1. Synthesis by diazotisation of α-amino acids. One of the most straightforward, reliable and inexpensive methods for the synthesis of α-hydroxy acids is diazotisation of α-amino acids. The reaction proceeds with retention of configuration,[20,21] and traces of the minor enantiomer, if present, can be removed by recrystallization.[22] We have chosen six amino acids **4b–g**, which were treated at 0 °C with excess of aqueous sodium nitrate(IV) in the presence of 0.5 M sulfuric acid. The reaction mixture was stirred

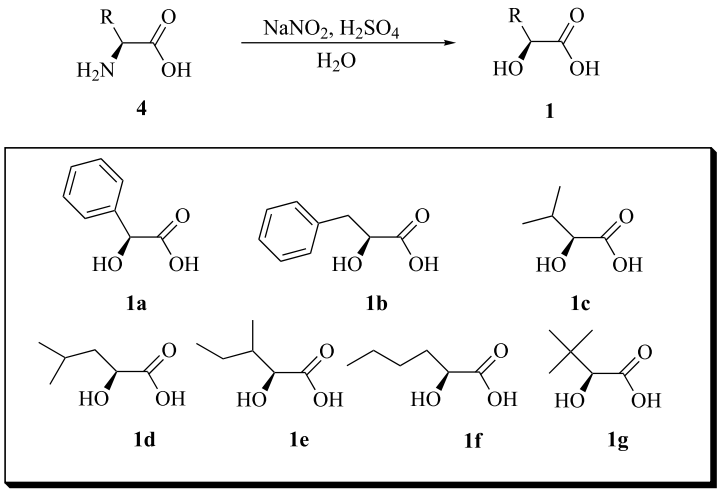


1



2 *S*-**3** *R*-**3**

Scheme 1. Diethylzinc addition to benzaldehyde in the presence of α-hydroxy acids as chiral ligands.



Scheme 2. Synthesis of α-hydroxy acids by diazotisation.

overnight at room temperature, and after work-up, the resulting α-hydroxy acids **1b–g** were crystallized from organic solvents (Scheme 2). For all thus prepared compounds, specific rotations were in good agreement with literature values, except the case of (*S*)-2-hydroxy-3,3-dimethylbutanoic acid (**1g**). For the sample prepared by us we measured $[\alpha]_D^{22}=+4.1$ ($c=1.83$, H_2O); commercially available (Aldrich) compound had $[\alpha]_D^{22}=+3.3$ (c 2.25, H_2O), while the literature value is $[\alpha]_D^{25}=+4.5$ ($c=1$[23] or $c=4$[24], H_2O). At this moment we are not able to say, whether the reason for this discrepancy is presence of the minor enantiomer or chemical impurities. The enantiomeric purity of (*S*)-2-hydroxy-3,3-dimethylbutanoic acid (**1g**), as well as rest of the α-hydroxy acids used, will be confirmed by other methods and the results will be reported in due course. This has to be taken into account during analysis of the results of diethylzinc addition.

2.1.2. Synthesis by diastereoselective Friedel–Crafts alkylation. In addition to α-hydroxy acids synthesized from α-amino acids we have also prepared two compounds bearing substituted phenyl rings. Lewis acid catalyzed addition of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**5**) to methoxy- and isopropoxy *tert*-butyl benzene (**6a** and **6b**, respectively) proceeded with good yield and diastereoselectivity. Hydrolysis of the chiral auxiliary under mild conditions gave hydroxy acids **1h** and **1i** (Scheme 3). The details of the synthesis are presented elsewhere.[25]

2.2. Enantioselective diethylzinc addition

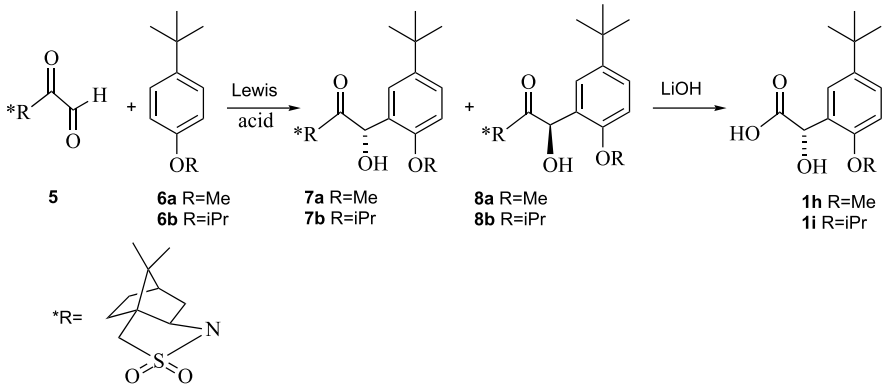
2.2.1. Enantioselective diethylzinc addition to aldehydes in the presence of (*S*)-mandelic acid. In order to confirm considerations presented above, we decided to use commercially available (*S*)-mandelic acid **1a** as a ligand and benzaldehyde **2** as a model carbonyl compound. The reaction was conducted at room temperature in methylene chloride in the presence of 0.2 equiv of mandelic acid, 3 equiv of diethylzinc and 1.4 equiv of titanium tetraisopropoxide. The reaction was stirred overnight, and after TLC showed complete conversion, quenched with aqueous hydrochloric acid. After work-up and chromatography 1-phenyl-1-propanol **3** was isolated in 88% yield. The enantiomeric excess (77% ee in favor of the product with 1*S* configuration) was determined by HPLC using a Chiracel OD column.

After this first successful experiment we started a systematic investigation of the factors influencing yield and asymmetric induction in this reaction. First, we noted that the reaction performed in the absence of $Ti(O^iPr)_4$ is very sluggish and proceeds with low asymmetric induction (Table 1, entry 1). On the other hand, increased bulkiness of the titanium reagent does not influence the reaction and in the presence of $Ti(O^tBu)_4$ we obtained similar yield and ee (Table 1, entry 3). Addition of zinc and titanium reagents in the reversed order did not influence enantioselectivity (Table 1, entry 2). To examine effect of the solvent the reaction was carried out in five typical solvents. Methylene chloride was the best one both for chemical yield and asymmetric induction (Table 1, entries 4–8).

Once the best solvent was found, we studied the influence of the amount of the ligand and its concentration. The asymmetric induction was only slightly influenced by increased amount of ligand, while the chemical yield dropped from 95 to 80% (Table 2). For further experiments, a concentration of 0.044 mmol/mL and 0.2 equiv of ligand was chosen. The next parameter studied was reaction temperature. Table 3 shows the influence of the temperature and the optimum regarding both yield and enantiomeric excess was observed for room temperature (22 °C).

The so-called 'aging' of the catalyst can seriously influence the results of the reaction. In order to find out, whether our system is prone to such phenomena we performed two series of experiments in which we measured the enantiomeric excess against time of the complexation with titanium and zinc compounds. In the first series, showed that the optimum complexation time for titanium tetraisopropoxide lies between 1 and 1.5 h. Therefore, in the next experiments, the ligand was stirred with $Ti(O^iPr)_4$ for 1.5 h. For diethylzinc this optimum was found after 45 min of complexation. The results are presented in Tables 4 and 5.

The last two parameters, the influence of which had to be



Scheme 3. Synthesis of α-hydroxy acids by diastereoselective Friedel–Crafts reaction.

Table 1. Diethylzinc addition in various solvents

Entry	Ligand	Solvent	Temperature (°C)	Time (h)	Yield (%)	ee (config.) (%)
1[a]	**1a**	CH_2Cl_2	22	66	73	40 (*S*)
2[b]	**1a**	CH_2Cl_2	22	23	90	76 (*S*)
3[c]	**1a**	CH_2Cl_2	22	23	79	77 (*S*)
4	**1a**	CH_2Cl_2	22	20	88	77 (*S*)
5	**1a**	Toluene	22	23	77	67 (*S*)
6	**1a**	*n*-Hexane	22	24	88	63 (*S*)
7	**1a**	THF	22	19	40	32 (*S*)
8	**1a**	Et_2O	22	19	75	65 (*S*)

[a] Reaction in the absence of $Ti(O^iPr)_4$.
[b] Addition order was reversed from $Ti(O^iPr)_4/Et_2Zn$ to $Et_2Zn/Ti(O^iPr)_4$.
[c] Reaction in the presence of $Ti(O^tBu)_4$ instead of $Ti(O^iPr)_4$.

Table 2. Influence of the ligand amount on the enantiomeric excess

Entry	Ligand	Amount (equiv)	Concentration (mmol/ml)	Temperature (°C)	Time (h)	Yield (%)	ee (config.) (%)
1	**1a**	0.2	0.034	22	20	88	77 (*S*)
2	**1a**	0.2	0.044	22	18	95	78 (*S*)
3	**1a**	0.4	0.044	22	18	88	79 (*S*)
4	**1a**	0.6	0.054	22	18	89	81 (*S*)
5	**1a**	0.8	0.064	22	18	85	81 (*S*)
6	**1a**	1.0	0.074	22	18	80	80 (*S*)

Table 3. Influence of the reaction temperature on the enantiomeric excess

Entry	Ligand	Temperature (°C)	Time (h)	Yield (%)	ee (config.) (%)
1	**1a**	22	18	95	78 (*S*)
2	**1a**	0	19	87	80 (*S*)
3	**1a**	−20	19	62	76 (*S*)
4	**1a**	−78	72	—	—

Table 4. Optimalization of the complexation time with $Ti(O^iPr)_4$

Entry	Ligand	Amount (equiv)	Complexation time (h)	Reaction time (h)	Yield (%)	ee (config.) (%)
1	**1a**	0.2	0.5	18	90	77 (*S*)
2	**1a**	0.2	1	18	94	78 (*S*)
3	**1a**	0.2	1.5	18	95	78 (*S*)
4	**1a**	0.2	2	18	87	78 (*S*)
5	**1a**	0.2	2.5	18	90	77 (*S*)

Table 5. Optimalization of the complexation time with Et_2Zn

Entry	Ligand	Amount (equiv)	Complexation time (h)	Reaction time (h)	Yield (%)	ee (config.) (%)
1	**1a**	0.2	0.5	18	95	78 (*S*)
2	**1a**	0.2	0.75	18	96	79 (*S*)
3	**1a**	0.2	1	19	94	78 (*S*)
4	**1a**	0.2	1.5	18	95	75 (*S*)
5	**1a**	0.2	2	18	87	75 (*S*)
6	**1a**	0.2	2.5	18	90	75 (*S*)

Table 6. Optimalization of amounts of Et_2Zn and $Ti(O^iPr)_4$ sufficient for the efficient addition

Entry	Ligand	Amount of **1a** (equiv)	Et_2Zn (equiv)	$Ti(O^iPr)_4$ (equiv)	Time (h)	Yield (%)	ee (config.) (%)
1	**1a**	0.2	3	1.4	18	96	79 (*S*)
2	**1a**	0.2	2.5	1.4	18	97	79 (*S*)
3	**1a**	0.2	2	1.4	18	92	80 (*S*)
4	**1a**	0.2	1.5	1.4	42	55	80 (*S*)
5	**1a**	0.2	1	1.4	42	41	80 (*S*)
6	**1a**	0.2	2	1.2	18	86	80 (*S*)
7	**1a**	0.2	2	1	18	88	80 (*S*)
8	**1a**	0.2	2	0.8	18	90	80 (*S*)
9	**1a**	0.2	2	0.6	18	85	78 (*S*)

established, were amounts of diethylzinc and titanium tetraisopropoxide sufficient for the good chemical yield and asymmetric induction. The optimum was found to be 2 equiv of Et_2Zn and 0.8 equiv of $Ti(O^iPr)_4$ (Table 6, entry 8). It is important to stress that substochiometric amounts of titanium are sufficient to produce *S*-**3** in 90% yield and 80% ee.

Having established all the important parameters of the reaction we carried out the enantioselective addition of diethylzinc to some representative aromatic and aliphatic aldehydes. As shown in the Table 7, for all but one aldehyde (cinnamaldehyde, entry 7) enantioselectivities were at levels comparable with that obtained for benzaldehyde, even for aliphatic and cycloaliphatic aldehydes (entries 8 and 9).

2.2.2. Enantioselective diethylzinc addition to aldehydes in the presence of various α-hydroxy acids. The positive results presented above prompted us to synthesize and use series of aromatic and aliphatic α-hydroxy acids with various steric demands. The results are presented in Table 8. The increased bulkiness of the acid substituent is reflected in the increased asymmetric induction. The individual character of each ligand means that conditions optimized for each one of them (e.g., mandelic acid **1a**) are not good for others (entry 1 vs 2, 3 vs 4, 10 vs 11), so we decided to use 'typical' (widely used in the literature) conditions −3 equiv of diethylzinc and 1.4 equiv of titanium tetraisopropoxide. The best results were obtained for two ligands **1g** and **1h**. Interestingly, ligand **1i** with more bulky isopropyl substituent, gave lower asymmetric induction than **1h**. Also, in this study, the bulkiness of the titanium reagent (entry 5) had an adverse effect on the asymmetric induction.

For relatively inexpensive and readily available ligand **1c** the influence of ligand amount and its concentration on ee was established (Table 9). The increased amounts of ligand **1c** gives slightly better enantiomeric excess but this effect is accompanied by longer reaction time and a serious drop of chemical yield (entry 1 vs entries 2–5 in Table 9). The reaction performed at 0 °C gave somewhat higher ee (entry 6), but the reaction stops at lower temperatures (entries 7 and 8).

The enantioselective addition of diethylzinc to some representative aromatic and aliphatic aldehydes was performed in the presence of ligand **1h**, which was easy to obtain in high chemical and enantiomeric purity, despite its multistep synthesis. The results are presented in Table 10. In general, the results obtained in the presence of ligand **1h** were better than in the presence of **1a**, with the exception of aliphatic aldehydes **16** and **17** that gave substantially lower enantiomeric excess.

2.2.3. Mechanistic considerations. The stereochemical outcome of the reaction performed in the presence of α-hydroxy acids can be rationalized as follows. The variation of the addition order of titanium and zinc reagents, leading to virtually identical asymmetric induction indicates a monometallic transition state, which has been postulated several times in the literature for other ligands.[26,27] We suggest that the reaction goes through one of the possible model transition states **I–III** depicted in Figure 1. For picture simplicity, addition of diethylzinc to benzaldehyde in the presence of mandelic acid is analyzed. In the model **I** *re* attack leads to products with the absolute configuration *R*,

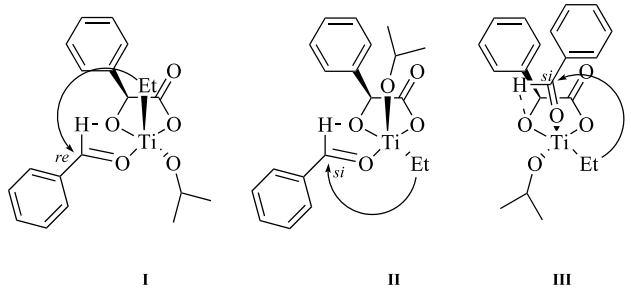
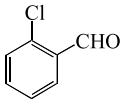
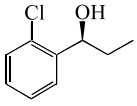
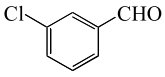
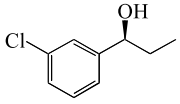
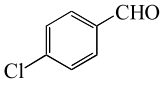
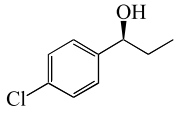
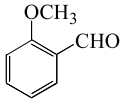
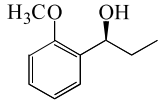
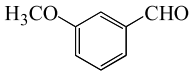
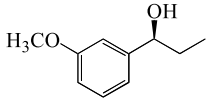
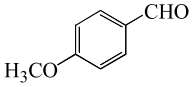
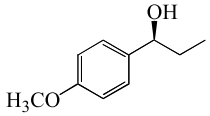
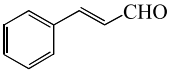
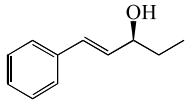
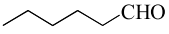
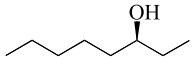
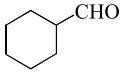
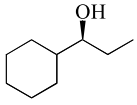


Figure 1. Stereochemical models for an ethylation of aldehydes.

Table 7. Et_2Zn addition to selected aldehydes in the presence of **1a**

Entry	**1a** (equiv)	Aldehyde		Temperature (°C)	Time (h)	Product		Yield (%)	ee (%)
1	0.2		**9**	28	19		*S*-**18**	75	76
2	0.2		**10**	28	18		*S*-**19**	90	70
3	0.2		**11**	28	19		*S*-**20**	97	72
4	0.2		**12**	28	19		*S*-**21**	88	79
5	0.2		**13**	28	19		*S*-**22**	97	77
6	0.2		**14**	28	18		*S*-**23**	96	80
7	0.2		**15**	28	17		*S*-**24**	91	52
8	0.2		**16**	28	17		*S*-**25**	75	78
9	0.2		**17**	28	19		*S*-**26**	81	77

opposite to that observed in experiments. In models **II** and **III** the *si* attack leads to the observed configuration, but the apical position of the bulky isopropoxy group in the model **II** is not very likely, due to a steric clash with the aryl (or alkyl) moiety of the α-hydroxy acid. The model transition state **III** in our opinion is the best explanation of the observed asymmetric induction. In all three we postulate the presence of hydrogen bonding between ligand's α-oxygen and formyl hydrogen of the coordinated aldehyde. Such bonding was already postulated by Corey, and was proved

Table 8. Addition of Et_2Zn to benzaldehyde in the presence of acids **1b–i**

Entry	Ligand	Amount of **1b–i** (equiv)	Amount of $Ti(O^iPr)_4$ (equiv)	Amount of Et_2Zn (equiv)	Time (h)	Yield (%)	Ee (config.) (%)
1	**1b**	0.2	1.4	3	19	80	85 (*S*)
2	**1b**	0.2	0.8	2	24	90	83 (*S*)
3	**1c**	0.2	1.4	3	19	85	85 (*S*)
4	**1c**	0.2	0.8	2	24	95	80 (*S*)
5[a]	**1c**	0.2	1.4	3	45	67	78 (*S*)
6	**1d**	0.2	1.4	3	19	73	80 (*S*)
7	**1e**	0.2	1.4	3	20	71	83 (*S*)
8	**1f**	0.2	1.4	3	20	88	77 (*S*)
9	**1g**	0.2	1.4	3	20	95	88 (*S*)
10	**1h**	0.2	1.4	3	20	95	87 (*S*)
11	**1h**	0.2	0.8	2	18	74	79 (*S*)
12	**1i**	0.2	1.4	3	20	95	79 (S)

[a] $Ti(O^tBu)_4$ instead of $Ti(O^iPr)_4$

Table 9. Influence of ligand amount on the enantiomeric excess in the addition of Et_2Zn to benzaldehyde

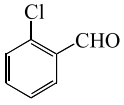
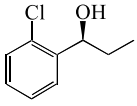
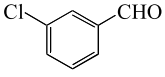
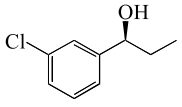
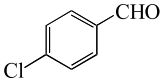
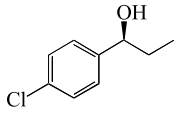
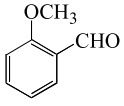
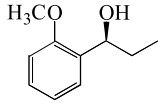
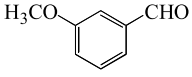
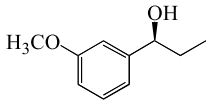
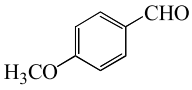
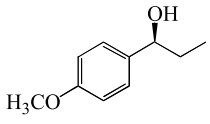
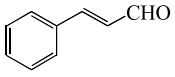
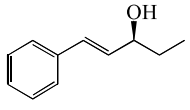
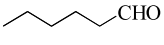
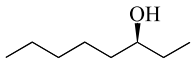
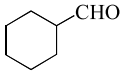
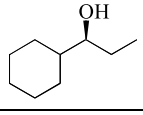
Entry	Ligand	Amount (equiv)	Concentration (mmol/ml)	Temperature (°C)	Time (h)	Yield (%)	ee (%)
1	**1c**	0.2	0.044	22	19	85	85 (S)
2	**1c**	0.4	0.044	22	24	79	87 (S)
3	**1c**	0.6	0.054	22	40	56	88 (S)
4	**1c**	0.8	0.064	22	42	54	91 (S)
5	**1c**	1.0	0.074	22	42	27	88 (S)
6	**1c**	0.2	0.044	0	20	82	86 (S)
7	**1c**	0.2	0.044	−23	48	—	—
8	**1c**	0.2	0.044	−78	48	—	—

to be a very important factor influencing asymmetric induction in enantioselective reactions.[28] Its presence substantially rigidifies transition states leading to good enantiomeric excess.

3. Conclusions

We have proposed a new class of chiral ligands applicable to enantioselective additions of diethylzinc to aldehydes. We have shown that reactions in the presence of α-hydroxy acids proceed with very good yield and good enantiomeric excess up to 90%. α-Hydroxy acids can catalyze the addition of diethylzinc to both aliphatic and aromatic aldehydes, are relatively inexpensive and are readily available. Further applications of α-hydroxy acids as ligands for enantioselective metalloorganic additions are under investigation and will be reported in due course.

Table 10. Et_2Zn addition to selected aldehydes in the presence of **1h**

Entry	Amount of **1h** (equiv)	Aldehyde		Temperature (°C)	Time (h)	Product		Yield (%)	ee (%)
1	0.2		**9**	21	24		*S*-**18**	95	76
2	0.2		**10**	21	19		*S*-**19**	94	77
3	0.2		**11**	21	24		*S*-**20**	83	82
4	0.2		**12**	21	19		*S*-**21**	85	89
5	0.2		**13**	21	18		*S*-**22**	96	78
6	0.2		**14**	21	18		*S*-**23**	95	83
7	0.2		**15**	21	18		*S*-**24**	87	59
8	0.2		**16**	21	23		*S*-**25**	70	65
9	0.2		**17**	21	23		*S*-**26**	70	68

4. Experimental

4.1. General

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Specific rotations were recorded using a Perkin–Elmer PE-241 polarimeter with a thermally jacketed 10-cm cell. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Varian 200 Unity Plus and Varian 500 Unity Plus spectrometers. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ, 0.00 ppm), and coupling constants (J) are measured in Hertz. Mass spectra were recorded on a Mariner instrument (Biosystem) using the LSIMS technique. Infrared spectra were recorded using a Beckmann IR-240 spectrometer. Reactions were carried under argon using Schlenk technique when necessary. Flash column chromatography was made on silica gel (Kieselgel-60, Merck, 230–400 mesh). High Performance Liquid Chromatography was conducted on Merck Hitachi D-7000 with diode array detector L-7455 using chiral column Diacel Chiracel OD. Gas Chromatography was conducted on Hewlett–Packard 5890 series II with FID detector using chiral column β-Dex, 30 m×0.25 mm I.D. (Supelco, Bellefonte, USA). Retention time is given in minutes.

4.2. Preparation of α-hydroxy acids form α-amino acids by diazotisation. General procedure

α-Amino acid (10 mmol) was dissolved in 0.5 M H_2SO_4 (40 mL, 20 mmol). This solution was cooled to 0 °C and a solution of $NaNO_3$ (4.14 g, 60 mmol) in H_2O (13.5 mL) was added slowly with stirring, while temperature was maintained below 5 °C. The reaction was stirred at this temperature for a further 3 h, and than allowed to warm up to room temperature and left for 24 h. The reaction mixture was extracted 3 times with ethyl ether (3×50 mL), combined organic layers were washed with brine (50 mL) and dried over anhydrous sodium sulfate. The drying agent was filtered off, and ether was evaporated in vacuo. The residual mass was recrystallized from hexane–ether to give respective α-hydroxy acid. All compounds have been previously reported and were characterized by comparison with their reported physical and spectroscopic data.

4.2.1. (*S*)-2-Hydroxy-3-phenylpropanoic acid (1b). Tiny, colorless needles with characteristic pleasant smell; yield 65% (1.08 g, 6.2 mmol). Mp 123–123 °C (ether–hexane); lit.[22] 123–124 °C. $[\alpha]_D^{20}=-21.3$ ($c=2.35$, H_2O); lit.[29] $[\alpha]_D=-20.0$ ($c=2$, H_2O).

4.2.2. (*S*)-2-Hydroxy-3-methylbutanoic acid (1c). Tiny, colorless needles with intensive unpleasant smell; yield 31% (0.37 g, 3.1 mmol). Mp 61–62 °C (ether–hexane) lit.[30] 62–63 °C. $[\alpha]_D^{20}=+17.3$ ($c=1.06$, $CHCl_3$); lit.[29] $[\alpha]_D=+17.3$ ($c=1$, $CHCl_3$).

4.2.3. (*S*)-2-Hydroxy-4-methylpentanoic acid (1d). Colorless needles yield; 40% (0.53 g, 4.0 mmol). Mp 76–77 °C (ether–hexane) lit.[22] 78–80 °C. $[\alpha]_D^{20}=-26.6$ ($c=1.2$, 1 M NaOH); lit.[29] $[\alpha]_D=-25.9$ ($c=1$, 1 M NaOH).

4.2.4. (2*S*,3*S*)-2-Hydroxy-3-methylpentanoic acid (1e). Tiny, colorless needles; yield 52% (0.69 g, 5.2 mmol). Mp 50–52 °C (ether–hexane) lit.[29]: 52–54 °C. $[\alpha]_D^{20}=+21.9$ ($c=1$, $CHCl_3$); lit.[31] $[\alpha]_D^{22}=+22$ ($c=1$, $CHCl_3$).

4.2.5. (*S*)-2-Hydroxyhexanoic acid (1f). White crystals; yield 30% (0.40 g, 3.0 mmol). Mp 59–60 °C (ether–hexane) lit.[32]: 60–61 °C. $[\alpha]_D^{20}=-16.3$ ($c=3.92$, 1 M NaOH); lit.[33] $[\alpha]_D^{25}=-15.3$ ($c=1.1$, 1 M NaOH).

4.2.6. (*S*)-2-Hydroxy-3,3-dimethylbutanoic acid (1g). Small colorless crystals; yield 47% (0.62 g, 4.7 mmol). Mp 47–48 °C (ether–hexane) lit.[34]: 49–51 °C. $[\alpha]_D^{22}=+4.1$ ($c=1.83$, H_2O); lit.[23] $[\alpha]_D^{25}=+4.5$ ($c=1$, H_2O); lit.[24] $[\alpha]_D^{25}=+4.5$ ($c=4$, H_2O).

4.3. General procedure for the addition of diethylzinc to aldehyde in the presence (*S*)-mandelic acid

In the oven dried Schlenk tube filled with argon and equipped with the stirring bar was placed (*S*)-mandelic acid (30.2 mg, 0.2 mmol), followed by methylene chloride (4.5 mL), $Ti(O^iPr)_4$ (0.24 mL, 0.8 mmol). After 1.5 h the solution was cooled to 0 °C and diethylzinc (1.1 M in toluene, 1.8 mL, 2 mmol) was added. The stirring was continued at this temperature for 45 min, aldehyde (1 mmol) was added and after additional 30 min of stirring at 0 °C the reaction mixture was allowed to warm up to room temperature. The progress of the reaction was controlled with TLC using CH_2Cl_2:MeOH 70:2. After completion the reaction was quenched with slow addition of 1 M HCl (CAUTION! Exothermic reaction). The precipitate was filtered off using funnel with cotton plug and filtrate was extracted three times with ethyl acetate (3×20 mL), combined extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$ and evaporated in vacuo. The resulting oil was purified by flash chromatography (CH_2Cl_2/MeOH 200:3 as eluent). All compounds have been previously reported and were characterized by comparison with their reported physical and spectroscopic data.

4.3.1. (*S*)-1-Phenyl-1-propanol (*S*-3). HPLC: $t_S=12.1$ $t_R=13.2$ (hexane/^{i}PrOH 97:3, flow 1 mL/min). $[\alpha]_D^{20}=-42.0$ ($c=1.0$, $CHCl_3$); for enantiomer *S* with ee=90.4%. lit.[35] $[\alpha]_D^{20}=-44.4$ ($c=1.01$, $CHCl_3$) for enantiomer *S* with ee=95.5%.

4.3.2. (*S*)-1-(2-Chlorophenyl)-1-propanol (*S*-18). GC: $t_R=51.0$, $t_S=54.2$ ($T_{column}=130$ °C, $P=100$ kPa). $[\alpha]_D^{20}=-48.6$ ($c=1.25$, benzene) for ee=85%.

4.3.3. (*S*)-1-(3-Chlorophenyl)-1-propanol (*S*-19). HPLC: $t_S=17.1$ $t_R=18.6$ (hexane/^{i}PrOH 96:4, flow 0.5 mL/min). $[\alpha]_D^{20}=-23.3$ ($c=1.21$, benzene) for enantiomer *S* with ee=78.8%. lit.[36] $[\alpha]_D^{20}=+26.6$ ($c=2.36$, benzene) for enantiomer *R* with ee=97%.

4.3.4. (*S*)-1-(4-Chlorophenyl)-1-propanol (*S*-20). HPLC: $t_S=22.4$ $t_R=24.3$ (hexane/^{i}PrOH 97:3, flow 0.5 mL/min). $[\alpha]_D^{20}=-23.6$ ($c=1.77$, benzene) for enantiomer *S* with ee=88.5%. lit.[35] $[\alpha]_D^{20}=-23.6$ ($c=1.73$, benzene) for enantiomer *S* with ee=93%.

4.3.5. (*S*)-1-(2-Metoxyphenyl)-1-propanol (*S*-21). HPLC: $t_S=27.5$ $t_R=29.6$ (hexane/^{i}PrOH 97:3, flow 0.5 mL/min). $[\alpha]_D^{20}=-50.8$ ($c=1.22$, toluene) for enantiomer *S* with ee=89.1%. lit.[35] $[\alpha]_D^{22}=-52.9$ ($c=1.02$, toluene) for enantiomer *S* with ee=91%.

4.3.6. (*S*)-1-(3-Metoxyphenyl)-1-propanol (*S*-22). HPLC: $t_S=80.3$ $t_R=76.6$ (hexane/^{i}PrOH 97:3, flow 0.3 mL/min). $[\alpha]_D^{20}=-26.8$ ($c=0.8$, toluene)) for enantiomer *S* with ee=92%.

4.3.7. (*S*)-1-(4-Metoxyphenyl)-1-propanol (*S*-23). HPLC: $t_S=38.1$ $t_R=33.6$ (hexane/:^{i}PrOH 97:3, flow 0.5 mL/min). $[\alpha]_D^{20}=-28.7$ ($c=1$, benzene)) for enantiomer *S* with ee=83%. lit.[35] $[\alpha]_D^{20}=-25.8$ ($c=1.1$, benzene) for enantiomer *S* with ee=74%.

4.3.8. (*S*)-1-Phenyl-1-penten-3-ol (*S*-24). HPLC: $t_S=13.0$ $t_R=9.0$ (hexane/^{i}PrOH 90:10, flow 1.0 mL/min). $[\alpha]_D^{20}=-4.87$ ($c=1$, $CHCl_3$) for enantiomer *S* with ee=63%. lit.[14] $[\alpha]_D^{20}=-6.3$ ($c=1.73$, $CHCl_3$) for enantiomer *S* with ee=59%.

4.3.9. (*S*)-3-Octanol (*S*-25). HPLC (as benzoate): $t_S=21.1$ $t_R=23.1$ (hexane, flow 0.5 mL/min). $[\alpha]_D^{20}=+7.6$ ($c=1.03$, $CHCl_3$); for enantiomer *S* with ee=77%. lit.[35] $[\alpha]_D^{20}=+5.87$ ($c=1$, $CHCl_3$), for enantiomer *S* with ee=60%.

4.3.10. (*S*)-1-Cyclohexyl-1-propanol (*S*-26). HPLC (as benzoate): $t_S=37.8$ $t_R=35.9$ (hexane/^{i}PrOH 99.9:0.1, flow 0.2 mL/min). $[\alpha]_D^{20}=-5.43$ ($c=1.14$, $CHCl_3$) for enantiomer *S* with ee=82.5%. lit.[35] $[\alpha]_D^{24}=-6.39$ ($c=1.05$, $CHCl_3$), for enantiomer *S* with ee=97%.

Acknowledgements

Financial support from the State Committee for Scientific Research (Grant 3 T09A 039 16) is gratefully acknowledged.

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2-(Arylsulfinylmethyl)oxazinanes: chiral carbonyl equivalents. Application to the asymmetric synthesis of 1,2,3,4-tetrahydro-β-carbolines

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Received 12 May 2004; revised 30 June 2004; accepted 23 July 2004

Available online 25 August 2004

Abstract—2-(*p*-Tolylsulfinylmethyl)oxazinane, a chiral carbonyl equivalent, has been synthesised and used for the diastereoselective synthesis of tetrahydro-β-carbolines including intermediates of yohimbine and herman alkaloids. A fair degree of diastereoselectivity, comparable with other approaches, has been achieved.

1. Introduction

The tetrahydroisoquinoline (THIQ) and tetrahydro-β-carboline (THBC) cores are structural motifs common to a diverse family of natural products, which display a variety of biological activities.[1] Most THBC and THIQ derivatives are optically active and have marked physiological activities[2] which are invariably different from those of their antipodes. The development of methods for enantioselective or diastereoselective synthesis of optically active 1-substituted THBCs is an important area in synthetic organic chemistry. The Pictet–Spengler reaction,[3] employing reaction of the biogenic amines with carbonyl substrates, is certainly one of the most powerful methods for the direct synthesis of THBC and THIQ derivatives.[4] Many other traditional synthetic methods are based on procedures that employ a stoichiometric amount of chiral building blocks, auxiliaries or reagents, catalytic asymmetric syntheses, catalytic asymmetric hydrogenation etc.[5] The chiral formamidine approach developed by Meyers et al.[6] has been extensively employed in the synthesis of both THBC and THIQ systems with high enantioselectivity. The use of a stereogenic sulfur centre of a chiral sulfoxide to achieve stereocontrol in asymmetric syntheses has been amply demonstrated.[7] Use of chiral acetylenic sulfoxides in the enantioselective synthesis of THBC and THIQ alkaloids through a tandem Michael addition/acid induced cyclisation reaction sequence has also been reported.[8] Chiral vinyl sulfoxides have been implemented,[9] via an intramolecular asymmetric conjugate addition of a nitrogen nucleophile to synthesise alkaloid systems. Since not many sulfoxide derivatives of the latter type are available, their use in asymmetric synthesis of THBCs and THIQs has been limited.

Using an unconventional approach we have been engaged in designing and mimicking[10] the reactivity pattern of a folate cofactor and investigating its use in the development of various types of synthetic strategies. Recently we reported[11] that simple and C-2 functionalised oxazinanes embodying a masked carbonyl substrate can be convincingly employed to synthesise otherwise inaccessible THBCs in a highly distereoselective manner and have thus been regarded as carbonyl equivalents. This has successfully addressed the problems associated with the direct use of carbonyl substrates (especially aliphatic carbonyls), in the diversification at the C-1 of THBCs, an attribute of potential utility in the total synthesis of indole alkaloids. These findings gave us additional impetus in developing optically active oxazinanes (chiral carbonyl equivalents)[12] with a possibility of further C-2 (at the oxidation level of the carbonyl) elaboration for exploration in asymmetric synthesis of THBCs and related systems. We now present a full account of our investigations on the synthesis of a new, stereochemically homogenous chiral oxazinane and its use as a two carbon synthon for enantio- and diastereoselective

Keywords: 2-(*p*-Tolylsulfinylmethyl)oxazinane; Carbonyl equivalents; Oxazinanes; Yohimbine alkaloids; Diastereoselective synthesis.
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0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.062

synthesis of THBCs, which can be converted into yohimbine and herman alkaloids.

2. Results and discussion

2.1. Synthesis of chiral carbonyl equivalent

The reaction of C-2 metallated (*n*-BuLi/THF) 2,4,4,6-tetramethyl-5,6-dihydro-(4H)-1,3-oxazine **1**[13,14]with (−)-(*S*)-menthyl *p*-toluenesulfinate[15] at −78 °C (Scheme 1) afforded 2-arylsulfinylmethyl oxazine **2** as a mixture of its diastereomers[16] in 85% overall yield, after crystallisation from hot hexane. On the basis of the fact that such Anderson type reactions proceed with inversion[17] of configuration at the sulfinyl sulfur atom, the absolute configuration (*R*) can be assigned at the sulfinyl sulfur of compound **2**. The assignments of all the protons have been made on the basis of NOE connectivity while the carbons have been distinguished by the HMQC spectrum. To further widen the synthetic scope, **2** was metallated and quenched with MeI to obtain further elaborated oxazine **4** which after reduction could be used to obtain C-1 elaborated THBCs.

2.2. Synthesis of THBCs

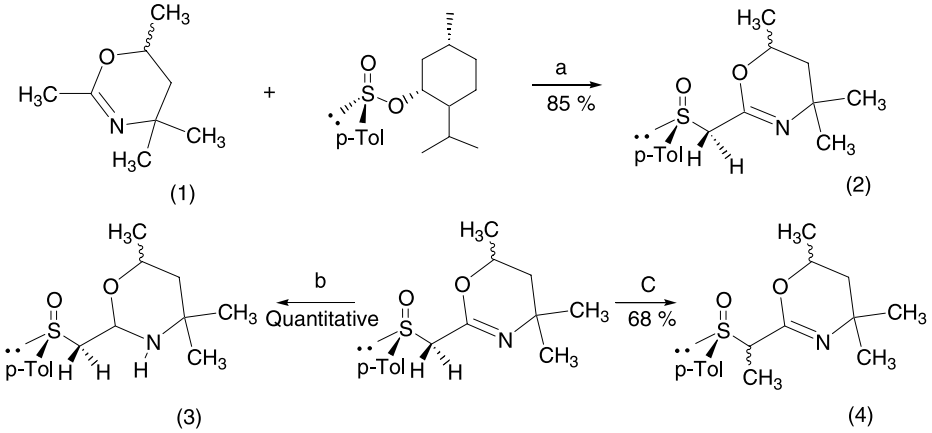
Acid catalysed reactions of **3** were performed with tryptamine and tryptophan derivatives **5a–d** to obtain THBCs which could be converted into the alkaloidal targets (Scheme 2). The chemical yields and the extent of stereoselectivity was comparable with the known syntheses.[8]

If a stoichiometric mixture of tryptamine **5a** and **3** in anhydrous MeCN/AcOH (10:1) solution is combined at ambient temperature, the following sequence takes place: formation of iminium intermediate **6** (tautomeric equilibrated, hydrogen bonded), spontaneous in situ conversion into a spiroindolenine[19] through acid induced intramolecular electrophilic attack of the iminium carbon at C-2 or at C-3 of the indole moiety and subsequent rearrangement-deprotonation. This furnishes THBCs **7a** and **8a** in a 70:30 (1*R*/1*S*) diastereomeric ratio (^{1}H NMR spectroscopy correlation),[20] out of which **7a** could be isolated in 40% yield. This sequence establishes the crucial carbon–nitrogen and carbon–carbon bond formations in a one-pot reaction and creates a new chiral centre at C-1 of the alkaloid system.

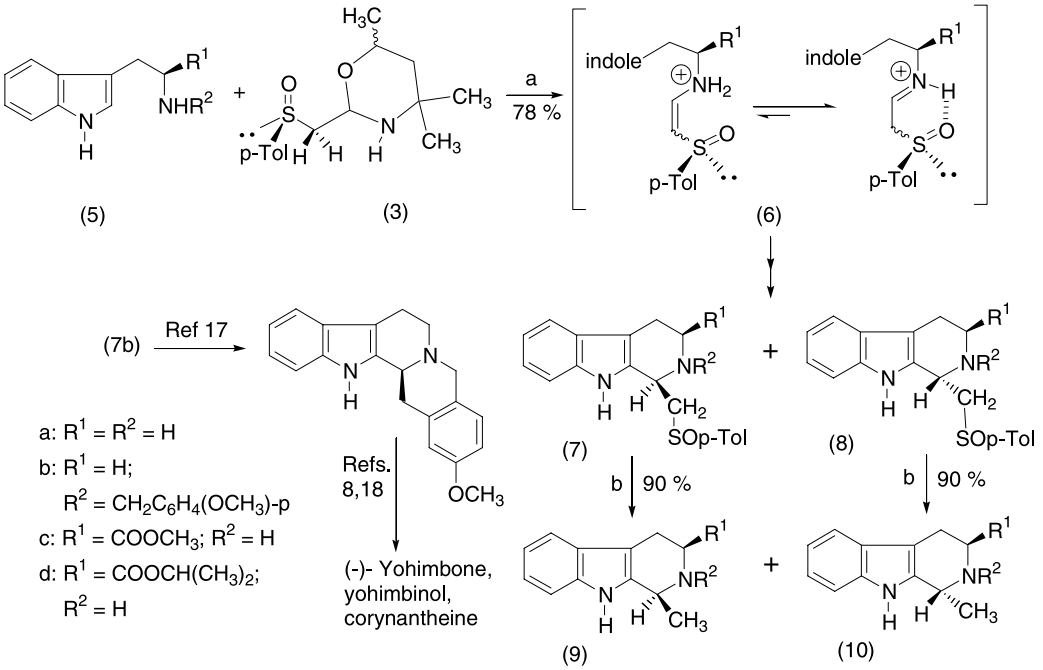
Similarly, secondary amine **5b**, which was prepared from tryptamine through reductive amination with *p*-methoxy benzaldehyde, reacts with **3** in MeCN/AcOH (10:1) at reflux temperature, yielding a mixture of two products, isolated by flash chromatography. The higher R_f component was minor and the lower one was the major component. These were assigned as **7b** and **8b**, respectively in 80% overall isolated yield and in a 30:70 (1*R*/1*S*) diastereomeric ratio. The NMR spectra and optical rotations were compared with the corresponding authentic data[17] and were thus assigned the appropriate absolute configuration at C-1. The THBC **7b** has also been converted into the homochiral pentacyclic intermediate **11**, which is a known precursor[18] of the pentacyclic yohimbine alkaloids (yohimbinol and corynantheine). Yohimbine alkaloids have a range of interesting biological properties and are used clinically in conventional medicines and folklore treatments. One interesting outcome of this methodology is reversal of the stereochemical bias in comparison with the chiral acetylenic approach. Switching from the chiral acetylenic sulfoxides to the oxazinane **3**, the stereochemical outcome of the reaction alters from **7a/8a** (30:70) and **7b/8b** (70:30) in the former method to **7a/8a** (70:30) and **7b/8b** (30:70) in the present approach.

Desulfurisation of the major component **8b** was conducted using Raney Ni and proceeded quantitatively to yield **10b**. The optical rotation of this enantiomer was found to be $[\alpha]_D^{21} = +25.0$ (*c* 0.126, CH_2Cl_2). On the basis of the correct spectral data and the fact that the starting **8b** is the 1*S* isomer, it can be assigned 1*R* configuration at C-1. Likewise, the minor component, **7b**, was also desulfurised under similar conditions and the product **9b** was assigned 1*S* configuration at C-1 {$[\alpha]_D^{21} = -24.0$ (*c* 0.126, CH_2Cl_2)}.

Similar reactions of a stoichiometric mixture of (L)-tryptophan methyl ester **5c** with **3** in anhydrous MeCN/AcOH (10:1) at ambient temperature furnished a mixture of THBCs, **7c** and **8c** (*cis*/*trans*: 33:66) in 76% isolated yield. *trans*-selectivity was favoured when the reaction was run at low temperature. The *cis* and *trans* isomers were distinguished as reported from the ^{13}C chemical shifts of the C-1 (*cis*: downfield, *trans*: upfield)[21] and also from the benzylic



Scheme 1. (a) *n*-BuLi, −78 °C, THF. (b) $NaBH_4$, THF/EtOH (1:1), −45 °C. (c) NaH, MeI, THF, 0 °C.



Scheme 2. (a) CH_3CN/AcOH (10:1). (b) Raney Ni, MeOH, 0 °C.

carbons (*trans*: upfield, *cis*: downfield),[19] which are easily distinguishable from rest of the signals (ca. 70 ppm). Also, both **7c** and **8c** were desulfurised using Raney Ni at 0 °C in methanol to obtain the corresponding known compounds[22] **9c** and 1**0c**, to further correlate the *cis* and *trans* stereochemistry. Likewise, reaction of tryptophan isopropyl ester **5d** with **3** under a similar set of conditions, yielded the THBCs **7d** and **8d** *cis*/*trans* diastereomers in 78% yield and similar diastereomeric ratio (Table 1). **7d** and **8d** were also desulfurised to obtain **9d** and **10d** to correlate the stereochemistry.

In view of the facile debenzylation[22] of **10b** and **9b**, and facile removal of the C-3 ester functions in **9d** and **10d** following the method of Yamada,[23] the above protocol constitutes a formal synthesis of optically pure eleagnine,[20] a herman alkaloid of known absolute configuration.

3. Conclusions

2-(*p*-Tolylsulfinylmethyl)oxazinane, a chiral carbonyl equivalent, has been synthesised and used for the diastereoselective synthesis of tetrahydro-β-carbolines including an intermediate of yohimbine alkaloids. The transformations depicted in Scheme 2 showed a fair degree of diastereoselectivity comparable with the reported methods,[8] when the chiral oxazinanes are employed as inductors. Also, precursors for the synthesis of optically pure eleagnine, a herman alkaloid have been synthesised. In addition, this strategy has scope for asymmetric synthesis of many more C-1 substituted THBCs and related compounds.

4. Experimental

4.1. General

All melting points are uncorrected. IR sectra were recorded on Shimadzu DR-8001 FT and Pye Unicam SP 3-300 spectrophotometer. ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra were run on Bruker AC 200 instrument using TMS as the internal standard. Mass (70 eV) spectra were performed on Shimadzu GCMS QP 2000 spectrometer. Elemental analyses of the samples were performed on and Perkin–Elmer 2400 CHN elemental analyser, respectively.

Table 1. Diastereocontrol in the reactions of **2** with tryptamine derivatives

Sr. no.	THBCs (**7**/**8**)	Reaction temperature	Diastereomeric ratio[a] of THBCs (**7**:**8**)	Reaction time (h)	Isolable yield (%)
1	$R^1=R^2=H$	rt	2.33:1 (1*R*:1*S*)[b]	12	40 (1*R*)
		Reflux	Decomposition	—	—
2	$R^1=H$	rt	Very slow reaction	—	—
	$R^2=CH_2C_6H_5(OCH_3)p$	Reflux	1:2.33 (1*R*:1*S*)[b]	24	80
3	$R^1=COOCH_3$ $R^2=H$	rt	1:2 (*c*/*t*)[a]	30	72
		Reflux	1:1.2 (*c*/*t*)[a]	10	78
4	$R^1=COOCH(CH_3)_2$	rt	1:2 (*c*/*t*)[c]	36	70
	$R^2=H$	Reflux	1:1.2 (*c*/*t*)[c]	12	75

[a] ±3% as determined from the integration of the C-3 ester signals in the ^1H NMR spectrum.
[b] Compared with the reported data.[12]
[c] Identified from the chemical shift of C-1 H signals.

TLC was performed on aluminium sheets coated with Silica gel 60 F_{254} (Merck). Optical rotations were measured using a Jasco DIP-360 digital polarimeter. All solvents MeCN (P_2O_5), THF (Na-benzophenone ketyl), hexane (sodium) and ethyl acetate (anhydrous K_2CO_3) were dried and distilled before use. Column chromatography was performed on silica gel (60–120 mesh).

L-Tryptophan methyl/isopropyl esters and 4-methoxy-benzyl tryptamine were prepared following the reported/modified procedures.[22] *p*-Toluene sulfinic acid, sodium salt hydrate (97%) and (1*R*,2*S*, 5$_R$)-(−)-menthol were purchased from Aldrich. (−)-(*S*)-Menthyl (*p*-tolunesulfinate) was synthesised following the reported procedure.[15]

4.1.1. Formation of 2-(arylsulfinylmethyl)-4,4,6-trimethyl-5,6-dihydro-(4H)-1,3-oxazine (2). A two necked round bottom flask (250 mL) equipped with a magnetic stirring bar, and pressure equalising additional funnel (75 mL) topped with rubber septum and a nitrogen inlet tube was evacuated and flushed with nitrogen, at least thrice in succession. Anhydrous THF (100 mL) and 2,4,4,6-tetramethyl-5,6-dihydro-(4H)-1,3-oxazine (14.1 g, 0.1 mol) was added using a hypodermic syringe through the rubber septum. The stirred solution was cooled (−78 °C) and *n*-BuLi in hexane (50 mL, 2.2 N) was injected into the addition funnel and added dropwise over a period of 1 h into the flask. After approximately 1 h, and after the addition of *n*-BuLi, a yellow precipitate was formed (indicative of the complete anion formation) and a solution of (−)-(*S*)-menthyl *p*-toluenesulfinate (14.7 g, 0.05 mol) in dry THF (60 mL) was injected into the addition funnel and slowly added to the reaction mixture over 1 h. After this addition, the reaction mixture was stirred at the same low temperature (−78 °C) for 1.5 h. The reaction was then quenched with saturated ammonium chloride solution (50 mL) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (2×50 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and evaporated in vacuo. The oily residue was dissolved in hot hexane and was allowed to crystallise at −5 °C. After the first crop, the mother liquor was concentrated and allowed once again to crystallise at −5 °C. This operation was repeated three times, and finally the product was crystallised once from hot hexane.

Yield: 84%; white amorphous solid, mp 54 °C; ν_{max} (KBr) 1597 (C=N), 1218 (C–O), 1041 (S=O) cm^{-1}. δ_H (200 MHz $CDCl_3$)† 1.03 (3H, s, Me), 1.06 (3H, s, Me), 1.10 (3H, s, Me), 1.13 (3H, s, Me), 1.17 (3H, d, *J*=6.1 Hz, Me), 1.23 (3H, d, *J*=6.1 Hz, C*H*$_2$), 1.40 (1H, m, C(5)*H*H), 1.65 (1H, m, C(5)H*H*), 2.40 (3H, s, Me), 3.43 (1H, distorted d, *J*=12.7 Hz, –C*H*HSO), 3.60 (2H, m, C*H*$_2$SO), 3.83 (1H, distorted d, *J*=12.7 Hz, CH*H*SO), 4.06 (1H, m, C(6)*H*), 7.29 (4H, d, *J*=8.0 Hz, Ph), 7.57 (4H, d, *J*=8.0 Hz, Ph); δ_C (50 MHz $CDCl_3$)†: δ 21.0, 21.3, 29.2, 29.4, 31.2, 41.3, 41.5, 50.4, 62.4, 62.7, 68.6, 124.7, 129.6, 139.2, 139.3, 141.9, 152.0. *m*/*z* 279 (M$^+$); [Found: C, 64.54; H, 7.58; N 4.98. $C_{15}H_{21}NO_2S$ requires C, 64.51; H, 7.52; N, 5.01].

4.1.2. Reduction of 2-(arylsulfinylmethyl)-4,4,6-trimethyl-5,6-dihydro-(4H)-1,3-oxazine. Formation of 2-(arylsulfinylmethyl)-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine (3). A solution of 2-(arylsulfinylmethyl)-4,4,6-trimethyl-5,6-dihydro-(4H)-1,3-oxazine (5 g, 0.017 mol) in a mixture of ethyl alcohol (95%) and THF (1:1 v/v, 60 mL) was taken in a round bottom flask (100 mL) and cooled to −45 °C. Hydrochloric acid (9 N) was added to this magnetically stirred solution until pH 7 was obtained. Sodium borohydride solution was prepared separately by dissolving sodium borohydride (0.681 g, 0.017 mol) in a minimum amount of water (1–2 mL) containing a drop of aqueous sodium hydroxide (40%) solution. The sodium borohydride solution and the 9 N hydrochloric solution were introduced to the stirred solution of dihydrooxazine alternatively, so that pH 7–8 was maintained throughout the course of reaction. After the addition of the borohydride solution was complete, the solution was stirred at the same low temperature (−45 °C) for an additional 1 h. During this period, pH 7 was maintained by the occasional addition of 9 N hydrochloric acid. The contents were then poured into water (approx. 50 mL) and made basic by the addition of aqueous sodium hydroxide solution (40%) (care was taken not to raise the temperature above 10 °C during this addition). Oil globules/turbidity appeared upon basification and the solution was extracted with ethyl acetate (2× 30 mL). The combined organic extracts were washed with saturated sodium chloride solution (50 mL) and dried over anhydrous potassium carbonate. The solvent was removed in vacuo to obtain the crude tetrahydrooxazine, which was purified using column chromatography employing a mixture of hexane and ethyl acetate (1:1, v/v) as the eluent.

Yield: quantitative; colourless oil at rt; ν_{max} ($CHCl_3$) 3390 (N–H), 1230 (C–O), 1045 (S=O) cm^{-1}. δ_H (200 MHz $CDCl_3$)† 1.10 (3H, s, Me), 1.43 (3H, s, Me), 1.20 (1H, m, C(5)*H*H), 1.40 (1H, dd, *J*=6.0, 2.2 Hz, C(5)H*H*), 1.47 (1H, dd, *J*=6.0, 2.2 Hz, C(5)*H*H), 2.40 (3H, s, Me), 2.75 (1H, dd, *J*=8.4, 6.1 Hz, C*H*HSO), 2.81 (1H, dd, *J*=8.4, 6.1 Hz, CH*H*SO), 3.09 (1H, t, *J*=13.2 Hz, C*H*HSO), 3.11 (1H, t, *J*=13.2 Hz, CH*H*SO), 3.85 (1H, m, C(6)*H*), 4.62 (1H, dd, *J*=6.1, 3.8 Hz, C(2)*H*), 4.66 (1H, dd, *J*=6.1, 3.8 Hz, C(2)*H*), 7.42 (4H, d, *J*=8.1 Hz, Ph), 7.43 (4H, d, *J*=8.1 Hz, Ph); δ_C (50 MHz $CDCl_3$)† 21.4, 22.1, 23.3, 23.7, 32.6, 45.0, 45.3, 49.2, 49.5, 62.2, 63.3, 69.2, 69.3, 78.3, 79.4, 124.3, 129.9, 141.0, 141.5. δ_C (50 MHz $CDCl_3$, DEPT-135) 21.4, 22.1, 23.3, 23.7, 32.6, 45.0 (−ve), 45.3 (−ve), 49.2, 49.5, 62.2 (−ve), 63.3 (−ve), 69.2, 69.3, 78.3, 79.4, 124.3, 129.9. *m*/*z* 281 (M$^+$); [Found: C, 63.99; H, 8.20; N, 4.95. $C_{15}H_{23}NO_2S$ requires C, 64.05; H, 8.18; N, 4.98].

4.1.3. Synthesis of oxazine 4. Dry THF (25 mL) was distilled directly from Na-benzophenone ketyl into a round bottom flask (50 mL), containing sodium hydride (0.90 g, 3.75 mmol), thoroughly prewashed with anhydrous hexane and dried. The flask was stoppered with a septum cap, flushed with nitrogen and cooled in ice, **2** (1.0 g, 3.5 mmol) dissolved in anhydrous THF (10 mL) was added dropwise and the colourless solution was stirred (0.5 h) at 0 °C. To this solution methyl iodide (1.0 mL, 16 mmol) was added dropwise and the reaction stirred for an additional 2 h at rt. The reaction was then quenched with saturated ammonium chloride solution (50 mL) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (2× 50 mL). The combined organic extracts were dried

† Extra signals appear owing to diastereomers.

(anhydrous sodium sulphate) and evaporated in vacuo. The oily residue was purified by column chromatography using ethyl acetate, hexane and their mixtures as eluents to obtain the pure product.

Yield: 74%; viscous oil; ν_{max} (KBr) 1590 (C=N), 1220 (C–O), 1035 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 0.95 (3H, d, $J=8.0$ Hz, Me), 1.20 (9H, m, 3×Me), 1.63 (2H, m, CH_2), 2.40 (3H, s, PhMe), 3.25 (0.6H, q, $J=8.0$ Hz, C*H*Me), 3.58 (0.4H, q, $J=8.0$ Hz, C*H*Me), 4.02 (1H, m, C*H*), 7.27 (2H, m, Ph), 7.53 (2H, m, Ph); δ_C (50 MHz $CDCl_3$) 21.0, 21.3, 29.1, 29.3, 29.5, 31.1, 31.3, 41.5, 41.7, 41.9, 41.9, 50.1, 50.2, 50.3, 63.9, 64.3, 66.7, 66.9, 68.2, 96.0, 125.3, 125.6, 130.5, 130.7, 138.8, 141.5. *m/z* 293 (M^+); [Found: C, 65.50; H, 7.81; N, 4.82 $C_{16}H_{23}NO_2S$ requires C, 65.52; H, 7.84; N, 4.77].

4.2. General procedure for the reaction of 2-(arylsulfinyl methyl)-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2 with L-tryptophan methyl/ isopropyl ester or N_b-4-methoxy benzyl tryptamine or tryptamine

2-(Arylsulfinylmethyl)-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2 (2.29 mmol), the appropriate tryptophan ester/ tryptamine derivative (2.29 mmol) and acetic acid (catalytic) in anhydrous acetonitrile (30 mL) were stirred at rt/ refluxed at 80 °C till the reaction completed (TLC). The reaction was basified with cold aqueous sodium carbonate (5%) solution and extracted with ethyl acetate (3×50 mL). The extract was washed once with cold water (50 mL) and dried (anhydrous Na_2SO_4). The solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh) using hexanes, ethyl acetate or their mixtures as eluents.

The reaction of L-tryptamine with oxazinanes provided the following product.

4.2.1. (1*R*,S$_R$)-1-(*p*-Tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]indole (7a).[20] Yield: 33%; white solid, mp 158–160 °C; ν_{max} (KBr) 3280 (N–H), 1028 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 2.41 (3H, s, Me), 2.76 (2H, m, NCH_2), 2.82 (1H, br, D_2O exchangeable, NH), 3.02 (1H, dd, $J=13.6$, 4.9 Hz, C*H*HSO), 3.20 (2H, m, $PhCH_2$), 3.40 (1H, dd, $J=13.6$, 4.9 Hz, CH*H*SO), 4.80 (1H, dd, $J=4.9$, 4.3 Hz, CH), 7.29 (4H, m, Ph), 7.48 (4H, 2×d $J=8.0$ Hz, ArH), 9.60 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.4, 22.2, 42.5, 50.0, 63.8, 108.9, 111.4, 118.1, 119.2, 121.9, 124.0, 126.9, 130.2, 133.4, 135.5, 140.2; [Found: C, 70.26; H, 6.30; N, 8.48 $C_{19}H_{20}N_2OS$ requires C, 70.34; H, 6.12; N, 8.63].

The reaction of N_b-4-methoxy benzyl tryptamine with oxazinanes furnished the following products.

4.2.2. (1*R*,S$_R$)-N-(*p*-Methoxybenzyl)-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]indole (7b). Yield: 24%; white solid, mp 157 °C; ν_{max} (KBr) 3280 (N–H), 1029 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 2.41 (3H, s, Me), 2.53 (1H, m, NCH_2CHH), 2.90 (3H, m, NCH_2CHH), 3.19 (1H, dd, $J=8.6$, 2.7 Hz, C*H*HSO), 3.33 (2H, m, CH_2Ph), 3.52 (dd, $J=8.6$, 2.7 Hz, CH*H*SO), 3.79 (3H, s, OMe), 4.06 (1H, dd, $J=8.6$, 2.7 Hz, CH), 6.90 (4H, 2×d, $J=8.5$ Hz, Ph), 7.16 (4H, m, Ph), 7.43 (4H, 2×d, $J=8.3$ Hz, Ph), 8.39 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 18.3, 21.3, 45.4, 51.2, 55.1, 56.4, 58.6, 107.8, 111.3, 113.6, 118.0, 119.0, 121.5, 124.2, 129.5, 129.9. 130.7, 132.7, 136.0, 138.5, 141.5 158.7; δ_C (50 MHz $CDCl_3$, DEPT-135) 18.3 (−ve), 21.3, 45.4 (−ve), 51.2, 55.2, 56.4 (−ve), 58.6 (−ve), 111.3, 113.6, 118.0, 119.0, 121.5, 124.2, 129.5, 129.9. *m/z* 444 (M^+); [Found: C, 72.98; H, 6.41; N, 6.28 $C_{27}H_{28}N_2O_2S$ requires C, 72.97; H, 6.30; N, 6.30]; $[\alpha]_D=+211.57$ (*c* 0.272, CH_2Cl_2).

4.2.3. (1*S*,S$_R$)-N-(*p*-Methoxybenzyl)-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]indole (8b). Yield: 56%; white solid, mp 82 °C; ν_{max} (KBr) 3265 (N–H), 1032 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 2.40 (3H, s, Me), 2.55 (1H, m, NCH_2CHH), 3.00 (3H, m, NCH_2CHH), 3.19 (2H, m, CH_2SO), 3.81 (3H, s, OMe), 3.86 (2H, m, CH_2Ph), 4.48 (1H, br t, $J=6.0$ Hz, C(1)H), 7.00 (4H, 2×d, $J=8.5$ Hz, Ph), 7.14 (4H, m, Ph), 7.42 (4H, 2×d, $J=8.6$ Hz, Ph), 9.28 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 17.2, 21.3, 43.5, 53.2, 55.1, 56.8, 63.2, 107.8, 111.3, 113.7, 117.9, 119.0, 121.5, 124.0, 126.9, 129.6, 130.0, 132.4, 136.2, 140.7, 141.5, 158.8. *m/z* 427 (M^+-OH), 291 ($M^+-CH_2SOC_6H_4Me$); [Found C, 72.85; H, 6.29; N, 6.42 $C_{27}H_{28}N_2O_2S$ requires C, 72.97; H, 6.30; N, 6.30]; $[\alpha]_D^{21}=+138.57$ (*c* 0.221, CH_2Cl_2).

Following the above procedure the reaction of L-tryptophan methyl ester with oxazinanes provided the following products.

4.2.4. (*cis*, S$_R$)-Methyl-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (7c). Yield: 35%; yellow viscous oil; ν_{max} ($CHCl_3$) 3430 (N–H), 1720 (C–O), 1030 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.91 (1H, br, D_2O exchangeable, NH), 2.41 (3H, s, C_6H_4Me), 3.07 (3H, m, C(4)H_2 and H_B of ABX of CH_2SO), 3.72 (3H, m, C(3)H and H_A of ABX CH_2SO), 3.76 (3H, s, OMe), 4.26 (1H, dd, $J=9.0$, 2 Hz, C(1)H), 7.23 (4H, m, Ph), 7.42 (4H, 2×d, $J=8.1$ Hz, Ph), 10.38 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.4, 25.5, 48.2, 52.2, 56.6, 57.8, 107.3, 111.6, 117.9, 119.2, 121.8, 124.3, 126.7, 130.3, 132.4, 136.0, 136.7, 142.0, 173.2; δ_C (50 MHz $CDCl_3$, DEPT-135) 21.4, 25.5 (−ve), 48.2, 52.2, 56.6, 57.8 (−ve), 111.6, 117.9, 119.2, 121.8, 124.3, 130.3. *m/z* 382 (M^+); [Found: C, 65.78; H, 5.84; N, 7.29 $C_{21}H_{22}O_3N_2S$ requires C, 65.96; H, 5.75; N, 7.32]; $[\alpha]_D=+253.97$ (*c* 0.175, $CHCl_3$).

4.2.5. (*trans*, S$_R$)-Methyl-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (8c). Yield: 43%; white solid, mp 215 °C; ν_{max} (KBr) 3210 (N–H), 1740 (C–O), 1045 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.85 (1H, br, D_2O exchangeable, NH), 2.41 (3H, s, C_6H_4Me), 3.05 (3H, m, C(4)H_2 and H_B of ABX of CH_2SO), 3.28 (1H, dd, $J=13.4$, 6.8 Hz, H_A of ABX of CH_2SO), 3.76 (3H, s, OMe), 3.85 (1H, dd, $J=7.2$, 5.3 Hz, C(3)H), 5.01 (1H, dd, $J=13.3$, 8.5 Hz, C(1)H), 7.26 (4H, m, Ph), 7.42 (4H, 2×d, $J=8.1$ Hz, Ph), 9.55 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.4, 25.2, 47.2, 52.2, 53.1, 64.2, 107.2, 111.4, 118.0, 119.3, 122.0, 124.0, 126.7, 130.2, 132.8, 136.2, 140.2, 142.0, 173.8. *m/z* 365 (M^+-OH^-), 229 ($M^+-CH_2SOC_6H_4CH_3$); [Found: C,

65.86; H, 5.78; N, 7.36 $C_{21}H_{22}O_3N_2S$ requires C, 65.96; H, 5.75; N, 7.32]; $[\alpha]^{21}=+698.39$ (*c* 0.112, $CHCl_3$).

The reaction of L-trptophan isopropyl ester with oxazinanes furnished the following products.

4.2.6. (*cis*, S_R)-Isopropyl-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (7d). Yield: 34.5%; yellow viscous oil; ν_{max} ($CHCl_3$) 3380 (N–H), 1725 (C–O), 1030 (S–O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.27 (6H, 2×d, *J*=6.2 Hz, $CH(Me)_2$), 2.16 (1H, br, D_2O exchangeable, NH), 2.43 (3H, s, C_6H_4Me), 2.85 (3H, m, C(4)H and H_B of ABX of CH_2SO), 3.60 (2H, m, C(3)H and H_A of ABX of CH_2SO), 4.18 (1H, br d, *J*=9.0 Hz, C(1)H), 5.09 (1H,heptet, *J*=6.2 Hz, $CH(Me)_2$), 7.26 (4H, m, Ph), 7.48 (4H, 2×d, *J*=8.1 Hz, Ph), 10.33 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.3, 21.7, 25.5, 48.1, 56.7, 57.8, 68.7, 107.4, 111.6, 112.0, 117.9, 119.1, 121.7, 124.3, 126.7, 130.2, 132.6, 135.8, 136.7, 141.9, 172.4; *m/z* 410 (M^+); [Found: C, 67.42; H, 6.35; N, 6.74 $C_{23}H_{26}N_2O_3S$ requires C, 67.31; H, 6.34; N, 6.82]; $[\alpha]_D=+212.19$ (*c* 0.250, $CHCl_3$).

4.2.7. (*trans*, S_R)-Isopropyl-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (8d). Yield: 40.5%; white solid, mp 225 °C; ν_{max} (KBr) 3300 (N–H), 1734 (C–O), 1027 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.28 (6H, 2×d, *J*=6.9 Hz, $CH(Me)_2$), 1.94 (1H, br, D_2O exchangeable, NH), 2.86 (1H, dd, *J*= 15.2, 8.2 Hz, H_A of ABX of $C(4)H_2$), 3.07 (2H,m, H_B of ABX of $C(4)H_2$ and H_A of ABX of CH_2SO), 3.28 (1H, dd, *J*=8.2, 4.9 Hz, H_B of ABX of CH_2SO), 3.77 (1H, dd, *J*= 8.2, 4.9 Hz, C(3)H), 5.02 (1H, br t, *J*=5.6 Hz, C(1)H), 5.11 (1H, heptet, *J*=6.9 Hz, $CH(Me)_2$), 7.25 (4H, m, Ph), 7.45 (4H, 2×d, *J*=8.1 Hz, Ph), 9.53 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.3, 21.7, 25.4, 47.1, 53.1, 64.3, 68.6, 107.2, 111.3, 117.9, 119.1, 121.8, 123.9, 126.7, 130.1, 132.9, 136.2, 140.3, 141.8, 172.8; *m/z* 393 (M^+-OH^-), 257 ($M^+-CH_2SOC_6H_4Me$); [Found: C, 67.32; H, 6.42; N, 6.83 $C_{23}H_{26}N_2O_3S$ requires C, 67.31; H, 6.34; N, 6.82]; $[\alpha]_D=+646.03$ (*c* 0.166, $CHCl_3$).

4.3. Desulfurisation of 7/8. General procedure

To an ice cooled solution of the appropriate **7** or **8** (1.5 mol) in methanol (30 mL) was added Raney nickel (excess). This mixture was stirred at 0 °C under a nitrogen atmosphere till the reaction completed (TLC), was then filtered through a bed of celite and the residue evaporated. The crude product was purified by column chromatography on silica gel (60–120 mesh) using hexane, ethyl acetate and their mixtures as eluents.

4.3.1. (1*S*)-N-(*p*-Methoxybenzyl)-1-methyl-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]indole (9b). Yield: quantitative; viscous oil; ν_{max} ($CHCl_3$) 3285 (N–H) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.44 (3H, d, *J*=6.6 Hz, Me), 2.67 (1H, m, PhC*H*H), 2.86 (2H, m, PhCH*H* and NC*H*H) 3.14 (1H, m, NCH*H*), 3.75 (2H, ABq, *J*=13.3 Hz, CH_2Ph), 3.80, (3H, s, OMe), 3.86 (1H, m, C(1)H), 7.14 (4H, 2×d, *J*=8.5 Hz, Ph), 7.17 (2H, m, Ph), 7.28 (1H, m, Ph), 7.46 (1H, m, Ph), 7.68 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 19.3, 19.4, 45.3, 52.0, 55.2, 56.6, 107.6, 110.7, 113.7, 118.1, 119.3, 121.4, 127.3, 130.0, 135.9, 136.1, 158.7; δ_C (50 MHz $CDCl_3$, DEPT-135) 19.3, 19.4 (−ve), 45.3 (−ve), 52.0, 55.2, 56.6 (−ve), 110.7, 113.7, 118.1, 119.3, 121.4, 130.0; *m/z* 306 (M^+); [Found: C, 78.45; H, 7.25; N, 9.19 $C_{20}H_{22}N_2O$ requires C, 78.43; H, 7.18; N, 9.15]; $[\alpha]_D=-24.0$ (*c* 0.154, CH_2Cl_2).

4.3.2. (1*R*)-N-(*p*-Methoxybenzyl)-1-methyl-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]indole (10b). Yield: quantitative; viscous oil; ν_{max} ($CHCl_3$) 3280 (N–H) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.44 (3H, d, *J*=6.7 Hz, Me), 2.62 (m, 1H, PhC*H*H), 2.85 (2H, m, PhCH*H* and NC*H*H), 3.19 (1H, m, NCH*H*), 3.70 (2H, ABq, *J*=13.3 Hz, CH_2Ph), 3.82 (3H, s, OMe), 3.89 (1H, m, C(1)H), 7.10 (4H, 2×d, *J*=8.5 Hz, Ph), 7.06 (2H, m, Ph), 7.29 (1H, m, Ph), 7.48 (1H, m, Ph), 7.66 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 19.21 19.2, 45.4, 51.9, 55.2, 56.6, 107.7, 110.6, 113.6, 118.0, 119.3, 121.4, 127.3, 129.9, 131.0, 135.9, 136.1, 158.7; δ_C (50 MHz $CDCl_3$, DEPT-135) 19.2, 19.2 (−ve), 45.4 (−ve), 51.9, 55.2, 56.6, 110.6, 113.6, 118.0, 119.3, 121.4, 129.9; [Found: C, 78.40; H, 7.29; N, 9.09 $C_{20}H_{22}N_2O$ requires C, 78.43; H, 7.18; N, 9.15]; $[\alpha]^{21}=+25.0$ (*c* 0.126, CH_2Cl_2).

4.3.3. (1*S*,3*S*) Methyl 1-methyl-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (9c).[22] Yield: 72%; viscous liquid; ν_{max} 3400 (N–H), 1725 (C=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.46 (3H d, *J*=6.5 Hz, Me), 1.89 (1H, br, D_2O exchangeable, NH), 3.15 (2H, m, $C(4)H_2$), 3.73 (3H, s, OMe), 4.02 (1H, m, C(3)H), 4.42 (1H, br, C(1)H), 7.10 (2H, m, Ph), 7.34 (1H, m, Ph), 7.52 (1H, m, Ph), 7.88 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.2, 24.8, 45.8, 52.2, 52.3, 106.4, 110.8, 118.1, 119.6, 121.9, 127.0, 136.0, 173.5; *m/z* 244 (M^+); [Found: C, 68.39; H, 6.23; N, 11.34 $C_{14}H_{16}N_2O_2$ requires C, 68.85; H, 6.55; N, 11.47].

4.3.4. (1*R*,3*S*) Methyl 1-methyl 1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (10c).[22] Yield: 75%; viscous liquid; ν_{max} ($CHCl_3$) 3405 (N–H), 1745 (C=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.49 (3H, d, *J*=6.7 Hz, Me), 1.92 (1H, br, D_2O exchangeable, NH), 2.90 (2H, m, $C(4)H_2$), 3.82 (3H, s, OMe), 3.90 (1H, m, C(3)H), 4.30 (1H, br, C(1)H), 7.14 (2H, m, Ph), 7.40 (2H, m, Ph), 7.83 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 20.3, 25.7, 48.2, 52.1, 56.3, 107.3, 110.7, 119.5, 119.6, 121.8, 127.0, 136.0, 173.3; *m/z* 244 (M^+); [Found: C, 68.41; H, 6.24; N, 11.43 $C_{14}H_{16}N_2O_2$ requires C, 68.85; H, 6.55; N, 11.47].

4.3.5. (1*S*,3*S*)-Isopropyl 1-methyl-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (9d). Yield: 89%; viscous liquid, ν_{max} ($CHCl_3$) 3405 (N–H), 1735 (C=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.22 (6H, 2×d, *J*=6.1 Hz, 2×Me), 1.47 (3H, d, *J*=6.3 Hz, CH_3), 2.64 (1H, br, D_2O exchangeable, NH), 2.99 (2H, m, $C(4)H_2$), 3.99 (1H, dd, *J*= 7.6, 5.2 Hz, C(3)H), 4.44 (1H, q, *J*=6.3 Hz, C(1)H), 5.15 (1H, heptet, *J*=6.1 Hz, $CH(Me)_2$), 7.13 (2H, m, Ph), 7.29 (1H, m, Ph), 7.52 (1H, m, Ph), 7.95 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.4, 21.7, 25.0, 45.9, 52.3, 68.6, 106.4, 110.8, 118.0, 119.4, 121.6, 127.0, 136.0, 172.9; *m/z* 272 (M^+); [Found: C, 70.62; H, 7.41; N,19.15 $C_{16}H_{20}N_2O_2$ requires C, 70.59; H, 7.35; N, 10.30].

4.3.6. (1*R*,3*S*)-Isopropyl 1-methyl-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (10d). Yield:

94%; viscous liquid, ν_{max} ($CHCl_3$) 3400 (N–H), 1725 (C=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.22 (6H, m, 2×Me), 1.40 (3H, d, J=6.3 Hz, Me), 1.67 (1H, br, D_2O exchangeable, NH), 2.68 (1H, m, C(4)*H*H), 2.98 (1H, m, C(4)H*H*), 3.65 (1H, dd, J=11.1, 4.3 Hz, C(3)H), 4.15 (1H, q, J=6.4 Hz, C(1)H), 5.03 (1H, heptet, J=6.3 Hz, C*H*$(Me)_2$), 7.09 (2H, m, Ph), 7.19 (1H, m, Ph), 7.38 (1H, d, J=7.1 Hz, Ph), 7.72 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 20.2, 21.7, 25.8, 48.3, 56.6, 68.6, 107.4, 110.8, 118.0, 119.5, 121.7, 127.2, 136.0, 172.5; *m/z* 272 (M^+); [Found: C, 70.60; H, 7.39; N, 10.20 $C_{16}H_{20}N_2O_2$ requires C, 70.59; H, 7.35; N, 10.30].

Acknowledgements

The authors thank CSIR, New Delhi, for the grant [(1653)/00-EMR-II]. KS thanks Prof. A.W.M. Lee for supplying spectral and physical data of some THBCs for comparison purpose.

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A synthetic approach toward taxol analogs: studies on the construction of the CD ring

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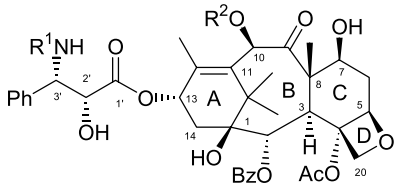
Received 29 April 2004; revised 23 July 2004; accepted 23 July 2004

Available online 27 August 2004

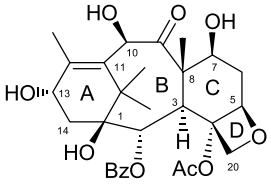
Abstract—Tricycle **6**, containing the CD ring of taxol, is constructed from (*S*)-(+)-carvone in 21 steps involving a Diels–Alder reaction with isoprene, a Baeyer–Villiger oxidation, an Oppenaurer oxidation and Meerwein–Ponndorf–Verley reduction, a stereospecific Grignard addition, and an intramolecular S_N2 reaction as the key steps.

1. Introduction

Paclitaxel (taxol®)[1] (**1**), the first member of a new group of anticancer drugs termed taxanes,[2] is a naturally occurring tetracyclic diterpenoid isolated[3] from the stem bark of Pacific Yew *Taxus brevifolia*. Taxol is recommended, in combination with *cis*-platin, for the treatment of primary ovarian cancer where standard platinum-containing therapy has failed, of metastatic breast cancer where anthracycline-containing thereapy has been unsuccessful or is inappropriate, and of nonsmall cell lung cancer when surgery and radiation therapy inappropriate.[4] The outstanding cytotoxic activity of taxol is believed to arise from its unique function as a mitotic inhibitor, hindering cell replication by preventing microtubules from depolymerization back to tubulin.[2] Docetaxel (taxotere®)[5] (**2**), a synthetic analog[6] of taxol (**1**), is recommended for use in advanced or metastatic breast cancer where adjutant cytotoxic chemotherapy (anthracycline or alkylation agent) has failed and in advanced nonsmall cell lung cancer where first line chemotherapy has failed.[4] Docetaxel (**2**) is twice as active as taxol (**1**) with regard to promoting the assembly and stability of microtubules.[7] Initially, the natural scarcity of taxol, the inefficient methods available for its isolation and its complex, strained framework attracted considerable attention from synthetic chemists. To date, 6 total syntheses of taxol have been published.[8–13] The shortest route is that reported by Wender et al.[11] starting from (1*R*)-(+)-verbenone and involving 37 steps in an overall yield of about 0.37%. Consequently, an industrial-scale production of taxol by total synthesis is unlikely to be economical. Fortunately, the supply problem of taxol has been adequately alleviated via semisynthesis from the naturally occurring 10-deacetylbaccatin III (**3**),[14] a renewable resource readily extractable in relatively high yield from the needles of the European Yew *Taxus baccata*. On the other hand, syntheses of structural analogs which might exhibit similar or improved biological activity has been an area of intense research.[2,15]



1 Taxol $R^1 = C_6H_5CO$, R^2 = Ac (Paclitaxel)
2 Taxotere R^1 = *t*-BuOCO, R^2 = H (docetaxel)



3 10-*O*-deacetylbaccatin III (10-DAB)

In our quest for the discovery of a structurally simplified, synthetically accessible taxol analog which possesses a comparable biological profile, we started a project to investigate a facile and flexible construction of the CD ring of taxol. The oxetane D ring is indispensable for

Keywords: Taxol analog; Diels–Alder reaction; Reduction.
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doi:10.1016/j.tet.2004.07.094

anti-cancer properties.[16] Our preliminary experiments have shown that the $EtAlCl_2$ catalyzed Diels–Alder reaction between (*R*)-(−)-carvone and isoprene occurred preponderantly in an *anti* orientation with respect to the isopropylene group to give decalin **4** (Scheme 1).[17] Such a decalin system **4**, containing a stereo-defined angular methyl group at C-9, would be a valuable synthetic precursor for the taxane C ring system. Regioselective dihydroxylation at the endocyclic double bond of the cycloadduct **4** followed by acetonation gave a crystalline acetonide **5**, the structure and stereochemistry of which were confirmed by an X-ray crystallographic analysis.[17] Hence the stereochemical outcome of the Diels–Alder reaction was established and to obtain the correct absolute configuration at the angular methyl group, (*S*)-carvone had to be employed in our synthesis. This paper describes in detail our effort in the stereocontrolled construction of the CD ring with functionalities suitable for elaboration into taxol analogs.[18]

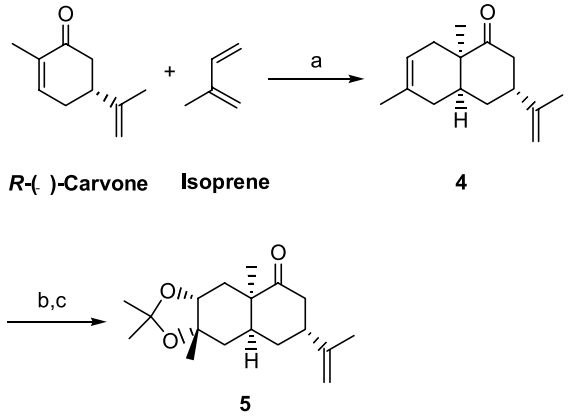
2. Results and discussion

2.1. Initial synthetic plan

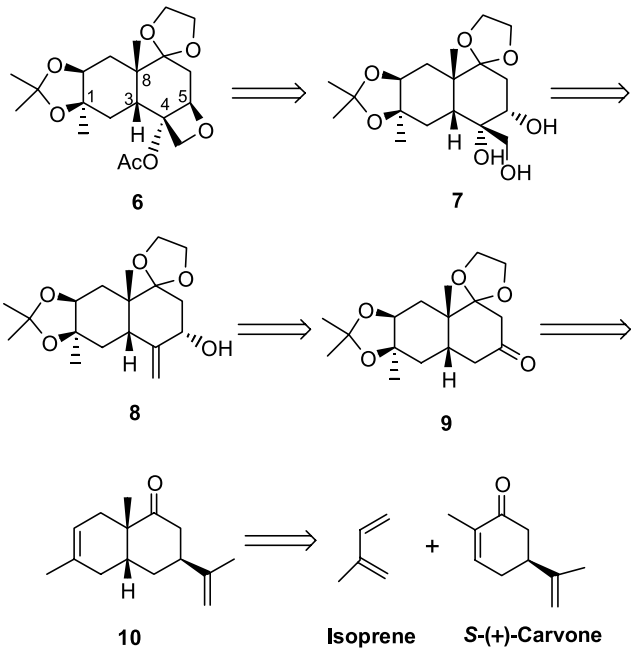
Retrosynthetic analysis of tricycle **6** containing a functionalized CD ring is shown in Scheme 2. We envisaged that the oxetane ring could be readily installed from the ring closure reaction between the hydroxyl groups at C-5 and C-11 in triol **7**. This triol could simply be obtained from dihydroxylation of the double bond in allylic alcohol **8** which would be transformed from ketone **9** via an aldol condensation with formaldehyde. The ketone **9** should be readily accessible from cycloadduct 10 through functional group manipulations. Finally intermolecular Diels–Alder reaction of *S*-(+)-carvone with isoprene should provide cycloadduct **10**.

2.2. Synthesis of ketone 9

The synthesis of the suitably protected ketone **9** is shown in Scheme 3. The intermolecular Diels–Alder reaction of *S*-(+)-carvone with isoprene using $EtAlCl_2$ as catalyst at room temperature afforded a mixture of major *anti*- and minor *syn*-cycloadducts, **10** and **11** respectively, in 92% combined

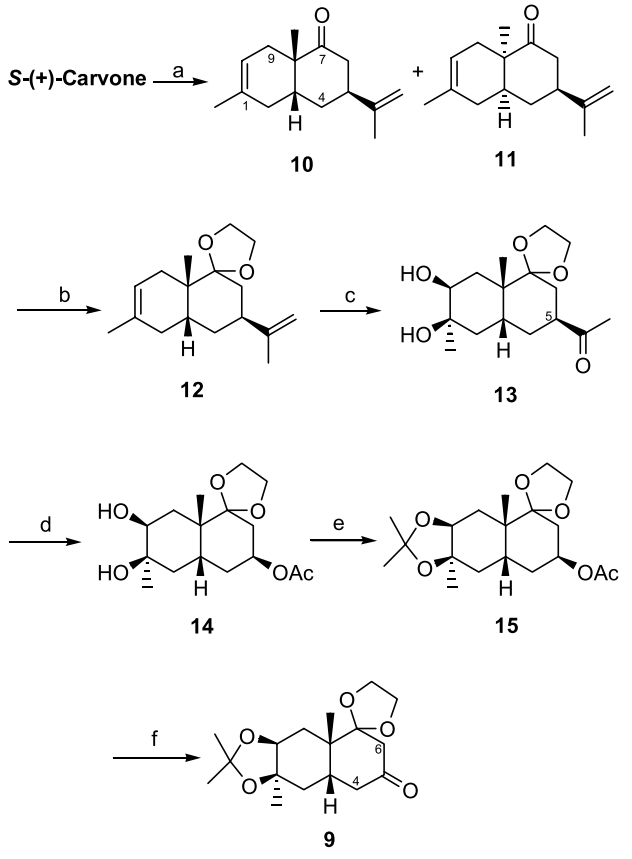


Scheme 1. Reaction conditions: (a) $EtAlCl_2$, rt, 48 h (100%); (b) OsO_4 (cat.), NMO, rt, 24 h (80%); (c) acetone, *p*-TsOH, reflux, 5 h (70%).



Scheme 2.

yield. The ratio of **10** to **11** was determined as 11.6:1 by GC-MS. This mixture which could not be separated by flash column chromatography on silica gel was directly put to the next step. Protection of the carbonyl group in octalones **10**



Scheme 3. Reaction conditions: (a) isoprene, $EtAlCl_2$, toluene (92%); (b) ethylene glycol, *p*-TsOH, PhH, reflux (89%); (c) OsO_4, NMO, acetone–H_2O (4:1) then $NaIO_4$ (74%); (d) *m*CPBA, CH_2Cl_2, rt (93%); (e) DMP, *p*-TsOH, CH_2Cl_2 (92%); (f) (i) K_2CO_3, MeOH; (ii) PCC, CH_2Cl_2 (90%).

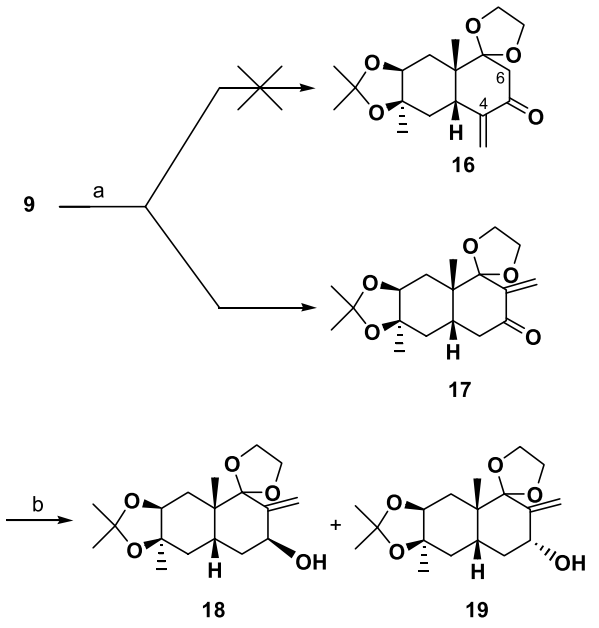
and **11** with ethylene glycol gave acetal **12** together with its diastereomer in 89% yield, which could not be fractionated on column chromatography either. Stereoselective dihydroxylation of the acetal **12** with a catalytic amount of osmium tetraoxide and *N*-methylmorpholine-*N*-oxide[19] furnished a tetraol in which the more reactive (containing a primary alcohol) exocyclic diol was selectively cleaved with 1 equiv of sodium metaperiodate,[20] and methyl ketone **13** could be isolated enantiopure in 74% overall yield from acetal **12**. Attack of OsO_4 was expected to occur at the less hindered convex face (β-face) of the bicyclic skeleton **12** to give, exclusively, the endocyclic β-diol as indicated in ketone **13**.

Installing an oxygen functionality at C-5 was effected with Baeyer–Villiger oxidation[21] of methyl ketone **13** using *meta*-chloroperbenzoic acid to give acetate **14** in 93% yield. At this point, protection of the free diol unit was necessary since manipulation of both alcohols would not be carried out in the present synthetic adventure. Thus, standard acidic acetonation of the diol moiety in **14** furnished acetonide **15** in 92% yield. Removal of the acetyl blocking group in acetate **15** with basic methanol followed by PCC oxidation of the liberated alcohol gave the desired ketone **9** in 90% overall yield.

2.3. Attempted aldol condensation of ketone 9

Since the D ring is situated across C-4 and C-5, homologation at C-4 was our next mission and the keto group in **9** should be assisting the elaboration. Initially, the obvious aldol condensation with formaldehyde,[22] following a regioselective deprotonation at C-4 of ketone **9**, was attempted in the hope to obtain enone **16**. Under kinetically controlled conditions, deprotonation of ketone **9** was speculated to take place at C-4 since the cyclic acetal blocking group should impose steric hinderance around C-6. Unfortunately, this step was found to be problematic. Our results (vide infra) indicated that standard strong base LDA reacted with ketone **9** to generate an enolate which attacked formaldehyde to yield enone **17** rather than the desired enone **16** (Scheme 4).

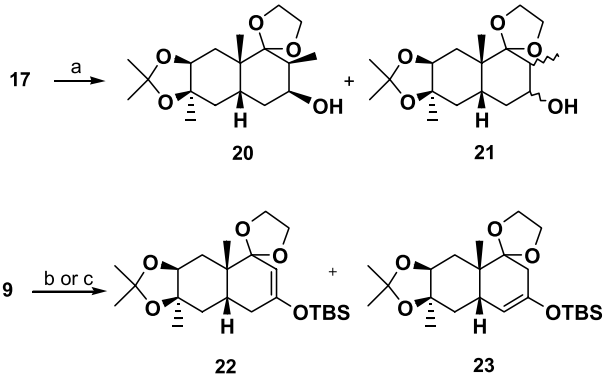
The enone **17** was found to be unstable at ambient conditions and a subsequent reduction was carried out in order to provide a stable compound. Thus Luche's reduction[23] of enone **17** immediately after the aldol condensation gave a mixture of diasteromeric allylic alcohols **18** and **19** in a respective ratio of 1:2. Since NMR spectral analysis could not confidently confirm the position of the methylene group inserted, two additional experiments were performed. As shown in Scheme 5, enone **17** was reduced with sodium borohyride in the absence of cerium chloride to give saturated alcohol **20** and its diastereomer **21** in 23% overall yield from **9**. An X-ray crystallographic analysis (CCDC-185889) of a single crystal from alcohol **20** confirmed its structure which proved that the aldol condensation had occurred at C-6. On the other hand, treatment of ketone **9** with LDA followed by trapping the resultant enolate with TBSOTf furnished silyl enol ethers **22** and **23** in a ratio of 2:1 and in a combined yield of 48%. Their structures were readily differentiated by ^{1}H NMR spectroscopy as the olefinic proton in **22** appeared



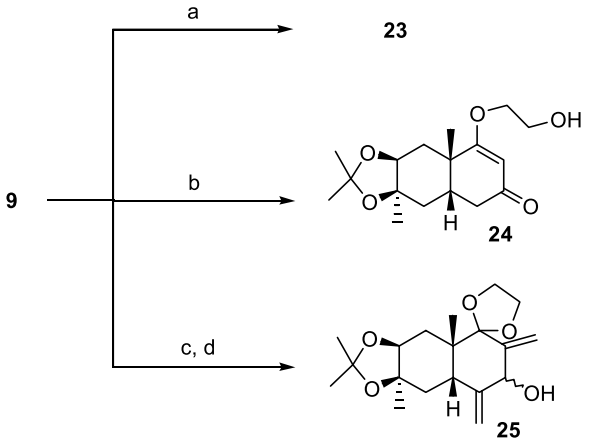
Scheme 4. Reaction conditions: (a) LDA, −78 °C gaseous HCHO, −30 °C; (b) $CeCl_3$, $NaBH_4$, MeOH, 0 °C (35%) (**18**:**19**=1:2).

as a singlet whereas that in **23** resonated as a doublet. Since enol ether **22** was the major product, deprotonation must have taken place at C-6 preponderantly. The regioselectivity of the deprotonation could be explained in terms of the interaction between the lithium ion and the oxygen atom of the cyclic acetal moiety. Hence, the methylene protons (H-6) closer to the cyclic acetal would be preferentially abstracted by LDA.

The setback with LDA was addressed with other bases and we turned to sodium *N*-hexamethyldisilazane (NaHMDS) first. However, only silyl enol ether **22** was produced in 50% yield when ketone **9** was treated with NaHMDS and TBSOTf. Since strong bases could not generate the desired C-4,5 enolate, weaker bases such as postassium carbonate, potassium *tert*-butoxide and sodium hydroxide were investigated. However, reactions with these bases afforded a stable enone **24** as the sole product, obtainable in high yields (Scheme 6). Again, deprotonation took place at C-6 rather than at C-4 to form an enolate which immediately caused β-elimination-opening of the cyclic acetal. Since all



Scheme 5. Reaction conditions: (a) $NaBH_4$, MeOH, 0 °C (23%); (b) LDA, −78 °C, TBSOTf (48%) (**22**:**23**=2:1); (c) NaHMDS, −78 °C, TBSOTf (50%) **22** only.



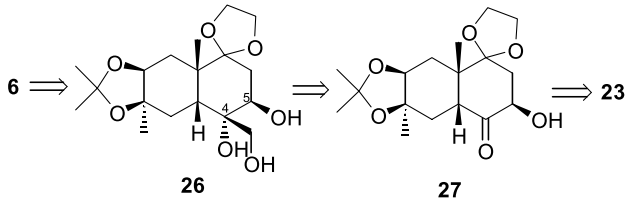
Scheme 6. Reaction conditions: (a) Et_3N, TBSOTf, −78 °C (88%); (b) NaOH, K_2CO_3 or BuOK, THF 0 °C (83%); (c) Eschensomer's salt, Et_3N, CH_2Cl_2, rt; (d) $CeCl_3$, $NaBH_4$, MeOH, 0 °C (40% from **9**).

metal bases could not furnish the desired enolate in good yields, organic bases might be suitable candidates to prevent the chelation effect of the cyclic acetal. Toward this end, ketone **9** was treated with Et_3N and TBSOTf[24] at −78 °C and we were delighted to learn that the desired silyl enol ether **23** could be obtained pure in 88% yield as the sole product (Scheme 6). With the regio-correct masked enolate **23** in hand, reaction with formaldehyde or *S*-trioxane under the Mukaiyama conditions[25] should provide an aldol adduct. Unfortunately, after tremendous experimentations, the Mukaiyama reaction of **23** under various conditions (Lewis acids, solvents and temperatures) were all unsuccessful.

An alternative approach towards the addition of a methylene unit at the α-position of a carbonyl group could in principle be achieved with Eschenmoser's salt.[26] Ketone **9**, in the absence of base, gave no reaction with the Eschenmoser's salt in refluxing CH_2Cl_2 or THF. With the addition of Et_3N,[27] the α-methylenation did occur but was unbearably sluggish in THF. Interestingly, the reaction proceeded at a moderate rate in CH_2Cl_2. However, both C-4 and C-6 were aminomethylated and elimination occurred concommitantly to give an enone which was unstable upon isolation. Its stable derivative, amenable for characterization, was obtained by Luche's reduction[23] of the carbonyl group, giving dialkenyl alcohol **25** in 40% overall yield. However, careful control of the reaction conditions could not afford the desired enone **16**. On the other hand, silyl enol ether **23** was inert towards Eschenmoser's salt. Since diene alcohol **25** could not contribute to the synthesis of the CD ring of taxol, this approach of direct functionalization of C-4 was therefore abandoned and an alternative avenue had to be pursued.

2.4. Revised synthetic plan

The retrosynthesis of a new approach is summarized in Scheme 7. Oxetane **6** would be constructed form triol **26** in which the functionalities at C-4 could be installed by inserting a hydroxymethyl group to α-hydroxy ketone **27**. The ketone **27** would be derived from silyl enol ether **23** via a series of functional group manipulations. In this new



Scheme 7.

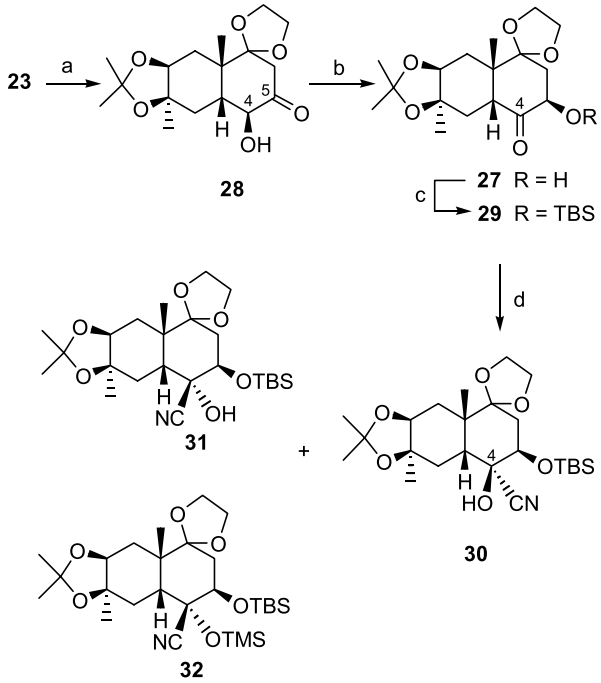
approach, the hydroxyl at C-5 would act as a nucleophile rather than a leaving group, which is different from the strategy reported [8-13] in the 6 total syntheses.

2.5. Synthesis of a highly functionalized precursor 33

The new approach started with silyl enol ether **23** which was hydroxylated using Oxone® and acetone[28] to give 4-hydroxy ketone **28** in 73% yield (Scheme 8). A 1-carbon homologation was required on C-4 and we planned to interconvert the ketone and hydroxy functionality between C-4 and C-5 so that the keto group at C-4 would be amenable for such elaboration.

This was accomplished by an intramolecular redox reaction: Oppenaurer oxidation and Meerwein–Ponndorf–Verley reduction[29] of 4-hydroxy ketone **28** using $Al(OiPr)_3$ as catalyst afforded 5-hydroxy ketone **27** in 79% yield. We believed that the transformation was thermodynamically controlled as the 1,3-diaxial interaction between the OH-4 and the angular methyl group was alleviated from **28** (Fig. 1).

To our knowledge, this is the first example of a direct interconversion between hydroxy and ketone groups intramolecularly in the presence of $Al(OiPr)_3$. It was reported that at least 1 equiv of $Al(OiPr)_3$ was required in



Scheme 8. Reaction conditions: (a) buffer, oxone, acetone, CH_3CN (73%); (b) $Al(OiPr)_3$ toluene (79%); (c) imidazol, DMAP, TBSCl, CH_2Cl_2 (93%); (d) see Table 1.

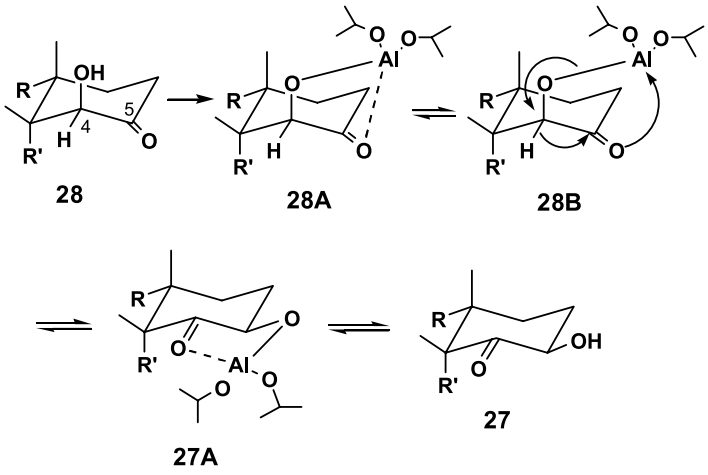


Figure 1. Proposed mechanism for the transformation of **28** into **27**. The cyclic acetal is not shown for clarity reason.

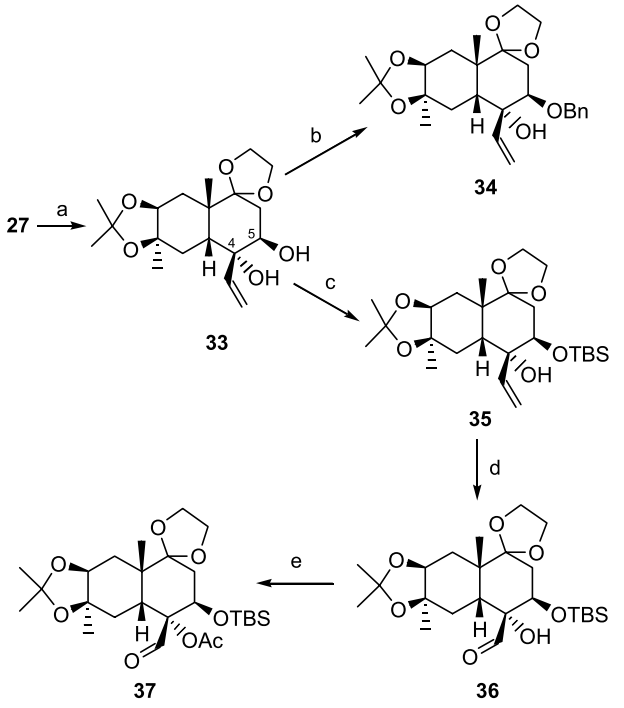
intermolecular reactions.[29] In our intramolecular case, the optimized yield was obtained with 0.5 equiv of $Al(OiPr)_3$ and the yield decreased dramatically with more than this amount. An X-ray crystallographic analysis (CCDC-185888) of a single crystal of **27** confirmed its structure and stereochemistry. Subsequent protection of the 5-hydroxy ketone **27** with TBSCl led to silyl ether ketone **29** in 93% yield. At this point, insertion of a hydroxymethyl group to the C-4 carbonyl group by nucleophilic addition became feasible. From a list of nucleophiles, TMSCN[30] should be a good choice since the nitrile moiety could be reduced to an aldehyde functionality by a number of reducing agents. Thus ketone **29** reacted with TMSCN at room temperature in the presence of 1.5 equiv (optimized) of $AlCl_3$ to give exclusively hydroxynitrile **30** in 66% yield whose stereochemistry at C-4 was confirmed undesirable by an X-ray crystallographic analysis (CCDC-185890). Interestingly, running the experiment at −35 °C afforded the desirable hydroxynitrile **31** and silyl ether nitrile **32** in 83% combined yield with a ratio of 3:1, respectively. These results revealed that at room temperature i.e. under thermodynamically controlled conditions, the bulkier nitrile group preferred to occupy the equatorial position and evaded the 1,3 diaxial interaction with the axial angular methyl group. On the other hand, under kinetically controlled conditions at −35 °C, the cyanide preferred to attack from the less hindered β-face due to the steric demand imposed by the *cis*-ring conformation. The yield of silyl ether nitrile **32** increased with the amount of $AlCl_3$ used and the best yield of **32** was achieved with 5 equiv of $AlCl_3$ (Table 1). It was clear that the hydroxy group of nitrile **31** could only be trimethylsilylated under forcing conditions.

The next step was the reduction of the nitrile group. To our disappointment, a number of reducing agents (DIBAL, LAH or Super hydride)[31a] or basic hydrolysis conditions[31b] could not reduce the nitrile group in **31** or **32** to an aldehyde or hydrolysed to the corresponding acid. For α-hydroxy nitrile **31**, the basic conditions caused retro-cyanohydrin formation to occur, affording the silyl ether ketone **29** in quantitative yield. The vicinity of the tertiary nitrile group might be sterically hindered by the angular methyl and the adjacent TBS group. This route was therefore abandoned and a Grignard reagent served as a hydroxymethyl equivalent was investigated. It has been well-known that Grignard reagent can attack a carbonyl group stereospecifically.[32] Vinyl magnesium bromide was chosen because the alkene moiety could be easily transformed into an aldehyde via a dihydroxylation-glycol cleavage protocol. However, α-silyl ether ketone **29** did not react the Grignard reagent attributable to the bulkiness of the TBS group. A straightforward method to alleviate this problem was to replace the TBS ether group with the less bulky TMS ether. Hence, transient protection of the free alcohol in 5-hydroxy ketone **27** as a TMS ether was followed by the addition of vinyl magnesium bromide, giving the corresponding allylic alcohol that was hydrolyzed with dilute HCl to give diol **33** in 90% overall yield (Scheme 9). It is noteworthy that the Grignard addition was stereospecific and only one stereoisomer was isolated in quantitative yield. The stereochemistry of the tertiary alcohol in diol **33** was confirmed desirable by an X-ray crystallographic analysis (CCDC-185891).

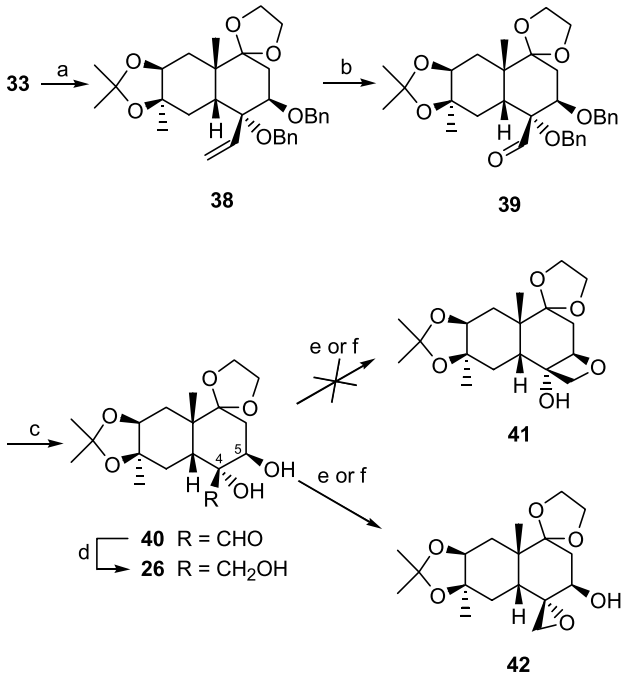
Table 1. Reactions of ketone **29** with TMSCN promoted by $AlCl_3$

Conditions	Isolated yield (%)	Product ratio **30**:**31**:**32**
TMSCN, 1.5 equiv $AlCl_3$, rt, 10 min	66	1:0:0
TMSCN, 1.5 equiv $AlCl_3$, −35 °C, 2 h	83	1:3:0
TMSCN, 5 equiv $AlCl_3$, −35 °C, 2 h	80	2:1:5

The onward steps were the selective protection of the secondary alcohol at C-5 followed by acetylation of the steric demanding tertiary hydroxy group at C-4. Thus, selective benzylation of the secondary alcohol in **33** afforded benzyl ether **34** in 86% yield without incident. To provide a variant for acetylation, selective silylation was also performed to furnish silyl ether **35** in 90% yield. To our regret, we could not acetylate the tertiary alcohol in **34** or **35** under various conditions and only unidentified decomposition products were isolated. Other research group[33] also encountered difficulty in carrying out acetylation in structurally similar systems. It was observed that the decomposition pattern of silyl ether **35** and benzyl ether **34** under various acetylation conditions were similar so only silyl ether **35** was selected for further studies. The reason for



Scheme 9. Reaction conditions: (a) (i) Et_3N, TMSCl, CH_2Cl_2; (ii) vinylMgBr, THF, −78 °C; (iii) 1 M HCl (90%); (b) NaH, BnBr, THF, 50 °C (86%); (c) imidazole, DMAP, TBSCl, CH_2Cl_2 (90%); (d) OsO_4, NMO, then $NaIO_4$ CH_2Cl_2:H_2O (8:1) (78%); (e) Pyr, DMAP, Ac_2O, reflux (35%).

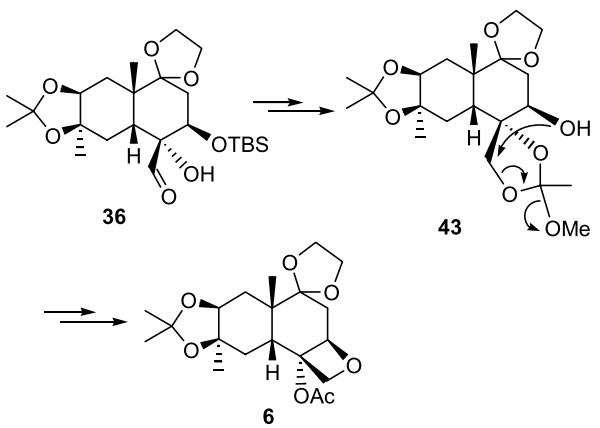


Scheme 10. Reaction conditions: (a) NaH, BnBr, THF, reflux (86%); (b) OsO_4, NMO, acetone–H_2O (4:1), then $NaIO_4$ (78%); (c) 10% Pd/C, EtOH, H_2 (78%); (d) $NaBH_4$, MeOH, 0 °C (80%); (e) (i) Et_3N, MsCl, CH_2Cl_2, 0 °C; (ii) NaH, THF, reflux (92%); (f) (i) Et_3N, MsCl, CH_2Cl_2, 0 °C; (ii) DBU, toluene, reflux (92%).

the unsuccessful acetylation was attributed to steric hindrance. We therefore postponed the acetylation stage until a less bulky aldehyde was installed from oxidative cleavage of the double bond. Accordingly, we transformed silyl ether **35** into TBS aldehyde **36** by the conventional dihydroxylation-glycol cleavage protocol[34] in 78% yield. Acetylation of the tertiary alcohol in **36** under various conditions was then examined. Only the classical method (Ac_2O and DMAP in refluxing pyridine) gave the desirable acetate aldehyde **37** in 35% yield accompanied by a number of unidentified side-products. The low yielding acetylation probably resulted from the steric factor and discouraged us to further investigate this route. Acetylation of the tertiary alcohol was scheduled to occur until the D-ring had been assembled.

As shown in Scheme 10, benzylation of the diol **33** in THF at reflux gave dibenzyl ether **38** in 86% yield. Dihydroxylation of the double bond in **38** followed by oxidative cleavage of the resulting diol afforded dibenzyl aldehyde **39** in 78% overall yield. Catalytic hydrogenolysis of dibenzyl ether **39** gave aldehyde diol **40** (78% yield) which underwent hydride reduction to generate triol **26** in 80% yield. To continue with our synthetic avenue, we allowed the tertiary hydroxyl unprotected in a hope that it would not participate in the intramolecular displacement during the oxetane ring formation. Thus selective mesylation of the primary alcohol in **26** gave the corresponding mesylate which would be attacked by the secondary C-5 alcohol to form oxetane **41** or by the tertiary alcohol at C-4 to produce epoxide **42**. Unluckily, the results indicated that the formation of the epoxide **42** was thermodynamically more stable. Even at prolonged reflux or with an excess amount of NaH or DBU, epoxide **42** could not be induced to undergo rearrangement to the desired oxetane **41**.[35] In principle, the rearrangement would occur if the C-5 hydroxyl and the leaving alkoxy group were arranged in an *anti*-periplanar fashion. However, it appeared that such alignment was not possible due to the ring strain of the C-ring. The formation of epoxide **42** as the sole product hinted at the importance of protecting the tertiary alcohol before the displacement reaction.

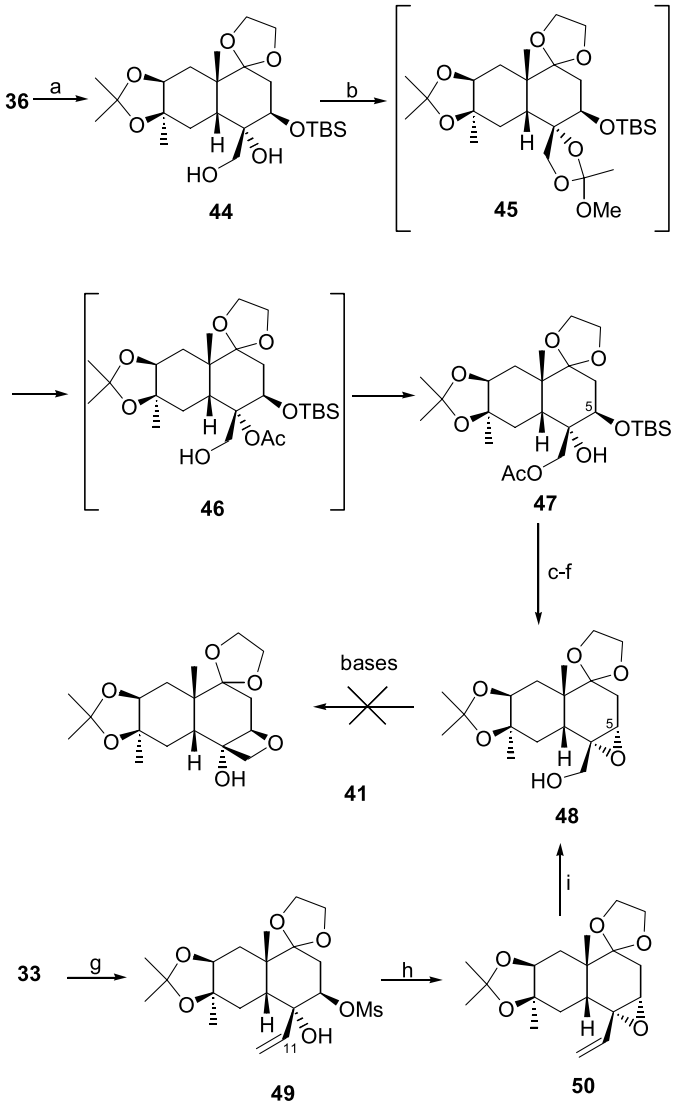
At this stage, we were tempted to make use of the trimethylorthroacetate[36] chemistry to construct the oxetane ring **6** (Scheme 11). Orthoester **43** would be assembled from the corresponding diol and it might serve the purpose of acetylation and oxetane formation since the C-5 hydroxyl could attack the orthoester to provide the oxetane and the C-4 acetate concomitantly.



Scheme 11.

As shown in Scheme 12, the aldehyde moiety in **36** was reduced to give diol **44** in 79% yield. Trimethylorthoacetate reacted with diol **44** in the presence of a stiochiometric amount of *p*-TsOH to give orthoester **45**. A catalytic amount of *p*-TsOH did not cause the reaction to take place. To our surprise, orthoester **45** was unstable even in the reaction mixture and the 5-membered ring readily hydrolyzed to form tertiary acetate **46**. Furthermore, another reaction was then involved which interfered with the isolation of the tertiary acetate **46**. Partial migration of the acetyl group from the tertiary position to the primary position took place readily in the reaction mixture to give a mixture of the tertiary acetate **46** and primary acetate **47**. The life time of the tertiary acetate **46** was too short for synthetic manipulation as facile rearrangement of tertiary acetate **46** to primary acetate **47** occurred quickly in weakly basic conditions (Et_3N/CH_2Cl_2). It was also found that **46** could be converted into **47** completely in silica gel so that the primary acetate **47** could be formed in 81% overall yield from diol **44**. Despite failure to obtain the desirable orthoester **45**, the acetate **47** could be a good candidate for a facile conversion into a CD ring precursor, i.e. oxirane **48**. Indeed, the TBS group in silyl ether **47** was smoothly erased with TBAF and the liberated C-5 hydroxyl was esterified with MsCl to give a mesylate. Intramolecular S_N2 displacement promoted by DBU in refluxing toluene followed by methanolysis of the acetate ester furnished epoxide **48** in 57% overall yield from silyl ether **47**.

The next hurdle to overcome was the isomerization of the oxirane moiety in **48** to an oxetane. Ideally, the freely rotating primary hydroxyl group in **48** should attack the epoxide at the less hindered C-5 in an *anti*-periplanar fashion to give oxetane **41**. However, attempts to isomerize the epoxide in **48** to the oxetane under different conditions failed. Bases such as $CsCO_3$ or K_2CO_3 in refluxing DMF or DBU in refluxing toluene gave no observable reactions. Reactions with ^{t}BuOK, NaH and LDA gave unidentified side-products. At this stage, we considered the possibility to invert the C-5 stereocenter in diol **33** with a bromide so that the C-11 primary hydroxyl, accessible from a dihydroxylation-glycol cleavage-reduction sequence, could displace the



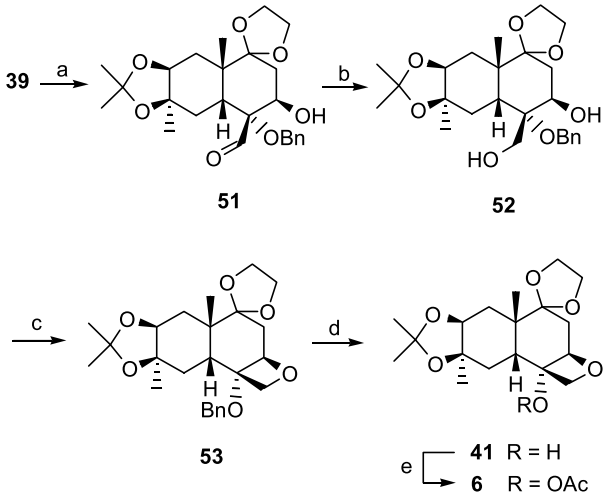
Scheme 12. Reaction conditions: (a) $NaBH_4$, MeOH, 0 °C (79%); (b) trimethylorthoacetate, *p*-TsOH, CH_2Cl_2, then SiO_2 (81%); (c) TBAF, THF; (d) Et_3N, MsCl, 0 °C; (e) DBU, toluene, reflux; (f) K_2CO_3, MeOh (57% from **47**); (g) Et_3N, MsCl, 0 °C (85%); (h) LiBr, CH_3CN (74%); or Bu_4NBr, PhH, reflux (40%); (i) (i) OsO_4, NMO, then $NaIO_4$; (ii) $NaBH_4$, MeOH, 0 °C (72%).

bromide to give oxetane **41**. Thus, selective mesylation of diol **33** gave monomesylate **49** and unfortunately, bromide ion generated by LiBr in CH_3CN or $^nBu_4NBr$ in benzene could not displace the mesylate group. Instead, the basic character of these reagents induced the tertiary hydroxyl to attack the mesylate group to form epoxide **50** in 74% and 40% yield, respectively. It was interesting to find that epoxide **50** could be transformed into oxirane **48** by a dihydroxylation-glycol cleavage-reduction sequence in 72% overall yield (Scheme 12).

2.6. Synthesis of the CD ring of taxol 6

The above results indicated that the tertiary alcohol had to be blocked before oxetane formation could be realized. After considering all the synthetic intermediates, we envisaged that retaining the tertiary benzyl group in dibenzyl ether **39** would be a good candidate for a successful venture.

Thus, catalytic and selective hydrogenolysis of the secondary benzyl group over the tertiary counterpart in dibenzyl ether **39** was investigated. After considerable efforts, it was observed that the choice of solvent could affect the rate and regioselectivity of the hydrogenolysis in our system. Only 5% palladium-on-charcoal in ethyl acetate could accomplish the task whereas the reaction in ethanol or THF showed very little selectivity. Under carefully controlled and monitored conditions, selective deprotection of the secondary benzyl group in **39** afforded, at best, aldehyde **51** in 70% yield, accompanied by the over-reduced diol **40** in 19% yield as shown in Scheme 13. Obviously, the selectivity was attributable to the less hindered secondary benzyl group. Subsequent reduction of the aldehyde in **51** with sodium borohydride in methanol furnished diol **52** in a quantitative yield. Selective mesylation of the primary C-11 hydroxyl group with MsCl and 2,4,6-collidine[37] at 0 °C gave a mesylate intermediate that was followed by an intramolecular S_N2 displacement[38] to give oxetane **53** for the first time in 83% yield. Hydrogenolysis of the tertiary benzyl ether in oxetane **53** with 10% palladium-on-charcoal in ethanol afforded alcohol **41** in 93% yield without incident. Finally, acetylation of the tertiary hydroxyl group was successfully achieved with Ac_2O and DMAP in refluxing pyridine to give the CD ring of taxol **6** in 56% yield. Thus the tricycle **6** was constructed from (*S*)-(+)-carvone in 21 steps with an overall yield of 4%.



Scheme 13. Reaction conditions: (a) 5% Pd/C, ethyl acetate, H_2 (70% for **51**, 19% for **40**); (b) $NaBH_4$, MeOH, 0 °C (100%); (c) (i) 2,4,6-collidine, MsCl, 0 °C; (ii) NaH, THF, reflux (83%); (d) 10% Pd/C, EtOH, H_2 (93%); (e) Pyr, DMAP, Ac_2O (56%).

In summary, we have presented a facile and stereocontrolled synthetic avenue for the construction of the functionalized CD ring in taxol. It is noteworthy that the BC ring in tricycle **6** or **41** is *cis*-fused and these tricycles may be versatile precursors for the preparation of taxol analogs with *cis*-fused BC rings and would provide excellent opportunities for structure-activity studies. The research in this direction is in progress.

3. Experimental

3.1. General

Melting points are reported in Celsius degrees and are uncorrected. Optical rotations were measured at 589 nm. GC-MS studies were performed on a GC with fused silica capillaries column and a GC/MS system with ion trap detector (ITD), injector temperature (250 °C), transfer line temperature (250 °C), oven temperature raised from 80 to 180 °C in a rate of 5 °C per min, EIMS by 70 eV electron beam. IR spectra were recorded on FT-IR spectrometer as a thin film or on a KBr disk. NMR spectra were measured at 300.13 MHz (^1H) or at 75.47 MHz (^{13}C) in $CDCl_3$ solutions, unless stated otherwise. All chemical shifts were recorded in ppm relative to tetramethylsilane ($\delta=0.0$). Spin–spin coupling constants (*J*) were measured directly from the spectra. MS and HRMS were performed at the Department of Chemistry, The Chinese University of Hong Kong, Hong Kong, China. Carbon and hydrogen elemental analyses were carried out by MEDAC Ltd, Department of Chemistry, Brunel University, Uxbridge, U.K. All reactions were monitored by analytical TLC on aluminum precoated with silica gel $60F_{254}$ (E. Merck) and compounds were visualized with a spray of 5% w/v dodecamolybdophosphoric acid in EtOH and subsequent heating. E. Merck silica gel 60 (230–400 mesh) was used for flash column chromatography. All solvents were reagent grade unless otherwise stated. Toluene, benzene, and THF were freshly distilled from Na/benzophenone ketyl under nitrogen. CH_2Cl_2 was freshly distilled from CaH_2 under N_2. Diisopropylamine was freshly distilled from Na under N_2. Other reagents were purchased from commercial suppliers and used without purification. All hexanes used are *n*-hexane.

3.1.1. Octalone 10 and 11. A molar solution of $EtAlCl_2$ in hexane (1.5 mL, 1.5 mmol) was added to a solution of *S*-(+)-carvone (751 mg, 5.0 mmol) in dry toluene (20 mL). The solution was stirred at room temperature under N_2 for 20 min for complexation. Isoprene (2.0 mL, 15.0 mmol) was added and the resulting solution was stirred at room temperature under N_2 for 28 h. Ice water was added to the reaction mixture which was extracted with Et_2O (3×). The combined organic extracts were dried ($MgSO_4$), filtered and

concentrated. The residue was fractionated by column chromatography (hexanes–Et_2O, 30:1) to give a mixture of octalones **10** and **11** as colorless oils (1.02 g, 92%, the ratio of **10**:**11** was determined by GC-MS to be 11.6:1): $[\alpha]_D^{20}=+3.7$ (*c* 0.27, $CHCl_3$); R_f 0.63 (hexanes–Et_2O, 10:1); IR (thin film) 2926, 1703, 1637, 896 cm^{-1}; ^1H NMR δ 1.15 (s, 3H), 1.62 (s, 3H), 1.73 (s, 3H), 4.69 (brs, 1H), 4.81 (brs, 1H), 5.30 (brs, 1H); ^{13}C NMR δ 21.9, 23.5 24.2, 30.8, 32.8, 33.4, 38.1, 41.6, 41.9, 47.5, 111.7, 118.5, 131.8, 147.9, 215.6; MS (EI) *m/z* (relative intensity) 218 (M^+, 16.9), 91 (100). Anal. calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.38; H, 10.10.

3.1.2. Acetal 12. The aforedescribed mixture of octalones **10** and **11** (20.0 g, 0.092 mol), ethylene glycol (39.7 g, 0.64 mol) and *p*-TsOH (10 mg) were dissolved in benzene (350 mL) and the resulting solution was heated at reflux for 12 h with continuous azeotropic removal of water by means of a Dean–Stark trap. The cooled mixture was then washed with aqueous $NaHCO_3$, saturated brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was fractionated by column chromatography (hexanes–Et_2O, 30:1) to give acetal **12** as a colorless oil (21.5 g, 89%): $[\alpha]_D^{20}=+5.8$ (*c* 0.2, $CHCl_3$); R_f 0.68 (hexanes–Et_2O, 10:1); IR (thin film) 2923, 2879, 1644, 886 cm^{-1}; ^1H NMR δ 0.84 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 3.89 (brs, 4H), 4.70 (brs, 2H), 5.32 (brs, 1H); ^{13}C NMR δ 17.9, 20.8, 23.7, 30.0, 33.8, 33.9, 35.2, 37.6, 39.8, 41.6, 64.9, 65.1, 108.5, 113.3, 117.8, 130.4, 149.5; MS (EI) *m/z* (relative intensity) 262 (M^+, 17), 91 (100); HRMS (EI) calcd for $C_{17}H_{26}O_2$ [M] 262.1927, found 262.1917.

3.1.3. Methyl ketone 13. A solution of acetal **12** (11.26 g, 43 mmol), NMO, (29 g, 215 mmol), and OsO_4 (50 mg) in 83% aqueous acetone (700 mL) was stirred at room temperature for 9 d. A solution of $NaIO_4$ (13.8 g, 64.5 mmol) in water (20 mL) was added at room temperature and precipitation occurred. The reaction mixture was stirred for 1 h and was then quenched with saturated aqueous $Na_2S_2O_3$. The resulting mixture was stirred for 24 h and was extracted with EtOAc (4×). The combined extracts were dried ($MgSO_4$) and filtered. Concentration of the filtrate under vacuum followed by flash column chromatography (hexanes–EtOAc, 1:1) afforded methyl ketone **13** as a white solid (9.5 g, 74%): mp 170–171 °C; $[\alpha]_D^{20}=+2.9$ (*c* 0.3, $CHCl_3$); R_f 0.43 (EtOAc); IR (thin film) 3479, 2966, 1703, 1042 cm^{-1}; ^1H NMR δ 1.07 (s, 3H), 1.24 (s, 3H), 1.39 (d, $J=9.9$ Hz, 1H), 1.662 (m, 2H), 2.11 (s, 3H), 2.71 (m, 1H), 3.75 (dd, $J=5.7$, 14.2 Hz, 1H), 3.91 (brs, 4H); ^{13}C NMR δ 26.4, 27.2, 27.8, 28.3, 32.1, 36.4, 37.7, 40.1, 41.4, 44.8, 63.8, 64.3, 71.3, 71.9, 112.5, 211.3; MS (FAB) *m/z* (relative intensity) 299 ($[M+H]^+$, 4), 281 (3), 255 (100). Anal. calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.36; H, 8.93.

3.1.4. Acetate 14. *m*-Chloroperbenzoic acid (9.1 g, 52 mmol) was added to a stirred solution of methyl ketone **13** (7.84 g, 26 mmol) in CH_2Cl_2 (150 mL). The solution was stirred at room temperature for 72 h. The milky solution was cooled with an ice bath and the precipitated *m*-chlorobenzoic acid was removed by filtration. The filtrate was concentrated and upon purification by flash chromatography (hexanes–EtOAc, 1:2) gave acetate **14** as a white solid (7.56 g, 93%): mp 179–180 °C; $[\alpha]_D^{20}=-15.1$(*c* 0.37, $CHCl_3$); R_f 0.53 (EtOAc); IR (thin film) 3461, 2966, 1732, cm^{-1}; ^1H NMR δ 1.13 (s, 3H), 1.24 (s, 3H), 2.02 (S, 3H), 3.73 (dd, $J=5.4$, 11.1 Hz, 1H), 3.92 (m, 4H), 4.96 (m, 1H); ^{13}C NMR δ 21.4, 26.7, 27.4, 31.6, 36.2, 36.3, 37.8, 40.5, 41.6, 63.9, 64.6, 68.9, 71.4, 72.3, 112.9, 170.4; MS (EI) *m/z* (relative intensity) 314 (M^+, 4), 271 (7), 255 (100), 236 (41). Anal. calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.42; H, 8.41.

3.1.5. Acetonide 15. To a stirred solution of acetate **14** (14.4 g, 45.9 mmol) in dry CH_2Cl_2 (350 mL) was added 2,2-dimethoxypropane (20 mL, 161 mmol) and a catalytic amount of *p*-TsOH (10 mg). The reaction mixture was stirred for 24 h at room temperature under N_2 and was then diluted with Et_2O. The organic phase was washed with saturated $NaHCO_3$, dried ($MgSO_4$) and filtered. Concentration of the filtrate gave a residue that was fractionated by column chromatography (hexanes–Et_2O, 2:1) to afford the acetonide **15** as a colorless oil (15.1 g, 92%): $[\alpha]_D^{20}=+21.9$ (*c* 1.5, $CHCl_3$); R_f 0.56 (hexanes–Et_2O, 1:2); IR (thin film) 2980, 1736 cm^{-1}; ^1H NMR δ 1.28 (s, 3H), 1.29 (s, 3H), 1.36 (s, 3H,), 1.45 (s, 3H), 1.84 (dd, $J=6.3$, 12.3 Hz, 1H), 1.91 (d, $J=3.3$ Hz, 1H), 1.96 (brs, 1H), 2.01 (s, 3H), 2.18 (m, 1H), 3.87 (m, 2H), 3.96 (m, 1H), 4.04 (m, 2H), 4.91 (m, 1H); ^{13}C NMR δ 21.3, 25.9, 26.3, 27.4, 27.6, 30.0, 32.7, 34.2, 34.9, 38.9, 39.8, 63.4, 65.1, 69.2, 79.8, 80.5, 106.6, 113.0, 170.3; MS (FAB) *m/z* (relative intensity) 354 ($[M]^+$, 5), 339 ($[M-CH_3]^+$, 25), 295 (100); HRMS (FAB) calcd for $C_{19}H_{31}O_6$ [M+H] 355.2120, found 355.2118.

3.1.6. Ketone 9. Deprotection of the acetyl group in acetonide **15** was effected by adding K_2CO_3 (29.4 g, 213 mmol) to a solution of **15** (15.1 g, 42.7 mmol) in MeOH (350 mL). The reaction mixture was stirred for 4 h at room temperature and then concentrated in vacuo. The residue was dissolved in Et_2O and H_2O, followed by acidification with 4 N aq. HCl until neutral. The solution was extracted with CH_2Cl_2 (3×) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration of the filtrate gave a white solid residue which was directly subjected to the next step.

To a stirred solution of the white residue in dry CH_2Cl_2 (400 mL) was added a mixture of 3 Å molecular sieves (70 g) and PCC (46 g, 213 mmol). The reaction mixture was stirred for 3 h at room temperature under N_2 and then filtered through a pad of Celite and silica gel. The residue was eluted with Et_2O. Concentration of the filtrate followed by flash column chromatography (hexanes–Et_2O, 1:1) gave ketone **9** as a white solid (153 mg, 90%): mp 69–70 °C; $[\alpha]_D^{20}=+40.5$ (*c* 0.4, $CHCl_3$); R_f 0.53 (hexanes–Et_2O, 1:2); IR (thin film) 2976, 1720 cm^{-1}; ^1H NMR δ 1.27 (s, 3H), 1.30 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.61–1.70 (m, 2H), 1.77 (d, $J=4.2$ Hz, 1H), 1.84 (dd, $J=3.3$, 15.3, 1H), 2.12–2.20 (m, 2H), 2.45 (bd, $J=16.2$ Hz, 1H), 2.61 (dd, $J=7.5$, 15.0 Hz, 2H), 3.93 (m, 4H), 4.13 (t, $J=3.6$ Hz, 1H); ^{13}C NMR δ 25.9, 26.2, 27.5, 27.6, 30.0, 34.3, 39.3, 41.1, 44.0, 46.4, 64.3, 64.9, 79.4, 79.7, 106.8, 113.6, 208.5; MS (FAB) *m/z* (relative intensity) 311 ($[M+H]^+$, 3), 149 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_5$ [M+H] 311.1858, found

311.1854. Anal. calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.89; H, 8.61.

3.1.7. Allylic alcohols 18 and 19. To a stirred solution of diisopropylamine (0.23 mL, 1.61 mmol) in dry THF (4 mL) was added a 1.6 M solution of *n*-butyllithium in *n*-hexane (1.0 mL, 1.61 mmol) under N_2 at −78 °C. The reaction mixture was stirred for 15 min and a solution of ketone **9** (100 mg, 0.323 mmol) in dry THF (4 mL) was then added dropwise. The reaction mixture was stirred for 30 min at −78 °C, warmed to −30 °C and an excess amount of HCHO (1 g) was added over a period of 20 min. The reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by purification with a short silica gel column chromatography (hexanes–Et_2O 2:1) gave the enone **17** which was used in the next reaction immediately.

To a stirred solution of the enone **17** and $CeCl_3\cdot 7H_2O$ (91 mg, 0.24 mmol) in MeOH (8 mL) was added $NaBH_4$ (23 mg, 0.61 mmol) in small batches over a period of 15 min at 0 °C. The reaction mixture was stirred for an additional 30 min and was then quenched with saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3×) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash column chromatography (hexanes–Et_2O, 10:1) afforded the β-hydroxy alkene **18** as a colorless oil (12 mg, 11%) and the α-hydroxy alkene **19** as a white solid (26 mg, 24%).

Data for **18**. $[\alpha]_D^{20}=+47.8$ (*c* 1.6, $CHCl_3$); R_f 0.40 (hexanes–Et_2O, 1:2); IR (thin film) 3420, 2930, 1072 cm^{-1}; ^1H NMR (CD_3OD) δ 1.13 (s, 3H), 1.26 (s, 3H), 1.33 (s, 3H), 1.39 (s, 3H), 1.59 (dd, $J=3.6$, 15.3 Hz, 1H), 1.67 (m, 2H), 2.01 (m, 3H), 3.75 (m, 2H), 3.89 (m, 1H), 3.99 (m, 1H), 4.11 (t, $J=3$ Hz, 1H), 4.27 (m, 1H), 5.04 (t, $J=1.8$ Hz, 1H), 5.18 (t, $J=2.1$ Hz, 1H); ^{13}C NMR (CD_3OD) δ 24.1, 24.4, 25.8, 28.9, 33.0, 37.1, 39.2, 39.5, 63.2, 63.3, 66.1, 79.3, 79.9, 104.8, 105.9, 112.3, 147.5; MS (FAB) *m/z* (relative intensity) 324 ($[M]^+$, 32), 307 (52), 249 ($[M-C_2H_4O_2-CH_3]^+$, 100); HRMS (FAB) calcd for $C_{18}H_{29}O_5$ [M+H] 325.2015, found 325.2023.

Data for **19**: mp 124–125 °C; $[\alpha]_D^{20}=-14.9$ (*c* 1.7, $CHCl_3$); R_f 0.36 (hexanes–Et_2O 1:2); IR (thin film) 3497, 2979, 1066 cm^{-1}; ^1H NMR (CD_3OD) δ 1.23 (s, 3H), 1.28 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.53 (m, 2H), 1.73 (m, 1H), 1.79 (d, $J=3$ Hz), 1.92 (m, 1H), 2.08 (bd, $J=10.8$ Hz), 3.85 (m, 4H), 3.99 (t, $J=3$ Hz, 1H), 4.21 (m, 1H), 5.10 (t, $J=2.1$ Hz, 1H), 5.20 (t, $J=2.1$ Hz, 1H); ^{13}C NMR (CD_3OD) δ 24.6, 26.5, 26.6, 27.8, 35.7, 37.8, 39.5 63.1, 64.6, 68.4, 76.9, 78.1, 105.0, 106.1, 117.5, 147.5; MS (FAB) *m/z* (relative intensity) 324 ($[M]^+$, 9), 249 ($[M-C_2H_4O_2-CH_3]^+$, 100), 187 (64); HRMS (FAB) calcd for $C_{18}H_{29}O_5$ [M+H] 325.2015, found 325.2000. Anal. calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.90; H, 8.82.

3.1.8. Alcohol 20. Enone **17** was prepared as above. To a stirred solution of the enone **17** in MeOH (15 mL) at 0 °C was added $NaBH_4$ (61 mg, 1.61 mmol) in small batches over a period of 15 min. The reaction mixture was stirred for 30 min and was then quenched with saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3×) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by column chromatography (hexanes–Et_2O, 1:1) gave alcohol **20** as a white solid (24 mg, 23%). A single crystal for X-ray crystallography was obtained from hexanes–Et_2O, 10:1.

Data for alcohol **20**: mp 151–152 °C; $[\alpha]_D^{20}=31.9$ (*c* 0.3, $CHCl_3$); R_f 0.32 (hexanes–Et_2O 1:2); IR (thin film) 3514, 2936, 1210 cm^{-1}; ^1H NMR δ 1.27 (s, 3H), 1.30 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.65 (m, 2H), 1.77 (d, $J=4.2$ Hz, 1H), 1.84 (dd, $J=3.3$, 15.3 Hz, 1H), 2.18 (m, 2H), 2.45 (bd, $J=16.2$ Hz, 1H), 2.61 (dd, $J=7.5$, 15.0 Hz, 2H), 3.93 (m, 4H), 4.13 (t, $J=3.6$ Hz, 1H); ^{13}C NMR δ 11.8, 19.5, 26.4, 28.2, 29.6, 33.6, 36.1, 38.2, 42.2, 67.1, 67.6, 71.7, 78.9, 106.9, 116.4; MS (EI) *m/z* (relative intensity) 326 ($[M]^+$, 7), 311 ($[M-CH_3]^+$, 17), 251 (26), 205 (100); HRMS (EI) calcd for $C_{18}H_{30}O_5$ [M] 326.2088, found 326.2083.

3.1.9. Silyl enol ether 22. To a stirred solution of diisopropylamine (0.1 mL, 0.73 mmol) in dry THF (4 mL) was added a 1.6 M solution of *n*-butyllithium in *n*-hexane (0.45 mL, 0.73 mmol) under N_2 at −78 °C. The reaction mixture was stirred for 15 min and a solution of the ketone **9** (45 mg, 0.15 mmol) in dry THF (4 mL) was added dropwise. After 30 min, *t*-butyldimethylsilyl trifluoromethanesulfonate (0.1 mL, 0.44 mmol) was added and the reaction mixture was stirred for 20 min at −78 °C. The reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried ($MgSO_4$) and filtered. Concentration of the filtrate under vacuum followed by fractionation of the residue by column chromatography (hexanes–Et_2O, 10:1) gave the silyl enol ether **22** as a white solid (20 mg, 32%) and the silyl enol ether **23** as a colorless oil (10 mg, 16%).

Data for **22**: mp 62–63 °C; $[\alpha]_D^{20}=-31.5$ (*c* 1.0, $CHCl_3$); R_f 0.53 (hexanes–Et_2O, 3:1); IR (thin film) 3743, 2959, 1368, 1220, 1087, 847 cm^{-1}; ^1H NMR δ 0.13 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 1.07 (s, 3H), 1.26 (s, 3H), 1.43 (s, 3H), 1.71 (m, 2H), 1.99 (m, 2H), 2.11 (dd, $J=7.8$, 14.7 Hz, 1H), 2.48 (ddd, $J=1.8$, 6.3, 17.8 Hz, 1H), 3.84 (m, 4H), 4.03 (t, $J=7.8$ Hz, 1H), 4.75 (d, $J=1.8$ Hz, 1H); ^{13}C NMR δ −4.5, −4.2, 17.9, 25.6, 25.8, 28.3, 29.5, 29.8, 33.1, 35.2, 36.9, 39.5, 40.6, 63.5, 64.4, 79.3, 80.9, 104.1, 107.7, 111.4, 152.5; MS (FAB) *m/z* (relative intensity) 425 ($[M+H]^+$, 100), 367 ($[M-C(CH_3)]^+$, 80), 305 (57); HRMS (FAB) calcd for $C_{23}H_{41}O_5Si$ [M+H] 425.2718, found 425.2726.

3.1.10. Silyl enol ether 23. Triethylamine (0.23 mL, 1.61 mmol) and TBDMSOTf (0.19 mL, 0.81 mmol) were added to a stirred solution of ketone **9** (100 mg, 0.32 mmol) in dry CH_2Cl_2 (8 mL) under N_2 at −78 °C. The reaction was stirred for 30 min −78 °C and quenched with saturated NH_4Cl. The aqueous phase was extracted with Et_2O (3×) and the combined organic layers were dried ($MgSO_4$), and filtered. The filtrate was concentrated under vacuum and the residue was fractionated by flash column chromatography (hexanes–Et_2O, 6:1) to give silyl enol ether **23** as a colorless oil (120 mg, 88%): $[\alpha]_D^{20}=+31.3$ (*c* 0.8, $CHCl_3$); R_f 0.63

(hexanes–Et_2O, 3:1); IR (thin film) 2954, 1203, 1086, 841 cm^{-1}; ^1H NMR δ 0.109 (s, 3H), 0.123 (s, 3H), 0.90 (s, 9H), 1.24 (s, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.47 (s, 3H), 1.64 (t, $J=12.6$ Hz, 2H), 1.73 (d, $J=2.7$ Hz, 2H), 2.06 (d, $J=16.5$ Hz, 1H), 2.32 (m, 2H), 3.97 (m, 4H), 4.11 (t, $J=3$ Hz, 1H), 4.70 (dd, $J=1.5$, 4.5 Hz, 1H); ^{13}C NMR δ −4.6, −4.3, 17.9, 25.5, 25.6, 27.2, 27.3, 28.3, 36.1, 26.4, 37.4, 39.5, 64.2, 65.1, 76.5, 76.9, 77.4, 79.8, 79.9, 106.6, 107.4, 112.7, 145.6; MS (FAB) *m/z* (relative intensity) 425 ($[M+H]^+$, 25), 365 ($[M+H\text{-}C_2H_4O_2]^+$, 100), 305 (90); HRMS (FAB) calcd for $C_{23}H_{41}O_5Si$ [M+H] 425.2718, found 425.2710. Anal. calcd for $C_{23}H_{40}O_5Si$: C, 65.05; H, 9.49. Found: C, 65.33; H, 9.67.

3.1.11. Enone 24. The experimental procedures for NaOH, ^{t}BuOK and K_2CO_3 were the same so that only the typical one was described. To a stirred solution of ketone **9** (40 mg, 0.13 mmol) in THF (4 mL) at 0 °C was added ^{t}BuOK (22 mg, 0.19 mmol). The reaction was warmed to room temperature slowly and stirred for 1 h. The reaction was quenched with NH_4Cl and the aqueous phase was extracted with EtOAc (3×). The combined organic layers were dried over $MgSO_4$ and filtered. Concentration of the filtrate followed by flash column chromatography (hexanes–EtOAc, 1:3) allowed the isolation of enone **24** as a white solid (33 mg, 83%): mp 110–111 °C; $[\alpha]_D^{20}=+92.3$ (*c* 0.6, $CHCl_3$); R_f 0.57 ($CHCl_3$M–MeOH, 10:1); IR (thin film) 3743, 3430, 1648, 1208 cm^{-1}; ^1H NMR δ 1.264 (s, 3H), 1.350 (s, 3H), 1.40 (d, $J=8.1$ Hz, 2H), 1.470 (s, 3H), 1.475 (s, 3H), 1.63 (m, 1H), 1.89 (s, 1H), 2.10 (dd, $J=1.8$, 16.5 Hz, 1H), 2.19 (dd, $J=3.6$, 15.9 Hz, 1H), 2.37 (m, 2H), 2.72 (dd, $J=6.3$, 16.5 Hz, 1H), 3.89 (m, 4H), 4.07 (t, $J=3$ Hz, 1H), 5.24 (s, 1H); ^{13}C NMR δ 25.3, 26.7, 26.9, 27.08, 33.2, 33.6. 37.5, 39.6, 39.6, 60.5, 69.7, 79.0, 79.7, 100.4, 107.0, 180.4, 198.7; MS (FAB) *m/z* (relative intensity) 310 ($[M]^+$, 20), 309 (100), 252 (17); HRMS (FAB) calcd for $C_{17}H_{27}O_5$ [M+H] 311.1858, found 311.1842. Anal. calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.81; H, 8.62.

3.1.12. Diene alcohol 25. Et_3N (0.045 mL, 0.32 mmol) was added to a stirred solution of ketone **9** (50 mg, 0.16 mmol) in dry CH_2Cl_2 (4 mL) at room temperature under N_2. The reaction mixture was stirred for 15 min and Eschensomer's salt (89 mg, 0.49 mmol) was added to the reaction mixture which was stirred for 96 h. The reaction was quenched with NH_4Cl and extracted with Et_2O (3×). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated under vacuum. The residue was directly subjected to the next step. $NaBH_4$ (30 mg, 0.98 mmol) was added to a stirred solution of the residue and $CeCl_3\cdot 7H_2O$ (120 mg, 0.31 mmol) in MeOH (5 mL) at 0 °C. The reaction mixture was stirred for 30 min and then quenched with saturated NH_4Cl. The aqueous phase was extracted with Et_2O (3×). The combined extracts were dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was fractionated by flash column chromatography (hexanes–Et_2O, 2:1) to furnish diene alcohol **25** as a colorless oil (22 mg, 40%): $[\alpha]_D^{20}=+46.7$ (*c* 0.9, $CHCl_3$); R_f 0.63 (hexanes–Et_2O, 1:2); IR (thin film) 3490, 2932, 1080 cm^{-1}; ^1H NMR δ 1.07 (s, 3H), 1.31 (s, 3H), 1.38 (s, 3H), 1.51 (s, 3H), 1.69 (dd, $J=3.6$, 15.6 Hz, 1H), 1.88 (bd, $J=15.6$ Hz, 1H), 2.07 (m, 2H), 2.75 (dd, $J=2.1$, 13.8 Hz, 1H), 3.94 (m, 4H), 4.13 (t, $J=3$ Hz, 1H), 4.84 (brs, 2H), 5.06 (d, $J=6$ Hz, 2H), 5.19 (brs, 1H); ^{13}C NMR δ 25.7, 26.1, 27.3, 27.4, 28.8, 39.8, 41.2, 44.2, 64.2, 64.4, 70.4, 79.8, 80.3, 106.3, 106.7, 106.9, 112.7, 146.2, 151.1; MS (FAB) *m/z* (relative intensity) 336 ($[M+H]^+$, 15), 261 ($[M-C_2H_4O_2\text{–}CH_3]^+$, 42), 207 (100); HRMS (FAB) calcd for $C_{19}H_{28}O_5$ [M] calcd 336.1931, found 336.1943.

3.1.13. 4-Hydroxy ketone 28. Buffer solution [4×10^{-4} M aqueous $Na_2(EDTA)$] (2 mL), acetone (0.1 mL, excess), Oxone (215 mg, 0.35 mmol) and $NaHCO_3$ (61 mg, 1 mmol) were sequentially introduced to a solution of silyl enol ether **23** (30 mg, 0.07 mmol) in CH_3CN (10 mL). The solution was stirred at room temperature for 4 h after which the reaction mixture was diluted with water and extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. Flash column chromatography (hexanes–Et_2O, 2:1) of the residue gave 4-hydroxy ketone **28** as a colorless oil (16 mg, 73%): $[\alpha]_D^{20}=+82.8$ (*c* 0.6, $CHCl_3$); R_f 0.42 (hexanes–Et_2O, 1:2); IR (thin film) 3477, 2977, 1718, 1102 cm^{-1}; ^1H NMR δ 1.21 (s, 3H), 1.36 (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.84 (m, 2H), 2.06 (m, 2H), 2.64 (dd, $J=18.3$, 42.9 Hz, 2H), 3.37 (d, $J=4.2$ Hz, 1H), 3.91 (m, 3H), 4.16 (m, 3H); ^{13}C NMR δ 26.0, 26.6, 27.6, 28.4, 28.9, 39.8, 40.2, 44.6, 45.3, 65.3, 65.6, 77.6, 107.4, 113.1, 209.9; MS (FAB) *m/z* (relative intensity) 327 ($[M+H]^+$, 26), 269 (30), 144 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_6$ [M+H] 327.1805, found 327.1814. Anal. calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.33; H, 7.96.

3.1.14. 5-Hydroxy ketone 27. $Al(O\textit{i}Pr)_3$ (10 mg, 0.05 mmol) was added to a stirred solution of 4-hydroxy ketone **28** (33 mg, 0.1 mmol) in dry toluene (2 mL) under N_2. The mixture was stirred at room temperature for 1 h, then was quenched with saturated NH_4Cl solution, and extracted with EtOAc (3×). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under vacuum. The residue was fractionated by column chromatography (hexanes–EtOAc, 3:1 to 1:1) to furnish 5-hydroxy ketone **27** as a white solid (15 mg, 79%) and recover starting material **28** (14 mg). A single crystal for X-ray crystallography was obtained from hexanes–Et_2O, 10:1.

Data for 5-hydroxy ketone **27**: mp 107–108 °C; $[\alpha]_D^{20}=+82.8$ (*c* 0.6, $CHCl_3$); R_f 0.47 (hexanes–Et_2O, 1:2); IR (thin film) 3742, 2975, 1708, 1080 cm^{-1}; ^1H NMR δ 1.26 (s, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.51 (s, 3H), 1.68 (dd, $J=3.3$, 15.3 Hz, 1H), 1.94 (m, 3H), 2.34 (dd, $J=6.9$, 12.9 Hz, 1H), 2.87 (dd, $J=2.4$, 13.8 Hz, 1H), 3.49 (d, $J=3.3$ Hz, 1H), 3.93 (m, 5H), 4.38 (ddd, $J=3.3$, 6.9, 12.6 Hz, 1H); ^{13}C NMR δ 25.3, 27.0, 27.2, 27.4, 28.2, 29.7, 36.8, 37.7, 41.9, 49.9, 63.8, 65.7, 71.1, 79.0, 79.2, 107.1, 111.6, 213.2; MS (FAB) *m/z* (relative intensity) 327 ($[M+H]^+$, 11), 311 ($[M+H\text{-}OH]^+$, 10), 269 (8), 115 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_6$ [M+H] 327.1805, found 327.1804. Anal. calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.29; H, 8.03.

3.1.15. Silyl ether ketone 29. Imidazol (25 mg, 0.368 mmol), dimethylaminopyridine (1 mg) and *tert*-butyldimethylsilyl chloride (27 mg, 0.184 mmol) were added to a solution of 5-hydroxy ketone **27** (12 mg, 0.037 mmol) in CH_2Cl_2 (3 mL) at room temperature under

N_2. The solution was stirred for 3 h and quenched with saturated NH_4Cl. The aqueous phase was extracted with Et_2O (2×) and the combined organic layers were dried over $MgSO_4$. After filtration and concentration of the filtrate under vacuum, the residue was subjected to flash column chromatography (hexanes–Et_2O, 4:1) to give silyl ether ketone **29** as a white solid (15 mg, 93%): mp 98–99 °C; $[\alpha]_D^{20}=11.7$ (*c* 0.4, $CHCl_3$); R_f 0.78 (hexanes–Et_2O, 3:1); IR (thin film) 2933, 1721, 1116 cm^{-1}; ^1H NMR δ 0.02 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 1.26 (s, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 1.49 (s, 3H), 1.65 (dd, $J=3.3$, 15.3 Hz, 1H), 1.92 (m, 3H), 2.09 (d, $J=2.1$ Hz, 1H), 2.12 (s, 1H), 2.74 (dd, $J=2.4$, 13.8 Hz, 1H), 4.04 (m, 5H), 4.43 (dd, $J=8.7$, 10.5 Hz, 1H); ^{13}C NMR δ −5.7, −4.7, 25.4, 25.6, 25.7, 27.1, 27.2, 28.2, 37.8, 41.5, 50.8, 63.8, 65.6, 72.7, 79.1, 79.3, 107.1, 112.1, 210.9; MS (FAB) *m/z* (relative intensity) 440 ($[M]^{\cdot+}$, 2), 426 ($[M+H\text{-}CH]_3)^+$, 16), 382 (100), 325 ($[M-C(CH)_3Si]^+$, 32), 263 (34); HRMS (FAB) calcd for $C_{23}H_{41}O_6$ [M+H] 441.2667, found 441.2679.

3.1.16. β-Hydroxy nitrile 30. $AlCl_3$ (5 mg, 0.035 mmol) and trimethylsilyl cyanide (9 μL, 0.069 mmol) were added to a solution of silyl ether ketone **29** (10 mg, 0.023 mmol) in dry toluene (2 mL) under N_2. The solution was stirred for 5 min at room temperature and quenched with saturated $NaHCO_3$. The solution was extracted with Et_2O (3×). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate concentrated. The oil residue was purified by flash column chromatography (hexanes–Et_2O, 5:1) to give β-hydroxy nitrile **30** as a white solid (7 mg, 66%). A single crystal for X-ray crystallography was obtained from hexanes–Et_2O, 10:1.

Data for β-hydroxy nitrile **30**: mp 192–193 °C; $[\alpha]_D^{20}=+11.2$ (*c* 1.3, $CHCl_3$); R_f 0.28 (hexanes–Et_2O, 3:1); IR (thin film) 3445, 2927, 1078, 779 cm^{-1}; ^1H NMR δ 0.14 (s, 3H), 0.19 (s, 3H), 0.93 (s, 9H), 1.33 (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.53 (s, 3H), 1.63 (m, 1H), 1.71 (m, 1H), 1.90 (m, 2H), 2.01 (m, 1H), 2.51 (dd, $J=2.1$, 14.1 Hz, 1H), 3.44 (brs, 1H), 3.96 (m, 5H), 4.10 (t, $J=3$ Hz, 1H); ^{13}C NMR δ −4.8, −4.5, 25.4, 25.7, 27.1, 27.2, 28.1, 29.7, 30.6, 33.0, 37.3, 39.1, 41.9, 63.7, 65.4, 71.3, 76.9, 79.2, 80.2, 107.2, 112.6, 120.6; MS (FAB) *m/z* (relative intensity) 452 ($[M-CH_3]^+$, 35), 383 ($[M+H\text{-}SiC(CH_3)_3]^+$, 100); HRMS (EI) calcd for $C_{23}H_{38}NO_6Si$ [M−CH_3] 452.2463, found 452.2463.

3.1.17. α-Hydroxy nitrile 31. Trimethylsilyl cyanide (56 μL, 0.42 mmol) was added to a solution of α-silyl ether ketone **29** (37 mg, 0.084 mmol) in dry toluene (6 mL) at −35 °C under N_2. The solution was stirred for 5 min and $AlCl_3$ (20 mg, 0.151 mmol) was introduced intermittently throughout 2 h. The mixture was stirred for a further 0.5 h and quenched with saturated $NaHCO_3$ and extracted with Et_2O (3×). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (hexanes–Et_2O, 6:1) to give the starting ketone **29** (6 mg), α-hydroxy nitrile **31** as a colorless oil (20 mg, 61% based on starting ketone consumed) and β-hydroxy nitrile **30** as a white solid (7 mg, 22%).

Data for α-hydroxy nitrile **31**. $[\alpha]_D^{20}=-5.6$ (*c* 0.25, $CHCl_3$); R_f 0.20 (hexanes–Et_2O, 3:1); IR (thin film) 3340, 2930, 2357, 1107 cm^{-1}; ^1H NMR δ 0.12 (s, 6H), 0.93 (s, 9H), 1.31 (s, 3H), 1.36 (s, 3H), 1.52 (s, 3H), 1.59 (s, 3H), 1.65 (d. $J=3.3$ Hz, 1H), 1.83 (dd, $J=4.2$, 13.5 Hz, 1H), 1.96 (m, 2H), 2.09 (m, 1H), 2.66 (dd, $J=2.1$, 13.5 Hz, 1H), 3.24 (s, 1H), 3.76 (dd, $J=4.2$, 12.0 Hz, 1H), 3.96 (m, 4H), 4.09 (t, $J=3$ Hz, 1H); ^{13}C NMR δ −4.7, −4.4, 18.5, 25.9, 26.3, 27.8, 28.2, 31.5, 32.7, 36.4, 41.5, 43.6, 64.3, 66.1, 72.1, 74.6, 79.6, 80.8, 107.7, 113.1, 122.6; MS (FAB) *m/z* (relative intensity) 468 ($[M+H]^+$, <1), 442 ($[M+H\text{-}CN]^+$, 20), 382 ($[M-SiC(CH_3)_3]^+$, 18), 229 (100); HRMS (FAB) calcd for $C_{24}H_{42}NO_6Si$ [M+H] 468.2776, found 468.2792.

3.1.18. TMS nitrile 32. Trimethylsilyl cyanide (14 μL, 0.1 mmol) was added to a solution of α-silyl ether ketone **29** (9 mg, 0.02 mmol) in dry toluene (3 mL) under N_2 at −35 °C. The solution was stirred for 5 min and $AlCl_3$ (11 mg, 0.08 mmol) was added intermittently throughout 20 min. The mixture was led to stir for further 2 h at −35 °C and then quenched with saturated $NaHCO_3$. The mixture was extracted with Et_2O (3×). The combined extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue was separated by flash column chromatography (hexanes–Et_2O, 9:1 to 5:1) to provide TMS nitrile **32** as a white solid (5 mg, 47%), α-hydroxy nitrile **31** (1 mg, 11%) and β-hydroxy nitrile **30** (2 mg, 22%).

Data for TMS nitrile **32**: mp 136–137 °C; $[\alpha]_D^{20}=+6.4$ (*c* 0.2, $CHCl_3$); R_f 0.44 (hexanes–Et_2O, 2:1); IR (thin film) 3734, 1517, 1127 cm^{-1}; ^1H NMR δ 0.064 (s, 3H), 0.081 (s, 3H), 0.29 (s, 6H), 0.91 (s, 9H), 1.26 (s, 3H), 1.38 (s, 3H), 1.50 (s, 3H), 1.59 (s, 3H), 1.76 (dd, $J=4.2$, 13.8 Hz, 1H), 1.90 (m, 2H), 2.09 (m, 1H), 2.51 (dd, $J=2.1$, 13.5 Hz, 1H), 3.68 (dd, $J=3.9$, 12.0 Hz, 1H), 3.93 (m, 4H), 4.10 (t, $J=3$ Hz, 1H); ^{13}C NMR δ −5.07, −4.13, 1.47, 25.2, 25.8, 27.2, 27.6, 27.7, 31.2, 33.0, 35.9, 41.0, 45.6, 63.7, 65.3, 71.9, 75.2, 78.9, 80.3, 107.0, 112.4, 121.8; MS (FAB) *m/z* (relative intensity) 540 ($[M+H]^+$, 11), 514 ($[M+H\text{-}CN]^+$, 25), 482 (18), 319 (100); HRMS (FAB) calcd for $C_{27}H_{50}NO_6Si_2$ [M+H] 540.3171, found 540.3150. Anal. calcd for $C_{27}H_{49}NO_6Si_2$: C, 60.07; H, 9.15; N, 2.59. Found: C, 60.07; H, 8.96; N, 2.45.

3.1.19. Diol 33. Et_3N (0.38 mL, 2.76 mmol), DMAP (3 mg) and TMS chloride (0.17 mL, 1.38 mmol) were added to a solution of 5-hydroxy ketone **27** (180 mg, 0.55 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred for 20 min at room temperature under N_2. The reaction mixture was quenched with saturated NH_4Cl and filtered through a short pad of silica gel which was eluted with Et_2O. The filtrate was removed under vacuum and the residue was put to the next step.

To a vigorously stirred suspension of magnesium powder (200 mg, 8.3 mmol) in dry THF (6 mL) under N_2 at −78 °C, was added dropwise vinyl bromide (2 mL, excess) by means of condensation with a cold finger containing dry ice and acetone. The suspension was stirred at room temperature and 1,2-dibromomethane (5 μL) was added as an initiator. When the solution started to boil, it was allowed to stir for further 30 min. The crude product from the previous step was dissolved in dry THF (4 mL) and the

solution was injected into the suspension at −78 °C. The reaction was complete within 10 min and saturated NH_4Cl was added. The resulting mixture was extracted with Et_2O (3×) and the combined organic layers were dried, filtered and the filtrate was concentrated under reduced pressure. The residue was redissolved in THF (4 mL) and 1 M HCl (1 mL) was added to the mixture. The reaction mixture was stirred for 30 min at room temperature and saturated $NaHCO_3$ was added for neutralization. The aqueous phase was extracted with EtOAc (3×). The combined extracts were dried ($MgSO_4$), filtered and the filtrate concentrated. Flash chromatography of the residue (hexanes–Et_2O, 2:1) provided diol **33** as a white solid (175 mg, 90%). A single crystal for X-ray crystallography was obtained from hexanes–Et_2O, 10:1.

Data for diol **33**: mp 150–151 °C; $[\alpha]_D^{20}=+24.1$ (*c* 0.3, $CHCl_3$); R_f 0.22 (hexanes–Et_2O, 1:2); IR (thin film) 3442, 2982, 1372, 1075 cm^{-1}; ^1H NMR δ 1.36 (s, 9H), 1.46 (s, 3H), 1.96 (m, 6H), 2.28 (m, 2H), 2.61 (m, 1H), 4.91 (m, 5H), 4.12 (t, $J=3.0$ Hz, 1H), 5.30 (d, $J=10.8$ Hz, 1H), 5.51 (d, $J=16.5$ Hz, 1H), 6.47 (m, 1H); ^{13}C NMR δ 25.5, 27.1, 29.1, 30.9, 34.0, 34.5, 40.7, 44.9, 63.7, 65.1, 71.7, 75.2, 79.2, 80.6, 106.1, 113.2, 116.0, 143.1; HRMS (FAB) calcd for $C_{19}H_{31}O_6$ [M+H] 355.2115, found 355.2112. Anal. calcd for $C_{19}H_{30}O_6$: C, 64.39; H, 8.53. Found: C, 64.68; H, 8.67.

3.1.20. Benzyl ether 34. A solution of the diol **33** (15 mg, 0.041 mol) in dry THF (2mL) was slowly added to a stirring suspension of 60% NaH (17 mg, 0.042 mmol) in dry THF (2 mL) under N_2 at 0 °C. The mixture was subsequently stirred at room temperature for 15 min and then 0 °C for 1 min. BnBr (6.2 μL, 0.05 mmol) was added to the mixture and the resulting mixture was stirred at 50 °C for 12 h. Saturated NH_4Cl was added and the mixture was extracted with Et_2O (3×), dried ($MgSO_4$), filtered and the filtrate was concentrated. The crude product was purified by column chromatography (hexanes–Et_2O, 6:1) to give benzyl ether **34** as a colorless oil (16 mg, 86%): $[\alpha]_D^{20}=+1.8$ (*c* 0.35, $CHCl_3$); R_f 0.58 (hexanes–Et_2O, 1:2); IR (thin film) 3595, 2982, 1075 cm^{-1}; ^1H NMR δ 1.33 (s, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.45 (s, 3H), 1.59 (dd, $J=3.3$, 15 Hz, 1H), 1.93 (m, 5H), 2.24 (dd, $J=2.4$, 13.8 Hz, 1H), 3.05 (brs, 1H), 3.59 (dd, $J=5.7$, 8.4 Hz, 1H), 3.94 (m, 4H), 4.11 (t, $J=3$ Hz, 1H), 5.19 (d, $J=10.8$ Hz, 1H), 5.50 (dd, $J=1.2$, 17.4 Hz, 1H), 6.42 (dd, $J=11.1$, 17.4 Hz, 1H); ^{13}C NMR δ 25.6, 27.2, 27.8, 28.6, 30.8, 32.9, 33.9, 40.1, 44.9, 63.7, 65.0, 72.2, 74.2, 79.4, 80.3, 80.7, 106.8, 113.5, 114.9, 127.6, 128.3, 138.7, 144.0; MS (EI) *m/z* (relative intensity) 444 ($[M]^+$, 1), 429 ($[M-CH_3]^+$, 13), 353 ($[M-OBn]^+$, 8), 309 ($[M-OBn\text{-}OH\text{-}vinyl]^+$, 81), 263 (100); HRMS (EI) calcd for $C_{26}H_{36}O_6$ [M] 444.2506, found 444.2494.

3.1.21. Silyl ether 35. Imidazol (46 mg, 0.68 mmol), DMAP (2 mg) and TBDMSCl (51 mg, 0.339 mmol) were added to a mixture of diol **33** (40 mg, 0.113 mmol) in CH_2Cl_2 (6 mL) at room temperature under N_2. The mixture was stirred for 96 h and quenched with saturated NH_4Cl, extracted with Et_2O (3×). The organic layers were combined, dried ($MgSO_4$) and filtered. Removal of the solvent in vacuo gave the residue which was fractionated by column chromatography (hexanes–Et_2O, 7:1) to give silyl ether **35** as a white solid (48 mg, 90%): mp 84–85 °C; $[\alpha]_D^{20}=+2.01$ (*c* 0.85, $CHCl_3$); R_f 0.45 (hexanes–Et_2O, 2:1); IR (thin film) 3460, 2953, 1108 cm^{-1}; ^1H NMR δ 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.33 (s, 3H), 1.36 (s, 3H), 1.46 (s, 3H), 1.48 (s, 3H), 1.64 (d, $J=3.6$ Hz, 1H) 1.95 (m, 4H), 2.22 (dd, $J=2.1$, 13.5 Hz, 1H), 3.31 (brs, 1H), 3.88 (m, 5H), 4.12 (t, $J=2.7$ Hz, 1H), 5.14 (d, $J=10.8$ Hz, 1H), 5.43 (d, $J=16.2$ Hz, 1H), 6.23 (dd, $J=11.1$, 17.1 Hz, 1H); ^{13}C NMR δ −4.8, −4.7, 25.6, 25.7, 17.1, 27.9, 28.5, 30.6, 34.0, 37.3, 39.6, 43.4, 63.9, 64.9, 73.6, 74.4, 79.4, 80.1, 106.8, 113.7, 114.4, 144.1; MS (FAB) *m/z* (relative intensity) 491 ($[M+Na]^+$, 18), 451 ($[M-OH]^+$, 65), 229 (100); HRMS (FAB) calcd for $C_{25}H_{44}O_6SiNa$ [M+Na] 491.2799, found 491.2762. Anal. calcd for $C_{25}H_{44}O_6Si$: C, 64.06; H, 9.46. Found: C, 64.18; H, 9.49.

3.1.22. TBS aldehyde 36. NMO (50 mg, 0.41 mmol) and OsO_4 (2 mg) were introduced into a stirring mixture of silyl ether **35** (48 mg, 0.01 mmol) in acetone–H_2O (4:1) (5 mL) at room temperature. The reaction mixture was stirred for 100 h and quenched with saturated aqueous $Na_2S_2O_3$ and stirred for a further 24 h. The resulting mixture was extracted with Et_2O (3×), dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. The crude product was dissolved in CH_2Cl_2–H_2O (8:1) (4 mL) and sodium metaperiodate (157 mg, 0.72 mmol) was added. The mixture was stirred at room temperature for 48 h followed by quenching with saturated $Na_2S_2O_3$ and was stirred for a further 2 h. The aqueous phase was extracted with Et_2O (3×), dried ($MgSO_4$) and filtered. The organic solvents were evaporated from the filtrate under vacuum and the residue was fractionated by flash column chromatography (hexanes–Et_2O, 3:1) to furnish TBS aldehyde **36** as a white solid (38 mg, 78%): mp 108–109 °C; $[\alpha]_D^{20}=+2.8$ (*c* 0.3, $CHCl_3$); R_f 0.75 (hexanes–Et_2O, 1:2); IR (thin film) 3437, 2933, 1721, 1094 cm^{-1}; ^1H NMR δ 0.02 (s, 3H), 0.04 (s, 3H), 0.83 (s, 9H), 1.32 (s, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.99 (m, 4H), 2.10 (dd, $J=11.7$, 13.8 Hz, 1H), 3.47 (s, 1H), 3.99 (m, 5H), 4.09 (t, $J=3$ Hz, 1H), 10.09 (s, 1H); ^{13}C NMR δ −4.9, −4.8, 17.9, 25.5, 25.6, 25.8, 27.1, 27.3, 28.2, 29.1, 30.7, 34.0, 35.9, 37.9, 40.2, 42.7, 63.8, 65.4, 65.6, 71.9, 79.1, 79.6, 80.2, 106.9, 112.6, 203.7; MS (EI) *m/z* (relative intensity) 470 ($[M]^+$, 4), 441 ($[M-CHO]^+$, 35), 425 ($[M-3CH_3]^+$, 98), 384 (100); HRMS (EI) calcd for $C_{24}H_{42}O_7Si$ [M] 470.2694, found 470.2695.

3.1.23. Acetate aldehyde 37. Acetic anhydride (0.1 mL, excess) and DMAP (1 mg) were added to a stirring mixture of tertiary alcohol **36** (10 mg, 0.021 mmol) in pyridine (2 mL) under N_2. It was heated under reflux for 100 h and quenched with saturated NH_4Cl. The aqueous phase was extracted with Et_2O (3×) and the combined extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated under vacuum and the crude residue was subjected to column chromatography (hexanes–EtOAc, 6:1) to give starting material **36** (2 mg) and acetate aldehyde **37** as a colorless oil (3 mg, 35% based on consumed starting material): $[\alpha]_D^{20}=+8.9$ (*c* 0.9, $CHCl_3$); R_f 0.57 (hexanes–Et_2O 2:1); IR (thin film) 2953, 1765, 1200 cm^{-1}; ^1H NMR δ 0.07 (s, 3H), 0.12 (s, 3H), 0.87 (s, 9H), 1.29 (s, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 1.54 (s, 3H), 1.68 (m, 2H), 1.98 (m, 2H), 2.14 (s, 3H), 2.99 (dd, $J=1.8$, 13.5 Hz, 1H), 3.94 (m, 4H), 4.09 (t, $J=3$ Hz, 1H), 4.21 (dd, $J=4.5$, 12.3 Hz, 1H), 9.67 (s, 1H); ^{13}C NMR δ −5.4, −5.0, 25.4, 27.1, 27.3, 29.1,

29.2, 29.7, 31.2, 35.4, 36.9, 40.9, 43.5, 63.8, 65.5, 69.4, 78.8, 80.1, 90.2, 106.9, 112.2, 163.5, 192.6; MS (FAB) *m/z* (relative intensity) 513 ($[M+H]^+$, 2), 441 ($[M+H-C(CH_3)_3-CH_3]^+$, 24), 425 (30), 399 (26), 383 (100); HRMS (FAB) calcd for $C_{26}H_{45}O_8Si$ [M+H] 513.2878, found 513.2850.

3.1.24. Dibenzyl ether 38. A solution of the diol **33** (93 mg, 0.263 mmol) in dry THF (3 mL) was slowly added to a stirring suspension of 60% NaH (44 mg, 1.05 mmol) in dry THF (4 mL) under N_2 which had been cooled for 5 min at 0 °C. The mixture was kept to stir at room temperature for 15 min and then 0 °C for 1 min. BnBr (0.1 mL, 0.79 mmol) was added to the mixture and the resulting solution was heated under reflux for 12 h. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O (3×). The combined organic extracts were dried ($MgSO_4$), filtered and the filtrate was concentrated under vacuum. The residue was subjected to flash chromatography (hexanes–Et_2O, 5:1) to furnish dibenzyl ether **38** as a white solid (121 mg, 86%): mp 91–92 °C; $[\alpha]_D^{20}=+6.5$ (*c* 0.9, $CHCl_3$); R_f 0.31 (hexanes–Et_2O, 4:1); IR (thin film) 3741, 2981, 1457, 1076 cm^{-1}; ^1H NMR δ 1.32 (s, 6H), 1.40 (s, 3H), 1.57 (s, 3H), 1.80 (m, 3H), 1.99 (dd, $J=2.4$, 12.6 Hz, 1H), 2.72 (d, $J=11.7$ Hz, 1H), 3.85 (m, 5H), 4.12 (t, $J=3$ Hz, 1H), 4.35 (dd, $J=11.4$, 33.3 Hz, 2H), 4.72 (dd, $J=11.7$, 82.8 Hz, 2H), 5.62 (m, 2H), 6.31 (dd, $J=11.4$, 18.3 Hz, 1H), 7.27 (m, 10H); ^{13}C NMR δ 25.4, 27.3, 29.9, 31.4, 33.4, 33.9, 39.1, 41.3, 63.3, 63.5, 65.2, 73.7, 79.3, 79.5, 80.7, 81.0, 106.7, 112.9, 120.3, 126.7, 127.1, 127.4, 127.6, 128.1, 128.2, 135.9, 139.5, 139.9; MS (FAB) *m/z* (relative intensity) 535 ($[M+H]^+$, 7), 427 ($[M-OBn]^+$, 78), 369 (36), 307 (100); HRMS (FAB) calcd for $C_{33}H_{43}O_6$ [M+H] 535.3054, found 535.3055. Anal. calcd for $C_{33}H_{42}O_6$: C, 74.13; H, 7.92. Found: C, 74.22; H, 7.96.

3.1.25. Dibenzyl aldehyde 39. NMO (53 mg, 0.45 mmol) and OsO_4 (2 mg) were introduced into a stirring solution of dibenzyl ether **38** (120 mg, 0.23 mmol) in acetone–H_2O (4:1) (4 mL) at room temperature. The reaction was stirred for 96 h followed by quenched with saturated aqueous $Na_2S_2O_3$. The mixture was stirred for a further 24 h and extracted with Et_2O (3×). The combined extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (hexanes–Et_2O, 5:1 then 1:1) to give the starting dibenzyl ether **38** (20 mg) and a mixture of diasteromeric diols as a colorless oil (90 mg, 88%). The diols were dissolved in acetone–H_2O (5:1, 4 mL) and sodium metaperiodate (105 mg, 0.48 mmol) was added. The mixture was stirred at room temperature for 48 h and quenched with saturated $Na_2S_2O_3$ and stirred for a further 2 h. The aqueous phase was extracted with Et_2O (3×). The combined extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated under vacuum and the residue was fractionated by column chromatography (hexanes–Et_2O, 3:1) to provide dibenzyl aldehyde **39** as a colorless oil (76 mg, 89%): $[\alpha]_D^{20}=+11.4$ (*c* 0.4, $CHCl_3$); R_f 0.69 (hexanes–Et_2O, 1:2); IR (thin film) 2982, 1719, 1079 cm^{-1}; ^1H NMR δ 1.14 (s, 3H), 1.32 (s, 3H), 1.39 (s, 3H), 1.63 (s, 3H), 1.65 (m, 2H), 1.82 (t, $J=12.9$ Hz, 1H), 1.97 (m, 2H), 2.95 (dd, $J=6.6$, 8.7 Hz, 1H), 3.88 (m, 5H), 4.12 (t, $J=3$ Hz, 1H), 4.39 (dd, $J=11.7$, 91.5 Hz, 2H), 4.79 (dd, $J=11.7$, 84.3 Hz, 2H), 7.29 (m, 10H), 10.16 (s, 1H); ^{13}C NMR δ 25.6, 26.9, 27.2, 28.9, 30.9, 32.7, 33.9, 34.6, 40.7, 63.4, 65.1, 65.3, 74.3, 79.5, 80.7, 82.2, 107.3, 112.2, 127.3, 127.4, 127.6, 127.7, 128.3, 138.5, 138.9, 200.4; MS (FAB) *m/z* (relative intensity) 537 ($[M+H]^+$, 24), 391 (99), 373 (41), 307 ($[M-2\ OBn\text{-}CH_3]^+$, 100); HRMS (FAB) calcd for $C_{32}H_{41}O_7$ [M+H] 537.2847, found 537.2862.

3.1.26. Aldehyde diol 40. 10% Palladium-on-charcoal (10 mg) was suspended in EtOH (2 mL). The mixture was degassed and refilled with hydrogen three times and then stirred for 10 min. A solution of the dibenzyl aldehyde **39** (32 mg, 0.059 mmol) in EtOH (2 mL) was added and the degas process was repeated and the mixture was stirred for 30 min under H_2 atmosphere (ballon). The resulting mixture was filtered and the filtrate was concentrated under vacuum. The residue was passed through a short pad of silica gel (hexanes–Et_2O, 1:1) to give aldehyde diol **40** as a white solid (17 mg, 78%): mp 188–189 °C; $[\alpha]_D^{20}=9.8$ (*c* 0.3, $CHCl_3$); R_f 0.29 (hexanes–Et_2O, 1:2); IR (thin film) 3442, 2979, 1709, 1070 cm^{-1}; ^1H NMR (CD_3OD) δ 1.13 (s, 3H), 1.21 (s, 3H), 1.24 (s, 3H), 1.33 (s, 3H), 1.47 (m, 3H), 1.89 (m, 3H), 2.06 (m, 1H), 2.16 (dd, $J=2.1$, 13.2 Hz), 3.85 (m, 5H), 4.03 (t, $J=3$ Hz, 1H), 9.85 (d, $J=0.9$ Hz, 1H); ^{13}C NMR δ 23.7, 25.4, 25.7, 26.8, 29.9, 32.2, 33.5, 39.8, 40.6, 62.8, 64.5, 69.4, 72.2, 78.6, 79.7, 106.1, 111.7, 202.7; MS (EI) *m/z* (relative intensity) 341 ($[M-CH_3]^+$, 5), 427 ($[M-CHO]^+$, 7), 205 (13), 122 (89), 105 (100); HRMS (EI) calcd for $C_{17}H_{25}O_7$ [M−CH_3] 341.1595, found 341.1599. Anal. calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.39; H, 7.86.

3.1.27. Triol 26. To a stirred solution of the aldehyde diol **40** (16 mg, 0.045 mmol) in MeOH (3 mL) at 0 °C was added $NaBH_4$ (5 mg, 0.13 mmol). The reaction mixture was stirred for 30 min and quenched with saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3×) and the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. Concentration of the filtrate followed by column chromatography (hexanes–EtOAc, 1:2) gave the triol **26** as a colorless oil (13 mg, 80%): $[\alpha]_D^{20}=+14.5$ (c 0.25, $CHCl_3$); R_f 0.33 ($CHCl_3$–MeOH, 15:1); IR (thin film) 3418, 2976, 1071 cm^{-1}; ^1H NMR (CD_3OD) δ 1.29 (s, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 1.47 (s, 3H), 1.54 (m, 2H), 1.80 (m, 2H), 1.92 (dd, $J=2.1$, 14.1 Hz, 1H), 1.74 (m, 2H), 2.02 (bd, $J=12.9$ Hz, 1H), 2.38 (dd, $J=1.8$, 13.2 Hz, 1H), 3.62 (d, $J=11.7$ Hz, 1H), 3.94 (m, 6H), 4.09 (t, $J=3$ Hz, 1H); ^{13}C NMR (CD_3OD) δ 24.9, 26.4, 26.9, 28.1, 29.8, 31.8, 33.9, 35.2, 39.8, 40.8, 63.7, 65.3, 65.9, 72.2, 74.9, 79.6, 81.1, 107.2, 113.2; MS (EI) *m/z* (relative intensity) 343 ($[M-CH_3]^+$, 2); HRMS (EI) calcd for $C_{17}H_{27}O_7$ [M−CH_3] 343.1751, found 343.1756.

3.1.28. Epoxide 42. DMAP (13 mg, 0.11 mmol) was added to a stirred solution of triol **41** (13 mg, 0.036 mmol) in dry CH_2Cl_2 (3 mL) under N_2 at 0 °C. The mixture was stirred for 15 min and MsCl (3 μL, mmol) was introduced and stirred at 0 °C for 12 h. The resulting solution was quenched with saturated NH_4Cl and the aqueous phase was extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated. The crude product was dissolved in THF (1 mL) and the resulting solution was added to a stirred suspension of

60% NaH (10 mg, 0.176 mmol) in THF (2 mL) under N_2. The mixture was heated under reflux for 5 h and saturated NH_4Cl was added which was followed by extraction with Et_2O (3×). The organic layers were combined, dried ($MgSO_4$), filtered and the filtrate was concentrated. Flash column chromatography of the residual oil (hexanes–Et_2O, 1:1 then $CHCl_3$–MeOH, 10:1) gave epoxide **42** as a colorless oil (7 mg, 92%) and recovered some unreacted triol **26** (5 mg).

Data for epoxide **42**. $[\alpha]_D^{20}=-8.3$ (*c* 0.3, $CHCl_3$); R_f 0.42 (hexanes–Et_2O 1:2); IR (thin film) 3448, 2976, 1372, 1077 cm^{-1}; ^1H NMR δ 1.32 (s, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.79 (m, 4H), 1.97 (dd, $J=3.3$, 15.6 Hz, 1H), 2.07 (dd, $J=4.8$, 12.9 Hz, 1H), 2.54 (d, $J=5.1$ Hz, 1H), 3.23 (d, $J=5.1$ Hz, 1H), 3.93 (m, 3H), 4.07 (m, 3H); ^{13}C NMR δ 25.6, 26.7, 27.3, 27.4, 29.5, 34.9, 35.9, 41.5, 41.7, 52.1, 61.7, 63.6, 63.9, 65.4, 79.5, 79.9, 106.7, 112.8; MS (FAB) *m/z* (relative intensity) 341 ($[M+H]^+$, 75), 283 ($[M-C(CH_3)_2-OH+H]^+$, 100), 265 (45); HRMS (FAB) calcd for $C_{18}H_{29}O_6$ [M+H] 341.1958, found 341.1953.

3.1.29. Diol 44. To a stirred solution of the silyl ether **36** (20 mg, 0.043 mmol) in MeOH (2 mL) at 0 °C was added with $NaBH_4$ (4 mg, 0.11 mmol) slowly. The reaction mixture was stirred for 30 min and quenched with saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3×) and the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. Concentration of the filtrate in vacuo followed by flash column chromatography (hexanes–Et_2O, 4:1) gave diol **44** as a colorless oil (16 mg, 79%): $[\alpha]_D^{20}=+4.7$ (*c* 1.0, $CHCl_3$); R_f 0.42 (hexanes–Et_2O, 1:1); IR (thin film) 3407, 2954, 1455, 1074 cm^{-1}; ^1H NMR δ 0.092 (s, 3H), 0.12 (s, 3H), 0.89 (s, 9H), 1.31 (s, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 1.47 (s, 3H), 1.56 (dd, $J=3.6$, 15 Hz, 1H), 1.95 (m, 4H), 2.09 (dd, $J=2.1$, 11.4 Hz, 1H), 2.97 (dd, $J=2.7$, 9.6 Hz, 1H), 2.29 (t, $J=$ 10.5 Hz, 1H), 3.95 (m, 5H), 4.09 (t, $J=3$ Hz, 1H), 4.31 (dd, $J=2.7$, 11.4 Hz, 1H); ^{13}C NMR δ −4.9, −4.8, 17.9, 25.5, 25.7, 27.1, 27.5, 28.7, 31.1, 33.8, 36.5, 40.2, 42.8, 63.8, 65.2, 68.8, 72.9, 75.3, 79.1, 80.3, 106.8, 113.2; MS (FAB) *m/z* (relative intensity) 473 ($[M+H]^+$, 50), 455 ($[M+H-H_2O]^+$, 45), 423 ($[M-OTBDMS\ -H_2O]^+$, 100), 229 (97); HRMS (FAB) calcd for $C_{24}H_{45}O_7Si$ [M+H] 473.2929, found 473.2920. Anal. calcd for $C_{24}H_{44}O_7Si$: C, 60.98; H, 9.38. Found: C, 61.20; H, 9.50.

3.1.30. Acetate 47. Trimethylorthoacetate (0.25 mL, 1.8 mmol) and *p*-TsOH (12 mg, 0.06 mmol) were added to a solution of diol **44** (30 mg, 0.06 mmol) in dry CH_2Cl_2 (4 mL) at room temperature under N_2. The mixture was allowed to stir for 5 h and made neutral by adding a few drops of Et_3N which was followed by concentration of the volatiles under vacuum. The residue was redissolved in CH_2Cl_2 (4 mL) and SiO_2 (200 mg) was added. The mixture was stirred at room temperature for 2 h and the SiO_2 was filtered. The filtrate was concentrated under vacuum and the crude product was subjected to flash column chromatography (hexanes–EtOAc, 6:1) to provide the acetate **47** as a white solid (25 mg, 81%): mp 114–115 °C; $[\alpha]_D^{20}=-1.6$ (*c* 1.0, $CHCl_3$); R_f 0.31 (hexanes–EtOAc, 4:1); IR (thin film) 3482, 2952, 1739, 1248, 1082 cm^{-1}; ^1H NMR δ 0.065 (s, 3H), 0.067 (s, 3H), 0.88 (s, 9H), 1.33 (s, 3H), 1.37 (s, 3H), 1.46 (s, 3H), 1.50 (s, 3H), 1.83 (m, 3H), 1.98 (dd, $J=6$, 14.1 Hz, 1H), 2.08 (s, 3H), 2.29 (dd, $J=2.1$, 13.5 Hz, 1H), 3.18 (brs, 1H), 3.92 (m, 5H), 4.12 (t, $J=3$ Hz, 1H), 4.31 (dd, $J=12$, 13.8 Hz, 2H); ^{13}C NMR δ −5.0, −4.9, 21.1, 25.5, 25.7, 27.0, 27.8, 28.2, 31.0, 34.5, 36.7, 38.8, 39.6, 63.9, 64.9, 67.9, 71.3, 73.7, 79.1, 80.1, 106.8, 113.4, 171.3; MS (FAB) *m/z* (relative intensity) 515 ($[M+H]^+$, 5), 437 ($[M-OAc\text{-}H_2O]^+$, 45), 397 (40), 229 (100); HRMS (FAB) calcd for $C_{26}H_{47}O_8Si$ [M+H] 515.3035, found 515.3030. Anal. calcd for $C_{26}H_{46}O_8Si$: C, 60.67; H, 9.01. Found: C, 60.73; H, 9.03.

3.1.31. Epoxide 48. A molar solution TBAF in THF (0.04 mL, 0.04 mmol) was added to a stirred solution of the acetate **47** (16 mg, 0.031 mmol) in THF (2 mL) under N_2. After 30 min, the reaction mixture was filtered through a pad of silica gel and eluted with Et_2O. Concentration of the filtrate gave a crude oil which was put to the next step. Et_3N (0.1 mL, 0.77 mmol) was added to a stirred solution of the crude oil in CH_2Cl_2 (3 mL) at 0 °C. MsCl (10 μL, 0.12 mmol) was then added to the mixture which was stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O (3×). The organic layers were combined, dried ($MgSO_4$), and filtered. A residue was obtained upon concentration of the filtrate under reduced pressure. The residue was then dissolved in toluene (2.5 mL) and DBU (12 μL, 0.08 mmol) was introduced into the solution that was heated under reflux for 30 min. The reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O (3×). The combined extracts were dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was dissolved in MeOH (2 mL) and K_2CO_3 (6 mg, 0.043 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and saturated NH_4Cl was added for neutralization. The mixture was extracted with CH_2Cl_2 (3×), dried ($MgSO_4$), filtered and the filtrate was concentrated. Purification of the residue by column chromatography (hexanes–EtOAc, 1:2) gave epoxide **48** as a white solid (6 mg, 57%): mp 159–160 °C; $[\alpha]_D^{20}=-2.3$ (*c* 0.5, $CHCl_3$); R_f 0.28 (hexanes–Et_2O 1:2); IR (thin film) 3460, 2923, 1072 cm^{-1}; ^1H NMR δ 1.25 (s, 3H), 1.31 (s, 3H), 1.36 (s, 3H), 1.47 (s, 3H), 1.54 (dd, $J=2.1$, 14.4 Hz, 1H), 1.69 (m, 3H), 2.02 (dd, $J=2.1$, 15.6 Hz, 1H), 2.16 (m, 2H), 3.39 (s, 1H), 3.62 (dd, $J=12.3$, 19.2 Hz, 2H), 3.81 (m, 2H), 4.03 (m, 2H), 4.11 (t, $J=3$ Hz, 1H); ^{13}C NMR δ 25.3, 26.5, 27.2, 27.8, 29.6, 35.6, 36.1, 36.9, 55.5, 59.5, 62.2, 63.7, 65.6, 79.6, 79.8, 106.7, 112.2; MS (EI) *m/z* (relative intensity) 340 ($[M]^+$, 11), 325 ($[M-CH_3]^+$, 18), 309 (16), 98 (100); HRMS (EI) calcd for $C_{18}H_{28}O_6$ $[M]^+$ 340.1880, found 340.1877. Anal. calcd for $C_{18}H_{28}O_6Si$: C, 63.51; H, 8.29. Found: C, 63.30; H, 8.25.

Another approach towards the epoxide **48** started with a dihydroxylation-glycol cleavage-reduction sequence from alkene epoxide **50**. NMO (23 mg, 0.19 mmol) and OsO_4 (2 mg) were introduced into a stirring solution of alkene epoxide **50** (22 mg, 0.065 mmol) in acetone–H_2O (4:1) (3 mL) at room temperature. After 48 h, the mixture was quenched with saturated $Na_2S_2O_3$ and stirred for a further 24 h. The resulting solution was extracted with Et_2O (3×), dried ($MgSO_4$) and filtered. Concentration of the filtrate in vacuo provided the residue which was dissolved in CH_2Cl_2–

H_2O (7:1) (3 mL) and sodium metaperiodate (25 mg, 0.12 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, quenched with saturated aqueous $Na_2S_2O_3$ and stirred for a further 2 h. The resulting mixture was extracted with Et_2O (3×), dried ($MgSO_4$) and filtered. The filtrate was concentrated under vaccum and a crude oil was obtained. Methanol (3 mL) was added to the crude which was stirred for 15 min at 0 °C. $NaBH_4$ (4 mg, 0.1 mmol) was slowly added to the reaction mixture which was subsequently stirred for 30 min. Saturated NH_4Cl was added to quench the reaction and the resulting mixture was extracted with CH_2Cl_2 (3×), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash column chromatography as mentioned above gave the epoxide **48** (16 mg, 72%).

3.1.32. Mesylate 49. Et_3N (0.1 mL, 0.77 mmol) was added to a stirred solution of diol **33** (40 mg, 0.11 mmol) in CH_2Cl_2 (4 mL) at 0 °C. It was kept stirring for 15 min and MsCl (9 μL, 0.12 mmol) was added to the mixture which was stirred for 3 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O (3×). The combined organic layers were dried ($MgSO_4$) and filtered. Evaporation of the solvent in vacuo followed by purification of the residue by column chromatography (hexanes–Et_2O, 2:1) gave mesylate **49** as a colorless oil (34 mg, 85% based on starting material **33** consumed) and recovered the starting material (6 mg).

Data for mesylate **49**. $[\alpha]_D^{20}=+2.3$ (*c* 1.0, $CHCl_3$); R_f 0.32 (hexanes–Et_2O 1:2); IR (thin film) 3505, 2987, 1349, 1172 cm^{-1}; ^1H NMR δ 1.32 (s, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.46 (s, 3H), 1.59 (m, 2H), 1.91 (dd, $J=2.4$, 15 Hz, 1H), 2.02 (dd, $J=1.8$, 14.1 Hz, 1H), 2.19 (m, 2H), 2.31 (dd, $J=1.8$, 13.5 Hz, 1H), 3.04 (s, 3H), 3.89 (m, 2H), 4.01 (m, 2H), 4.10 (t, $J=3$ Hz, 1H), 4.67 (dd, $J=6.0$, 9.9 Hz, 1H), 5.28 (d, $J=10.8$ Hz, 1H), 5.53 (dd, $J=17.4$ Hz, 1H), 6.42 (dd, $J=10.8$, 17.4 Hz, 1H); ^{13}C NMR δ 25.4, 27.1, 27.5, 28.6, 30.8, 32.7, 34.2, 38.1, 40.3, 46.0, 63.8, 65.2, 73.3, 79.1, 80.4, 83.2, 106.9, 112.5, 116.3, 142.3; MS (EI) *m/z* (relative intensity) 417 ($[M-CH_3]^+$, 50), 321 ($[M-CH_3-SO_2CH_3-OH]^+$, 100); HRMS (EI) calcd for $C_{19}H_{27}O_8S$ $[M-CH_3]$ 417.1578, found 417.1581.

3.1.33. Epoxide 50. LiBr (66 mg, 0.76 mmol) was added to a mixture of mesylate **49** (33 mg, 0.076 mmol) in dry CH_3CN (5 mL) at room temperature under N_2. The resulting mixture was stirred at room temperature for 12 h and saturated NH_4Cl was added. The aqueous phase was extracted with Et_2O (3×) and the combined organic layers were dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and purification of the crude product was accomplished by flash column chromatography (hexanes–Et_2O, 2:1) to afford epoxide **50** as a white solid (15 mg, 74% based on starting material **49** consumed) and recover the starting material (7 mg).

Data for expoxide **50**: mp 62–63 °C; $[\alpha]_D^{20}=+17.7$ (*c* 0.5, $CHCl_3$); R_f 0.56 (hexanes–Et_2O, 1:2); IR (thin film) 2978, 1204, 1066, 673 cm^{-1}; ^1H NMR δ 1.28 (s, 3H), 1.31 (s, 3H), 1.37 (s, 3H), 1.51 (s, 3H), 1.67 (m, 3H), 2.11 (m, 2H), 2.51 (dd, $J=3.6$, 11.7 Hz, 1H), 3.11 (t, $J=1.8$ Hz, 1H), 3.80 (m, 2H), 4.03 (m, 2H), 4.13 (t, $J=3$ Hz, 1H), 5.19 (dd, $J=1.2$, 10.5 Hz, 1H), 5.40 (dd, $J=1.2$, 17.4 Hz, 1H), 5.62 (dd, $J=10.5$, 17.1 Hz, 1H); ^{13}C NMR δ 25.3, 26.6, 27.2, 27.3, 27.9, 29.9, 35.5, 36.7, 36.9, 59.0, 61.3, 63.7, 65.6, 79.7, 79.9, 102.7, 106.6, 111.9, 116.4, 139.2; MS (FAB) *m/z* (relative intensity) 337 ($[M+H]^+$, 24), 277 ($[M+H-C_2H_4O_2]^+$, 20), 185 (90), 93 (100); HRMS (FAB) calcd for $C_{19}H_{29}O_5$ [M+H] 337.2010, found 337.1989.

3.1.34. Alcohol 51. 5% Palladium-on-charcoal (40 mg) was suspended in EtOAc (5 mL) and the mixture was degassed and then filled with hydrogen gas three times and was stirred for 10 min. A solution of the aldehyde **39** (80 mg, 0.15 mmol) in EtOAc (4 mL) was added and the mixture was continuously monitored by TLC so that the starting material was estimated to be about 80% consumed. The resulting mixture was filtered through filter paper and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (hexanes–Et_2O, 3:1 to 1:3) to afford the starting aldehyde **39** (7 mg), alcohol **51** as a colorless oil (43 mg, 70%) and the aldehyde diol **40** (9 mg, 19%).

Data for alcohol **51**. $[\alpha]_D^{20}=+9.4$ (*c* 0.25, $CHCl_3$); R_f 0.42 (hexanes–Et_2O, 1:2); IR (thin film) 3737, 2981, 1715, 1074 cm^{-1}; ^1H NMR δ 1.15 (s, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.60 (s, 3H), 1.98 (m, 4H), 2.63 (brs, 1H), 2.91 (dd, $J=3.3$, 11.4 Hz, 1H), 3.98 (m, 5H), 4.13 (t, $J=3$ Hz, 1H), 4.44 (dd, $J=11.4$, 82.8 Hz, 2H), 7.34 (m, 5H), 10.03 (s, 1H); ^{13}C NMR δ 25.5, 26.9, 27.2, 28.8, 30.9, 32.4, 33.7, 34.9, 41.1, 63.5, 65.4, 65.6, 70.1, 79.4, 80.5, 80.6, 107.2, 111.9, 127.7, 127.9, 128.4, 137.9, 200.2; MS (FAB) *m/z* (relative intensity) 447 ($[M+H]^+$, 14), 417 ($[M-CHO]^+$, 36), 309 (95), 281 (92); HRMS (FAB) calcd for $C_{25}H_{35}O_7$ [M+H] 447.2377, found 447.2344.

3.1.35. Diol 52. To a stirred solution of the alcohol **51** (8 mg, 0.017 mmol) in MeOH (4 mL) at 0 °C was added with $NaBH_4$ (5 mg, 0.13 mmol) in small batches over a period of 5 min. The reaction mixture was stirred for 30 min and quenched with saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3×) and the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. Concentration of the filtrate followed by flash column chromatography (hexanes–Et_2O, 1:1) afforded diol **52** as a colorless oil (8 mg, 100%): $[\alpha]_D^{20}=+10.6$ (*c* 0.45, $CHCl_3$); R_f 0.35 (hexanes–Et_2O, 1:2); IR (thin film) 3313, 1378 cm^{-1}; ^1H NMR δ 1.31 (s, 3H), 1.32 (s, 3H), 1.37 (s, 3H), 1.51 (s, 3H), 1.89 (m, 5H), 2.24 (m, 1H), 3.06 (brs, 1H), 3.22 (brd, $J=5.4$ Hz, 1H), 3.92 (m, 6H), 4.09 (brs, 1H), 4.46 (d, $J=12.6$ Hz, 1H), 4.61 (dd, $J=9.9$, 52.5 Hz, 2H), 7.36 (m, 5H); ^{13}C NMR δ 25.4, 27.0, 29.2, 31.6, 33.5, 34.5, 39.9, 40.8, 63.5, 65.3, 73.3, 79.1, 79.3, 80.7, 106.9, 112.6, 127.5, 128.3, 128.4, 138.6; MS (EI) *m/z* (relative intensity) 417 ($[M-CH_2OH]^+$, 88), 359 ($[M-CH_2OH-C(CH_3)_2-OH+H]^+$, 100); HRMS (EI) calcd for $C_{24}H_{33}O_6$ $[M-CH_2OH]$ calcd 417.2272, found 417.2270.

3.1.36. Oxetane 53. 2,4,6-Collidine (0.32 mol, 2.49 mol) was added to a stirred solution of the diol **52** (140 mg, 0.313 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C under N_2. After 15 min, MsCl (0.028 mL, 0.36 mmol) was added to the reaction mixture which was kept stirring at 0 °C for 48 h. The mixture was quenched with NH_4Cl and extracted with

Et_2O (3×). The combined organic extracts were dried ($MgSO_4$) and filtered. Concentration of the filtrate gave a crude oil which was put to the next step.

The crude oil was added to a suspension of NaH (24 mg, 0.62 mmol) in dry THF (5mL) and the resulting mixture was heated under reflux for 4 h under N_2. The reaction was quenched with NH_4Cl and the aqueous phase was extracted with Et_2O (3×). The combined organic extracts were dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was fractionated by flash column chromatography (hexanes–Et_2O, 2:1 to 1:2) to give pure oxetane **53** as a white solid (70 mg, 83%) and the starting diol **52** (52 mg).

Data for oxetane **53**: mp 173–174 °C; $[\alpha]_D^{20} = +16.4$ (*c* 0.65, $CHCl_3$); R_f 0.56 (hexanes–Et_2O, 1:2); IR (thin film) 2880, 1516, 1078 cm^{-1}; ^1H NMR δ 1.29 (s, 3H), 1.36 (s, 3H), 1.48 (s, 3H), 1.57 (s, 3H), 1.74 (dd, $J=3.3$, 15.0 Hz, 1H), 1.84 (dd, $J=2.4$, 15.3 Hz, 1H), 1.96 (dd, $J=3.6$, 14.7 Hz, 1H), 2.18 (m, 2H), 2.38 (dd, $J=3.6$, 11.4 Hz, 1H), 3.94 (m, 4H), 4.11 (t, $J=3$ Hz, 1H), 4.54 (d, $J=7.2$ Hz, 1H), 4.66 (s, 2H), 4.77 (d, $J=7.2$ Hz, 1H), 4.96 (m, 1H); ^{13}C NMR δ 25.6, 26.9, 27.3, 27.6, 30.6, 34.5, 35.0, 38.8, 42.7, 64.4, 64.7, 65.9, 78.6, 79.1, 79.6, 79.8, 83.8, 106.7, 112.3, 127.1, 127.3, 128.3, 138.9; MS (FAB) *m/z* (relative intensity) 431 ($[M+H]^+$, 6), 323 ($[M-OBn]^+$, 100), 309 (37), 265 (47); HRMS (FAB) calcd for $C_{25}H_{35}O_6$ [M+H] 431.2428, found 431.2430. Anal. calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.68; H, 8.04.

3.1.37. Alcohol 41. 10% Palladium-on-charcoal (10 mg) was suspended in EtOH (3 mL). The mixture was degassed and then filled with hydrogen gas three times and was stirred for 10 min at room temperature. A solution of the oxetane **52** (27 mg, 0.063 mmol) in EtOH (2 mL) was added and the resulting mixture was stirred for 30 min under hydrogen (balloon). The mixture was filtered and the filtrate was concentrated under vacuum. The residue was eluted through a short pad of silica gel (hexanes–Et_2O, 2:1) to give alcohol **41** as a colorless oil (20 mg, 93%): $[\alpha]_D^{20} = -25.2$ (c 0.7, $CHCl_3$); R_f 0.30 (hexanes–Et_2O, 1:2); IR (thin film) 1378 cm^{-1}; ^1H NMR δ 1.35 (s, 3H), 1.38 (s, 3H), 1.28 (s, 3H), 1.53 (s, 3H), 1.77 (d, $J=3$ Hz, 2H), 1.95 (dd, $J=5.4$, 14.4 Hz, 1H), 2.09 (m, 2H), 2.34 (dd, $J=5.4$, 9.3 Hz, 1H), 2.55 (brs, 1H), 3.94 (m, 4H), 4.10 (t, $J=3$ Hz, 1H), 4.43 (dd, $J=6.3$, 5.25 Hz, 2H), 4.74 (dd, $J=6$, 8.7 Hz, 1H); ^{13}C NMR δ 25.9, 26.5, 27.3, 27.5, 28.9, 32.8, 34.3, 38.1, 43.6, 64.6, 64.9, 72.5, 78.8, 78.9, 84.1, 88.3, 106.8, 113.3; MS (FAB) *m/z* (relative intensity) 341 ($[M+H]^+$, 3), 307 (70), 289 (24), 154 (100); HRMS (FAB) calcd for $C_{18}H_{29}O_6$ [M+H] 341.1958, found 341.1916.

3.1.38. Acetate 6. Acetic anhydride (0.1 mL, excess) and DMAP (2 mg) were added to a stirring solution of the alcohol **41** (19 mg, 0.056 mmol) in pyridine (5 mL). The resulting mixture was heated under reflux for 9 h and quenched with saturated NH_4Cl. The aqueous phase was extracted with Et_2O (3×). The combined organic layers were dried ($MgSO_4$) and filtered. Concentration of the filtrate gave a crude oil which was purified by flash chromatography (hexanes–Et_2O, 2:1 to 1:2) to give acetate **6** as a white solid (10 mg, 56% based on starting material **41** consumed) and unreacted alcohol **41** (3 mg).

Data for acetate **6**: mp 131–132 °C; $[\alpha]_D^{20} = +6.1$ (*c* 0.25, $CHCl_3$); R_f 0.50 (hexanes–Et_2O, 1:2); IR (thin film) 3742, 2934, 1697, 1077 cm^{-1}; ^1H NMR δ 1.27 (s, 3H), 1.35 (s, 3H), 1.50 (s, 3H), 1.63 (s, 3H), 1.73 (m, 2H), 2.13 (s, 3H), 2.19 (m, 1H), 2.29 (dd, $J=9$, 14.7 Hz, 1H), 2.75 (dd, $J=2.7$, 13.5 Hz, 1H), 3.86 (m, 1H), 3.99 (m, 3H), 4.11 (t, $J=3$ Hz, 1H), 4.76 (dd, $J=8.4$, 10.8 Hz, 2H), 4.82 (dd, $J=5.1$, 9.3 Hz, 1H); ^{13}C NMR δ 21.3, 25.5, 26.9, 27.2, 27.3, 29.7, 30.7, 34.7, 36.5, 38.6, 40.9, 64.3, 64.9, 78.9, 79.8, 80.5, 82.0, 84.5, 107.0, 112.3, 169.8; MS (FAB) *m/z* (relative intensity) 383 ($[M+H]^+$, 5), 307 ($[M-C_2H_4O_2-CH_3]^+$, 100); HRMS (FAB) calcd for $C_{20}H_{31}O_7$ [M+H] 383.2064, found 383.2060. Anal. calcd for $C_{20}H_{30}O_6$: C, 62.81; H, 7.91. Found: C, 62.86; H, 8.00.

Acknowledgements

Financial support from CUHK Direct Grant (account no. 2060203) is gratefully acknowledged.

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Tetrahedron 60 (2004) 9199–9204
Tetrahedron

An expedient synthesis of spiroketals: model studies for the calyculin C_{16}–C_{25} fragment

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Received 28 April 2004; revised 30 June 2004; accepted 23 July 2004

Available online 27 August 2004

Abstract—A new short strategy to prepare the spiroketal fragment of calyculins is presented. A novel Seyferth–Gilbert type homologation of hindered lactols to the corresponding alkynes has been achieved for the first time. The spirocyclization was achieved efficiently via a DIHMA (double intramolecular hetero-Michael addition) process of this hindered ynone. The spirocyclization rate is not dependent on the stereochemistry of the alkoxy substituent in the oxolane ring.

1. Introduction

The 1,6-dioxaspiro[4.5]decane ring system is a common motif, occurring in nearly 100 natural products.[1] It is noteworthy that in most of these structures, the configuration of the stereogenic carbon atom is dictated by double anomeric effect, placing the oxygen in the oxolane ring axial with respect to the oxane ring (Fig. 1).[2] Due to the wide occurrence of such structures, a rapid and reliable entry into the spirocyclic structure is highly desirable. This was of special interest to us because of our ongoing efforts towards the total synthesis of calyculin C, a potent protein phosphatase inhibitor.[3,4] In this paper we report our recent results on a highly convergent strategy to achieve this goal.[5]

Our retrosynthetic strategy for the model spiroketal is based on a convergent strategy (Scheme 1). The actual spiroketal formation is based on the DIHMA (double intramolecular hetero-Michael addition) process of a suitably derived ynone.[6] Thus, our penultimate goal became the ynone **13**, which would be available through a nucleophilic addition of the alkyne **8** onto the Weinreb amide **12**, in turn available via Evans aldol methodology from propionyloxazolidinone **9** and benzyloxypropanal. The alkyne was envisioned to arise through a Seyferth–Gilbert-type homologation[7] of the aldehyde (or lactol) corresponding to lactone **4**.

Although seemingly well precedented, several questions remained to be answered. First, the electrophilic end of the ynone **13a**,**b** is highly sterically crowded, which might affect the cyclization rate. Secondly, the formation of the highly substituted alkyne **8** is not trivial. Thirdly, the existence of the requisite alkoxy group in the oxolane ring might affect the cyclization rate and/or the stability of the ensuing spirocycle. To shed light on this latter question, we decided to enter the spirocyclization with enantiopure **12** and racemic **8**. Rate differences between the diastereomers would thus become evident experimentally.

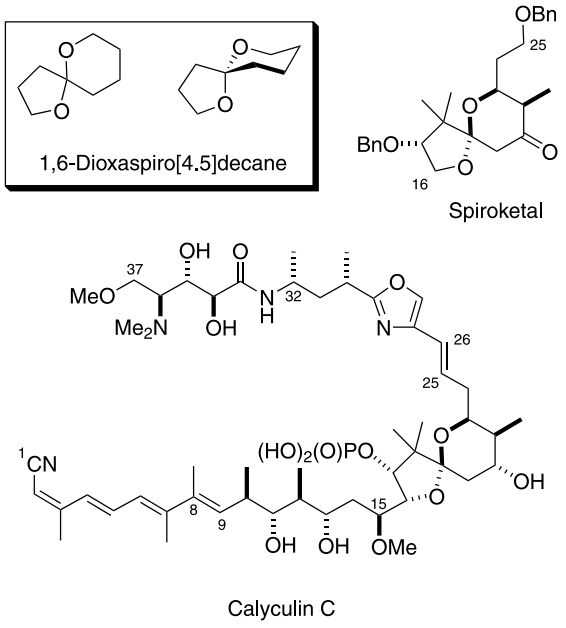

Figure 1. Spiroketal fragment of calyculin C.

Keywords: Enantioselectivity; Natural product; Spiroketals.
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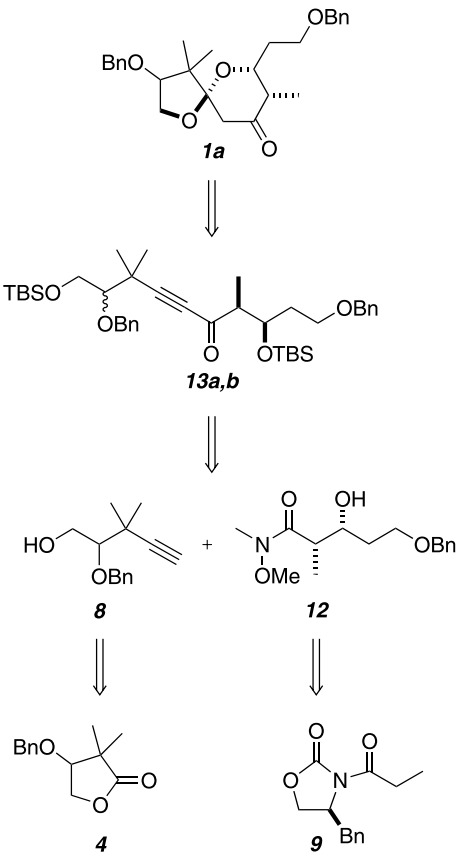
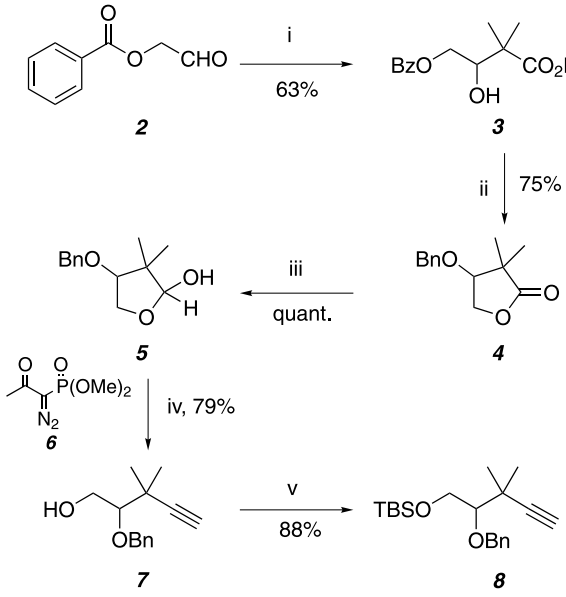
doi:10.1016/j.tet.2004.07.059



Scheme 1. Retrosynthetic analysis of spiroketal **1a**.

2. Results

The alkyne **8** was prepared as shown in Scheme 2, beginning with an addition of the ester enolate of ethyl isobutyrate to 2-benzoyloxyacetaldehyde **2** affording the hydroxy ester **3** in 63% yield. Protection of the hydroxy group (NaH, BnCl, 75%) and DIBAL-H reduction of the lactone gave lactol **5** in near quantitative yield, ready for the Seyferth–Gilbert type homologation to the alkyne without further purification. If the initial ester aldol reaction was allowed to warm to higher temperatures, the intermediate alkoxide corresponding to **3** further reacted, by intramolecular benzoate transfer and ring closure, to give the hydroxy lactone directly. Quenching the reaction mixture with benzyl chloride gave **4** in a one-pot operation, however, with yields typically below 25%. We therefore decided to rely on the more reproducible two step operation.

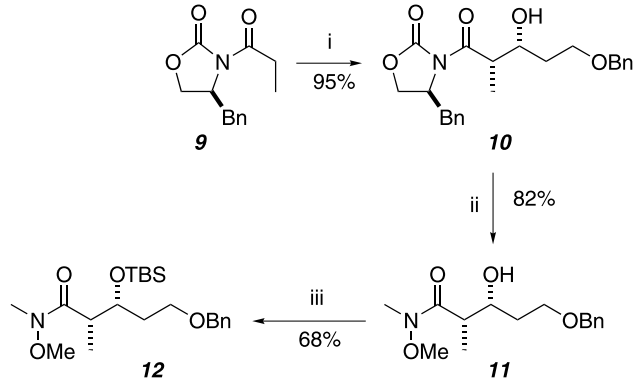


Scheme 2. Reagents: (i) LDA, Me_2CHCO_2Et, THF, −78 °C, then **2**; (ii) NaH, BnCl, DMF, THF, 0 °C; (iii) DIBAL-H, PhMe, −78 °C; (iv) **6**, K_2CO_3, MeOH, 36 °C; (v) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

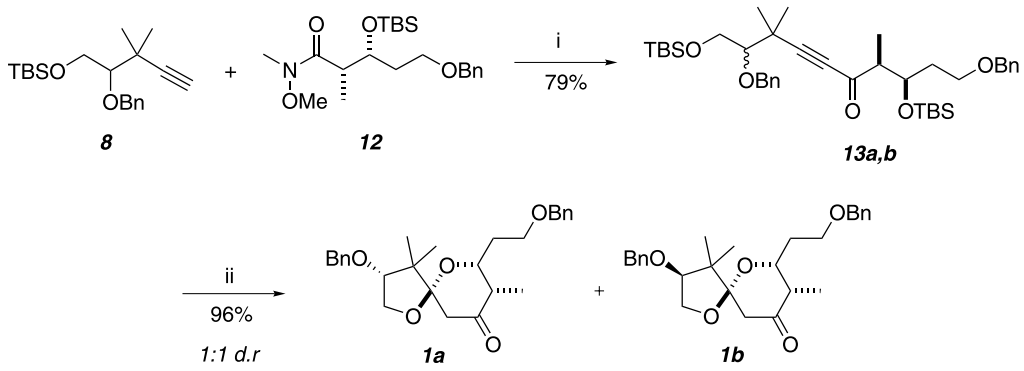
Ohira's reagent **6** is a mild alternative to the original Seyferth–Gilbert homologation, widely used to transform an aldehyde to the corresponding alkyne.[8] In our case, the lactol **5** was used as the aldehyde surrogate.[9] The relative sluggishness of the lactol for ring-chain tautomerism was evident experimentally: Ohira's reagent **6** had to be added slowly (in five ca. 50 mol% portions over 5 days), and the reaction temperature had to be kept low (between 36 and 44 °C) in order to achieve acceptable yields reproducibly (60–79%, based on recovered starting material). Higher reaction temperatures or faster addition of reagent **6** and the base led to decomposed products. This successful procedure represents the first successful example of using a hindered lactol in the Seyferth–Gilbert homologation. Finally, the secondary hydroxyl was protected (TBSOTf, lutidine, 88%) to give the alkyne **8** ready for coupling.

The enantiopure fragment, Weinreb amide **12**, was prepared using the diastereoselective Evans *syn*-aldol reaction from the known propionyloxazolidinone **9** and 3-benzyloxypropionaldehyde (Scheme 3). Thus, reaction of the dibutylboron *Z*-enolate of **9** and the aldehyde gave the desired **10** in 95% yield. Conversion of **10** to the Weinreb amide **11** (82%), followed by TBS protection under standard conditions[10] gave the coupling partner **12** (68%).

Fragments **8** and **12** were coupled using the Weinreb–Nahm procedure to produce alkynone **13a**,**b**.[11] Spirocyclization with the DIHMA procedure was then attempted using a stepwise protocol.[11] In the first step, the TBS protections were cleavage by CSA in MeOH. Some spirocyclization occurred already at this stage (TLC). Thus, the solvent was removed and replaced with benzene, and addition of *p*-TsOH took the spirocyclization to completion. Because



Scheme 3. Reagents: (i) **9**, Bu_2BOTf, Et_3N, CH_2Cl_2; then $BnOCH_2CH_2$-CHO, −77 °C; (ii) MeOMeNH·HCl, $AlMe_3$, THF, 0 °C; (iii) TBSCl, Im, DMF, 0 °C.



Scheme 4. Coupling of **8** and **12** and spirocyclization. Reagents: (i) BuLi, **8**, then **12**, THF −78 °C; (ii) CSA, MeOH, then *p*-TsOH, PhH, rt.

the alkyne **8** was not optically pure, the two diastereoisomers **1a** and **1b** were observed in a 1:1 diastereomeric ratio (Scheme 4). This supports the conclusion that the cyclization rate is not critically dependent on the existence of a directing alkoxy group in the oxolane ring.

3. Conclusions

We have presented a new strategy to prepare the spiroketal fragment of calyculins. A novel Seyferth–Gilbert type homologation of hindered lactols to the corresponding alkynes has been achieved for the first time. The spirocyclization was achieved efficiently via a DIHMA (double intramolecular hetero-Michael addition) process. The spirocyclization rate is not dependent on the stereochemistry of the alkoxy substituents in the oxolane ring. Application of this protocol in the total synthesis of calyculin C will be reported in due course.

4. Experimental

4.1. General

All reactions were conducted under a positive pressure of argon. THF was distilled prior to use from sodium-benzophenone, MeOH from $Mg(OMe)_2$ and toluene from sodium. Other solvents were pro analysis grade.

Melting points were determined on a Gallenkamp melting point apparatus MFB-595 and are uncorrected. TLC was conducted on Merck 0.25 mm silica gel 60 F plates and samples were visualized with UV light, anisaldehyde, PMA or ninhydrin staining. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh) as a stationary phase. HPLC was performed with Waters 501 pump, Waters 486 tunable absorbance detector, Waters 746 data module using the following columns: Shandon Hypersil Silica Column with Waters Guard-Pak™ precolumn fitted with Resolve™ silica inserts for normal phase chromatography and Daicel Chiralcel OD 25 cm×0.46 cm with Daicel Chiracel OD 5 cm×0.46 cm precolumn for chiral chromatography. Optical rotations were measured at 20 °C on a Perkin–Elmer polarimeter 343. IR spectra were measured with Perkin–Elmer Spectrum One.

Elemental analyses were performed with Perkin–Elmer Elemental Analyzer 2400 CHN. HRMS spectra were measured with Jeol JMS-DX 303 and Micromass LCT. NMR spectra were measured with Bruker AMX 400 (^{1}H 400.13 MHz, ^{13}C 100.61 MHz).

4.1.1. 3-(Ethoxycarbonyl)-2-hydroxy-3-methylbutyl benzoate 3. Diisopropylamine (2.82 mL, 20.1 mmol, 110 mol%) was dissolved in freshly distilled THF (20 mL) at 0 °C. BuLi (2.3 M, 8.7 mL, 20.1 mmol, 110 mol%) was added during 10 min and the light yellow solution was cooled to −78 °C. Ethyl isobutyrate (2.69 mL, 20.1 mmol, 110 mol%) was added dropwise during 5 min. The light yellow reaction mixture was stirred 1.5 h at −78 °C and aldehyde **2** (3.0 g, 18.3 mmol, 100 mol%) in THF was added dropwise over 20 min. After 2 h stirring at −78 °C, the reaction was quenched with sat. NH_4Cl (20 mL) and allowed to warm up to rt. The aqueous phase was washed three times with 30 mL of Et_2O, the combined organic phases were washed once with brine (20 mL) and dried with Na_2SO_4. The product was purified by flash column chromatography (30% EtOAc/hexane) affording **3** 3.25 g (63%). R_f (50% EtOAc/hexane, UV/PMA)=0.49; IR (ν_{max}, film) 1141, 1366, 1386, 1581, 1598, 1737, 3565 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J=7.1 Hz, 3H), 1.29 (s, 3H), 1.32 (s, 3H), 3.15 (d, J=6.6 Hz, 1H), 4.05 (m, 1H), 4.14 (dd, J=7.1, 4.9 Hz, 2H), 4.37 (dd, J=7.3, 11.7 Hz, 1H), 4.48 (dd, J=2.9, 11.7 Hz, 1H), 7.44 (m, 2H), 7.57 (m, 1H), 8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.9, 22.6, 45.4, 61.0, 66.2, 75.1, 128.4, 128.9, 129.7, 133.1, 166.7, 176.8; HRMS (TOF MS EI$^+$) calcd for $C_{15}H_{21}O_5Na$ 303.1208, found 303.1221.

4.1.2. 4-(Benzyloxy)-dihydro-3,3-dimethylfuran-2(3*H*)-one 4. NaH (60% oil dispersion, 476 mg, 11.9 mmol, 110 mol%) in dry DMF was cooled to 0 °C. Ester **3** (3.03 g, 10.8 mmol, 100 mol%) in THF (6 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 5 min at 0 °C and 15 min at rt. BnCl (1.37 mL, 11.9 mmol, 110 mol%) was added dropwise and the reaction was stirred for 4 h at rt. After quenching at 0 °C with sat. NH_4Cl, the aqueous phase was extracted three times with 25 mL of Et_2O, the combined organic phases were washed once with brine (50 mL) and dried with $MgSO_4$. After flash column chromatography (15% EtOAc/hexane) lactone **4** was isolated (1.77 g, 75%). R_f (30% EtOAc/hexane, UV/PMA)=0.27; IR (ν_{max}, film) 1773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.28 (s, 3H), 3.91 (dd, J=4.0, 5.1 Hz, 1H), 4.15 (dd, J=4.0, 10.1 Hz, 1H), 4.31 (dd, J=5.1, 10.1 Hz, 1H), 4.59 (d, J_{AB}=

11.1 Hz, 2H), 7.30–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 23.3, 42.9, 68.9, 72.1, 81.8, 127.5, 128.0, 128.5, 137.4, 180.6; HRMS (EI^+) calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1092.

4.1.3. 4-(Benzyloxy)-tetrahydro-3,3-dimethylfuran-2-ol 5. Lactone **4** (0.273 g, 1.24 mmol, 100 mol%) in toluene (12 mL) was cooled to −78 °C. DIBAL-H (1 M in toluene, 2.11 mL, 2.11 mmol, 170 mol%) was added during 5 min. After 14 min, the reaction was quenched by adding MeOH (0.5 mL) and allowed to warm up to rt. The solution was partitioned between 20 mL of 1 M HCl and 20 mL of EtOAc, the phases were separated and the aqueous phase was extracted three times with 15 mL of EtOAc. The combined organic phases were washed once with 10 mL of brine, dried with $MgSO_4$ and evaporated affording crude **5** 0.267 g, which was used without purification in the next reaction. R_f (50% EtOAc/hexane, UV/PMA)=0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.24 (s, 3H), 3.58 (d, J=12.1 Hz, 1H), 3.61 (d, J=3.7 Hz, 1H), 4.05 (dd, J=10.5, 3.8 Hz, 1H), 4.23 (d, J=10.2 Hz, 1H), 4.54 (d, J_{AB}=11.8 Hz, 2H), 4.81 (d, J=11.9 Hz, 1H), 7.29–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 24.0, 46.6, 70.9, 72.0, 85.3, 105.3, 127.6, 127.9, 128.5, 137.4; HRMS (TOF MS EI^+) calcd for $C_{13}H_{18}O_3Na$ 245.1154, found 245.1180.

4.1.4. 2-Benzyloxy-3,3-dimethylpent-4-yn-1-ol 7. Lactol **5** (0.214 g, 0.963 mmol, 100 mol%) was diluted in 10 mL of dry MeOH and dimethyl 1-diazo-2-oxopropyl phosphonate **6** (0.370 g, 1.925 mmol, 200 mol%) and K_2CO_3 (0.266 g, 1.925 mmol, 200 mol%) were added. The reaction was warmed to 36 °C and allowed to stir for 5 days, during which more phosphonate **6** (0.092 g, 0.481 mmol, 50 mol%) and K_2CO_3 (0.067 g, 0.481 mmol, 50 mol%) in 0.5 mL of dry MeOH were added five times once a day. The blue–green reaction mixture was evaporated to dryness and dissolved in 30 mL of 1:1 mixture of Et_2O and H_2O. The phases were separated and the aqueous one was extracted four times with 10 mL of Et_2O and dried with $MgSO_4$. Crude **7** was purified by column chromatography (15% EtOAc/hexane) affording 0.122 g (58%) of a slightly yellow oil. R_f (50% EtOAc/Hex, UV/anisaldehyde)=0.50; IR (ν_{max}, film) 1096, 1382, 2254, 3306, 3690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.30 (s, 3H), 1.86 (dd, J=7.3, 5.3 Hz, 1H), 2.19 (s, 1H), 3.40 (dd, J=6.6, 3.8 Hz, 1H), 3.77 (ddd, J=11.9, 6.6, 5.3 Hz, 1H), 3.92 (ddd, J=11.7, 7.5, 3.9 Hz, 1H), 4.75 (d, J_{AB}=11.9 Hz, 2H), 7.29–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.7, 34.7, 62.6, 69.8, 74.7, 85.6, 89.7, 127.8, 127.9, 128.5, 138.3; HRMS (TOF MS EI^+) calcd for $C_{14}H_{18}O_2NaSi$ 241.1204, found 241.1216.

4.1.5. (2-(Benzyloxy)-3,3-dimethylpent-4-ynyloxy)-*tert*-butyldimethylsilane 8. The alcohol **7** (0.120 g, 0.550 mmol, 100 mol%) was dissolved in dry CH_2Cl_2 (6 mL) and cooled to 0 °C. 2,6-Lutidine (0.256 mL, 2.2 mmol, 400 mol%) was added and the reaction mixture was allowed to stir for 36 min before TBSOTf (0.253 mL, 1.1 mmol, 200 mol%) was added. After 12 min the reaction was quenched with 3 mL of sat. K_2CO_3. The mixture was partitioned between water (10 mL) and Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted three times with 10 mL of Et_2O and the combined organic phase dried with Na_2SO_4. Crude **8** was purified by column chromatography (15% EtOAc/hexane) affording pure product (0.161 g, 88%) as a slightly yellow oil. R_f (50% EtOAc/hexane, UV/PMA)=0.67; IR (ν_{max}, film) 839, 1096, 1257, 1383, 2254, 3306, 3690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.92 (s, 9H), 1.20 (s, 3H), 1.27 (s, 3H), 2.13 (s, 1H), 3.36 (dd, J=7.3, 2.7 Hz, 1H), 3.80 (dd, J=10.8, 7.3 Hz, 1H), 4.10 (dd, J=10.8, 2.7 Hz, 1H), 4.78 (d, J_{AB}=11.4 Hz, 2H), 7.24–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −5.3, 18.2, 24.4, 25.9, 27.1, 34.7, 65.4, 69.1, 74.5, 86.1, 90.0, 127.3, 127.8, 128.2, 139.0; HRMS (TOF MS EI^+) calcd for $C_{20}H_{32}O_2NaSi$ 355.2069, found 355.2110.

4.1.6. (*S*)-4-Benzyl-3-((2*S*,3*R*)-5-benzyloxy-3-hydroxy-2-methylpentanoyl)-2-oxazolidinone 10. (*S*)-4-Benzyl-3-propionyl-2-oxazolidinone **9** was dissolved in 100 mL of dry CH_2Cl_2 and cooled to 0 °C before dibutylboron triflate (1 M in CH_2Cl_2, 41.2 mL, 41.2 mmol, 120 mol%) was added dropwise keeping the internal temperature below 2 °C. The color changed to dark red-brown but when Et_3N (6.23 mL, 44.7 mmol, 130 mol%) was added (T ≤ 2 °C) it turned to yellow. After 40 min, the reaction mixture was cooled to −77 °C and 3-benzyloxy-propionaldehyde (6.2 g, 37.8 mmol, 110 mol%) dissolved in 10 mL CH_2Cl_2 was added slowly (45 min) keeping the internal temperature stable. Stirring was continued for a further 3 h at −77 °C and then for 30 min at 0 °C. Phosphate buffer (80 mL, pH 7.0) and methanol (60 mL) were added, and the mixture was cooled to −10 °C before slow (15 min) addition of 120 mL of (1:1) H_2O_2 (30%) and MeOH. The mixture was then stirred for 30 min at 0 °C before organic solvents were evaporated, Et_2O was added and reaction was cooled to 0 °C. Sat. $Na_2S_2O_3$ (120 mL) was added slowly (30 min) and the phases were separated. The aqueous phase was extracted three times with 80 mL Et_2O and the combined organic phases were washed once with 80 mL of sat. $NaHCO_3$ and 50 mL of brine and dried with Na_2SO_4. The crude product was purified by flash column chromatography (25% EtOAc/Hex) affording pure **10** (9.7 g, 71%). R_f (50% EtOAc/Hex, UV/PMA)=0.31; $[\alpha]_D^{20}$=+44.7 (*c* 1.0; $CHCl_3$); IR (ν_{max}, film) 1111, 1694, 1780, 3480 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J=7.0 Hz, 3H), 1.74 (m, 1H), 1.89 (m, 1H), 2.78 (dd, J=13.2, 9.5 Hz, 1H), 3.26 (dd, J=13.5, 3.3 Hz, 1H), 3.29 (d, J=2.6 Hz, 1H), 3.69 (m, 2H), 3.82 (dq, J=7.0, 3.7 Hz, 1H), 4.18 (m, 1H), 4.19 (m, 2H), 4.52 (s, 2H), 4.68 (m, 1H), 7.34–7.19 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 33.7, 37.8, 42.6, 55.2, 66.1, 68.4, 70.4, 73.3, 127.4, 127.7, 128.4, 129.0, 129.4, 135.1, 138.0, 153.1, 176.7; HRMS (EI^+) calcd for $C_{23}H_{27}NO_5$ 397.1889, found 397.1880.

4.1.7. (2*S*,3*R*)-5-(Benzyloxy)-3-hydroxy-*N*-methoxy-*N*,2-dimethylpentanamide 11. A 25 mL 2-neck flask was charged with *N*,*O*-Dimethyl hydroxylamine hydrochloride (1.08 g, 11.1 mmol, 220 mol%) and 4 mL THF. The suspension was cooled to −10 °C in a NaCl/ice-bath and $AlMe_3$ (5.3 mL, 10.6 mmol, 210 mol%) was added over 5 min. After 12 min, the cooling bath was removed and the reaction mixture was allowed to stir for 1 h at rt before it was cooled again to −10 °C. Oxazolidinone **10** (2.0 g, 5.0 mmol, 100 mol%) dissolved in a mixture (4:5) of CH_2Cl_2 (2.9 mL) and THF (3.5 mL) was slowly added.

The mixture was stirred for 1 h at 0 °C and then poured into a pre-cooled 0 °C mixture of aqueous HCl [0.5 M] (16 mL) and CH_2Cl_2 (16 mL). This was stirred for 1 h 15 min at 0 °C and the phases were separated. The aqueous phase was extracted three times with 60 mL of CH_2Cl_2 and the combined organic phases were washed once with 50 mL of brine and dried with $MgSO_4$. The crude product was purified by step gradient column chromatography (1:3, 2:5, 1:1 and 3:5 EtOAc / hexane in 900 mL fractions) affording **11** as a light yellow oil (1.16 g, 82%). R_f (50% EtOAc/Hex, UV/PMA)=0.12; $[\alpha]_D^{20}=+11.4$ (*c* 1.0; $CHCl_3$); IR (ν_{max}, film) 1102, 1637, 3468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, $J=7.3$ Hz, 3H), 1.89–1.66 (m, 2H), 2.93 (br s, 1H), 3.18 (s, 3H), 3.63–3.73 (m, 2H), 3.66 (s, 3H), 3.92 (s, 1H), 4.05 (m, 1H), 4.52 (s, 2H), 7.26–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 31.9, 34.0, 39.5, 61.5, 68.3, 70.3, 73.2, 127.6, 127.6, 128.4, 138.2, 177.8; HRMS (TOF MS EI^+) calcd for $C_{15}H_{23}NO_4Na$ 304.1525, found 304.1550.

4.1.8. (2*S*,3*R*)-5-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*,2-dimethylpentanamide 12. Alcohol **11** (0.50 g, 1.78 mmol, 100 mol%) and imidazole (0.61 g, 8.89 mmol, 500 mol%) were dissolved in 5 mL of dry DMF and cooled to 0 °C. TBSCl (0.54 g, 3.55 mmol, 200 mol%) in 5 mL DMF was added dropwise over 10 min to the reaction after which the reaction was allowed warm up to rt. After stirring for 43 h, the reaction was quenched with 20 mL of EtOAc and 20 mL of brine and stirred for 30 min. The phases were separated and the aqueous phase was washed three times with 20 mL of Et_2O. The combined organic phases were dried over $MgSO_4$. The crude product was purified by column chromatography (5% MTBE/Hex) affording the product **12** (0.48 g, 68%). R_f (50% EtOAc/Hex, UV/PMA)=0.46; $[\alpha]_D^{20}=-2.4$ (c 1.0; $CHCl_3$); IR (ν_{max}, film) 836, 1103, 1663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.13 (d, $J=$ 7.0 Hz, 3H), 1.82–1.88 (m, 2H), 2.99 (br s, 1H), 3.13 (s, 3H), 3.49–3.56 (m, 2H), 3.59 (s, 3H), 4.03 (td, $J=8.0$, 5.1 Hz, 1H), 4.47 (d, $J_{AB}=12.1$ Hz, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, −4.4, 14.5, 18.1, 25.9, 32.1, 35.4, 41.2, 61.2, 66.5, 71.3, 72.9, 127.4, 127.7, 128.3, 138.6, 176.3; HRMS (EI^+) calcd for $C_{21}H_{37}NO_4Si$ 395.2492, found 395.2512.

4.1.9. (3*R*,4*S*,9*R*/*S*)-1,9-Bis(benzyloxy)-3,10-di(*tert*-butylsilyloxy)-4,8,8-trimethyldec-6-yn-5-one 13a,b. The alkyne **8** (0.057 g, 0.172 mmol, 200 mol%) was dissolved in 1.7 mL of dry THF and cooled to −78 °C. BuLi (2.27 M, 83 µl, 0.189 mmol, 220 mol%) was added and the reaction was allowed to stir for 1 h before the Weinreb amide **12** (0.034 g, 0.086 mmol, 100 mol%) in 0.9 mL of dry THF was added. After 50 min, the reaction mixture was allowed to warm up to rt and after another 2 h 15 min it was quenched with 5 mL of H_2O. Et_2O (10 mL), H_2O (5 mL) and brine (5 mL) were added and the phases were separated. The aqueous phase was extracted three times with 10 mL of Et_2O and the combined organic phases were dried with $MgSO_4$. The crude product was purified by step gradient chromatography (150 mL 5% EtOAc/hexane, 150 mL 10% EtOAc/hexane) affording **13a,b** (0.045 g, 79%). R_f (50% EtOAc/Hex, UV/PMA)=0.66; IR (ν_{max}, film) 838, 1095, 1257, 1669, 2208, 2247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.84 (s, 9H), 0.91 (s, 9H), 1.13 (d, $J=6.9$ Hz, 3H), 1.23 (s, 3H), 1.28 (s, 3H), 1.76–1.92 (m, $J=14.0$, 6.4 Hz, 2H), 2.53–2.60 (m, $J=13.9$, 6.9 Hz, 1H), 3.38 (dd, $J=7.1$, 3.0 Hz, 1H), 3.49 (t, $J=6.5$ Hz, 2H), 3.78 (dd, $J=10.8$, 7.1 Hz, 1H), 4.00 (dd, $J=10.8$, 3.0 Hz, 1H), 4.75 (d, $J_{AB}=11.5$ Hz, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −5.4, −4.5, −4.4, 9.5, 9.6, 18.1, 18.2, 23.9, 24.0, 25.8, 25.9, 26.1, 35.4, 35.7, 53.5, 65.1, 65.1, 66.7, 70.0, 73.0, 74.5, 81.3, 85.5, 85.5, 99.3, 127.4, 127.4, 127.5, 127.7, 127.7, 128.2, 128.3, 138.4, 138.7, 138.8, 190.2; HRMS (TOF MS EI^+) calcd for $C_{39}H_{62}O_5NaSi_2$ 689.4034, found 689.4025.

4.1.10. (7*R*,8*S*)-3-Benzyloxy-7-(2-benzyloxy-ethyl)-4,4,8-trimethyl-1,6-dioxa-spiro[4.5]decan-9-one 1a and 1b. The mixture of ynones **13a,b** (13 mg, 19.5 µmol, 100 mol%) was dissolved in 0.5 mL of dry MeOH, and camphor sulphonic acid (0.7 mg, 3.0 µmol, 15 mol%) was added. The reaction was allowed to stir at rt for 2 h 20 min before the solvent was evaporated. The residue was dissolved in 1 mL benzene and the reaction was stirred for 3 h 30 min, after which time *p*-TsOH (1.4 mg, 7.4 µmol, 38 mol%) was added. Stirring was continued for another 15 h, and the reaction was quenched by adding TEA (0.02 mL) followed by 1 mL of sat. $NaHCO_3$. The phases were separated and the aqueous one was extracted three times with 3 mL of toluene. The combined organic phases were extracted once with 5 mL of brine and dried with $MgSO_4$. The crude product was first purified by step gradient column chromatography (5, 10, 15 and 20% EtOAc/hexane in 50 mL portions) affording the two diastereomers **1a** and **1b** (8.2 mg, 96%). The diastereomers were separated with HPLC chromatography, which afforded (4.1 mg each).

(Fraction 1) R_f (50% EtOAc/Hex, UV/PMA)=0.59; R_t (Shandon Hypersil 5µ column, EtOAc/hexane, 1:20, flow rate 1.0 mL/min, $\lambda=254$ nm)=30.52 min; $[\alpha]_D^{20}=+105$ (*c* 0.1; $CHCl_3$); IR (ν_{max}, film) 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.07 (d, $J=7.0$ Hz, 3H), 1.60 (s, 3H), 1.64–1.72 (m, 1H), 1.81–1.90 (m, 1H), 2.33 (qd, $J=7.0$, 2.6 Hz, 1H), 2.45 (dd, $J_{AB}=14.8$ Hz, 2H), 3.46–3.54 (m, 2H), 3.59 (dd, $J=8.8$, 6.7 Hz, 1H), 3.59 (dd, $J=8.7$, 7.8 Hz, 1H), 4.12 (dd, $J=7.7$, 6.7 Hz, 1H), 4.24 (td, $J=9.8$, 3.0 Hz, 1H), 4.47 (dd, $J_{AB}=11.9$ Hz, 2H), 4.49 (dd, $J_{AB}=11.8$ Hz, 2H), 7.28–7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 17.2, 20.3, 29.7, 40.8, 47.6, 66.9, 67.2, 69.3, 72.9, 73.1, 84.5, 110.0, 127.4, 127.7, 127.7, 128.4, 128.4, 138.2, 138.4, 209.9; HRMS (TOF MS EI^+) calcd for $C_{27}H_{34}O_5Na$ 461.2304, found 461.2318.

(Fraction 2) R_f (50% EtOAc/Hex, UV/PMA)=0.59; R_t (Shandon Hypersil 5µ column, EtOAc/hexane, 1:20, flow rate 1.0 mL/min, $\lambda=254$ nm)=35.69 min; $[\alpha]_D^{20}=+90$ (*c* 0.1; $CHCl_3$); IR (ν_{max}, film) 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.11 (d, $J=7.1$ Hz, 3H), 1.25 (s, 3H), 1.59–1.67 (m, 1H), 1.85–1.94 (m, 1H), 2.34 (qd, $J=7.2$, 2.0 Hz, 1H), 2.42 (dd, $J_{AB}=14.5$ Hz, 2H), 3.54–3.67 (m, 2H), 3.61 (dd, $J=6.4$, 3.1 Hz, 1H), 3.67 (dd, $J=9.7$, 3.2 Hz, 1H), 4.16 (dd, $J=9.7$, 6.4 Hz, 1H), 4.28 (td, $J=10.6$, 2.5 Hz, 1H), 4.30 (dd, $J_{AB}=12.1$ Hz, 2H), 4.49 (dd, $J_{AB}=12.1$ Hz, 2H), 7.23–7.36 (m, 10H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 10.7, 16.6, 24.5, 29.7, 41.1, 49.0, 66.6, 67.0, 71.3, 72.5, 72.8, 85.4, 108.8, 127.1, 127.4, 127.5, 127.5, 128.3, 128.3, 128.4, 138.6, 138.6, 210.4; HRMS (TOF MS EI^+) calcd for $C_{27}H_{34}O_5Na$ 461.2304, found 461.2317.

Acknowledgements

Funding and financial support provided by the Finnish Academy, the Ministry of Education, Jenny and Antti Wihuri Foundation and Emil Aaltonen Foundation are gratefully acknowledged. We would like to thank Mr. Y. Masuda for the valuable work with the lactone fragment and Päivi Joensuu at the University of Oulu for providing the high resolution mass spectroscopy data.

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Alkyl and dialkylammonium tetrafluoroborate catalyzed *cis–trans* isomerization of 1,3,5-trimethyl-1,3,5-triphenylcyclotrisiloxane

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Received 27 April 2004; revised 9 July 2004; accepted 23 July 2004

Available online 27 August 2004

Abstract—Alkyl and dialkylammonium tetrafluoroborate promoted *cis–trans* isomerization of 1,3,5-trimethyl-1,3,5-triphenylcyclotrisiloxane (**1**) in DMSO-d_6 were studied. The isomerization equilibrium constant K are within the range of 3.74–3.30 from 22 to 47 °C. Thermodynamic parameters of ΔH° and ΔS° for the isomerization were −0.95 kcal/mol and −0.59 cal/mol-K respectively. The isomerization rate is first order in [*cis*-**1**] and second order in [$R_nNH_{4-n}BF_4$]. Both components of $R_nNH_{4-n}^+$ and BF_4^- are essential for the catalytic *cis–trans* isomerization. The catalytic strength follows the decreasing order of $^+H_3N(CH_2)_6NH_3^+ > n\text{-}C_8H_{17}NH_3^+ > n\text{-}C_{16}H_{33}NH_3^+ > Me_3CNH_3^+ > PhCH_2NH_3^+ > Et_2NH_2^+ \gg Ph_2CHNH_3^+$, Et_3NH^+. Inversion region was observed in the plot of $\ln(k_f/T)$ versus $(1/T)$ with the ceiling located at around 38 °C. The positive activation enthalpy of 9 kcal/mol was estimated at 22–32 °C. The activation enthalpy turns to be slightly negative at $T > 38$ °C.

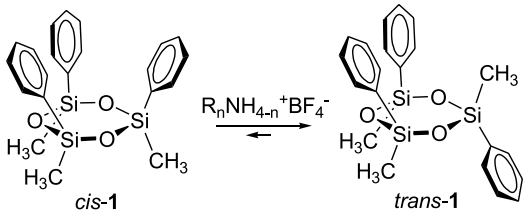
1. Introduction

Because of their special physical properties and chemical stability, polysiloxanes have been widely used in electrical, textile, plastic, paper, automobile, with minor amounts going into food and medical products.[1] Among the synthetic approaches for polysiloxanes, cationic and anionic ring opening polymerization of cyclic siloxanes attract many research teams to study.[2] In particular, the ring-opening process has been considered as a key step to control the kinetics and mechanisms of the polymerization.[3] Many research results suggested that chelation of metal cations by the siloxane moieties would importantly affect the polymerization process.[4] Explorations of the interactions between siloxane monomers and metal cations or R_4N^+ ions have been reported.[5] However, systematic studies on the interactions between cyclic siloxanes and $R_nNH_{4-n}^+$ are rare. As our continuous interest in hydrogen bonding interactions as well as cation binding,[6] we have recently investigated the possibility of using hydrogen bond donor as a catalyst to activate cyclic siloxanes for reaction. Herein we report novel conditions of alkyl or dialkylammonium tetrafluoroborate promoted *cis–trans* isomerization of *cis*-1,3,5-trimethyl-1,3,5-triphenyl-cyclotrisiloxane (*cis*-**1**) (Scheme 1).

cis–trans Isomerization of *cis*-**1** by $ZnCl_2$ or $FeCl_3$ as the catalyst in CH_3NO_2 at elevated temperature has been first reported by Spielvogel and Frye.[7] Later on, the use of pyridinium chloride or $PhNH_3Cl$ in DMF as a catalyst for the isomerization has also been reported.[8] However, pyridinium acetate was found to be inactive under similar conditions, implying that the counter anion indeed plays an important role on the above isomerization process. A ring opening reaction mechanism was proposed by the authors in that case.

1.1. R_nNH_{4-n} BF_4 promoted *cis–trans* isomerization of *cis*-1

The synthesis of *cis*-**1** has been reported in previous literature.[9] The structure of *cis*-**1** was further confirmed by X-ray crystallographic analysis before use.[10,11] ^1H NMR of *cis*-**1** in DMSO-d_6 (Fig. 1) shows a singlet of methyl protons at δ 0.55 ppm, which is corresponding to the resonance of the methyl protons. *cis*-**1** (14.9 mM) is stable in DMSO-d_6



Scheme 1.

Keywords: *cis–trans* Isomerization; Isomerization; Polymerization.
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doi:10.1016/j.tet.2004.07.074

for several days without causing any change on the spectrum. On addition of $NH_3(CH_2)_6NH_3(BF_4)_2$ or n-$C_8H_{17}NH_3BF_4$ (5 mM), two additional methyl singlets of the *trans*-isomer at δ 0.46 and 0.41 ppm, with the integration ratio of 2:1, gradually appeared. These results suggested that the ammonium salt acts as a catalyst to promote the *cis–trans* isomerization.

To elucidate the role of the salt in this reaction, contrast experiments were run for comparison. When *cis*-**1** (0.1 M) was treated with n-$C_8H_{17}NH_3Cl$ (0.1 M) at 25 °C for three days, no reaction was observed. On the other hand, polymerization of *cis*-**1** (0.1 M), instead of *cis–trans* isomerization, slowly proceeded in the presence of $LiBF_4$ (0.1 M). When *cis*-**1** (0.1 M) was treated with a mixture of n-$C_8H_{17}NH_3Cl$ and $LiBF_4$, *cis–trans* isomerization occurred along with some degree of polymerization. On the contrary, LiCl (0.08 M) would lead to *cis–trans* isomerization but in much slower rate. Even in the presence of relatively high concentration of LiCl, only 5% of *trans*-**1** was observed after one day.

All these results indicate that the *cis–trans* isomerization requires the coexistence of both n-$C_8H_{17}NH_3^+$ and BF_4^- as the catalysts. Either n-$C_8H_{17}NH_3^+$ or BF_4^- alone does not effectively promote the *cis–trans* isomerization. The same reaction occurred in CD_3CN, along with some degree of polymerization. On the other hand, when BF_4^- had been replaced by ClO_4^- ion, a complicated reaction mixture was obtained. All this indicated that BF_4^- should have a specific role for this isomerization.

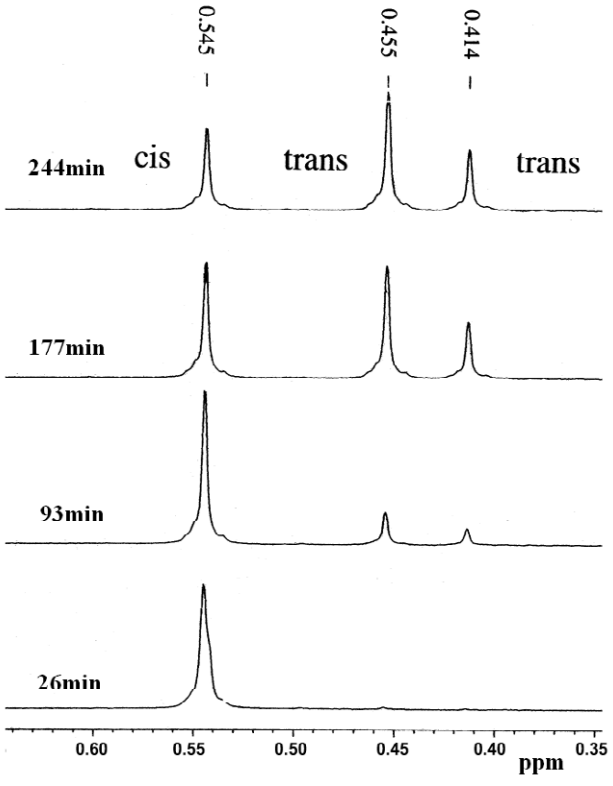


Figure 1. ^{1}H NMR spectra of $NH_3(CH_2)_6NH_3(BF_4)_2$ (4.46 mM) catalyzed *cis–trans* isomerization of *cis*-**1** (14.9 mM) at 25.0±0.1 °C in DMSO-d_6 at: (a) 26 min; (b) 93 min; (c) 177 min; (d) 244 min.

1.2. Kinetics and thermodynamics

Kinetic studies revealed that the isomerization of *cis*-**1** to *trans*-**1** is first order in [*cis*-**1**].[8] The equilibrium constants for the *cis–trans* isomerization of **1**, defined as $K=k_f^{cat}/k_b^{cat}=[trans]_{eq}/[cis]_{eq}$, were evaluated at various temperatures in

$$cis\text{-}\mathbf{1} \underset{k_b^{cat}}{\overset{k_f^{cat}}{\rightleftharpoons}} trans\text{-}\mathbf{1}$$

DMSO-d_6 and are listed in Table 1. The equilibrium constants K are within the range of 3.74–3.30 from 22–47 °C. Thermodynamic parameters of ΔH° and ΔS° were determined from a linear plot of ln K versus $1/T$ and were found to be −0.95 kcal/mol and −0.59 cal/mol-K respectively. Although the sign of ΔH° is consistent with the prediction based on the ring strain energy (E_s) measurements, in which *cis*-cyclotrisiloxane isomer has slightly higher ring strain than the *trans* one,[12] the ΔH° of −0.95 kcal/mol is relatively small in comparison to the reported ΔE_s of −2.1 kcal/mol. The negative entropy of −0.59 cal/mol-K may be attributed to the siloxane-DMSO interactions that restricted the degree of freedom of the solvent molecules. Noteworthy to mention are the facts that the literature values of [*trans*]/[*cis*] were found to be nearly equal to 3 either in methylcyclohexane[13] or in nitromethane,[7] indicating that the solvent effects on the equilibrium are small.

The mathematical expression for the first order kinetics described above is shown as the following equation.

$$\ln\left(\frac{[cis\text{-}\mathbf{1}]_t}{[cis\text{-}\mathbf{1}]_0}-\frac{1}{K+1}\right)=-k_f^{cat}\left(1+\frac{1}{K}\right)t+\ln\left(\frac{K}{K+1}\right)$$

In the kinetic expression, $[cis\text{-}\mathbf{1}]_o$ is the initial concentration of [*cis*-**1**], k_f^{cat} is the rate constant for the forward reaction, t is the reaction time elapsed, $[cis\text{-}\mathbf{1}]_t$ is the concentration of [*cis*-**1**] at time t.[14] Linear regression of $\ln\{[cis\text{-}\mathbf{1}]_t/[cis\text{-}\mathbf{1}]_0-1/(K+1)\}$ versus t gave a slope of $-k_f^{cat}(1+1/K)$. Since the equilibrium constant K had been measured in the previous equilibrium experiments, the values of k_f^{cat} could then be calculated. In most of the kinetic runs, the data were collected up to 80% conversion and the linearity of the plots are usually good with the correlation coefficient larger than 0.99. Since the value of k_f^{cat} obtained above should be a function of concentration of the catalyst, we tentatively proposed an empirical formula of $k_f^{cat}=k_f[R_nNH_{4-n}BF_4]_o^P$, in which $[R_nNH_{4-n}BF_4]_o$ is the concentration of the alkylammonium tetrafluoroborate used in the reaction, and the original first order kinetic equation could be re-expressed as follows.

Table 1. Equilibrium constants $K=[trans]_{eq}/[cis]_{eq}$ and the Gibbs free energy change for the *cis–trans* isomerization of *cis*-**1** at various temperatures

Temperature (°C)	K	ΔG° (kcal/mol)
22.0±0.2	3.74	−0.774
26.0±0.2	3.65	−0.770
37.0±0.2	3.44	−0.761
47.0±0.2	3.30	−0.759

Table 2. Determination of the reaction order P from a plot of $\ln[k_f^{cat}]$ versus $\ln[R_nNH_{4-n}BF_4]$

$R_nNH_{4-n}^+$	Reaction order
n-$C_8H_{17}NH_3^+$ [a]	2.53
$PhCH_2NH_3^+$ [a]	2.07
$^+H_3N(CH_2)_6NH_3^+$ [a]	2.05
n-$C_8H_{17}NH_3^+$ [b]	2.14

[a] At $T=25.0\pm0.1$ °C.
[b] At $T=47.0\pm0.1$ °C.

$$-\frac{d[cis\text{-}\mathbf{1}]}{dt} = k_f^{cat}[cis\text{-}\mathbf{1}] = k_f[R_nNH_{4-n}BF_4]_o^p[cis\text{-}\mathbf{1}].$$

Table 2 summarized the reaction orders p obtained from the slope of the plots of $\ln(k_f^{cat})$ versus $\ln[R_nNH_{4-n}BF_4]_o$. For the ammonium salts we studied, the p values at 25 °C were found to be or slightly larger than 2 with an average of 2.2 ± 0.2. Fractional order in pyridinum chloride catalyzed *cis–trans* isomerization has been previously reported in literature.[8]

Although the reaction order obtained above is not exactly equal to 2, particularly in the case of $C_8H_{17}NH_3BF_4$ where the p value was found to be 2.53 in the regression, their second order plots of k_f^{cat} versus $[R_nNH_{4-n}BF_4]^2$ are very linear with the correlation coefficient larger than 0.99. Therefore, we tentatively assigned the reaction order p as 2. To compare the catalytic strength of different alkylammonium tetrafluoroborates, their k_f values (Table 3) were evaluated at 25 ± 0.1 °C with $[R_nNH_{4-n}BF_4]_o$ around 6 mM. Their reactivity follows the decreasing order of $^+H_3N(CH_2)_6NH_3^+ > n$-$C_8H_{17}NH_3^+ > n$-$C_{16}H_{33}NH_3^+ > Me_3CNH_3^+ > PhCH_2NH_3^+ > Et_2NH_2^+ \gg Ph_2CHNH_3^+$, Et_3NH^+. Less hindered primary alkylammonium cations such as n-$C_8H_{17}NH_3^+$, n-$C_{16}H_{33}NH_3^+$ and $^+H_3N(CH_2)_6NH_3^+$ show highest reactivity for the *cis–trans* isomerization. For ammonium cations bearing larger substituent such as $Me_3CNH_3^+$ and $PhCH_2NH_3^+$, or secondary alkylammonium cations such as $Et_2NH_2^+$, their k_f values drop significantly by almost one order of magnitude. In addition, very sterically hindered $Ph_2CHNH_3^+$ and Et_3NH^+ or tetraalkylammonium tetrafluoroborates such as Et_4NBF_4 basically show no catalytic reactivity in our study.

The *cis–trans* isomerization also proceeds in CD_3CN but in much slower rate. The isomerization kinetics was found to be second order in $[C_8H_{17}NH_3BF_4]$ with the k_f value of 1.6 min^{-1} M^{-2} under the condition of $[R_nNH_{4-n}BF_4]_o=6$ mM, which is 2 order of magnitude slower than that in DMSO-d_6.

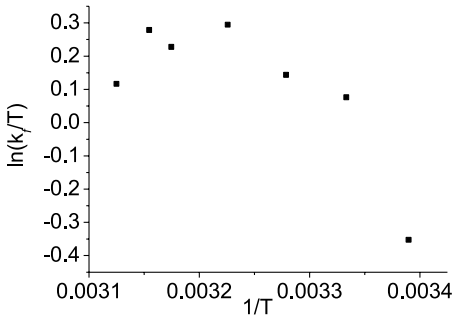


Figure 2. A plot of $\ln(k_f/T)$ versus $1/T$.

To further understand the reaction mechanism of the *cis–trans* isomerization, temperature variation experiments were carried out, in which n-$C_8H_{17}NH_3BF_4$ was used as the catalyst. The order p in $[n$-$C_8H_{17}NH_3BF_4]$ in the kinetic expression changed slightly from 2.53 to 2.14 when the temperature was varied from 25 °C to 47 °C. Although variation of the reaction order with temperature could be attributed to the intrinsic behavior of this reaction, experimental errors arising from independent kinetic runs as well as linear regression may also lead to similar extents of uncertainty. Since the variation of the reaction order is relatively small, we keep therefore our assumption that the order of p is equal to 2 for the following evaluation. The k_f for n-$C_8H_{17}NH_3BF_4$ were measured at seven different temperatures and the data are shown in Figure 2. Inversion region was observed in the plot of $\ln(k_f/T)$ versus $(1/T)$ with the ceiling at around 38 °C. The positive activation enthalpy of 9 kcal/mol was estimated at the temperature region of 22–32 °C.[8] The activation enthalpy turns to slightly negative at the temperature region higher than 38 °C. This observation suggested a complex reaction mechanism for the catalytic isomerization. Nevertheless, the existence of the inversion region could possibly be rationalized by an associative mechanism with a pre-complexation step followed by a rate determining *cis–trans* isomerization step. When the temperature increases, the rate determining *cis–trans* isomerization step is accelerated while the pre-complexation step is retarded. When the temperature is high enough, the entropically less favored pre-complex formation may become unfavorable that the pre-equilibrium kinetics is no longer valid. This will lead to a non-linear plot of $\ln(k_f/T)$ versus $(1/T)$ in the temperature variation experiments.

Although the explanation for the slightly negative activation enthalpy at the high temperature region may not be immediately obvious, the associative mechanistic argument of pre-complex formation is consistent with at least two

Table 3. Catalytic rate constants k_f for various alkylammonium tetrafluoroborates

$R_nNH_{4-n}^+$	$[R_nNH_{4-n}BF_4]$ (10^{-3} M)	k_f^{cat} (min^{-1})	k_f [k_{rel}] (min^{-1} M^{-2})
n-$C_8H_{17}NH_3^+$ (**2**)	5.37	1.04×10^{-2}	360 [1]
$^+H_3N(CH_2)_6NH_3^+$ (**3**)	5.78	1.53×10^{-2}	459 [1.3]
n-$C_{16}H_{33}NH_3^+$ (**4**)	5.99	5.07×10^{-3}	141 [0.39]
$Me_3CNH_3^+$ (**5**)	6.37	1.23×10^{-3}	30 [0.103]
$PhCH_2NH_3^+$ (**6**)	6.18	1.12×10^{-3}	29 [0.078]
$Et_2NH_2^+$ (**7**)	5.86	6.00×10^{-4}	18 [0.046]
Et_3NH^+ (**8**)	5.83	Very slow	—
$Ph_2CHNH_3^+$ (**9**)	7.73	Very slow	—
$PheNH_3^+$ (**10**)	5.89	Very slow	—

features: (1) Sterically hindered alkylammonium salts that do not favor the pre-complex formation usually show low catalytic activity for the reaction; (2) Heat releasing but entropically unfavored pre-complex formation may be a key reason for the slightly negative activation enthalpy at higher temperature region.[15]

Since hydrogen bonding between organic acids and cyclotrisiloxane has long been proposed in literature,[16] it is reasonable to suggest that hydrogen bond complexation may involve in this *cis–trans* isomerization. However, the chemical instability of *cis*-**1** in the ammonium salt solution hampered the direct study of the hydrogen bond intermediate. To elucidate the possibility of hydrogen bond complex formation, we selected a system of hexamethylcyclotrisiloxane (D_3)/$PhCH_2NH_3BF_4$ in CD_3CN as the model to investigate. D_3 is chemically stable and would not lead to other products in the presence of RNH_3BF_4. In addition, $PhCH_2NH_3BF_4$ is the least reactive primary alkylammonium salt in the list we have studied. Furthermore, the reactivity of the isomerization in CD_3CN is lower according to previous results.

In CD_3CN, up-field shift of the N–H signal of $PhCH_2NH_3BF_4$ (0.09 M), from 6.5 ppm approaching to 5.9 ppm, was observed when the added amount of D_3 gradually increased. The data is summarized in Table 4. These results suggested that hydrogen bond complexation of $RNH_3^+\cdots D_3$ occurs in this case. The unusual direction of upfield-shift of the N–H signal may be due to the change of the coordination shell throughout complexation. Hydrogen bond accepting properties of nitriles have recently been studied by combining crystallographic data as well as theoretical calculation.[17] Before complexation, the RNH_3^+ should be coordinated with either CD_3CN or BF_4^-. Since both of them will have hydrogen bonding with RNH_3^+, the N–H signal is relatively down-field shift. On complexation, the coordination shell of RNH_3^+ will be partially occupied by a D_3 molecule, leading to an up-field shift of the N–H signal. Similar results were obtained for *n*-$C_{16}H_{33}NH_3BF_4$. Since DMSO and acetonitrile are hydrogen bond acceptors with similar polarity,[18] we expected that formation of $RNH_3^+\cdots$*cis*-**1** as a reactive intermediate in DMSO is possible.

The role of BF_4^- is also an interesting target to study. Perfluorinated complex anions such as BF_4^-, or PF_6^- have been regarded as non-nucleophilic and inert of innocent anions.[19] If BF_4^- involves in the catalytic process, one may expect that changing the concentration of BF_4^- would lead to significant effect on the reaction rate. Therefore, we have attempted using Et_4NBF_4 as independent BF_4^- source to control the BF_4^- concentration. However, addition of Et_4NBF_4 to the solution of RNH_3BF_4 does not significantly alter the reaction rate of isomerization. We tentatively attributed this result to the ion pair association of Et_4NBF_4.[20] In particular, in the absence of hydrogen bond interactions, solvation of the bulky Et_4N^+ with DMSO is expected to be poor. Furthermore, we have observed the reactivity-suppression effects of Et_4NCl on RNH_3BF_4. In an independent experiment, we discovered that the catalytic strength of *n*-$C_{16}H_{33}NH_3BF_4$ (5.9 mM) was reduced by 60% in the presence of Et_4NCl (14 mM). This result is consistent with the above assumption of ion-pair formation. Addition of Et_4N^+ salt to a solution of RNH_3BF_4 would lead to Et_4NBF_4 ion-pair formation, reducing the effective concentration of free BF_4^- ions, and hence suppressing the catalytic reactivity of the RNH_3BF_4 solution.

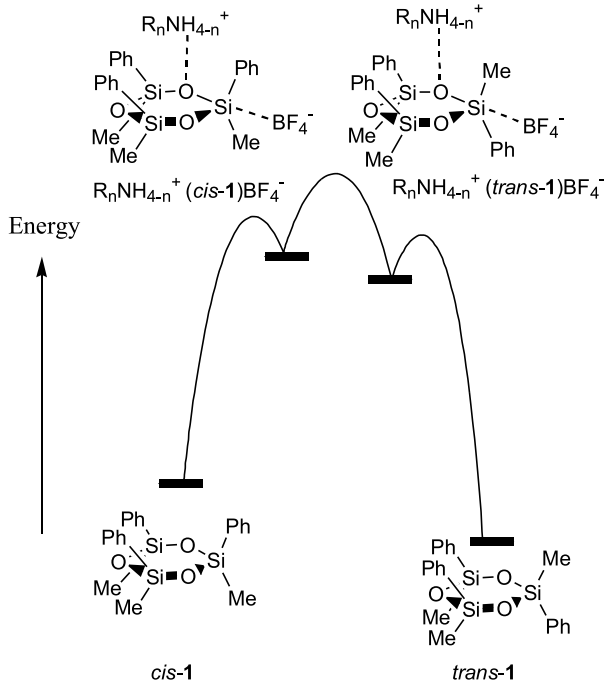
Since ion pair association in organic solvents is complicated,[21] detailed study of the reaction order would be relatively difficult. Although it is known that BF_4^- would dissociate into BF_3+F^- at high temperature,[19,22] it is unlikely to undergo this process in our case because the reactions were carried out only at room temperature or slightly above room temperature. Furthermore, the present of F^- would lead to polymerization[23] that has not been observed during *cis–trans* isomerization. On the other hand, BF_4^- has been proposed to act as a nucleophile to coordinate directly and react with group IV compound.[24] Although mechanistically we do not have evidence for the complexation of *cis*-**1** with BF_4^-, our results again indicated that BF_4^- is not truly innocent.

Although the details of the mechanism are not completely understood, pre-complexation involving $R_nNH_{4-n}^+$, BF_4^- and *cis*-**1** before isomerization to the *trans* isomer is plausible. We therefore proposed a mechanistic schematic diagram shown in Scheme 2. We believed that a push–pull mechanism involving hydrogen bond interaction between

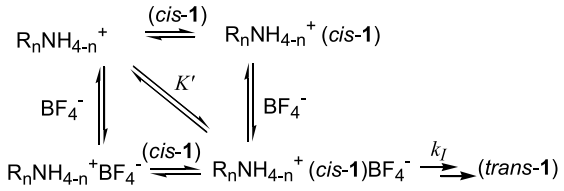
Table 4. N–H Chemical shifts of $PhCH_2NH_3BF_4$ in the presence of various amounts of D_3

$[D_3]/[PhCH_2NH_3BF_4]$	δ (N–H) (ppm)
0	6.51
0.21	6.39
1.85	6.18
3.15	6.05
4.64	5.98
6.33	5.93

At $T=25.0\pm0.1$ °C with $[PhCH_2NH_3BF_4]=0.09$ M.



Scheme 2.



Scheme 3.

$R_nNH_{4-n}^+$ and the oxygen atom of the Si–O–Si units, and probably coordination of BF_4^- with the silicon atoms are operating for the *cis–trans* isomerization.

On the basis of this assumption, a putative mechanism is proposed as shown in Scheme 3. We have already discussed the possibility of $R_nNH_{4-n}^+$(*cis*-**1**) complex formation. Since there is a positive charge on $R_nNH_{4-n}^+$(*cis*-**1**), further formation of a reactive ion pair intermediate of $R_nNH_{4-n}^+$(*cis*-**1**)BF_4^- is not impossible. On the other hand, the possibility of the formation of $R_nNH_{4-n}^+$(*cis*-**1**) BF_4^- through the ion pair of $R_nNH_{4-n}^+BF_4^-$ could not be eliminated. Once the $R_nNH_{4-n}^+$(*cis*-**1**)BF_4^- is formed, pseudorotational isomerization of $R_nNH_{4-n}^+$(*cis*-**1**)BF_4 at the pentacoordinated silicon atom may occur to give $R_nNH_{4-n}^+$(*trans*-**1**)BF_4^-, followed by dissociation of the ion-pair complex would give *trans*-**1** as the product. This type of pseudorotational mechanism is known as the Berry pseudorotation and turnstile twists that have been studied and reviewed in literature.[25]

A rate equation could then be derived on the basis of the reaction scheme, in which $K'=[R_nNH_{4-n}^+(cis\text{-}\mathbf{1})BF_4^-]/[R_nNH_{4-n}^+][BF_4][cis\text{-}\mathbf{1}]$ is the overall equilibrium constant for $R_nNH_{4-n}^+$(*cis*-**1**)BF_4^- formation, and k_I is the isomerization rate constant from $R_nNH_{4-n}^+$(*cis*-**1**)BF_4^- to the *trans* isomer.

$$-\frac{d[cis\text{-}\mathbf{1}]}{dt} = k_1[R_nNH_{4-n}^+(cis\text{-}\mathbf{1})BF_4^-]$$

$$= k_1K'[R_nNH_{4-n}^+][BF_4^-][cis\text{-}\mathbf{1}]$$

However, this equation does not straightly explain for the observeation of the second reaction order in $[R_nNH_{4-n}BF_4]_o$, unless we assumed that dissociation of $R_nNH_{4-n}BF_4$ in DMSO is extensive. This may be plausible due to strong hydrogen bond interactions between R_nNH_{4-n} BF_4 If the assumption is valid, each equivalent of $R_nNH_{4-n}BF_4$ would dissociate to give respectively one equivalent of $R_nNH_{4-n}^+$ and BF_4^-, and therefore $[R_nNH_{4-n}^+]$ and $[BF_4^-]$ are both equal to $[R_nNH_{4-n}BF_4]_o$. Substitution these into the above equation would give the following equation,

$$-\frac{d[cis\text{-}\mathbf{1}]}{dt} = k_f[R_nNH_{4-n}BF_4]_0^2[cis\text{-}\mathbf{1}]$$

where k_IK could be combined and denoted as the k_f. The second order kinetics in $[R_nNH_{4-n}BF_4]_o$ could then be explained.

2. Experimental

All reactions were performed under nitrogen. Acetonitrile was dried over CaH_2. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity plus (400 MHz). All 400 MHz ^1H NMR spectra were recorded in $CDCl_3$ deuterated acetonitrile (CD_3CN) and deuterated dimethylsulfoxide (DMSO-d_6) and are reported in ppm as δ. The kinetic experiments were carried out in DMSO-d_6. The ^1H NMR assignments for *cis*-**1** and *trans*-**1** were previously reported in literature.[7,8,13] Infrared spectra were obtained with KBr using Nicolet MAGNA-IR 550 spectrometer series type FT-IR and are reported in ν as cm^{-1}. Elemental analysis was performed by Heraeus CHN-O Rapid.

2.1. General procedure for the kinetic measurements

The kinetic measurements were performed by using ^1H NMR spectroscopy (Varian Unity plus (400 MHz)) with temperature control. Solution of *cis*-**1** and solution of the ammonium salt with known concentrations in DMSO-d_6 were prepared before measurement. Both solutions were pre-warmed to the desired temperature, mixed, and subjected to the NMR spectrometer for data collection. The concentrations of *cis*-**1** after mixing were set within the range of 8.48 to 25.5 mM. The concentrations of the ammonium salts were set within the range of 1.19 to 12.6 mM. The progress of the isomerization of *cis*-**1** to *trans*-**1** was monitored by taking the NMR spectrum for every 15 to 30 min. ^1H NMR of *cis*-**1** in DMSO-d_6 shows a singlet of methyl protons at δ 0.55 ppm, which is corresponding to the resonance of the methyl protons. On addition of the ammonium salt solution, two additional methyl singlets of the *trans*-isomer at δ 0.46 and 0.41 ppm gradually appeared. The ratio of [*trans*-**1**]/[*cis*-**1**] at a time could be determined on the basis of the methyl proton integrations. For the temperature variation experiments, the temperature range of 25–47 °C was used. The rate constant was determined according to the equation

$$\ln\left(\frac{[cis\text{-}\mathbf{1}]_t}{[cis\text{-}\mathbf{1}]_0} - \frac{1}{K+1}\right) = -k_f^{cat}\left(1+\frac{1}{K}\right)t + \ln\left(\frac{K}{K+1}\right)$$

By using linear least square fitting of $\ln([cis\text{-}\mathbf{1}]_t/[cis\text{-}\mathbf{1}]_o - (1/K+1))$ versus t, a slope of $-k_f^{cat}(1+1/K)$could be obtained. The value of k_f^{cat} could then be calculated.

2.2. General procedure for the preparation of alkylammonium tetrafluoroborates

Following is a typical preparative procedure for alkylammonium tetrafluoroborates. Alkyl or phenyl ammonium tetrafluoroborates were prepared according to the literature procedures of Kukhar.[26] They were prepared by reaction of the corresponding alkylammonium chlorides with triethyloxonium tetrafluoroborate in acetonitrile. Since most of the salts are hygroscopic, they are collected under nitrogen, sealed and sent for microanalysis.

2.2.1. Octylammonium tetrafluoroborate (2). To a solution of 1-octylamine (10 mL, 56.9 mmol) in CH_2Cl_2 (20 mL) in an ice bath were slowly added concentrated hydrochloric acid (4.75 mL, 56.9 mmol). The mixture was

stirred for another 5 h. White suspension was collected by filtration and further purified by recrystallization from CH_2Cl_2. The crystals were collected under nitrogen and dried in vacuum to give colorless octylammonium chloride (6.69 g, 71%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 3H), 2.70 (t, J=7.6 Hz, 2H), 1.55–1.50 (m, 2H), 1.35–1.20 (m, 10H), 0.84 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 38.7, 31.2, 28.5, 26.9, 25.9, 22.1, 14.0; IR (KBr) ν 3400–2700 cm^{-1} (NH_3^+, br, s). To a solution of octylammonium chloride (3 g, 18 mmol) in dried acetonitrile (18 mL) under nitrogen at room temperature was added triethyloxonium tetrafluoroborate ($Et_3O^+BF_4^-$, 18 mmol). The solution was refluxed for 24 h until outgassing of alkyl chloride was no longer observed. In some occasion, the completion of reaction was traced by ^{1}H NMR. The solid obtained after evaporation of the solvent was further purified by recrystallization from ethyl acetate. The product was collected by filtration under nitrogen, and dried in vacuum to give colorless crystals. (2.76 g, 71%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 3H), 2.75 (t, J=7.6 Hz, 2H), 1.52–1.46 (m, 2H), 1.35–1.20 (m, 10H), 0.85 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 41.4, 32.5, 29.8, 29.7, 27.7, 26.9, 23.4, 14.4; IR (KBr) ν 3400–3200 cm^{-1} (NH_3^+, br), 1200–1000 cm^{-1} (B–F, br). Anal. calcd for $C_8H_{20}BF_4N$: C, 44.27; H, 9.29; N, 6.45. Found: C, 44.79; H, 9.42; N, 6.50.

2.2.2. 1,6-Hexanediammonium bistetrafluoroborate (3). 1,6-Hexanediammonium dichloride obtained was purified by washing with methanol and CH_2Cl_2 to give colorless solid (75%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 6H), 2.73 (t, J=7.6 Hz, 4H), 1.57–1.53 (m, 4H), 1.31–1.28 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 39.2, 27.4, 26.0; IR (KBr) ν 3400–2700 cm^{-1} (NH_3^+, br). 1,6-Hexanediammonium bistetrafluoroborate obtained was recrystallized from acetonitrile to give colorless solid. (46%): ^{1}H NMR (400 MHz, CD_3CN) δ 5.82 (s, 6H), 2.95 (t, J=7.6 Hz, 4H), 1.66–1.59 (m, 4H), 1.41–1.31 (m, 4H); ^{13}C NMR (100 MHz, CD_3CN) δ41.2, 27.3, 26.1; IR (KBr) ν 3300–3200 cm^{-1} (NH_3^+, br), 1200–1000 cm^{-1} (B–F, br). Anal. calcd for $C_6H_{18}B_2F_8N_2$: C, 24.69; H, 6.22; N, 9.60. Found: C, 25.02; H, 6.22; N, 9.43.

2.2.3. Hexadecylammonium tetrafluoroborate (4). Hexadecyl-ammonium chloride obtained was recrystallized from $CHCl_3$ to give colorless solid (79%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 3H), 2.72 (t, J=7.6 Hz, 2H), 1.53–1.48 (m, 2H), 1.35–1.15 (m, 26H), 0.84 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 38.7, 31.4, 29.1, 29.1, 29.0, 28.9, 28.8, 28.6, 27.0, 25.9, 22.2, 14.1; IR (KBr) ν 3200–2700 cm^{-1} (NH_3^+, br). Hexadecyl ammonium tetrafluoroborate was recrystallized from THF to give colorless solid (53%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (s, 3H), 2.7 (t, J=7.6 Hz, 2H), 1.51–1.45 (m, 2H), 1.36–1.18 (m, 26H), 0.84 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 38.9, 31.3, 29.1, 29.0, 28.9, 28.8, 28.6, 27.1, 25.8, 22.2, 14.1; IR (KBr) ν 3300–3100 cm^{-1} (NH_3^+, br), 1200–1000 cm^{-1} (B–F, br). Anal. calcd for $C_{16}H_{36}BF_4N$: C, 58.36; H, 11.02; N, 4.25. Found: C, 58.68; H, 11.00; N, 4.26.

2.2.4. *tert*-Butylammonium tetrafluoroborate (5). *tert*-Butylammonium chloride was crystallized from ethanol to give colorless solid. (69%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 51.2, 27.4; IR (KBr) ν 3200–2900 cm^{-1} (NH_3^+, br, m). *tert*-Butylammonium tetrafluoroborate was recrystallized from acetonitrile to give colorless solid (39%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 51.7, 27.7; IR (KBr) ν 3300–3100 cm^{-1} (NH_3^+, br), 1300–1000 cm^{-1} (B–F, br). Anal. calcd for $C_4H_{12}BF_4N$: C, 29.85; H, 7.51; N, 8.70. Found: C, 29.79; H, 7.65; N, 8.43.

2.2.5. Benzylammonium tetrafluoroborate (6). Benzylammonium chloride obtained was crystallized from MeOH to give colorless solid (87%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 3H), 7.50–7.36 (m, 5H), 3.99 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 134.1, 128.9, 128.5, 128.4, 42.1; IR (KBr) ν 3200–2700 cm^{-1} (NH_3^+, br), 1600 cm^{-1} (C=C). Benzylammonium tetrafluoroborate obtained was crystallized from acetonitrile to give colorless solid (75%): ^{1}H NMR (400 MHz, CD_3CN) δ 7.48–7.43 (m, 5H), 6.46 (s, 3H), 4.15 (s, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 133.1, 130.4, 130.4, 130.1, 44.9; IR (KBr) ν 3300–3100 cm^{-1} (NH_3^+, br), 1615 cm^{-1} (C=C), 1200–1000 cm^{-1} (B–F). Anal. calcd for $C_7H_{10}BF_4N$: C, 43.12; H, 5.17; N, 7.18. Found: C, 43.44; H, 5.15; N, 7.24.

2.2.6. Diethylammonium tetrafluoroborate (7). Diethylammonium chloride obtained was recrystallized from acetonitrile and followed by washing with hexane and ether to give colorless solid (68%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 2H), 2.90–2.81 (m, 4H), 1.17 (t, J=7.6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.2, 10.9; IR (KBr) ν 3300–2700 cm^{-1} (NH_2^+, br). Diethylammonium tetrafluoroborate obtained was recrystallized from ethyl acetate to give colorless solid (44%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 2H), 3.02 (q, J=7.2 Hz, 4H), 1.15 (t, J=7.6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 42.0, 11.7; IR (KBr) ν 3200–2900 cm^{-1} (NH_2^+, br), 1300–900 cm^{-1} (B–F, br). Anal. calcd for $C_4H_{12}BF_4N$: C, 29.85; H, 7.51; N, 8.70. Found: C, 29.83; H, 7.67; N, 8.58.

2.2.7. Triethylammonium tetrafluoroborate (8).[27] Triethylammonium chloride prepared was recrystallized from acetonitrile to give colorless solid (48%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 3.06–3.00 (m, 6H), 1.19 (t, J=7.6 Hz, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 45.2, 8.4; IR (KBr) ν 3200–2900 cm^{-1} (NH^+, br). Triethylammonium tetrafluoroborate obtained was precipitated from ethyl acetate to give colorless solid (38%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 3.08 (q, J=7.2 Hz, 6H), 1.16 (t, J=7.6 Hz, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ46.0, 8.9; IR (KBr) ν 3200–2900 cm^{-1} (NH^+, br), 1300–900 cm^{-1} (B–F, br). Anal. calcd for $C_6H_{16}BF_4N$: C, 38.13; H, 8.53; N, 7.41. Found: C, 38.30; H, 8.73; N, 7.37.

2.2.8. (1,1-Diphenylmethyl)ammonium tetrafluoroborate (9). (1,1-Diphenylmethyl)ammonium chloride obtained was recrystallized from ethanol to give colorless solid (91%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 3H), 7.56 (d, J=7.2 Hz, 4H), 7.40 (t, J=7.6 Hz 4H), 7.33 (t, J=7.6 Hz, 2H), 5.61 (s, 1H);^{13}C NMR (100 MHz, DMSO-d_6) δ 138.8, 129.2, 128.7, 127.8, 57.6; IR (KBr) ν

3300–2600 cm^{-1} (NH_3^+, br), 1610 cm^{-1} (C=C, s). (1,1-Diphenylmethyl)ammonium tetrafluoroborate obtained was recrystallized from CH_2Cl_2 to give colorless solid (57%): ^1H NMR (400 MHz, CD_3CN) δ 7.49–7.26 (m, 10H), 7.26 (s, 3H), 5.69 (s, 1H);^{13}C NMR (100 MHz, CD_3CN) δ 137.2, 130.3, 130.3, 128.4, 60.0; IR (KBr) ν 3300–3100 cm^{-1} (NH_3^+, br), 1597 cm^{-1} (C=C), 1200–900 cm^{-1} (B–F, br). Elemental analysis suggested that the salt is a monohydrate. Anal. calcd for $C_{13}H_{14}BF_4N\cdot(H_2O)$: C, 54.01; H, 5.58; N, 4.85. Found: C, 54.87; H, 5.38; N, 4.92.

2.2.9. L-Phenylalanine methyl ester ammonium tetrafluoroborate (10). To a solution of L-phenylalanine (5.0 g, 29.8 mmol) in distilled MeOH (50 mL) under nitrogen at at 0 °C was added distilled thionyl chloride (3.28 mL, 44.7 mmol) dropwise. After addtion, the mixture was stirred at room temperature for 24 h. The reaction was followed by TLC, using BAW (butanol–acetic acid–H_2O=4:1:1) as the mobile phase. After completion of the reaction, methanol was removed by distillation. Ether (400 mL) was added to precipitate the product. The solid product was collected by suction filtration under nitrogen, followed by washing with iced ether, and dried under vacuum to give L-phenylalanine methyl ester ammonium chloride (5.91 g, 91%): ^1H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 3H), 7.35–7.23 (m, 3H), 7.22 (d, J=6.8 Hz, 2H), 4.28 (t, J=6.8 Hz, 1H), 3.66 (s, 3H), 3.14 (dd, J=14.0, 6.0 Hz, 1H); 3.06 (dd, J=13.8, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 134.4, 129.2, 128.4, 127.1, 53.2, 52.5, 35.9; IR (KBr) ν 3300–2700 cm^{-1} (NH_3^+, br), 1766 cm^{-1} (C=O). 1600 cm^{-1} (C=C). L-phenylalanine methyl ester ammonium tetrafluoroborate obtained was precipitated from CH_2Cl_2 to give colorless solid. (18%): ^1H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 3H), 7.37–7.22 (m, 3H), 7.21 (d, J=6.8 Hz, 2H), 4.32 (t, J=6.8 Hz, 1H), 3.68 (s, 3H), 3.12–3.02 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.5, 134.5, 129.4, 128.7, 127.4, 53.2, 52.7, 36.0; IR (KBr) ν 3300–2800 cm^{-1} (NH_3^+, br), 1747 cm^{-1} (C=O), 1609 cm^{-1} (C=C), 1200–900 cm^{-1} (B–F, br). Anal. calcd for $C_{10}H_{14}BF_4NO_2$: C, 44.98; H, 5.28; N, 5.25. Found: C, 44.78; H, 5.25; N, 5.32.

Acknowledgements

We thank the National Science Council of Republic of China for the financial support. (NSC 92-2113-M-002-020).

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Tetrahedron 60 (2004) 9213–9222
Tetrahedron

Synthesis, complete NMR assignments, and NOE versus GIAO data assisted ab initio modelling the overall conformations of amide 3,4′-diquinolinyl sulfides in solution. Another approach to analysis of flexible systems

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Received 27 April 2004; revised 28 June 2004; accepted 23 July 2004

Abstract—Two isomeric amide sulfides **3** and **4** were prepared by the treatment of 6-substituted thioquinanthrene (**2**) with sodium methoxide and methyl iodide. Product structures were determined by ^{1}H and ^{13}C NMR spectroscopy in solution, including 2D experiments HSQC and HMBC at 11.75 T. The time-averaged conformations were elucidated, based on best fitting the measured data δ_C and δ_H to those computed by the ab initio GIAO NMR method at the HF/6-31G* level. All used input molecular models had been pre-selected before in the light of NOE experimental data. Excellent two-nuclear linear correlations $\delta^{exp}_{C,H}$ vs. $\delta^{calc}_{C,H}$ were achieved ($R>0.999$). Spatial orientations of the ring substituents [SMe and, especially, of C(O)NMe$_2$] in both isomers were considered to rationalise the NMR spectra of these and other related amide systems. A protocol for the three-step conformational analysis is described in detail.

1. Introduction

NMR spectroscopy is an extremely powerful tool for investigating the structure of organic systems. It enables the constitution/configuration elucidation and a conformational analysis of such molecular objects. These possibilities became considerably enhanced in recent years for the common spin-1/2 nuclei X by the parallel use of two supporting methods of computational chemistry, i.e. the GIAO prediction of field-dependent chemical shifts δ_Xs and/or the FPT evaluation of spin–spin coupling constants $^{n}J_{AB}$s.[1]

As reported previously,[2] thioquinanthrene[§] **1** reacts with free *C*-radical species derived from DMF under the Minisci-reaction[3] conditions giving 6-(*N*,*N*-dimethylcarbamoyl)-thioquinanthrene **2**, along with two other polycyclic azahetarenes. In the presence of nucleophiles, compound **1** leads to 3(β)-quinolinyl-4′(γ′)-quinolinyl sulfides, as the attack of such reagents typically results in a cleavage of the carbon–sulfur bond of the 1,4-dithiin-ring moiety. These latter processes give molecules with large conformational flexibility,[4] mainly due to presence of the sulfide bridge. In the case of **2**, a bulky *N*,*N*-dimethylcarbamoyl (hereafter noted DMC) group differentiates two γ-C–S bonds. Thus, nucleophilic splitting of **2** followed by *S*-methylation gave two isomers **3** and **4** as viscous liquids formed via an attack on atoms C-14a and C-7a, respectively (Scheme 1).[2c,5]

In this paper, we report the high-field NMR identification and conformational analysis of products **3** and **4**. Moreover, their δ_Xs were compared with those found previously for parent compound **5**,[4c] to better recognise the 'structure vs spectral image' relations concerning this kind of species. Indeed, 3,4′-diquinolinyl sulfides **5** (Z=OR, SR, Cl) exhibit many non-typical NMR properties, such as (i) up to 0.87 ppm deshielding of the H-5 and H-5′ protons induced most likely by the *peri* effect of 4-hetero- and 4′-thio-substituents, (ii) large differences in δ_Hs of α-quinolinyl protons (δ_H 7.85–8.88), and (iii) substantial nuclear Overhauser effects (NOEs) between the 3′-methylthio group and H-2′. The majority of these findings were interpreted in terms of stereoelectronic effects of lone pair-bearing heteroatoms (Z, bridged-S)[4c,d] and/or shielding zones due to the ring-current of the γ′-quinoline moiety.[6] Some of

Keywords: Thioquinanthrene; Sulfanes; Conformational constraints; Anisotropic shielding; Chemical shifts correlation.
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† Azinyl sulfides, part LXXX. For part LXXIX, see ref. 4.
‡ Physical image vs structure relation, part 11. For part 10, see Ref. 41.
§ [1,4]Dithiino[2,3-*c*;5,6-*c*′]diquinoline (*Chem. Abstr.* name) or 7,14-dithia-5,12-diaza-dibenzo[*a*,*h*]anthracene (AutoNom).

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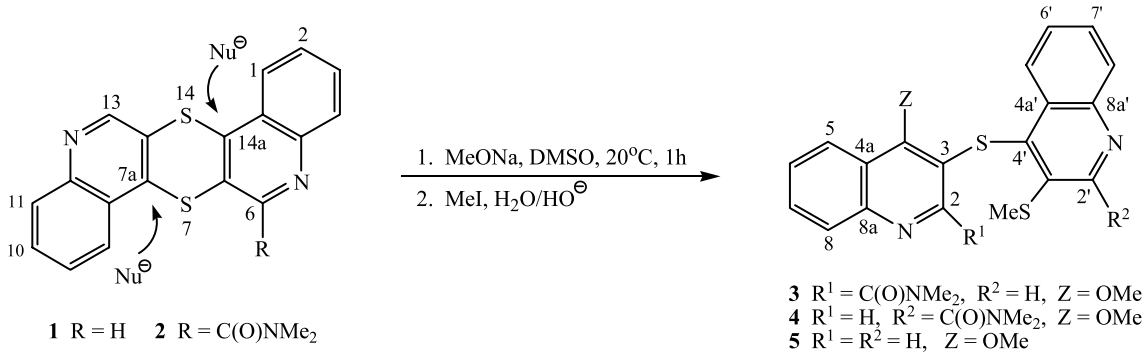
doi:10.1016/j.tet.2004.07.058



Scheme 1. Synthesis of sulfides **3** and **4** starting from compound **2**.

these NMR observations were supported by single-crystal X-ray analyses of sulfides **5** (where Z=OMe, SMe).[4c,6b] Skew conformations with an interring angle θ_R of 73.7[4c,7] or 81.4°,[7] respectively, and very short contacts between the *ortho*-situated sulfur atoms are particularly worthy of mention.

Since X-ray crystal structures of **3** and **4** could not be established, the only method for elucidating their constitution was a spectroscopic study. Thus, these isomeric structures were determined in $CDCl_3$ solution using NMR techniques, especially two-dimensional (2D) correlation experiments. This allows an unequivocal assignment of all ^1H and ^{13}C signals. Moreover 1D NOE spectra were recorded, in order to obtain a better insight into spatial arrangement around the central sulfide bridge.[2c,5] Measured values δ_X (δ_X^{exp}) were compared with calculated ones (δ_X^{calc}). Some preliminary findings were announced earlier, based on the 'MMX randomisation[8] and AM1 (MNDO/d) modelling vs. TNDO/2' results.[9] The present study covers ab initio computations and GIAO predictions[1a,10] of σ_Xs at the HF level. All starting geometries of the title compounds had been pre-selected before in the light of NOE results.[5] Finally, least-squares regression was applied for best fitting the δ_X^{exp}s to corresponding theoretical values. The latter 'experimental NMR data vs. molecular modelling and spectra calculations' approach enabled us to propose the most probable overall conformations of **3** and **4** in solution. The results achieved were reported in part very recently.[11]

In all cases of conformationally flexible species, a presence of populations of different interconverting forms gives rise to time-averaged NMR parameters, and this averaging is not always linear. Such results on flexible molecules will be highly skewed in favour of conformers with smaller internuclear distances, because NOE responses depend on the distance r between interacting protons as r^{-6}. This effect introduces complications in interpretation of the NOEs, especially when only a small number of these values can be measured.[12] Fortunately, δ_Xs as well as $^nJ_{AB}$s (not applicable in this work) are spectral parameters averaged linearly, and thus their interpretation in the presence of large mobility is, in principle, less prone to error. Hence, an elaboration of an other approach to a structural analysis of this kind of objects, based inter alia on values δ_X and NOE, seemed to be of crucial importance.

A joint approach used here can be applied to other flexible systems (especially carbo- and heteroaromatic), if their nuclei X are responsible for sufficiently different δ_Xs. Indeed, one should realise that the vast majority of contemporary ab initio or DFT studies on medium-sized species are usually performed with equilibrium structures of the free molecules at near 0 K. Consequently, some problems occur in extrapolation of such results to bulk solution (liquid) states usually studied at ambient temperature, due to total neglect of the specific solute (solvent)–solvent interactions (solvent sorting). Therefore, an additional use of the NOE-based conformational constraints in the analyses is very useful.

2. Results and discussion

2.1. NMR assignments and qualitative conformational results (by the standard NOE approach)

An initial analysis of ^1H NMR spectra of amide sulfides **3** and **4** revealed that the former bears the DMC group in position 2, whereas the latter in 2′. This finding resulted from the comparison of δ_Hs for the protons H-2 and H-2′ (Table 1) with those for **5**. This latter reference compound was investigated before, including an X-ray single-crystal study and full interpretation of NMR spectra.[4c,d] Its signals due to H-2 and H-2′ resonate at 8.12 and 8.83 ppm, respectively.

Additional evidence for the constitution of **3** was supplied with the 2D HSQC and HMBC spectra. The most important observations were long-range connectivities from H-2′ to C-4a′ and from 3′-methylthio protons to C-2′. Thus, it was possible to achieve an unambiguous elucidation of the structure of the pyridine ring in the 'right-hand' (primed) quinoline part of the molecule. Moreover, its DMC group was localised at the position 2, as there was not the observed signal of the second α-quinolinyl proton. In addition, full identification of the three closely resonating methyl groups was possible; δ_H 2.51 (SCH_3), 2.55 and 2.58 (two NCH_3). Among all carbons in **3**, only its C-3 atom (δ_C 117.3) was found to not interact with the remaining protons. Analogous C,H-signal correlations used for sulfide **4** are summarised in Table 1. Especially important were 2D connectivities from H-2 and from the OCH_3 protons to C-4. The above data allowed the determination of the 'left-hand' quinoline moiety.

Table 1. Relative chemical shifts δ_X (in ppm) and set of ^1H–^{13}C NMR correlations for sulfides **3** and **4** (for $CDCl_3$ solution)

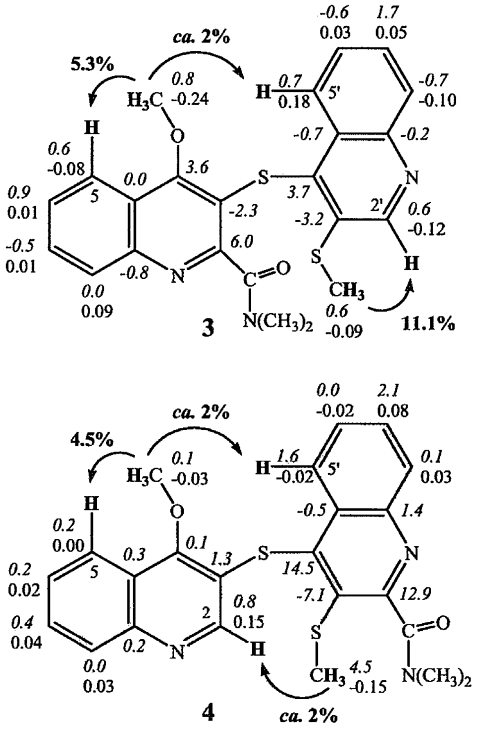
δ_H			δ_C, one-bond coupling			δ_C, two-bond coupling			δ_C, three-bond coupling			δ_C, four-bond coupling		
H[a]	**3**	**4**	C[a]	**3**	**4**	C	**3**	**4**	C	**3**	**4**	C	**3**	**4**
H-2	—	8.27	C-2	—	151.3	C-3	—	120.9	C-4	—	160.6	C-4a	—	123.7
									C-8a		148.7			
H-5	7.99	8.07	C-5	122.0	121.6				C-4	164.1	160.6			
									C-7	128.9	129.8			
									C-8a	147.7	148.7			
H-6	7.56	7.57	C-6	127.9	127.2				C-4a	123.4	123.7			
									C-8	129.6	129.6			
H-7	7.65	7.68	C-7	128.9	129.8				C-5	122.0	121.6			
									C-8a	147.7	148.7			
H-8	8.05	7.99	C-8	129.6	129.6				C-4a	123.4	123.7			
									C-6	127.5	127.2			
OCH_3	3.95	4.16	OCH_3	62.7	62.0				C-4	164.1	160.6			
H-2′	8.71	—	C-2′	146.9	—	C-3′	136.1	—	C-4′	137.5	—	C-4a′	130.5	—
									C-8a′	145.8				
H-5′	8.58	8.38	C-5′	125.3	126.2				C-4′	137.5	148.3			
									C-7′	130.5	130.9			
									C-8a′	145.8	147.4			
H-6′	7.58	7.53	C-6′	127.9	128.5				C-4a′	129.1	129.3			
									C-8′	129.5	130.3			
H-7′	7.70	7.73	C-7′	130.5	130.9				C-5′	125.3	126.2			
									C-8a′	145.8	147.4			
H-8′	8.00	8.13	C-8′	129.5	130.3				C-4a′	130.5	129.3			
									C-6′	127.9	128.5			
NCH_3^T	2.55	2.86	NCH_3^T	37.9	37.9				C=O	166.5	168.2	C-2	156.5	151.3
NCH_3^C	2.58	3.20	NCH_3^C	34.2	34.6				C=O	166.5	168.2	C-2	156.5	151.3
SCH_3	2.51	2.45	SCH_3	16.4	20.3				C-3′	136.1	132.2	C-2′	146.9	159.2

[a] Superscripts T and C stand for the *N*-methyl signals due to nuclei X lying *trans* and *cis* to the C=O group, respectively (see text).

Our results on **3** and **4** are consistent with observation that *cis*- (to the carbonyl oxygen) and *trans*-groups on an amide nitrogen give well-separated signals whenever restricted rotation through the amide plane occurs at a rate which is slow on the ^1H NMR timescale, owing to partial double-bond character of the N-CO bond.[13] Both amides can be treated as asymmetrical *ortho*-substituted aromatics, and so they are atropisomeric enantiomers at low temperatures (due to molecular dissymmetry arising from a sufficiently slow rotation about the chiral C-CO axis), but racemise very rapidly under normal conditions.[14] Indeed, only one set of their ^1H and ^{13}C signals were observed. Thus, they are both highly flexible systems, especially taking into account an additional occurrence of ring substituents (OMe, SMe) and the central sulfide bridge. These latter fragments contain C-heteroatom bonds practically unrestricted rotationally at room temperature; long C–S linkages are especially important in this regard.

A 'differential analysis' of the δ_Xs (Scheme 2) led to a tentative result that the voluminous DMC group in **3** is responsible for a larger modification in the arrangement of its quinoline moieties, with respect to **5**, compared to **4**. All δ_H data for protons around the triad *H-5*–OCH_3–*H-5′* in **3** were strongly changed, whereas those for protons *H-2*–H_3CS in **4** were only slightly modified. The latter finding was in agreement with a prior expectation, as resulted from the close neighbourhood of an amide function. Instead, all δ_Cs strongly suggested that the spatial environment of the SMe group in **3** is very similar to that in **5**.

In sharp contrast to the above findings, a similar overall conformation around the diquinolinyl-bridged sulfur was suggested based on the NOEs alone (Scheme 2). Especially concerning a similar net increase of integrated intensities experienced by signals of quinolinyl protons in the *H-5*–OCH_3–*H-5′* triad, on the selective pre-irradiation of the OMe proton frequency. Moreover for **3** (with the 11.1%



Scheme 2. Experimental ^1H (roman)/^{13}C (italic) NMR chemical shift differences between isomer **3** (or **4**) and reference **5** ($\Delta\delta_X=\delta_3-\delta_5$ or $\delta_4-\delta_5$, in ppm, $CDCl_3$), and ^1H–^1H NOE enhancements measured at the ArH signals of both studied compounds ($CDCl_3$).[2c,5]

NOE for H-2′) it was expected that its SMe group adopts an orientation analogous to that in compound **5**, for which the 10.3% NOE effect in the SCH_3 (irradiated)–*H-2′* fragment was measured.[4c] It is worth noting that both heavy atoms in the SMe group of this reference are, in the crystalline state, almost strictly coplanar with the parent pyridine ring (torsion angle C2′–C3′–S–C of 0.2°).[4c,7]

Moreover, a wide variety in δ_Hs associated with two different *N*-methyls of the DMC groups was found for both amides in question; $\Delta\delta_H$Me of 0.03 and 0.34 ppm for **3** and **4**, respectively. The latter difference was close to that found for **2** ($\Delta\delta_H$ 0.41 ppm; δ_H 2.91, 3.32).[2] The intermediate $\Delta\delta_H$Me values were reported for structurally related heteroaromatic amides, e.g. $0.15 \leq \Delta\delta_H \leq 0.22$ ppm refers to two isomeric 2,6-disubstituted 3-(*N*,*N*-dimethylcarbamoyl)-pyridines (δ_H^A 2.93, 2.87, δ_H^B 3.08, 3.09),[13b] and similar data concern *N*,*N*-dimethylbenzamide (δ_H 2.96, 3.10).[13a] In this context, it is worth noting that both *N*-Me groups in **3** resonate at a relatively low frequency (high field), δ_H 2.55, 2.58. Obviously, any suggested overall conformations of **3** and **4** should rationalise all (or, at least, the vast majority) of the aforementioned NMR data.

2.2. Molecular modelling justified statistically by the δ_X^{calc} vs δ_X^{exp} relationship

The modelling study was performed to elucidate the molecular structures of compounds **3** and **4**, especially taking their great mobility into account (Section 4). The relatively large size of both objects forced us to make most of these calculations without considering the solvent influences. It turned out that the majority of generated low-energy structures did not satisfy rather rigid conformational constraints derived from complementary NOE data, i.e. average H–H distances. So, examination of the computed models (with respect to their structural goodness for solution) was of crucial importance, as many good geometric candidates reflected only local and not global energy minima. This 'solution criterion' revealed to be the strongest determinant for such goodness, besides the fundamental 'minimum-energy criterion'. Usually recommended[1b,15] calculations weighted with respect to the Boltzmann population analysis of the lowest energy forms, were practically not possible at this stage.

Finally, agreement of δ_Xs (X = H, C), measured and predicted for various geometries, were used in statistical testing[16] of the obtained structures as correct models of the solution conformations. Values δ_X^{calc} were found from isotropic chemical shieldings σ_X computed by an ab initio GIAO magnetic perturbation methodology.[1a,10] All σ_Xs were predicted on the in vacuo designed molecules, considering that the effects of $CDCl_3$ solvent should not significantly affect these parameters. Undoubtedly, both systems do not participate strongly in intermolecular interactions. Therefore, the NMR spectra predicted in this way reflect reasonably well a situation in dilute solution.[17]

In the case of **3**, such an approach gave three 3-21G**-structures, namely two forms $\mathbf{A}_p$ and $\mathbf{B}_p$ of type **I** (differing in the DMC group orientation) and the form $\mathbf{C}_p$ of type **II**. Type **I** means the geometry is similar to that found in the crystal of **5**,[4c] while the subscript p indicates a local planar arrangement applied (Section 4). Indeed, in all these forms, the SCH_3 group was frozen in a pyridine-ring plane, to reflect the strong NOE. Omissions of this torsion angle constraint afforded rotamers giving poorer correlations δ_X^{exp} vs δ_X^{calc}. Consequently, this fragment was initially considered as a molecular unit rotating sufficiently fast between two limiting forms to result in the NMR spectra being time-averages of two conformers (see also below). Instead, our choice for **4** covered only two 3-21G** structures, viz. the form **D** of type **I** and the form **E** of type **II**, in which both *N*-methyl groups are not equivalent in space.

Some geometric, computational and statistical[16] results on pertinent models of **3** and **4** are listed in Table 2. Inspection of the content revealed that a skew form **A** is the most probable overall conformation of **3** (Fig. 1(a)). The contact OCH_3–H-5′ and $\delta_H(NMe_2)$s appeared to be particularly important arguments in this choice. The latter values found for this form (henceforth called $\mathbf{3A}_p$) are different, but of the order being in agreement with the experiment. $\mathbf{3B}_p$ was disqualified by $\delta_H(NMe_2)$ 1.49, whereas $\mathbf{3C}_p$—by too short OCH_3–H-5′ and too high frequency of $\delta_H(NMe_2)$s; it is well exemplified by the lower and higher values of $R(\delta_H)$ and $s(\delta_H^{calc})$, respectively. For **4**, a skew form **D** (Fig. 1(b)) seems to be the most likely conformation, for which good agreement with $\delta_H(NMe_2)^{exp}$s was found. An alternative form **4E** (of lower energy in the gas phase) has too short OCH_3–H-5′ and too long SCH_3–H-2.

A little lower value of $R(\delta_C)$ obtained at the 3-21G** level for $\mathbf{3A}_p$, with respect to that for the ruled out form $\mathbf{3B}_p$, can be explained with the used gas-phase approximation. Although even lower $R(\delta_X)$s characterise **4D**, nevertheless correlations achieved for geometries $\mathbf{3A}_p$ and **4D** are fully satisfying (vide infra). Therefore, these forms can be considered as averaged conformations of the analysed systems, as all structural data both measured and computed can only be accommodated in these structures. Thus, similar magnitudes of NOEs result, generally, in comparable H–H distances in these models (Scheme 2, Table 2). Indeed, slightly longer (compared to those in $\mathbf{3A}_p$) contacts OCH_3–H-5′ in **4D** are responsible for a smaller through-space interaction between the respective atoms (*peri* effect). This results in a high-frequency shift of the H-5′ signal of **3**, in accord with observation. Obviously, it can realise that all the NMR data were interpreted in terms of the overall *non-solvated* conformations as representations of real *solvated* conformers; see also Ref. 18. So, a small violation of some NOE distance constraints is permissible.

To gain a deeper insight into the electronic properties, more advanced calculations on structures $\mathbf{3A}_p$ and **4D** were performed at the higher HF/6-31G* level; final geometries are shown in Figure 1. Moreover, distinct rotamers about the C3′-SMe axis in **3A** were considered (Table 2). Two rotational forms $\mathbf{3A}_{in}$ and $\mathbf{3A}_{out}$ were found, where index indicates a relative orientation of the SMe group with respect to the skew molecular conformation. In addition, the Gibbs-free-energy difference between these conformers was predicted (Section 4), $\Delta G^\circ_{298} = 7.16$ kJ mol^{-1}, in favour of $\mathbf{3A}_{out}$. However, subsequent NMR data resulted again in poorer correlations $\delta_{C,H}^{exp}$ vs. $\delta_{C,H}^{calc}$ and, especially, δ_C^{exp} vs δ_C^{calc}

Table 2. Selected structural, energetic, ^{1}H NMR and regression data calculated for the forms **A**–**E** of sulfides **3** and **4**

Geometry or calculational result[a]	**3A**$_p$		**3A**$_{in}$[b]	**3A**$_{out}$[b]	**3B**$_p$	**3C**$_p$	**4D**		**4E**
SC*H*–H-2′ (Å)	2.26, 2.26	*2.28*, *2.28*	*2.30*, *3.14*	*3.30*, *4.38*	2.26, 2.26	2.27, 2.28		—	
OC*H*–H-5 (Å)	2.76, 3.37	*2.66*, *3.35*	*2.70*, *3.37*	*2.66*, *3.36*	2.84	2.64, 3.47	2.80, 3.42	*2.68*, *3.39*	2.58
OC*H*–H-5′ (Å)	3.50, 3.55	*3.72*, *3.78*	*3.61*, *3.68*	*3.66*, *3.72*	3.57, 3.61	2.65, 3.09	3.62, 3.65	*3.97*, *4.04*	2.64, 3.00
SC*H*–H-2 (Å)					—		2.35, 3.57	*2.51*, *3.50*	4.01, 4.19
C2–C3–S–C4′ (°)[c,d]	77.0	*73.2*	*77.9*	*74.9*	69.2	131.4	67.4	*60.2*	119.2
C3–S–C4′–C3′(°)[c,e]	−121.9	*−123.8*	*−125.9*	*−123.5*	−121.3	−65.9	−122.1	*−123.1*	−67.4
Angle θ_R (°)[c,f]	79.4	*83.5*	*82.2*	*82.6*$_5$	87.9	76.9	88.4	*84.1*$_5$	88.5
Angle θ_P (°)[g]	65.5	*78.3*	*76.8*	*76.5*	67.2	45.8	60.5	*73.7*	67.7
ΔE_T (kJ mol^{-1})[h]	5.69	*6.77*	*2.27*	*0.00*[i]	5.57	0.00[j]	2.96	[k]	0.00[l]
$\delta_H(NMe_2)^{calc}$ (ppm)[m]	2.67, 3.09	*2.53*, *2.93*	*2.42*, *2.90*	*2.52*, *2.97*	1.49, 2.92	3.31, 3.29	2.64, 3.17	*2.52*, *3.08*	2.32, 3.00
$\delta_H(NMe_2)^{exp}$ (ppm)					2.55 and 2.58			2.86 and 3.20	
$R(\delta_C)$, $s(\delta_C)$ (ppm)[n]	0.9979, 2.76	0.9977, 2.89	*0.9961*, *3.81*	*0.9928*, *5.20*	0.9980, 2.70	0.9978, 2.77	0.9967, 3.48	*0.9974*, *3.14*	0.9963, 3.74
$R(\delta_H)$, $s(\delta_H)$ (ppm)[n]	0.9940, 0.29	*0.9964*, *0.23*	*0.9971*, *0.21*	*0.9946*, *0.29*	0.9892, 0.42	0.9867, 0.44	0.9925, 0.32	*0.9971*, *0.20*	0.9753, 0.63
$R(\delta_{C,H})$, $s(\delta_{C,H})$ (ppm)[n]	0.9994, 2.32	*0.9992*, *2.60*	*0.9988*, *3.15*	*0.9979*, *4.20*	0.9994, 2.30	0.9994, 2.25	0.9991, 2.81	*0.9991*, *2.77*	0.9989, 3.11

[a] For 3-21G** (roman) and 6-31G* (italic) structures.
[b] A geometrically unconstrained *in* or *out* rotamer (see text).
[c] In **5** (X-ray study,[4c,7] the CSD refcode SOPHOU).
[d] 69.3(2)°.
[e] −105.2(2)°.
[f] 73.7(1)°.
[g] Interplanar angle between a least-squares plane of the DMC group (formed by 4 or 5 heavy atoms) and the pyridine ring.
[h] Relative changes in total energy E_T at the RHF//6-31G*/3-21G** (SP results, roman) or RHF/6-31G* level (italic).
[i] E_T of *−1991.28546* au. (1 au=1 hartree ≈ 2625.50 kJ mol^{-1}).
[j] E_T of *−1991.27844* au.
[k] E_T of *−1991.29027* au.
[l] E_T of −1991.28396 au.
[m] For *trans*- (to C=O) and *cis*-Me groups, respectively.
[n] Correlation coefficient R and RMS error s (standard deviation of δ_X^{calc}s about the best-fit regression line of the type $\delta_{Xi}^{calc}=a+b\delta_{Xi}^{exp}$).[16]

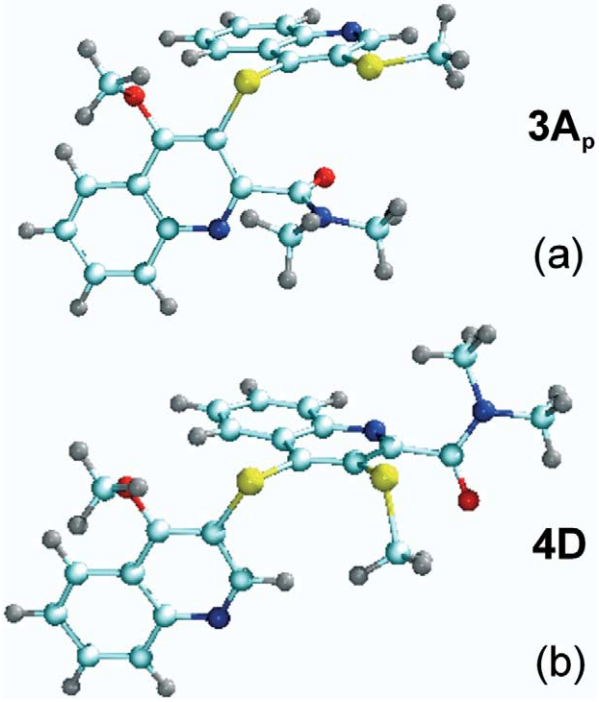


Figure 1. 3D plots of the ab initio HF/6-31G*-optimised structures of the NOE and GIAO supported overall conformations of compounds **3** (upper part a, form $\mathbf{3A}_p$) and **4** (lower part b, form **4D**) in solution.

(Table 2). Surprisingly, this concerned particularly δ_Xs for the preferred conformer $\mathbf{3A}_{out}$ and those computed in the simple Boltzmann-weighted consideration[1b,15] of both rotational forms, i.e. for the virtual rotamer $\mathbf{3A}_{out/in}$ consisting of $\mathbf{3A}_{out}$ (94.7%) and $\mathbf{3A}_{in}$ (5.3%). Therefore we assumed that in solution this molecular unit exists as a rapidly interconverting equilibrium mixture of both these rotamers (and/or other forms similar in shape), that is represented quite well by an overall structure $\mathbf{3A}_p$.

An energetic aspect of the two competitive nucleophilic additions is also interesting. Thus, sulfide **4** appears to be thermodynamically favoured compared to **3** [ΔE_T of 14.5 kJ mol^{-1} (single-point HF/6-31G*//3-21G** result for $\mathbf{3C}_p$ and **4E**) or 19.4 (12.6) kJ mol^{-1} as found for $\mathbf{3A}_p$ ($\mathbf{3A}_{out}$) and **4D** recomputed at the HF/6-31G* level; Table 2, footnotes h–l]. So, preparation of **3** and **4** in the ratio ca. 3:2 indicates that their formation is governed mainly by kinetic control. The sterically favoured γ-attack on C-14a in **2** was expected, considering the influence of the voluminous DMC group.

2.3. Spatial orientation of ring substituents vs NMR spectra

In both structures $\mathbf{3A}_p$ and **4D** groups OMe and C(O)NMe_2 (strictly, its bulkier NMe_2 unit) are *out* oriented with respect to the skew conformations. Accordingly, the SMe group in **4D** is *in* oriented to minimise steric interactions with an adjacent DMC group (Fig. 1(b)). Moreover, all δ_Hs predicted for *N*-Me protons in the latter substituents (Table 2) are consistent with an empirical rule for *N*,*N*-disubstituted aromatic amides, that signals of *N*-groups *cis* to the carbonyl oxygen are shifted to high frequency relative to those *cis* to an aromatic ring.[14,21]

As regards the amide fragment, in both cases the C(O)NMe_2 plane is twisted ca. 76° out of a parent pyridine ring (HF/6-31G* result).[22] Our finding is midway between arrangements observed crystallographically for **1** possessing the *in*-oriented NMe_2 group ($\theta_P=55.0°$)[6] and 2-substituted *N*,*N*-dialkylaryl amides (alkyl = *i*-Pr), in which steric hindrance totally dominates conformations (both planes lie more or less perpendicular).[23] Thus, small shielding of protons of one of two *N*-Me groups in $\mathbf{3A}_p$, i.e. the group *cis* to the C=O and *transoid* to OMe at C-4, can be rationalised by a classical shielding influence of the γ′-quinoline-ring current. (A similar 0.71 ppm low-frequency shift of H-2 was found for **5**.[4c,d]) In addition, this Me group is closely placed to the γ-quinoline-ring plane, and so its protons are deshielded, at the same time. As the above anisotropic effects are opposing one another, this group suffers a magnetic influence practically similar to that experienced by the second Me group (inside the γ-ring shielding zone). Consequently, all *N*-Me protons in $\mathbf{3A}_p$ should be NMR equivalent (or nearly so) and, simultaneously, they should resonate at a lower frequency compared to those for **2** or **4**. These predictions are in accordance with the experiment (two discrete Me signals only 0.03 ppm apart, $0.28 \le \Delta\delta_H Me \le 0.77$ ppm).

On the contrary, solely deshielding influence of the γ′-quinoline moiety may be considered for **4D**, in which the two *N*-Me groups are not spatially equivalent. The first of them (*cis* to the C=O group, more deshielded) is nearly in the plane of a parent heteroaryl ring, whereas the second one is located above this plane. An analogous arrangement was found in the crystal of **2**.[2b] Such a different magnetic environment of these two chemically equivalent *N*-Me groups results in significant NMR non-equivalency of their protons, in agreement with the observation; $\Delta\delta_H Me$ of 0.41 and 0.34 ppm for **2**[2b] and **4**,[2c,5] respectively.

2.4. Some remarks on statistical correlation analysis

Scatter diagrams, least-squares lines, and values of *a* and *b* for final geometries $\mathbf{3A}_p$ and **4D** are given in Figure 2. For every of them, calculated and measured δ_Xs matched very well; $R(\delta_{C,H})>0.999$, $R(\delta_C)=0.997$–0.998 and $R(\delta_H)=0.996$–0.997 for 36, 23 and 13 data points, respectively. Similar values of *R* and *s* were reported in the GIAO DFT analysis of conformationally rigid heteroaromatics; $R(\delta_C)=0.998$, $s(\delta_C^{calc})=2.30$ ppm.[24] $R(\delta_C)$s of 0.995–0.999 were also found in the HF/6-31G* study on medium-sized natural products.[25] Parameters $-0.24 \le a \le -0.15$ and $0.996 \le b \le 0.997$ obtained for $\mathbf{3A}_p$ and **4D** at the HF/6-31G*//3-21G** level are especially worth mentioning, as they are very close to ideal values of 0.0 and 1.0, respectively. However, much better δ_Hs and related statistics were found at the 6-31G* level (Table 2). On the whole, our statistical results can be regarded as the best proof of the correctness of these overall conformations for solution.

Two resulted scatter graphs of type δ_{Xn}^{calc} vs. δ_{Xn}^{exp}, where $n \ge 2$[26] (Fig. 2), showing very strong two-nuclear linear

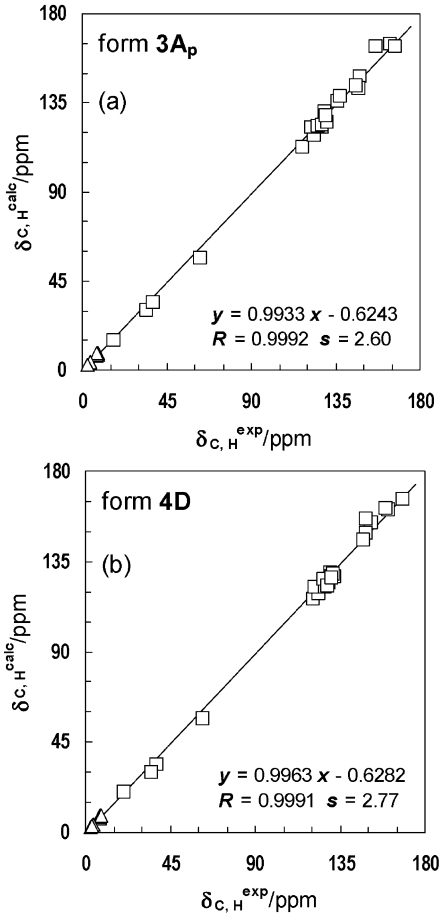


Figure 2. Scatter plots of isotropic $\delta_{C,H}^{calc}$ vs. $\delta_{C,H}^{exp}$ for the most probable overall HF/6-31G* structures of compounds **3** (part a, top, form **3A**$_p$) and **4** (part b, bottom, form **4D**) in solution; see Table 2, footnote n. The δ_C and δ_H data points are shown as squares and triangles, respectively.

regressions between different δ_Xs for the same object, merit some comment. Double sets of values δ_C and δ_H (calculated and measured) are usually considered as two independent series of the NMR parameters. Frequently, such separate mathematical operations involve several structurally close molecules.[1,24] However, there is no reason against performing the multi-nuclear regression analyses, provided that appropriate standards of δ_Xs are applied. The latter approach was reported only occasionally in the literature.[27]

2.5. Position, scope and limitations of the method

The used approach, including some NOE-based constrains and resulting in elucidation of the *overall conformation*, reminds the 3D NMR solution structure determination of macromolecules. In the latter case, numerous torsion angle constraints (derived largely from *J*-couplings) and, especially, a wide variety of H–H distances and connectivities detected by homo- and heteronuclear correlation experiments are of the fundamental value. Computationally intensive procedures are employed to convert NOE cross-peak intensities into H–H distance constraints, usually using the corrections to account for motional averaging, interactions involving Me groups, etc. The final *single representative conformer* is identified as the structure that best satisfies the NMR constraints, as the energy-minimised structure derived from the averaged co-ordinates of an entire ensemble of conformers, or as the structure that is closest to the averaged co-ordinates of the ensemble.[28] Some aspects of such an application of solution-state NMR spectroscopy to proteins and nucleic acids were briefly outlined.[29]

So, the NMR-derived structure is represented by the single geometry, both for the macromolecular and medium-sized object. An average structure of the former is calculated from a large collection of experimental constraints. On the contrary, the measured NMR spectra are fitted (as δ_X^{exp}s) to several tentative sets of δ_X^{calc}s GIAO computed for various ab initio molecular models pre-selected before in line with not numerous NOE constraints, for the latter. The geometry refinement and/or the structure choice (validation or rejection) are performed by statistical analysis in both protocols.

As to the proposed method, it seems that it can be applied to flexible proton-containing carbo- and heteroaromatics as well as to some related, moderately flexible semi- and saturated systems, if (i) their NMR-active nuclei X are responsible for sufficiently different δ_Xs, and (ii) their molecules do not participate strongly in solute-solvent interactions. The fulfilment of the latter requirement guarantees a larger reliability of the GIAO calculational results.

3. Conclusions

The great importance of both adequate molecular modelling (followed by the GIAO predictions of σ_Xs) and NOE-based interproton distances for selection of preferred conformational states of the title compounds in solution was demonstrated. The balance between the fundamental *energetic* (gas-phase theoretical result) criterion and the *geometric* (NOEs for solution) criterion must be taken into account in making all choices of this kind. However the best fitting the δ_X^{exp}s (i.e. magnitudes of values of *R* and *s*) was the *statistical*, most verificative criterion of these choices. Two-nuclear $\delta_{C,H}^{calc} = f(\delta_{C,H}^{exp})$ relations were discussed in detail, but very strong correlations exist also for δ_Cs and δ_Hs alone. Most likely, this is the case for the majority of flexible systems. A disclosure of subtle stereoelectronic effects of quinoline rings and heteroatoms as NMR shielding influences operative in molecules **3** and **4**, fully confirmed the correctness of the structural choices that were taken.

It is apparent that the overall forms **3A**$_p$ and **4D** represent whole families of closely related conformational states, rather than single species. Moreover these molecular models, obtained in the three-stage 'NMR data (δ_X, NOE, 2D connectivities) analysis/ab initio modelling and spectra prediction/statistical δ_{Xn}^{calc} vs. δ_{Xn}^{exp} treatment' protocol, correspond to local and not global energy minima (in the sense of simulating the structure of an isolated molecule). This finding is in agreement with the well-known importance of solvents as surrounding media modifying the shapes of flexible objects. It is likely that more advanced, Boltzmann-weighted considering the large quantity of conformers (undoubtedly closely related to **3A**$_p$ and **4D**)

based on the NOE vs. distance constraints and supported with suitable calculations of solvent effects, will give still better results. However, molecular size of these systems efficiently prevents such computations at the current time.

4. Experimental

4.1. Preparation of sulfides 3 and 4

A suspension of **2**[2a] (0.40 g, 1 mmol) and MeONa (0.16 g, 3 mmol) of in dry DMSO (10 mL) was stirred at ca. 293 K for 0.5 h. The resulting mixture was poured into 20 mL of 15% aq. NaOH, filtered and methyl iodide (0.08 mL, 1.2 mmol) of was added to the filtrate with intensive stirring. Stirring was continued for 15 min and mixture was extracted with $CHCl_3$ (3×10 mL). Combined extracts were washed with water, dried ($MgSO_4$), filtered and evaporated in vacuo to give a yellow viscous liquid consisting of **3** (32%), **4** (24%), and unchanged substrate **2** (27%) [by quantitative TLC: SiO_2 (Merck, 60 F_{254} plates), $CHCl_3$–EtOH (19:1, v/v), UV visualisation]. This mixture was separated by column chromatography on SiO_2 (Merck, 100–200 mesh) using the aforementioned solvent system as an eluent.

4.1.1. 2-(*N*,*N*-Dimethylcarbamoyl)-3-(3-methylsulfanyl-quinolin-4-ylsulfanyl)-4-methoxy-quinoline (3). Pale yellow oil. R_f=0.36. ^{1}H NMR: δ 8.71 (s, 1H, ArH), 8.59–8.55 (m, 1H, ArH), 8.08–7.99 (m, 3H, ArH), 7.72–7.62 (m, 2H, ArH), 7.60–7.52 (m, 2H, ArH), 3.95 (s, 3H, OMe), 2.58 (s, 3H, NMe), 2.55 (s, 3H, NMe), 2.51(s, 3H, SMe). ^{13}C NMR: see Table 1. LR MS, *m*/*z* (rel intensity, %): 435 (*M*, 2), 388 (13), 363 (100), 345 (15), 330 (15). HR MS: $C_{23}H_{21}O_2N_3S_2$ requires *M*=435.1075, found *M*=435.1083.

4.1.2. 2-(*N*,*N*-Dimethylcarbamoyl)-4-(4-methoxy-quinolin-3-ylsulfanyl)-quinoline (4). Pale yellow oil. R_f=0.43. ^{1}H NMR: δ 8.40–8.36 (m, 2H, ArH), 8.27 (s, 1H, ArH), 8.15–7.96 (m, 1H, ArH), 7.75–7.65 (m, 3H, ArH), 7.60–7.49 (m, 2H, ArH), 4.16 (s, 3H, OMe), 3.20 (s, 3H, NMe), 2.86 (s, 3H, NMe), 2.45 (s, 3H, SMe). ^{13}C NMR: see Table 1. LR MS, *m*/*z* (rel intensity, %): 435 (*M*, 13), 392 (26), 363 (31), 331 (20), 277 (100). HR MS: $C_{23}H_{21}O_2N_3S_2$ requires *M*=435.1075, found *M*=435.1064.

R_f of the starting material **2**: 0.48 (TLC conditions and visualisation, as above).

4.2. Spectroscopy

The ^{1}H and ^{13}C NMR spectra of **3** and **4** were recorded at 303 K for ca. 0.1 mol L^{-1} $CDCl_3$ solutions on a Bruker MSL 500 spectrometer operating at 500.133/125.769 MHz for ^{1}H/^{13}C nuclei. All δ_Xs were referenced to internal tetramethylsilane (TMS). Samples for NOE difference experiments were carefully flushed with argon. The ^{1}H–^{13}C correlation information was obtained with an usual combination of the inverse-detected one-bond and long-range 2D experiments HSQC and HMBC, respectively. Low- and high-resolution electron-impact mass spectra (MS) were taken on an AMD 604 spectrometer (70 eV).

The HSQC (heteronuclear single-quantum correlation) experiments were performed on a 1600×2048 data matrix (F_1, F_2) with 2 scans per t_1 increment, using the gradient selection pulse sequence *invietgs*. Spectral widths (SWs) were 19–25 kHz in the ^{13}C evolution dimension (F_1) and 1.5–4 kHz in the ^{1}H acquisition dimension (F_2), 90 and 180° ^{1}H pulses (P1, P2) 7.0–7.5 and 14.0–15.0 μs, 90 ^{13}C pulses (P3) 13.0 μs, acquisition times (AQ) 0.23–0.34 s, and the *garp* composite-pulse-decoupling (^{13}C) sequence applied during the acquisition. The HMBC (heteronuclear multiple-bond correlation) experiments were performed on a 1600×2048 matrix (F_1, F_2) with 4–8 scans per t_1 increment, using the pulse program *inv4gplplrnd* that includes a low-pass *J* filter to suppress one-bond cross-peaks. SW's were 19–23 kHz (F_1) and 3–4.5 kHz (F_2), 90 and 180° ^{1}H pulses (P1, P2) 7.0–7.5 and 14.0–15.0 μs, the 90° ^{13}C pulse (P3) 13.0 μs, and AQ of 0.23–0.49 s. The 1D NOE difference experiments were performed with the sequence *noemul*. SW's were ca. 6 kHz, 32 K data points (TD), 90° ^{1}H pulse time (PL1) 8.8 ms, power level for the NOE build-up (PL14) 84 dB, AQ of 2.7 s, relaxation delay (D1) 1.0 s, irradiation time (D20) 0.06 s, and 96 scans for each multiplet.

4.3. Molecular modelling

A wide search for minima on potential energy hypersurfaces was carried out initially with an external co-ordinate Monte Carlo (MC) technique. The molecular-mechanics searching protocol[30] applying the randomisation procedure of Saunders-type[8] was used within PCMODEL (MMX force field).[31] Typically, 800–1000 MC steps were used within the 21 kJ mol^{-1} energy window; a bulk value of the relative permittivity being applied for the gas phase, ε=1.50.[32] All low-energy forms were justified in the light of experimental NOE data[2c,5] and applied as starting points in a further geometry refinement using the MM+ force field[33] of HyperChem.[34] Resulting molecular models were selected, fully optimised by the PM3 method (HyperChem) and verified again in view of both NOE results and NMR spectra predicted for geometries such obtained.

Fully relaxed (or slightly conformationally constrained for **3**, by freezing the torsion angle C4′–C3′–S–C to 180°) geometry optimisations were performed at the ab initio restricted Hartree–Fock level using the Gaussian 98W electronic structure package.[20] A fully polarised 3-21G** basis set was applied due to the sulfur atoms; use of larger basis functions was practically impossible, at this stage. Some computations were also realised for the simulated presence of solvent, by employing the Onsager's model reaction field.[19,20] Finally, the HF/6-31G* level computations were carried out on models $\mathbf{3A}_p$ and **4D**. Moreover, frequency calculations[35] were performed to determine the standard Gibbs free energies (G°) for rotamers $\mathbf{3A}_{out}$ and $\mathbf{3A}_{in}$ at 298.15 K; the scale factor of 0.9135[35,36] was used. Geometric calculations of angles θ_i were carried out with PLATON.[37] Computed structures were visualised as their ray-traced pictures applying the rendering program POV-Ray,[38] on the basis of graphic outputs from PCMODEL V 8.5.[39] The Intel 1.5 or 2.6 GHz Pentium 4 class PCs running under MS Windows® XP Professional were used.

4.4. NMR spectra prediction

Single-point GIAO-CPHF (gauge including atomic orbital, coupled-perturbed Hartree–Fock)[10] calculations of absolute isotropic nuclear magnetic shielding tensors (σ_Xs) were performed with standard routines in the Gaussian 98W.[20] The relative chemical shift of a given nucleus X in the molecule was defined as δ_X^{calc} [ppm]$=\sigma_X^{ref}-\sigma_X^{calc}$. For the ^{1}H and ^{13}C spectra, σ_X^{ref} is equal to 32.9701 and 202.0729 ppm (32.9034 and 201.7279 ppm), respectively, as found on the HF/3-21G** (or 6-31G*) geometry of the dual-reference δ_X standard (TMS of the T_d symmetry).[26] Statistical analysis was carried out by the MS Excel® 97 spreadsheet.

Acknowledgements

The authors thank Professor A. Maślankiewicz for his guidance in the early stages of research and continuing interest in this work.

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Experimental and theoretical approaches into the C- and D-ring problems of sterol biosynthesis. Hydride shift versus C–C bond migration due to cation conformational changes controlled by the counteranion

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Received 26 June 2004; revised 21 July 2004; accepted 22 July 2004

Abstract—The C- and D-ring problems of sterol biosynthesis, how an enzyme overcomes the Markovnikov wall, were investigated by using a model compound from an experimental as well as theoretical standpoint. When model diol **20** was treated with $BF_3 \cdot Et_2O$, $SnCl_4$, TiF_4, $Sc(OTf)_3$, $FeCl_3$, or TfOH, spirocyclic ether **21** was formed as the sole product via a *tert*-cationic intermediate **16** through 1,2-hydride shift. However, the treatment with $TiCl_4$ afforded six-membered ring products **22**, **23**, **24**, **25**, **26**, and **27** via the ring expansion into the unstable six-membered ring secondary cation **17**. Occurrence of both α and β chloride **23** and **24** is distinctive evidence of the existence of secondary cation **17**, ruling out the idea of the concerted mechanism. Molecular mechanics calculations of the naked cation **15** elucidated two possible conformers, parallel **15-I** (five membered ring and cationic plane) that is favorable for the hydride shift generating **16** and perpendicular **15-II** leading to C–C bond migration to **17**. The first ab initio calculation of the cation conformation in the presence of counteranions such as $[TiCl_4OH]^-$, $[TiF_4OH]^-$, $[BF_3OH]^-$, and $[OTf]^-$ entirely supported our experimental results. Although the counteranion $[TiCl_4OH]^-$ stabilizes perpendicular cation **15-II**, it destabilizes the parallel conformer **15-I** significantly, and thus, the C–C bond migration to **17** becomes the only possible pass. On the other hand, $[TiF_4OH]^-$, $[BF_3OH]^-$, and $[OTf]^-$ stabilize parallel conformer **15-I** and the hydride shift to **16** becomes the only possible pass. The relative location or distance of the counteranion from the cation should be the biggest factor to control the stability and, thus, the conformation of the cation. Our results indicate that the carboxylate anions in the enzyme cavity enable to control the conformation of pre-C-ring cationic intermediate **3** to be perpendicular leading to six-membered C-ring secondary cation **4**. The parallel conformation of the cation **5** could lead to hydride shift to give tirucallanoids or lanostanoids. Therefore, this result is the first example that overcame the big Markovnikov wall experimentally and theoretically at least to our knowledge.

1. Introduction

Remarkable enzymatic cyclization of squalene and oxidosqualene has been achieved by a wide range of microorganisms and higher eukaryotes to yield polycyclic triterpenoides.[1,2] Today, the biosynthesis of phytosterols such as dammaranoid, lupanoid, oleananoid, and tirucallanoid are explained by the stepwise cyclization of oxidosqualene via the monocyclic cation **1**, the bicyclic cation **2**, the tricyclic 6/6/5-cation (pre-C ring cation) **3**, the secondary 6/6/6-cation **4**, and the 6/6/6/5-cation **5**.[3,4] Hydride shift (*a*) and C–C bond migration (*b*) from **5** are competing processes leading to tirucallanoids and tetrahymanoids, respectively. In the animal kingdom, steroids are also constructed through the corresponding boat-form B-ring intermediates (Scheme 1).[1b,5,6]

In 1985, we achieved the cyclization of geranylgeranyl acetate **6** with our original cyclization agent, $Hg(OTf)_2$–dimethylaniline complex,[5] in the presence of water when the mono-, bi-, and tricyclic cationic intermediates were trapped to give *tert*-alcohols **7**–**9**.[6] This is the first experimental evidence that the biomimetic olefin cyclization takes place via conformationally flexible cationic intermediates. In 1984, we also achieved the cyclization of **6** without water and found that the chair/chair cyclization competed with the chair/boat cyclization in 5:1 ratio to give **10**, **11**, and **12** after bromination.[7] This result served as the first example to show that the boat-form B-ring product was formed by means of biomimetic olefin cyclization.[8] Recently, we have shown that the 6/5-*trans*-selective

Keywords: Steroid biosynthesis; C-ring problem; $TiCl_4$; *anti*-Markovnikov rearrangement; Cation conformation with counteranion.
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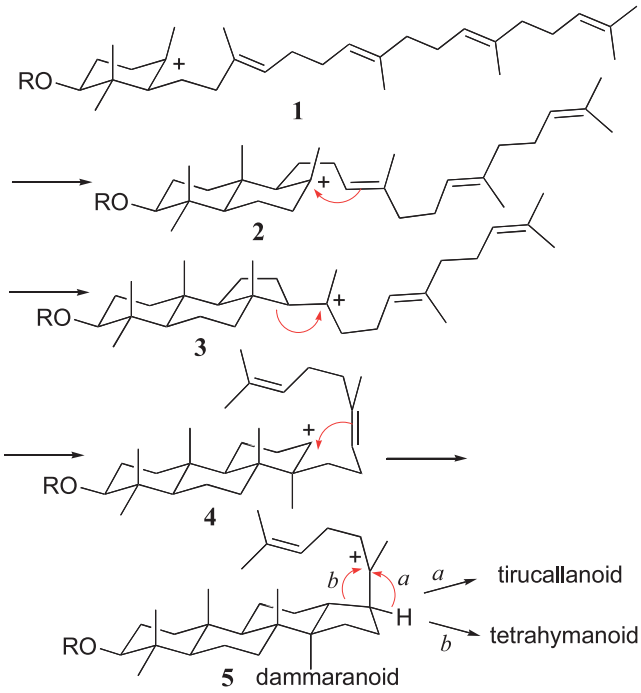
doi:10.1016/j.tet.2004.07.064

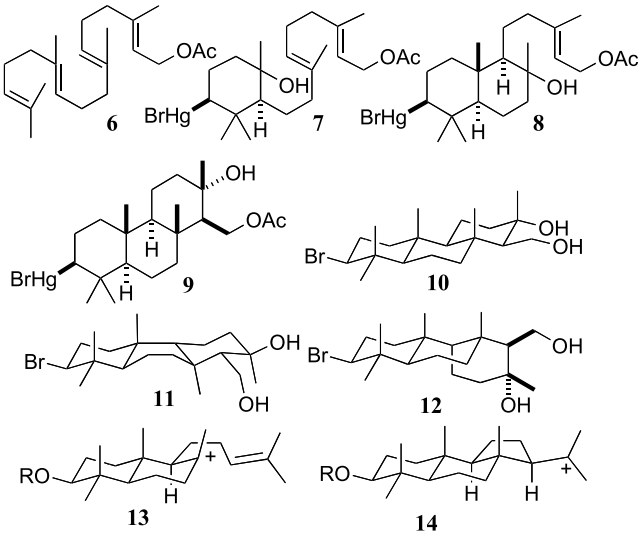


Scheme 1.

cyclization of **2** into **3** does not depend upon any special enzyme power by achieving a similar 6/5-*trans*-selective cyclization of **13** into **14** by a chemical process promoted by a Lewis acid.[9] The next mystery to be solved was the enzymatic rearrangement of the stable *tert*-cation **3** to the unstable six-membered ring *secondary*-cation **4**, how the enzyme overcomes the formidable Markovnikov wall (Scheme 2).[1a,3b,3e,10,11]

2. Results and discussion

The transformation of **3** into **4** involves ring expansion of a *tert*-cation into an unstable *sec*-cation.[3b] To achieve a similar transformation through organic synthesis, we planned to generate a model cation such as **15** and

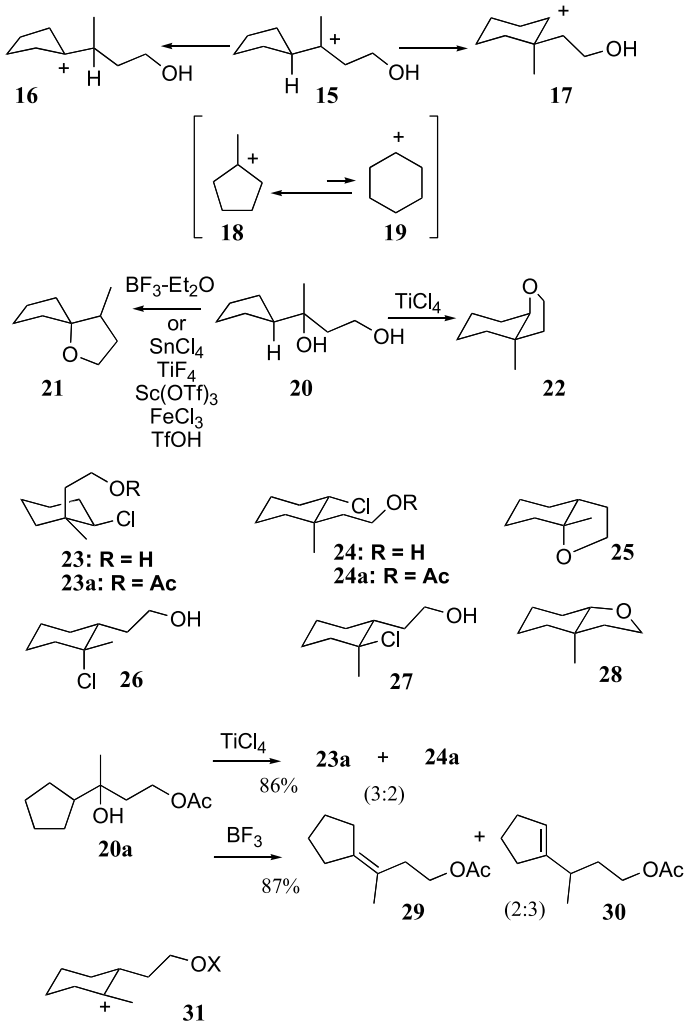


Scheme 2.

investigate its chemical behaviour. The hydride shift to the *tert*-cation **16** corresponds to the hydride shift *a* in the dammaranoid cation **5**. Likewise, ring enlargement to the *anti*-Markovnikov cation **17** corresponds to the carbon–carbon bond migration *b* in the cation **5** leading to the formation of the six-membered D-rings and C-ring formation from **3**. Olah has pointed out that the equilibrium between the cyclopentylmethyl cation **18** and the cyclohexyl cation **19** favors overwhelmingly **18** based on NMR experiments.[12] Harding has also reported a similar tendency through the synthesis of 1-acetyl-2-methylcyclopentene from cyclohexane and CH_3COCl in the presence of $AlCl_3$.[13] Theoretical calculations of model cations have also pointed out the energetical disadvantage of the latter process.[11a] Therefore, we investigated the reactions of the diol **20** with a variety of Lewis acids. Although most of the Lewis acids afforded only the *spiro*-product **21** via a hydride shift by generating the cation **16**, $TiCl_4$ surprisingly generated the *anti*-Markovnikov cation **17** selectively and afforded the six-membered ring compound **22** along with other related products.[14] The remarkable selectivity achieved with $TiCl_4$ was explained by the counteranion-controlled conformational changes in the cation.[15] These were, in fact, the first theoretical calculations on cation conformations in the presence of counteranions (Scheme 3).

Although the diol **20** was inert to $BF_3{\cdot}Et_2O$ (3 equiv) in CH_2Cl_2 at 0 °C, a rapid reaction took place at 25 °C to afford the spirocyclic species **21** as the sole product in 82% yield (Table 1, entry 1). The reactions of **20** with 3 equiv each of $SnCl_4$, $Sc(OTf)_3$, $FeCl_3$, TiF_4, and CF_3SO_3H in CH_2Cl_2 at 25 °C for 30 min also provided only the *spiro*-ether **21**. However, the reaction of **20** with 3 equiv of $TiCl_4$ in CH_2Cl_2 at 25 °C afforded an entirely different result. Intensive purification of the complicated reaction mixture provided the 6/5 *cis*-fused ether **22** (16%), the *cis*-chloro alcohol **23** (13%) and its *trans*-isomer **24** (26%), the 6/5 *cis*-fused ether **25** (9%), the *cis*-chloro alcohol **26** (16%), and the *trans*-chloro alcohol **27** (7%) along with 1% of **21** (Table 1, entry 8). The 6/5 *trans*-fused ether **28** was not detected from any of these reactions. When the corresponding acetate **20a** was treated with $TiCl_4$, a very clean reaction took place to afford a 3:2 mixture of the chlorinated products **23a** and **24a** in 86% yield. On the other hand, the reaction of **20a** with $BF_3{\cdot}Et_2O$ afforded a 2:3 mixture of the olefins **29** and **30**. Thus, the latter reaction induced only a hydride shift corresponding to the transformation of **15** into **16**. The reaction of **20** with $AlCl_3$ and $ZrCl_4$ under identical conditions provided an alternative result. Only the 5/6 *cis*-product **25** was obtained in 87% and 84% yields, respectively (entries 12 and 13). The products **25**–**27** should be generated via the cation **31** through 1,2-migration of the side chain from **17**. Treatment of **20** with $FeCl_2$, $TiCl_2(O\text{-}i\text{-}Pr)_2$, $ZnCl_2$ and $Zn(OTf)_2$ provided no product and the starting material was recovered almost quantitatively.

The diol **20** was prepared from 3-*tert*-butyldimethylsilyloxypropanal (**32**).[16] Grignard reaction of **32** with cyclopentylmagnesium bromide afforded the alcohol **33** which, following oxidation and methylation, provided the *tert*-alcohol **35**. Cleavage of the TBS group by TBAF provided the diol **20**, and acetylation afforded the acetate **20a**. Structural studies of the cationic reaction products were



Scheme 3.

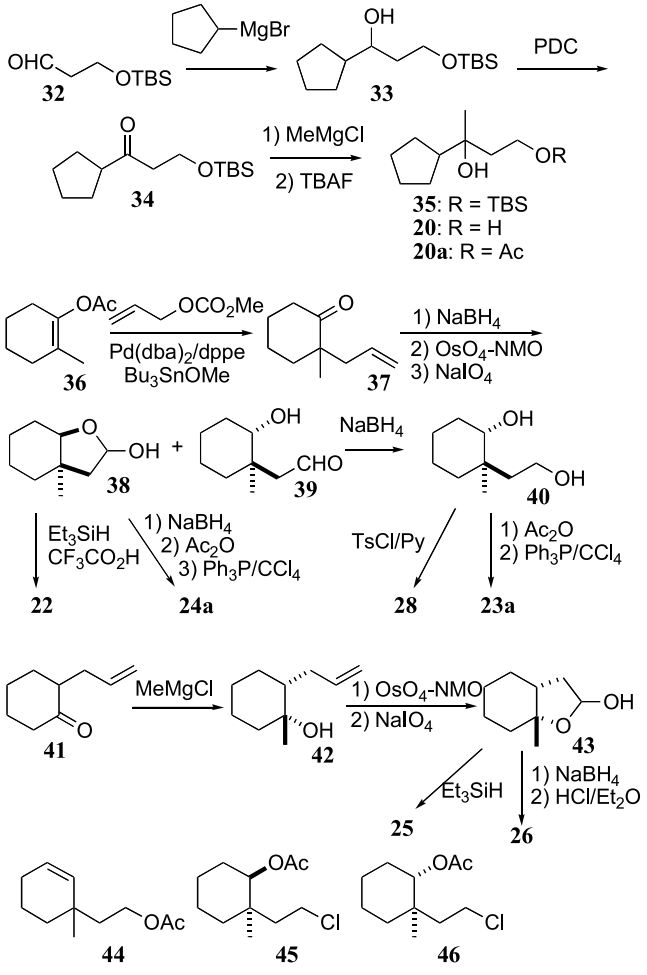
carried out carefully by preparing authentic materials. The spirocyclic ether **21** was derived from the known 1-(3-hydroxy-1-methylpropyl)cyclopentanol on reaction with *p*-TsCl in pyridine in 95% yield.[17] Regioselective allylation of the enol acetate **36** according to Tsuji's protocol afforded the ketone **37** in 90% yield.[18] $NaBH_4$ reduction of **37** followed by treatments with OsO_4-NMO and $NaIO_4$, in that order, afforded the *cis*-fused hemiacetal **38** and the *trans*-hydroxy aldehyde **39** in 38 and 25% yields, respectively. The reaction of the hemiacetal **38** with triethylsilane in the presence of CF_3COOH provided the 6/5 *cis*-fused ether **22** in 83% yield.[19] The alcohol obtained from $NaBH_4$ reduction of **38** was acetylated and then chlorinated with (Ph_3P–CCl_4)[20] to give **24a** (13%), **44** (40%), and **45** (13%). $NaBH_4$ reduction of **39** afforded the *trans*-diol **40**. Part of **40** was converted into the 6/5-*trans*-fused ether **28** on treatment

Table 1. Reaction of diol **20** with acid and Lewis acids in CH_2Cl_2

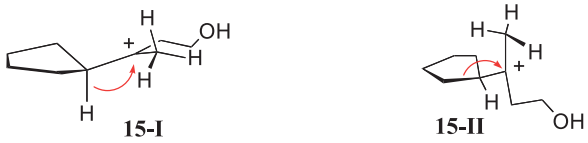
Entry	Acid	Product (% yield)						
		21	**22**	**23**	**24**	**25**	**26**	**27**
1	BF_3Et_2O	82	—	—	—	—	—	—
2	$SnCl_4$	90	—	—	—	—	—	—
3	$Sc(OTf)_3$	51	—	—	—	—	—	—
4	$FeCl_3$	76	—	—	—	—	—	—
5	$FeCl_2$	—	—	—	—	—	—	—
6	CF_3SO_3H	88	—	—	—	—	—	—
7	TiF_4	76	—	—	—	—	—	—
8	$TiCl_4$	1	16	13	26	9	16	7
9	$TiCl_4(O\text{-}i\text{-}Pr)_2$	—	—	—	—	—	—	—
10	$ZnCl_2$	—	—	—	—	—	—	—
11	$Zn(OTf)_2$	—	—	—	—	—	—	—
12	$AlCl_3$	—	—	—	—	87	—	—
13	$ZrCl_4$	—	—	—	—	84	—	—

with *p*-TsCl in 33% yield. Alternatively, the acetylation of **40** followed by its chlorination afforded **23a** (13%), **44** (26%), and **46** (18%). Hydrolyses of **23a** and **24a** using NaOMe in MeOH afforded **23** and **24**, respectively, in quantitative yields. The stereochemical assignments of **23** and **24** were achieved by NOE experiments. Clear NOE cross-peaks between the axial methyl and the axial protons of 1,3-relationship were detected for **24**; **23** did not show any distinctive NOE cross-peaks. 2-Allylcyclohexanone **41**, prepared from 1-acetoxycyclohexene using Tsuji's protocol,[18] was treated with MeMgCl to give the *cis*-carbinol **42** in 73% yield. Cleavage of the double bond of **42** using OsO_4-NMO followed by oxidation with $NaIO_4$ gave the hemiacetal **43** in 62% yield. Treatment of **43** with Et_3SiH in the presence of CF_3COOH provided the *cis*-fused ether **25** in 76% yield.[19] $NaBH_4$ reduction of **43** and further treatment with concd HCl in ether afforded the *cis*-chloroalcohol **26** in 30% yield. Although the formation of the *trans*-isomer **27** was not detected from this chlorination, the stereochemical assignments of **26** and **27** were confirmed by NOE experiments as well (Scheme 4).

It is exciting to consider how the above clear selectivity comes about.[16] MM2 calculations of the cation **15** using the CAChe-CONFLEX-MOPAC programs elucidated the existence of two conformers **15-I** and **15-II**.[21] The conformer **15-I**, that takes parallel alignment of the five-membered ring and the cationic plane, is geometrically suited to hydride shift to generate the cation **16**. The conformer **15-II**, that assumes a perpendicular relationship of the cationic plane and the five-membered ring, should instead result in a marked carbon–carbon bond migration and afford the *anti*-Markovnikov cation **17**. Detection of the actual conformational changes reflecting the nature of the counteranion is the next target of our research (Scheme 5).



Scheme 4.



Scheme 5.

Not only our MM2 calculations but also almost all other publications dealing with the calculations of carbocations[11,22] have been carried out without any counteranion; only the stabilities of the naked cations were discussed. Recently, Farcasiu and co-workers[23] have studied carbocations in ion pairs using ab initio MO methods to understand the behaviour of carbocations in media of low to moderate dielectric constants and where the reaction pathway was determined by transformation of carbocations forming tight ion pair conditions. As indicated by these studies and our own recent calculations,[15] the major stabilization of a cation is likely to come from a counteranion through electrostatic effects. The location of the counteranion in respect of the cation should, therefore, constitute the most important factor for the conformational control of the latter. Thus, we undertook the first calculations of the conformers **15-I** and **15-II** in the presence of counteranions $[TiCl_4OH]^-$, $[TiF_4OH]^-$, $[BF_3OH]^-$, and $[OTf]^-$. As expected, the counteranion indeed contributed significantly to the stabilization of the carbocation that led us to conclude that the rearrangement of the cation **3** to **4** was a reasonable pathway.[15]

Recently, the conversion of pre-C-ring cation **3** to C-ring cation **4** has also been explained by a concerted mechanism.[11b–e] Our non-selective chlorination to give **23** and **24** from **20** (as well as **23a** and **24a** from **20a**) are the distinctive evidence of the existence of the six-membered ring secondary cation **17**. Although the cyclization to form **22** took place stereoselectively, it is quite natural by considering the stability of 6/5 *cis*-fused system over *trans* based system upon the ring strain. Therefore, the present result definitively denied the idea of concerted mechanism from **3** to **4**.

We performed ab initio Hartree Fock molecular orbital calculations with the 6-31G* basis set.[24] The cations **15-I**, **15-II**, **16**, and **17** and the anions $[TiCl_4OH]^-$, $[TiF_4OH]^-$, $[BF_3OH]^-$, and $[OTf]^-$ were completely optimized separately using the Berny optimization algorithm[25,26] of the Gaussian 98 package.[27] The anions were slowly brought in from a distance to the cation and, at each point, the interaction energy of the two was calculated using supermolecule approach. These interaction energies are without the incorporation of the basis set superposition error (BSSE) correction. Since we are interested only in the relative

stabilities of various supermolecules, the BSSE will almost cancel out. In this manner, the optimal cation–anion distance was estimated as the one at which the attractive interaction energy was the maximum. The counteranion was then placed at this optimal distance and the cation was completely optimized in its presence to locate the stationary point for the supermolecule. Although the anion was kept frozen in a particular orientation and the stationary point was found using only partial optimization, all gradients were found to be within the convergence criterion.[28] The anion was then rotated to a different orientation and the resultant supermolecule was optimized for yet another stationary point. The stationary points corresponding to several possible orientations of the counteranion were located. The energetically most favoured orientations of cation and counteranion are reported here.

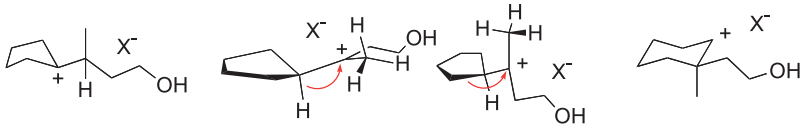
The fully optimized conformations and the relative energies of the naked cations **15-I**, **15-II**, **16**, and **17** are collected in Figure 1. The perpendicular cation **15-II**, that is suitable for carbon–carbon bond migration, is energetically more favored than the parallel cation **15-I** that is suitable for hydride transfer. As expected, the conversion of **15-II** into the *anti*-Markovnikov cation **17** is an unfavorable process with an energy requirement of 9.8 kcal/mol that is comparable to 12 kcal/mol reported by Jorgensen.[11a] In contrast, the transition of the cation **15-I** to **16** is favored by 4.5 kcal/mol. The cations **15-I** and **15-II**, being in equilibrium due to a small energy difference (2.6 kcal/mol), are therefore expected to rearrange to **16** in preference to **17**. This, however, contrasts with our experimental findings.

In this study we demonstrate the stabilization of a cation by a counteranion and its effect on the energetics of the reaction and, thus, the fate of the cation. The relative stabilities of the energetically most favored conformations of cations in the presence of $[TiCl_4OH]^-$ indicate that it stabilizes preferentially the cation **15-II** that is suitable for carbon–carbon bond migration. A close examination reveals that the counteranion approached closer ($C^+\cdots Ti=4.82$ Å) to the cation **15-IIa** than to the cation **15-Ia** ($C^+\cdots Ti=5.5$ Å) (Fig. 1). This allows for better electrostatic interactions in **15-IIa** than in **15-Ia**. An estimate of the electrostatic interaction energy helps us to understand its contribution to preferential stabilization of one cation over the other. We note that 14.8 kcal/mol out of a total difference of 17.4 kcal/mol is due solely to the difference in electrostatic interactions; the remaining difference is of conformational origin. However, minor anion-induced conformational changes in the cation do take place to allow for any possible H-bonds or to maximize interactions with the counteranion.

The relative energies of the optimized product cations in the presence of counteranion $[TiCl_4OH]^-$ (**16a** and **17a**) indicate that **15-Ia**, once formed, will quickly rotate to **15-IIa** and initiate a carbon–carbon bond migration to **17a** even though it is an endothermic reaction. The conversion of **15-IIa** back to **15-Ia** and then to **16a** is unlikely as was indeed observed from our model study (Scheme 6).

From the above discussion, the shape and size of the counteranion appear to be important in determining its electrostatically most favored disposition in respect of the cation that, in turn, may determine the fate of the cation itself. To further understand this, we considered calculations with $[TiF_4OH]^-$ that carries the same Ti metal but has a smaller ligand (F vs Cl). It can be seen clearly that the counteranion can now penetrate much closer to the cation ($C^+\cdots Ti=4.00$ Å in **15-IIb** as compared to $C^+\cdots Ti=4.82$ Å in **15-IIa**) to benefit from greater electrostatic stabilization. The relative energies indicate that the energetics are now controlled largely by the electrostatic interactions and that the conformational effects are reduced to marginal, if not negligible, due to the smaller size of the counteranion. From rotationally isomeric **15-Ib** and **15-IIb**, **15-Ib** is transformed to **16b** via hydride shift in a process that is predicted to be exothermic by 5.2 kcal/mol (8.9 kcal/mol from **15-IIb**). On the contrary, the transformation of **15-IIb** to **17b** via carbon–carbon migration is predicted to be endothermic with an energy requirement as high as 17.2 kcal/mol. This is supported from our experimental results as we observed only the product of hydride migration.

Further, we have performed calculations on the cations in the presence of $[BF_3OH]^-$ and $[OTf]^-$ as the counteranions. The shape and size of these counteranions is such that they can penetrate close to both the rotationally isomeric cations, i.e. (**15-Ic** and **15-IIc**), and (**15-Id** and **15-IId**) and stabilize them to almost equal extent ($C^+\cdots B=3.5$ Å for **15-Ic** and **15-IIc** both); ($C^+\cdots S=3.5$ Å for **15-Id** and **15-IId** both). The relative energies of **15-Ic** and **15-IIc** indicate that they will exist in equilibrium with a small energy difference of 1.39 kcal/mol. This difference is further reduced in the case of $[OTf]^-$ counteranion; **15-Id** and **15-IId** will exist in equilibrium with an energy difference of only 0.91 kcal/mol. This difference is due to the minor differences in electrostatic interactions with the counteranion and almost negligible contribution from the



16: X = none	**15-I**: X = none	**15-II**: X = none	**17**: X = non
16a: X = $TiCl_4OH^-$	**15-Ia**: X = $TiCl_4OH^-$	**15-IIa**: X = $TiCl_4OH^-$	**17a**: X = $TiCl_4OH^-$
16b: X = TiF_4OH^-	**15-Ib**: X = TiF_4OH^-	**15-IIb**: X = TiF_4OH^-	**17b**: X = TiF_4OH^-
16c: X = BF_3OH^-	**15-Ic**: X = BF_3OH^-	**15-IIc**: X = BF_3OH^-	**17c**: X = BF_3OH^-
16d: X = OTf^-	**15-Id**: X = OTf^-	**15-IId**: X = OTf^-	**17d**: X = OTf^-

Scheme 6.

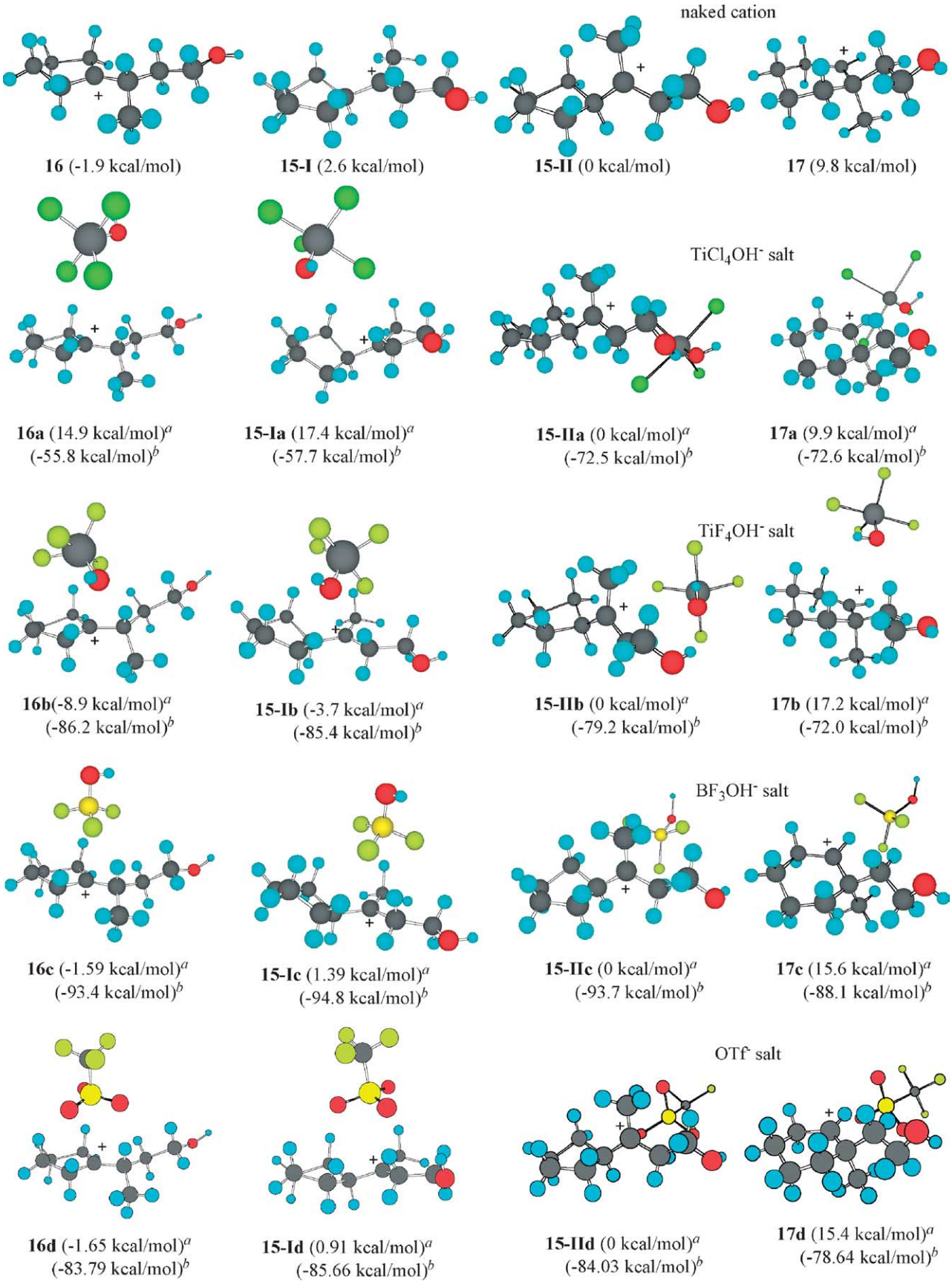


Figure 1. Conformation of cation. (a) Relative energy, (b) Interaction energy.

conformational aspects due to the small size of the ligand and the compact size of the counteranion in both the cases. The equilibrium will be driven to the exothermic hydride transfer process (1.6 kcal/mol from **15**-**IIc**; 1.65 kcal/mol from **15**-**IId**) as compared to carbon–carbon bond migration that is highly endothermic. These calculations support our experimentally observed major hydride transfer product with $BF_3 \cdot Et_2O$ (82% yield) and TfOH (88% yield; c.f. Table 1).

We have, therefore, succeeded in overcoming the formidable Markovnikov wall by changing the counteranion and, in turn, by changing the conformation of the cation. We know the significance of solvent effects. However, the solvent effects cannot outweigh the electrostatic aspects. According to Jorgensen, solvent effect on the similar transformation of his model compound did not exceed 2 kcal/mol.[11a] The relative location or distance of the counteranion from the cation should be the biggest factor to control the stability and, thus, the conformation of the cation. In the enzymatic sterol biosynthesis, the possible counteranion should be limited to the carboxylates of aspartic acid and glutamic acid residues. The relative location of these carboxylates and the cationic center in an enzymatic cavity enable to control the conformation of the pre-C-ring cation **3** or D-ring cation **5** to take the perpendicular conformation leading to carbon–carbon bond migration to give the six-membered ring *sec*-cation or the parallel conformation leading to hydride shift to give tirucallanoids or lanostanoids.[1a,1b,3d,e,4,29]

3. Experimental

3.1. General

All commercially available chemicals were used without further purification. All reactions were carried out with dry glassware under argon atmosphere. Analytical TLC was carried out on Merck 60 F_{254} silica gel plate and column chromatography was performed on Merck 60 silica gel (230–400 mesh). IR spectra were recorded on a JASCO FT/IR-410 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity-600, Varian Mercury-300, Varian Unity-200, Varian Gemini-200, and JEOL JMNGX-400 apparatus. Mass spectra were taken on JEOL AX-500.

3.1.1. Reaction of 3-cyclopentylbutane-1,3-diol (20) with $BF_3 \cdot OEt_2$. To a stirred solution of **20** (91 mg, 0.58 mmol) in dichloromethane (16 mL) was added $BF_3 \cdot Et_2O$ (220 μL, 1.80 mmol) at 0 °C and the mixture was stirred at 25 °C for 30 min. After addition of saturated aqueous $NaHCO_3$, the organic phase was dried and concentrated. Column chromatography using hexane and ether afforded 4-methyl-1-oxa-spiro[4.4]nonane (**21**) (67 mg, 82%) as a colorless oil. FT-IR (film) 2958, 2873, 1454, 1376, 1332, 1184, 1049 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.97 (3H, d, J=6.6 Hz), 1.61–1.48 (6H, m), 1.77–1.68 (3H, m), 2.04 (1H, dddd, J=14.2, 7.4, 7.2, 6.8 Hz), 2.17–2.07 (1H, m), 3.74 (1H, dd, J=15.1, 7.7 Hz), 3.80 (1H, ddd, J=8.5, 4.7, 3.8 Hz); ^{13}C NMR (50 MHz in $CDCl_3$) δ 15.39 (q), 23.73 (t), 24.25 (t), 31.76 (t), 34.13 (t), 36.95 (t), 39.65 (d), 64.40 (t), 93.42 (s); MS (CI) *m/z* 140 (M^+), 111, 98 (base), 85, 55, 44; HR-MS (EI) *m/z* calcd for $C_9H_{16}O$ (M^+) 140.1187; Found 140.1207. Reactions of **20** with $SnCl_4$, $Sc(OTf)_3$, $FeCl_3$, CF_3COOH, and TiF_4 were carried out essentially in the same manner.

3.1.2. Reaction of 20 with $TiCl_4$. To a stirred solution of **20** (530 mg, 3.35 mmol) in dichloromethane (10 mL) was added $TiCl_4$ (1.14 mL, 10.38 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. After addition of saturated aqueous sodium hydrogen carbonate, the organic phase was dried and concentrated. Column chromatography using hexane and ethyl acetate afforded Fractions I and II. Fraction I was further purified by HPLC using YMC-Pack R and D SIL-5 (20×250 mm) column and hexane–ethyl acetate (90:1, 20 mL/min) to give **22** (74 mg, 16%): FT-IR (film): 2935, 2868, 1462, 1381, 1159, 1090, 1053, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, s), 1.86–1.11 (10H, m), 3.43 (1H, dd, J=3.3, 2.7 Hz), 3.97–3.80 (2H, m); ^{13}C NMR (75 MHz in $CDCl_3$) δ 20.57 (t), 21.95 (t), 22.26 (q), 26.37 (t), 32.94 (t), 39.31 (t), 40.74 (s), 64.90 (t), 82.09 (d); MS (CI) *m/z* 140 (M^+), 139, 122 (base), 107, 96, 84, 67, 55, 49, 41; HR-MS (EI) *m/z* calcd for $C_9H_{16}O$ (M^+) 140.1201; Found 140.1171, **25** (42 mg, 9%): FT-IR (film) 2937, 2873, 1448, 1373, 1271, 1180, 1122, 1086, 1049, 954 cm^{-1}; ^1H NMR (300 MHz in $CDCl_3$) δ 1.19 (3H, s), 1.74–1.25 (8H, m), 1.88–1.77 (2H, m), 2.11–1.98 (1H, m), 3.97–3.82 (2H, m); ^{13}C NMR (75 MHz in $CDCl_3$) δ 22.40 (t), 22.82 (t), 25.58 (q), 27.11 (t), 30.58 (t), 34.12 (t), 42.63 (d), 64.34 (t), 80.30 (s); HR-MS (EI) *m/z* calcd for $C_9H_{16}O$ (M^+) 140.1201; Found 140.11, along with **21** (7 mg, 1%). Fraction II was further purified by HPLC using three straight connections of YMC-Pack R and D SIL-5 (20×250 mm) column and hexane–ethyl acetate (7.5:1, 12 mL/min) to give **23** (75.3 mg, 13%): FT-IR (film) 3336, 2938, 2866, 1452, 1051 cm^{-1}; ^1H NMR (600 MHz in $CDCl_3$) δ 1.08 (3H, s), 1.14 (1H, ddd, J=14.0, 9.1, 4.9 Hz),1.29 (1H, br s), 1.41–1.34 (1H, m), 1.51–1.42 (2H, m), 1.89–1.70 (5H, m), 2.00–1.95 (1H, m), 3.74 (2H, ddd, J=10.2, 9.1, 6.1 Hz), 3.88 (1H, dd, J=9.3, 3.8 Hz); ^{13}C NMR (150 MHz in $CDCl_3$) δ 20.96 (t), 24.42 (t), 25.45 (q), 31.78 (t), 35.45 (t), 36.57 (t), 37.78 (t), 59.15 (s), 71.04 (d); MS (CI) *m/z* 177 (M^++1), 159, 141 (base), 124, 95, 81; HR-MS (EI) *m/z* calcd for $C_9H_{18}OCl$ (M^++1) 177.1046; Found 177.1033, **24** (148.4 mg, 26%): FT-IR (film) 3346, 2939, 2862, 1446, 1381, 1053, 972 cm^{-1}; ^1H NMR (600 MHz in $CDCl_3$) δ 1.03 (3H, s), 1.33 (2H, m), 1.46 (3H, m), 1.63 (1H, dddd, J=9.3, 5.8, 3.6, 2.2 Hz), 1.69 (1H, ddd, J=14.0, 8.2, 6.8 Hz), 1.80 (3H, m), 1.99 (1H, dddd, J=13.5, 5.3, 4.2, 1.1 Hz), 3.75 (2H, ddd, J=10.4, 7.9, 6.6 Hz), 3.91 (1H, dd, J=11.0, 4.1 Hz); ^{13}C NMR (150 MHz in $CDCl_3$) δ 18.6 (q), 21.0 (t), 25.9 (t), 32.6 (t), 36.6 (t), 38.4 (s), 44.1 (t), 58.9 (t), 69.5 (d); HR-MS (EI) *m/z* calcd for $C_9H_{18}OCl$ (M^++1) 177.1046; Found 177.1041, **26** (92.1 mg, 16%): FT-IR (film) 3338, 2935, 2812, 1446, 1055, 1014 cm^{-1}; ^1H NMR (600 MHz in $CDCl_3$) δ 1.23 (1H, m), 1.35 (1H, ddd, J=13.2, 11.3, 3.6 Hz), 1.44 (3H, m), 1.56 (2H, m), 1.59 (3H, s), 1.67 (1H, dddd, J=11.0, 4.7, 3.3, 1.4 Hz), 1.74 (2H, m), 1.98 (2H, m), 3.65 (1H, ddd, J=10.5, 8.8, 5.8 Hz), 3.75 (1H, ddd, J=10.8, 7.5, 4.7 Hz); ^{13}C NMR (150 MHz in $CDCl_3$) δ 22.2 (t), 25.6 (t), 27.6 (t), 31.7 (q), 34.1 (t), 42.9 (t), 44.2 (d), 60.8 (t), 76.0 (s); HR-MS (CI) *m/z* calcd for $C_9H_{18}OCl$ (M^++1) 176.6864; Found 177.1019, and **27** (39.2 mg, 7%): FT-IR (film) 3340, 2935,

2862 cm^{-1}; ^1H NMR (600 MHz in $CDCl_3$) δ 1.13 (1H, dddd, $J=12.0$, 8.7, 6.0, 3.5 Hz), 1.36 (4H, m), 1.50 (3H, s), 1.66 (2H, m), 1.83 (1H, dddd, $J=13.2$, 5.7, 3.8, 1.9 Hz), 1.89 (1H, dddd, $J=13.8$, 6.3, 3.9, 2.5 Hz), 1.97 (1H, ddd, $J=12.9$, 9.1, 3.8 Hz), 2.14 (2H, m), 3.66 (1H, ddd, $J=10.4$, 8.2, 6.3 Hz), 3.76 (1H, ddd, $J=10.6$, 7.6, 4.9 Hz); ^{13}C NMR (150 MHz in $CDCl_3$) δ 23.5 (q), 24.2 (t), 25.2 (t), 29.5 (t), 34.1 (t), 44.4 (t), 45.8 (d), 61.4 (t), 76.3 (s); HR-MS (CI) *m/z* calcd for $C_9H_{18}OCl$ ($M^+ + 1$) 177.1046; Found 177.1039.

3.1.3. Reaction of 3-cyclopentyl-3-hydroxybutyl acetate (20a) with $TiCl_4$. $TiCl_4$ (1.33 g, 7.0 mmol) was added to a stirred solution of **20a** (530 mg, 2.65 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the mixture was stirred at 25 °C for 1 h. After cooling to 0 °C, aqueous $NaHCO_3$ solution was added and extracted with CH_2Cl_2. The dried and concentrated extract was subjected to column chromatography using hexane and ethyl acetate to give a 3:2 mixture of **23a** and **24a** (498 mg, 86%). The mixture was purified by HPLC using YMS-Pack R and D SIL D-SIL-5 20×250 mm column and hexane–ethyl acetate (50:1, 20 mL/min) to give **23a** and **24a** as colorless oils. **23a**: FT-IR (film) 2943, 2846, 1747, 1456, 1367, 1252, 1142, 1034 cm^{-1}; ^1H NMR (200 MHz in $CDCl_3$) δ 1.08 (3H, s), 1.19 (1H, m), 1.42 (3H, m), 1.85 (6H, m), 2.05 (3H, s), 3.85 (1H, dd, $J=5.0$, 4.0 Hz), 4.14 (2H, dddd, $J=7.0$, 3.6, 2.6, 1.6 Hz); ^{13}C NMR (50 MHz in $CDCl_3$) δ 20.8 (t), 20.9 (q), 24.5 (t), 25.3 (q), 31.8 (2C, t), 35.3 (t), 37.7 (s), 61.0 (t), 70.7 (d), 171.0 (s); HR-MS (CI) *m/z* calcd for $C_{11}H_{20}O_2Cl$ ($M^+ + 1$) 219.1152; Found 219.1147. **24a**: FT-IR (film) 2941, 2866, 1747, 1448, 1367, 1250, 1034, 973 cm^{-1}; ^1H NMR (200 MHz in $CDCl_3$) δ 1.04 (3H, s), 1.64 (10H, m), 2.05 (3H, s), 3.85 (1H, dd, $J=6.2$, 4.4 Hz), 4.16 (2H, dddd, $J=7.4$, 0.8, Hz); ^{13}C NMR (50 MHz in $CDCl_3$) δ 18.0 (q), 20.7 (2C, t), 25.6 (t), 32.3 (q), 36.0 (t), 38.0 (t), 39.3 (s), 60.4 (t), 68.7 (d), 170.6 (s); HRMS (CI) *m/z* calcd for $C_{11}H_{20}O_2Cl$ ($M^+ + 1$) 219.1152; Found 219.1147.

3.1.4. Reaction of 20a with $BF_3 \cdot Et_2O$. $BF_3 \cdot Et_2O$ (78.5 mg, 0.55 mmol) was added to a stirred solution of acetate **20a** (52 mg, 0.26 mmol) in CH_2Cl_2 (5 mL) at 0 °C and the mixture was stirred at 25 °C for 30 min. After cooling to 0 °C, aqueous $NaHCO_3$ was added, and extracted with CH_2Cl_2. The dried and concentrated extract was subjected to column chromatography using hexane and ethyl acetate to give a 2:3 mixture of **29** and **30** (41 mg, 87%). **29**: ^1H NMR (200 MHz in $CDCl_3$) δ 1.05 (3H, d, $J=$ 6.8 Hz), 1.80 (4H, m), 2.04 (3H, s), 2.30 (5H, m), 4.09 (2H, m), 5.36 (1H, m); ^{13}C NMR (50 MHz in $CDCl_3$) δ 19.5 (q), 21.0 (q), 26.7 (d), 27.0 (t), 30.4 (t), 32.2 (t), 33.8 (t), 62.9 (t), 123.4 (d), 139.7 (s), 171.2 (s). **30**: ^1H NMR (200 MHz in $CDCl_3$) δ 1.64 (3H, m), 1.80 (4H, m), 2.04 (3H, s), 2.30 (6H, m), 4.09 (2H, m); ^{13}C NMR (50 MHz in $CDCl_3$) δ 19.1 (q), 21.0 (q), 23.3 (t), 30.8 (t), 32.0 (t), 32.2 (t), 34.8 (t), 63.2 (t), 120.6 (s), 148.2 (s), 171.2 (s).

3.1.5. 4-Methyl-1-oxaspiro[4.4]nonane (21). *p*-TsCl (482 mg, 2.52 mmol) was added to a solution of 1-(3-hydroxy-1-methylpropyl)cyclopentanol (200 mg, 1.26 mmol) in pyridine (10 mL) at 0 °C and the mixture was stirred for 43 h at 25 °C. After addition of aqueous $NaHCO_3$, the organic material was extracted into ether. The ether extract was successively washed with aqueous 2 M HCl, NH_4Cl, and $NaHCO_3$. The dried and concentrated extract was subjected to column chromatography to give **21** (167 mg, 95%) as a colorless oil. Spectral data were identical with that of the acid reaction product.

3.1.6. 3-(*tert*-Butyldimethylsilyloxy)-1-cyclopentylpropan-1-ol (33). To a stirred solution of Grignard reagent prepared from magnesium (3.62 g, 150 mmol) and bromocyclopentane (4.45 g, 30 mmol) in THF (100 mL) was added a solution of 3-(*tert*-butyldimethylsilyloxy)-propanal (**32**) (5.74 g, 30 mmol) in THF (60 mL) dropwise at −40 °C and the resultant mixture was stirred for 2 h at this temperature. After addition of aqueous NH_4Cl, the organic material was extracted into ether. The dried and concentrated extract was subjected to column chromatography using hexane and ethyl acetate to give alcohol **33** in 65% yield as a colorless oil. FT-IR (film) 3458, 2962, 2861, 2738, 1471, 1389, 1362, 1257, 1103 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 1.95–1.13 (11H, m), 3.66–3.55 (1H, m), 3.97–3.76 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.68 (2o), 17.97 (e), 25.55 (e), 25.75 (3o), 28.63 (e), 28.86 (e), 37.29 (o), 46.24 (e), 62.84 (e), 76.04 (o); MS (CI) *m/z* 259 ($M^+ + 1$), 189, 109, 67 (base); HR-MS (CI) *m/z* calcd for $C_{14}H_{31}O_2Si$ ($M^+ + 1$) 259.2093; Found 259.2098.

3.1.7. 3-(*tert*-Butyldimethylsilyloxy)-1-cyclopentylpropan-1-one (34). To a stirred solution of alcohol **33** (1.1 g, 4.26 mmol) in dichloromethane (15 mL) was added pyridinium dichromate (3.2 g, 8.5 mmol) at 0 °C and the mixture was stirred for 46 h at 25 °C. After addition of ether (200 mL) and then Celite (20 g), the mixture was stirred for another 10 min. This was filtered through a celite pad and concentrated. The residue was subjected to column chromatography using hexane and ethyl acetate to give the ketone **34** (11.7 g, 59%) as a colorless oil. FT-IR (film) 2954, 2858, 1711, 1471, 1389, 1362, 1255, 1095 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.87 (9H, s), 1.67–1.55 (4H, m), 1.87–1.68 (4H, m), 2.56 (2H, t, $J=6.3$ Hz), 2.89 (1H, dddd, $J=8.0$, 7.7 Hz), 3.94 (2H, t, $J=6.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.86 (2q), 17.80 (t), 25.53 (3q), 25.69 (2t), 27.99 (2t), 44.16 (t), 51.68 (d), 58.56 (t), 210.97 (s).

3.1.8. 4-(*tert*-Butyldimethylsilyloxy)-2-cyclopentylbutan-2-ol (35). To a stirred solution of MeMgCl (3.0 M in THF, 1.80 mL, 3.95 mmol) was added a solution of the ketone **34** (0.95 g, 3.71 mmol) in THF (5 mL) at 0 °C and the mixture was stirred for 2 h at the same temperature and another 2 h at 25 °C. After addition of aqueous NH_4Cl, the organic material was extracted with ether. The dried and concentrated extract was subjected to column chromatography using hexane and ethyl acetate to give the alcohol **35** (1.00 g, 99%) as a colorless oil. FT-IR (film) 3512, 2954, 2860, 1471, 1389, 1255, 1088 cm^{-1}, 1H NMR (200 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.90 (9H, s), 1.18 (3H, s), 1.68–1.43 (10H, m), 1.99–1.76 (1H, m), 4.01–3.81 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.99 (q), −5.96 (9), 17.71 (t), 23.57 (q), 25.54 (3q), 25.64 (t), 25.66 (t), 26.33 (t), 26.90 (t), 40.71 (t), 50.08 (d), 60.43 (t), 73.60 (t).

3.1.9. 3-Cyclopentylbutane-1,3-diol (20). To a solution of the alcohol **35** (3.15 g, 11.56 mmol) in THF (20 mL) was added *n*-Bu_4NCl (1.0 M THF solution, 17.3 mL, 17.3 mmol) at 0 °C and the mixture was stirred for 3 h at

25 °C. After addition of water, the organic material was extracted into ethyl acetate and the dried and concentrated extract was subjected to column chromatography using hexane and ethyl acetate to give the diol **20** (1.74 g, 95%) as a colorless oil. FT-IR (film) 3361, 2958, 2868, 1454, 1052, 1016 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$) δ 1.22 (3H, s), 1.33–1.26 (1H, m), 1.46–1.40 (1H, m), 1.64–1.51 (5H, m), 1.72–1.64 (2H, m), 1.88 (1H, ddd, $J=14.3$, 9.1, 4.7 Hz), 2.02 (1H, ddd, $J=17.5$, 9.6, 8.2 Hz), 2.22 (1H, br s), 2.88 (1H, br s), 3.85–3.82 (1H, m), 3.95 (1H, ddd, $J=8.2$, 3.3, 3.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.92 (q), 25.90 (q), 25.91 (t), 26.60 (t), 27.25 (t), 40.81 (t), 50.45 (d), 59.87 (t), 75.57 (t); MS (CI) *m/z* 159 ($M^+ +1$), 141, 123, 113, 95 (base), 89, 81, 43; HR-MS (CI) *m/z* calcd for $C_9H_{18}O_2$ ($M^+ +1$) 159.1385; Found 159.1370.

3.1.10. 2-Allyl-2-methylcyclohexanone (37). To a solution of the enol acetate **36** (2.0 g, 13.0 mmol) in dioxane (50 mL) was successively added allyl methyl carbonate (3.0 g, 25.9 mmol), 1,2-bis(diphenylphosphino)ethane (520 mg, 1.3 mmol), and tris(dibenzylidene-acetone)dipalladium(0)-chloroform adduct (670 mg, 0.65 mmol), and the mixture was stirred for 10 min at 25 °C. After addition of tributyltin methoxide (840 mg, 2.62 mmol), the mixture was heated to reflux for 10 h and then cooled to 25 °C. Saturated aqueous NaCl and ice were added and the organic material was extracted into ether. The organic phase was washed with aqueous $NaHCO_3$. The dried and concentrated extract was chromatographed using hexane and ethyl acetate to give **37** (1.78 g, 90%) as a colorless oil. FT-IR (film) 3076, 2935, 2868, 1712, 1639, 1452, 1377, 1313, 1215, 1124, 995, 914 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.07 (3H, s), 1.72 (6H, m), 2.30 (4H, m), 5.31 (2H, m), 5.70 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.8 (t), 22.3 (q), 27.1 (t), 38.3 (t), 38.4 (t), 41.7 (t), 48.1 (s), 117.4 (t), 133.5 (d).

3.1.11. *cis*-Octahydro-3a-methylbenzofuran-2-ol (38) and *trans*-(2-hydroxy-1-methylcyclohexyl)-acetaldehyde (39). $NaBH_4$ (57 mg, 1.5 mmol) was added to a solution of **37** (152 mg, 1.0 mmol) in 2-propanol (5 mL) at 0 °C and the mixture was stirred at 25 °C for 4 h. After cooling to 0 °C, 2 M aqueous HCl was added and the organic material was extracted into ether. The dried and concentrated extract was dissolved in aqueous CH_3CN (2:1, 6 mL) and mixed with 4-methylmorpholine *N*-oxide (194 mg, 1.66 mmol) and 2% aqueous OsO_4 (4.0 mL, 0.08 mmol). The resulting mixture was stirred at 25 °C for 10 h. After addition of aqueous sodium thiosulfate at 0 °C, the organic material was extracted into ethyl acetate, and the extract was washed with aqueous 1M HCl and saturated $NaHCO_3$. The dried and concentrated extract was subjected to column chromatography using hexane and ethyl acetate to give a mixture of triols. The crude product was dissolved in aqueous THF (3:1, 8 mL), and mixed with $NaIO_4$ (195 mg, 0.91 mmol) at 0 °C. The mixture was stirred at 0 °C for 3.5 h and then water was added. The dried and concentrated ether extract was subjected to column chromatography using hexane and ether to give the crude material. HPLC using YMC-Pack R and D Sil D-SIL-5 10×250 column and hexane–ether 3:1, 15 mL/min) afforded hemiacetal **38** (60 mg, 38%) and hydroxy aldehyde **39** (39 mg, 25%) as colorless oils. Hydroxy aldehyde **39**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, s), 1.53 (8H, m),2.09 (2H, dd, $J=12.6$, 5.5 Hz), 3.33 (1H, br s), 3.43 (1H, m), 9.90 (1H, dd, $J=3.3$, 2.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9 (q), 20.8 (t), 24.5 (t), 35.3 (t), 37.6 (t), 39.6 (s), 56.0 (t), 76.1 (d), 203.9 (s).

3.1.12. *cis*-Octahydro-3a-methylbenzofuran (22). To a solution of triethylsilane (64 mg, 0.55 mmol) and trifluoroacetic acid (62 mg, 0.55 mmol) in dichloromethane (5 mL) was added a solution of the hemiacetal **38** (29 mg, 0.18 mmol) in dichloromethane (3 mL) at −78 °C. The mixture was stirred for 2 h at 0 °C. After aqueous workup, the dried and concentrated ether extract was chromatographed using pentane and ether to give the *cis*-ether **22** (21 mg, 83%) as a colorless oil. Spectral data were identical with that of the product formed from the reaction of **20** with $TiCl_4$.

3.1.13. *trans*-2-(2-Chloro-1-methylcyclohexyl)ethyl acetate (24a). $NaBH_4$ (57 mg, 1.5 mmol) was added to a solution of **37** (193 mg, 1.2 mmol) in 2-propanol (3 mL) at 0 °C and the mixture was stirred at room temperature for 7 h. After cooling to 0 °C, aqueous 2 M HCl was added and the organic material was extracted into ether to give the crude diol. This was dissolved in dichloromethane (2 mL) and mixed with pyridine (0.2 mL) and CH_3COCl (95 mg, 1.2 mmol). The mixture was stirred for 30 min at 0 °C. After aqueous workup, the dried and concentrated organic extract was subjected to column chromatography using hexane and ethyl acetate to give the mono acetate 171 mg (69% in two steps). FT-IR (film) 3467, 2933, 2862, 1738, 1722, 1454, 1392, 1367, 1247, 1136, 1053, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (3H, s), 1.43 (10H, m), 2.04 (3H, s), 3.40 (1H, dd, $J=4.6$, 3.0 Hz), 4.16 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9 (t), 21.0 (q), 23.1 (t), 24.0 (q), 29.7 (t), 31.9 (t), 34.9 (t), 36.9 (s), 61.6 (t), 76.3 (d), 171.3 (s); HR-MS (EI) *m/z* calcd for $C_{11}H_{20}O_3$ (M^+) 200.1412; Found 200.1395. The *cis*-monoacetate (150 mg, 0.75 mmol) was dissolved in CCl_4 (10 mL) and triphenylphosphine (294 mg, 1.1 mmol) was added. The mixture was heated to reflux for 58 h. After addition of hexane, the mixture was filtered through a celite pad. The concentrated filtrate was subjected to column chromatography using hexane and ethyl acetate to give the crude mixture. Purification by HPLC using YMC-Pack R and D SIL D-Sil-5 10×250 mm column and hexane–ethyl acetate 40:1, 15 mL/min) gave **24a** (21 mg, 13%), **43** (54 mg, 40%), and **44** (21 mg, 13%). The material **24a** was identical with the reaction product of **20a** and $TiCl_4$. **43**: FT-IR (film) 3012, 2931, 2866, 2837, 1741, 1458, 1389, 1365, 1234, 1034, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, s), 1.68–1.34 (6H, m), 1.98–1.89 (2H, m), 2.03 (3H, s), 4.116–4.08 (2H, m), 5.44–5.37 (1H, m), 5.62 (1H, dt, $J=6.0$, 1.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.19 (t), 21.18 (q), 25.08 (t), 27.73 (q), 33.53 (t), 35.03 (t), 40.75 (t), 61.87 (s), 126.21 (d), 135.59 (d), 171.24 (s). **44**: FT-IR (film) 2939, 2864, 1739, 1454, 1373, 1250, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.74–1.16 (8H, m), 2.00–1.82 (2H, m), 2.06 (3H, s), 3.62–3.47 (2H, m), 4.60 (1H, dd, $J=3.5$, 3.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.91 (t), 21.33 (q), 23.19 (t), 23.81 (q), 26.64 (t), 35.31 (t), 37.18 (t), 37.95 (t), 40.97 (t), 78.44 (d), 170.57 (s); MS (CI) *m/z* 219 ($M^+ +1$), 159, 123 (base), 95, 43; HR-MS (CI) *m/z* calcd for $C_{11}H_{20}O_2Cl$ ($M^+ +1$) 219.1152; Found 219.1154.

3.1.14. *trans*-2-(2-Chloro-1-methylcyclohexyl)-ethanol (24). Sodium methoxide (28% solution in MeOH, 0.6 μL, 0.003 mmol) was added to a solution of **24a** (7 mg, 0.32 mmol) in methanol (2 mL) and the mixture was stirred at 25 °C for 3 h. Amberlite IR-120B was added to neutralize the reaction mixture which was then filtered through a celite pad and concentrated. The residue was subjected to column chromatography using hexane and ethyl acetate to give **24** (5.7 mg, 99%). The spectral data were identical with that of the reaction product of **20** and $TiCl_4$.

3.1.15. *trans*-2-(2-Chloro-1-methylcyclohexyl)ethanol (40). $NaBH_4$ (19 mg, 1.0 mmol) was added to a solution of **39** (156 mg, 1.0 mmol) in 2-propanol (3 mL) at 0 °C and the mixture was stirred at 25 °C for 4 h. After cooling to 0 °C, aqueous 2 M HCl was added and the organic material was extracted into ether. The dried and concentrated extract was subjected to column chromatography using hexane and ethyl acetate to give the *trans*-diol (129 mg, 82%) as a colorless oil. FT-IR (film) 3320, 2937, 2867, 2360, 1450, 1147, 1076, 979 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (3H, s), 1.47 (10H, m), 3.28 (2H, br s), 3.39 (1H, dd, $J=7.0$, 4.0 Hz), 3.74 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7 (q), 21.2 (t), 25.0 (t), 30.0 (t), 38.0 (t), 39.2 (t), 46.7 (t), 57.8 (t), 76.0 (d); MS (EI) $m/z(M^+-H_2O)$ 140.

3.1.16. *trans*-Octahydro-3a-methylbenzofuran (28). *p*-TsCl (197 mg, 1.0 mmol) was added to a solution of the diol **40** (78 mg, 0.49 mmol) in pyridine (5 mL), and the mixture was stirred for 5 h at 25 °C. After aqueous workup, extraction of the product into ether, and concentration of the dried extract furnished the crude product that was subjected to column chromatography using hexane and ethyl acetate to give **28** (23 mg, 33%) as a colorless oil. FT-IR (film) 2935, 2873, 2360, 1456, 1377, 1279, 1147, 1070, 1031 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (3H, s), 1.53 (10H, m), 3.06 (1H, dd, $J=3.8$, 3.2Hz), 3.87 (2H, ddd, $J=8.4$, 6.6, 3.2 Hz); ^{13}C NMR (50 MHz in $CDCl_3$) δ 16.8 (q), 21.1 (t), 24.6 (t), 25.4 (t), 35.8 (t), 40.1 (t), 40.3 (s), 65.0 (t), 84.6 (d); HR-MS (CI) m/z calcd for $C_9H_{16}O$ (M^+-1) 139.1123; Found 139.1133.

3.1.17. *cis*-2-(2-Chloro-1-methylcyclohexyl)ethyl acetate (23a). CH_3COCl (25 mg, 0.32 mmol) was added to a solution of the diol **40** (43 mg, 0.27 mmol) in dichloromethane (2 mL) and pyridine (44 μL), and the mixture was stirred at 0 °C for 30 min. Aqueous workup and column chromatography of the crude material using hexane and ethyl acetate furnished the monoacetate (43 mg, 80%) as a colorless oil. FT-IR (film) 3458, 2929, 2862, 1738, 1714, 1365, 1236, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (3H, s), 1.55(10H, m), 2.05 (3H, s), 3.39 (1H, dd, $J=$ 6.4, 3.8 Hz), 4.19 (2H, t, $J=7.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6(q), 20.9 (q), 20.9(t), 24.2 (q), 30.3 (t), 35.8 (t), 37.4 (s), 39.3 (t), 61.4 (t), 75.4 (d), 171.2 (s); HR-MS (EI) m/z calcd for $C_9H_{18}O_2$ (M^+) 158.2407; Found 158.2411.

The above acetate (43 mg, 21.5 mmol) was dissolved in CCl_4 (5 mL) and triphenylphosphine (84 mg, 0.32 mmol) was added. The mixture was heated to reflux for 68 h. After addition of pentane, the mixture was filtered through a celite pad. The concentrated filtrate was subjected to column chromatography using hexane and ethyl acetate to give a crude mixture. Purification by HPLC using YMC-Pack R and D SIL D-Sil-5 10×250 mm column and hexane–ethyl acetate 40:1, 15 mL/min) afforded **23a** (6 mg, 13%), **44** (10 mg, 26%), and **46** (8 mg, 18%). This **23a** was identical with the reaction product of **20a** and $TiCl_4$. **46**: FT-IR (film) 2937, 2866, 1743, 1450, 1373, 1251, 1032, 985 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, s), 1.90–1.24 (10H, m), 2.05 (3H, s), 3.60–3.46 (2H, m), 4.60 (1H, dd, $J=3.9$, 3.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.12 (q), 20.91 (t), 21.37 (q), 23.79 (t), 26.94 (t), 35.64 (t), 37.45 (t), 40.57 (t), 43.88 (s), 77.52 (d), 170.66 (s); MS (CI) m/z 219 ($M^+ + 1$), 159, 123 (base), 95; HR-MS (CI) m/z calcd for $C_{11}H_{20}O_2Cl$ ($M^+ + 1$) 219.1152; Found 219.1153.

3.1.18. *cis*-2-(2-Chloro-1-methylcyclohexyl)-ethanol (23). Sodium methoxide (28% in methanol, 0.6 μL, 0.003 mmol) was added to a solution of **23a** (7 mg, 0.32 mmol) in methanol (2 mL), and the mixture was stirred at 25 °C for 3 h. Amberlite IR-120B was added to neutralize the reaction mixture which was filtered through a celite pad and concentrated. The residue was subjected to column chromatography using hexane and ethyl acetate to give **23** (4.6 mg, 81%). The spectral data were identical with that of the reaction product of **20** and $TiCl_4$.

3.1.19. *cis*-2-Allyl-1-methyl-cyclohexanol (42). MeMgCl (3 M THF solution, 0.45 mL, 1.24 mmol) was added to a solution of **41** (700 mg, 5.1 mmol) in THF (5 mL) at 0 °C, and the mixture was stirred for 30 min at the same temperature. Aqueous workup following chromatography of the concentrated ether extract using hexane and ethyl acetate gave **42** (585 mg, 73%). FT-IR (film) 3365, 2937, 2862, 1651, 1446, 1377, 1265, 1159, 1056, 1018 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (3H, s), 1.52 (10H, m), 3.70 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.0 (t), 25.7 (t), 26.9 (t), 28.7 (q), 32.5 (t), 40.0 (t), 43.4 (t), 59.6 (t), 70.9 (s); HR-MS (EI) m/z calcd for $C_9H_{18}O_2$ (M^+) 158.2407; Found 158.2404.

3.1.20. *cis*-Octahydro-7a-methylbenzofuran-2-ol (43). To a solution of **42** (305 mg, 2.0 mmol) in aqueous acetonitrile (2:1, 15 mL) was added 4-methylmorpholine *N*-oxide (469 mg, 4.0 mmol) and 2% aqueous solution of OsO_4 (1.0 mL, 0.02 mmol). The resulting mixture was stirred at 25 °C for 3 h. After addition of sodium thiosulfate at 0 °C, the organic material was extracted into ethyl acetate, and the extract was washed with aqueous 1M HCl and saturated $NaHCO_3$. The dried and concentrated extract was subjected to column chromatography using hexane and ethyl acetate to give the desired triols. The crude product was dissolved in aqueous THF (3:1, 16 mL) and mixed with $NaIO_4$ (381 mg, 1.78 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 h, and then water was added. The dried and concentrated ether extract was subjected to column chromatography using hexane and ether to give **43** as a colorless oil.

3.1.21. *cis*-Octahydro-7a-methylbenzofuran (25). To a solution of triethylsilane (110 mg, 0.95 mmol) and trifluoroacetic acid (108 mg, 0.95 mmol) in dichloromethane (5 mL) was added a solution of hemiacetal **43** (50 mg, 0.32 mmol) in dichloromethane (3 mL) at −78 °C. The mixture was stirred for 2 h at 0 °C. Aqueous workup and chromatography

of the concentrated ether extract using pentane and ether gave **25** (35 mg, 76%) as a colorless oil. The spectral data were identical with that of the reaction product of **20** and $TiCl_4$.

3.1.22. *cis*-2-(2-Chloro-2-methylcyclohexyl)-ethanol (26). $NaBH_4$ (14 mg, 0.37 mmol) was added to a solution of **43** (115 mg, 0.74 mmol) in 2-propanol (5 mL) at 0 °C, and the mixture was stirred at 25 °C for 4 h. After cooling the reaction mixture to 0 °C, aqueous 2M HCl was added and the organic material was extracted into ether to give the crude diol that was purified by column chromatography using hexane and ethyl acetate; 100 mg (85%). FT-IR (film) 3365, 2937, 2862, 1651, 1446, 1377, 1265, 1159, 1056, 1018 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (3H, s), 1.52 (10H, m), 3.70 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.0 (t), 25.7 (t), 26.9 (t), 28.7 (q), 32.5 (t), 40.0 (t), 43.4 (t), 59.6 (t), 70.9 (s); HR-MS (EI) *m/z* calcd for $C_9H_{18}O_2$ (M^+) 158.2407; Found 158.2411.

The above diol (75 mg, 0.47 mmol) was dissolved in ether (5 mL), and water (10 μL) and concd HCl (35%, 30 μL) were added at 25 °C. The mixture was stirred for 15 min at this temperature. After aqueous workup, the concentrated ether extract was chromatographed using hexane and ether to give **26** (25 mg, 30%) as a colorless oil. The spectral data were identical with that of the reaction product of **20** and $TiCl_4$.

Acknowledgements

This study was financially supported by a Grant-in-Aid from Yamada Science Foundation and by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japanese Government.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2004.07.064

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Facile conversion of *O*-silyl protected sugars into their corresponding formates using $POCl_3 \cdot DMF$ complex

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Received 10 June 2004; revised 8 July 2004; accepted 22 July 2004

Available online 28 August 2004

Abstract—The direct *O*-formylation of two selectively protected sugar derivatives using the Vilsmeier–Haack (V–H) complex $POCl_3 \cdot DMF$ was studied. Primary *O*-TBDMS and *O*-TBDPS ethers of sucrose, the most common disaccharide, underwent regio and chemoselective *O*-formylation with this formylating agent. This conversion was also studied with a monosaccharide analogue.

1. Introduction

Carbohydrates are fundamental to life. They are involved in many essential biological processes: they act as an energy source, in biological signalling and recognition mechanisms and as basic building blocks, for example, they are part of DNA, RNA, starch, cellulose, chitin and cotton.[1] The great advantage in the use of carbohydrates is that they are natural products produced in large quantities; glucose is the most abundant organic molecule on the planet (mostly in the form of its polymer cellulose); sucrose is the most common sugar and its annual production exceeds 120 million tons.

Sugars contain numerous functional groups and chiral centres, so the problem of protecting groups is one of the fundamental tasks in carbohydrate chemistry. A specific differentiation of the hydroxyl groups can be achieved by etherification procedures, such as tritylation or silylation, which are now widely used and well described.[2,3]

The selective derivatisation of sugars with unsaturated moieties is one of the easiest routes to the preparation of polymers[4–8] and for the construction of asymmetric molecules using sugars as chiral auxiliaries.[9–12] One of the potentially most useful and versatile functional groups to be introduced is the formyl group. It is useful as a protecting group which can be removed easily and selectively. Formate esters can also serve as intermediates for C–C chain extension reactions particularly through Wittig type olefinations.

Several one-step formylation methods have been reported over the years, using formylation agents such as formyl fluoride, formic anhydride, acetic-formic anhydride,[13] 2-(*N*-methyl-*N*-formylamino)pyridine, dimethylchloromethyl-ammonium chloride, *N*-formylbenzotriazole[14] and *N*,*N*-dimethylformamide,[15] among many others.[16] In particular, the one step conversion of silyl ethers into their corresponding formates was described using PPh_3/CBr_4 in $HCOOEt/H_2O$[17] and more recently by the use of the Vilsmeier–Haack (V–H) complex $POCl_3$/DMF.[18–20]

In this work, we extend the above cited formylation method with the Vilsmeier–Haack complex to the conversion of *O*-TBDPS and *O*-TBDMS ethers of mono and disaccharides into the corresponding formates. We have proven its usefulness in the fast, easy and selective preparation of 6-*O*-formates of glucose and we have also explored the chemo and regioselectivity, as well as the applicability to acid sensitive and more complex substrates, such as sucrose, without the need for addition of a base, which retards the reaction.[18–20]

2. Results and discussion

Compounds **1–9** (Scheme 1), having variable silyl protections at the primary positions, were studied for their direct conversion into formates with the view to determining the efficiency and the selectivity of the reaction (Scheme 2). We opted only to study the reaction at the primary positions, which are more reactive than the secondary ones. It had

Keywords: Carbohydrates; Vilsmeier–Haack (V–H) complex; Regio and chemoselective *O*-formylation.
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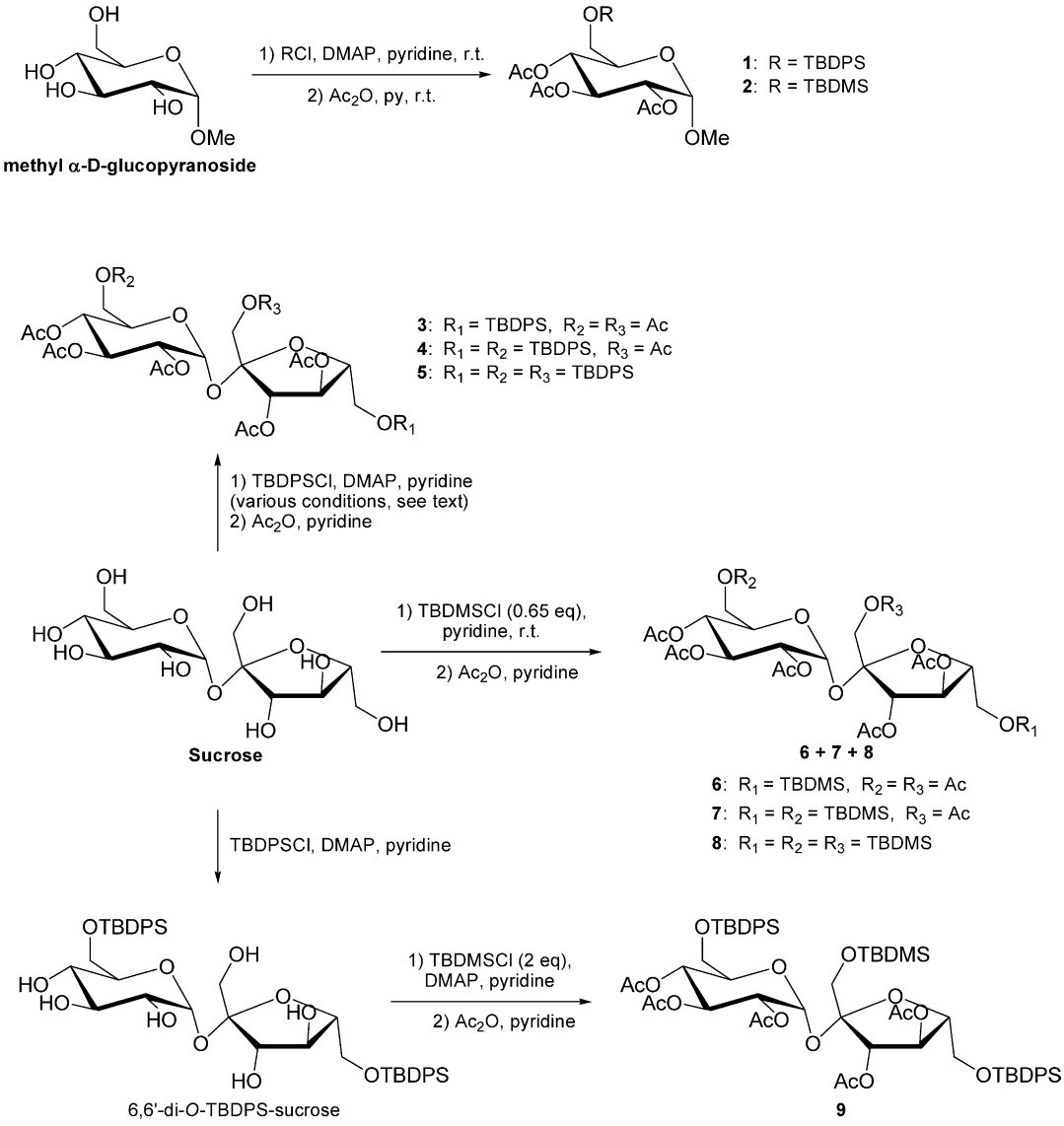
doi:10.1016/j.tet.2004.07.056



Scheme 1. Preparation of silyl precursors of the sugars.

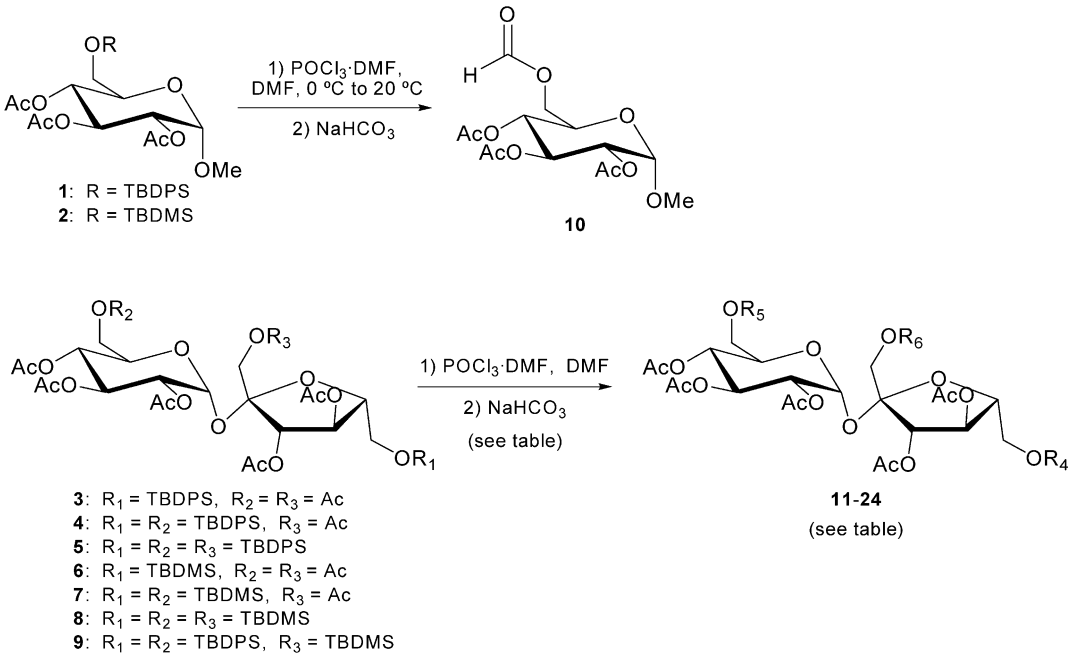
already been shown by Lellouche during studies with D-glucal that the primary positions are preferred to the secondary ones, even using large excess of the silylating agent,[19] but the regioselective conversion in a molecule with more that 1 primary position was not explored. The chemoselectivity between TBDMS and TBDPS was also forgotten by the authors, and the two were only compared in terms of speed of reaction, and never used together in the same molecule.

2.1. Selective protection at the primary positions with silyl ethers

Sugar derivatives **1** and **2** were prepared in one step from methyl α-D-glucopyranoside with yields above 90%. Silyl protection at the primary (6) position was achieved according to described procedures,[3] followed by acetylation of the secondary hydroxyls with acetic anhydride.

Selective *O*-TBDPS protection for sucrose substrates **3**–**5** was carried out based upon Khan's protocol,[21] with slight changes that permitted an increasing in the yields. Mono substituted compound **3** was prepared by dropwise addition of 1 equiv. of TBDPSCl to the sugar dissolved in dry pyridine, using catalytical amount of DMAP, at room temperature. The yield for this step was increased to 85%, though the product did not need to be isolated and could be immediately acetylated to afford **3** with an overall yield of 80%.

For the di-*O*-TBDPS protection, following the procedure described by Khan,[21] and contrary to his observations, we obtained mainly the tri-protected derivative and only small amounts of the desired di-protected compound. For this reason, we modified the described method, heating sucrose in pyridine (and catalytic DMAP) with 1.1 equiv. of TBDPSCl at 70 °C for 4 h, followed by addition of another 1.1 equiv. of silylating agent at room temperature and 24h stirring at room temperature. 6,6′-Di-*O*-TBDPS-sucrose was obtained with 84% yield. The product was sufficiently pure to proceed without isolation, thus addition of acetic anhydride to the reaction mixture, followed by column purification afforded compound **4** in 78% overall yield.



Scheme 2. Reaction of the sugar *O*-silylated precursors with 1.1 equiv. of $POCl_3 \cdot DMF$.

Compound **5** was obtained in 75% yield from unprotected sucrose in two steps by first adding 4.6 equiv. of TBDPSCl to the solution containing sucrose and DMAP in anhydrous pyridine and heating at 70 °C during 24 h, followed by acetylation of the secondary positions and isolation by column chromatography.

The TBDMS group is smaller and consequently less hindered than the TBDPS, and so selective protection is not so easy to achieve. Following the procedure of Franke,[3] the *O*-TBDMS protected sucrose was obtained with different degrees of protection and with variable yields. The addition of 0.65 equiv. of TBDMSCl to a solution of sucrose in pyridine and stirring overnight at room temperature followed by acetylation with acetic anhydride afforded a mixture of products, which includes the mono-, di- and tri-protected products needed for our further reactions. Column chromatography allowed the isolation of compounds **6–8**.

Sucrose derivative **9** was obtained from 6,6′-di-*O*-TBDPS-sucrose by reaction in pyridine with 2 equiv. of TBDMSCl in the presence of catalytical amount of DMAP, at room temperature.[22] This afforded 75% of 1′-*O*-TBDMS-6,6′-di-*O*-TBDPS-sucrose, after column purification using ethyl acetate/hexane 1:4. Acetylation with acetic anhydride in pyridine gave 92% of **9**.

2.2. Vilsmeier–Haack (V–H) *O*-formylation

The monosaccharides **1** and **2** underwent formylation with 1.1 equiv. of the V–H reagent to afford the 6-formate ester **10** with good yields. As expected, the reaction was much faster for the TBDMS protected compound (see Table 1, entries 1 and 2).

The results obtained with sucrose require a closer examination. For the mono silylated substrates **3** and **6** (entries 3 and 6), *O*-formylation was achieved with yields and times comparable with those for the monosaccharide precursors. When protected with TBDMS the precursors were converted faster than in the case of the TBDPS ether (30 min vs. 24 h) and with similar yield range (82 and 88% respectively). These results were confirmed by ^1H NMR spectroscopy, which gave

Table 1. Results obtained by *O*-formylation of the sugar substrates

Entry	Precursor	Time	Products obtained (yield)
1	**1**	24 h	**10** (85%)
2	**2**	5 min	**10** (84%)
3	**3**	24 h	**11** R_4=CHO, R_5=R_6=Ac (88%)
4	**4**	24 h	**12** R_4=CHO, R_5=TBDPS, R_6=Ac (45%) **13** R_4=TBDPS, R_5=CHO, R_6=Ac (13%) **14** R_4=R_5=CHO, R_6=Ac (5%) **4** recovered (22%)
5	**5**	24 h	**15** R_4=CHO, R_5=R_6=TBDPS (59%) **16** R_4=R_5=CHO, R_6=TBDPS (16%) **5** recovered (21%)
6	**6**	30 min	**11** R_4=CHO, R_5=R_6=Ac (82%)
7	**7**	30 min	**14** R_4=R_5=CHO, R_6=Ac (77%)
8	**7**	5 min	**17** R_4=CHO, R_5=TBDMS, R_6=Ac (15%) **18** R_4=TBDMS, R_5=CHO, R_6=Ac (18%) **14** R_4=R_5=CHO, R_6=Ac (37%) **7** recovered (17%)
9	**8**	30 min	**19** R_4=CHO, R_5=R_6=TBDMS (10%) **20** R_4=R_6=TBDMS, R_5=CHO (13%) **21** R_4=R_5=CHO, R_6=TBDMS (31%) **22** R_4=R_5=R_6=CHO (5%) **8** recovered (32%)
10	**9**	21 h	**23** R_4=R_5=TBDPS, R_6=CHO (69%) **24** R_4=R_6=CHO, R_5=TBDPS (21%)

All reactions were performed using 1.1 equiv. of $POCl_3$; addition of V–H complex was made dropwise to the sugar solution cooled with an ice bath; the ice bath was then removed and the mixture maintained at RT for the indicated time, except entries 8 and 9, where the reactions were carried out at 0–5 °C.

a singlet at 8.15 ppm corresponding to the formate proton and a deshielding of the protons at position 6′ from 3.38 and 3.82 for **3** and **6**, respectively to 4.43 ppm.

From these results we can conclude that the *O*-formylation of TBDMS ethers with equimolar amount of $POCl_3$ is much faster than with TBDPS ethers (some minutes versus one day).

The challenge now was to convert one silyl ether group selectively in the presence of others. For the di- and tri-*O*-TBDMS protected sucrose compounds **7** and **8** respectively, this objective failed. Reaction of **7** with 1.1 equiv. of $POCl_3$ at room temperature afforded uniquely the diformylated compound **14** (entry 7) after 30 min reaction at room temperature in 77% yield. By lowering the temperature to 0 °C (entry 8), we obtained after 5 min, a mixture which contained the mono formylated compounds **17** and **18** in low yields, 37% of diformate **14** and 17% of the starting sugar recovered. Increasing the time of reaction led to the formation of more diformylated derivative. In an attempt to improve the results, the reaction was also carried out at −50 °C, but all the starting material was recovered after 2 h.

The assignment of the structures was made by 2 dimensional NMR studies (HMQC and COSY). For compound **7** the chemical shift in the ^{1}H NMR for the C(6) protons was 3.81 ppm and for the C(6′), 3.70 ppm. For compound **17**, the formyl proton appeared at 8.14 ppm and the 6′ protons were shifted to 4.40 ppm; for compound **18**, the singlet corresponding to the formyl appeared at 8.06 and C(6) protons were deshielded to 4.26 ppm. Slight shifts for 5 and 5′ protons were also be observed and supported these results. For compound **14**, the two formyl singlets appeared at 8.09 and 8.12 ppm.

Attempts to selectively formylate the trisilylated precursor **8** were also unsuccessful (entry 9). A complex mixture of products was obtained after 30 min of reaction, from which were isolated and characterized the mono-, di- and triformylated compounds **19–22**, with very poor yields. Lowering the temperature did not change the results. When the reaction was left for a longer time (21 h), the formation of more diformylated compound and disappearance of the mono derivatives was observed.

Fortunately, better results were obtained when sucrose was protected with TBDPS. Adding 1.1 equiv. of Vilsmeier–Haack reagent to disilylated compound **4** (entry 4), formate **12** (45%) was formed as major product, with the formate ester group at position 6′ (**4**: $\delta_{6'}=3.80$ ppm; **12**: $\delta_{6'}=4.33$ ppm, $\delta_{CHO}=8.03$ ppm). Formylation at position 6 also occured but at lesser extent (13%) to give **13** (**4**: $\delta_6=3.56$ ppm; **13**: $\delta_6=4.41$ ppm, $\delta_{CHO}=8.15$ ppm).

The same trend was observed with the tri-*O*-TBDPS ether **5** (entry 5). By addition of 1.1 equiv. of the formylating agent was obtained 59% of **15**, formylated at position 6′ (**5**: $\delta_{6'}=3.79$ ppm; **15**: $\delta_{6'}=4.30$ ppm, $\delta_{CHO}=8.03$ ppm), as well as 16% of compound **16** and 21% of starting sugar **4** recovered.

From these results we can conclude:

- The conversion of primary TBDMS ethers of sugars into formates is much faster than for the TBDPS ethers (the same trend is observed with glucose and sucrose).
- The *O*-formylation of TBDPS ethers of sucrose with equimolar amount of $POCl_3\cdot$DMF is regioselective, and the order of reactivity is $6'>6\gg1'$. In fact, reaction at position 1′ was never observed.
- Very poor selectivity was found for the conversion of primary TBDMS ethers of sucrose, and the reaction occured at all three primary positions, that is, $6'=6=1'$.

Bearing in mind these results, we expected that it would be possible to convert selectively TBDMS ethers to formates in the presence of TBDPS ethers. In order to verify this, we prepared compound **9**, with two TBDPS groups in the positions 6 and 6′, and TBDMS group in the most hindered position 1′. Using 1.1 equiv. of $POCl_3$ to generate the V–H reagent (entry 10) we obtained 69% of formate **23**, corresponding to the conversion at the hindered position 1′. ^{1}H NMR of this compound showed a singlet at 8.05 ppm which was assigned to the formate proton; the signals corresponding to the methyl group of TBDMS had disappeared and the aromatic protons from TBDPS were still present, together with a singlet at 1.02 ppm corresponding to 18 protons of the *tert*-butyl groups. The 1′ protons, which appeared at 3.84 and 3.55 ppm in **10**, were deshielded to 4.30 ppm in the product **23**. As a secondary product, we obtained 22% of **24**, resulting from reaction at positions 1′ and 6′ (**10**: $\delta_{6'}=3.78$ ppm; **24**: $\delta_{6'}=4.34$ ppm, $\delta_{CHO}=8.06$ and 8.05 ppm). We were never able to eliminate this unwanted transformation, even making the formylation at lower temperatures.

From these results we can finally conclude that the *O*-formylation of the silyl ethers in primary positions of sucrose with equimolar amount of $POCl_3\cdot$DMF is chemoselective, and TBDMS ethers are more reactive than TBDPS ethers.

3. Experimental

3.1. General

All solvents were purified before use.[23] $POCl_3$ was distilled immediately before use. All reactions were run under dry argon atmosphere. All reactions were monitored by thin layer chromatography, which was performed on aluminium-backed silica gel Merck 60 F_{254} plates, and compounds were detected by ultraviolet light or by staining with 10% solution of H_2SO_4 in ethanol followed by heating. Flash chromatography was carried out using silica gel from Macherey–Nagel (Kieselgel 60 M). Preparative layer chromatography was performed on glass plates coated with 1 mm of silica gel (Mackerey–Nagel, Kieselgel DGF_{254}). Melting points were determined with a capillary apparatus and are uncorrected. Elemental analyses were performed on Thermo Finnigan-CE Flash EA 1112 CHNS series analyser. Mass spectra were determined on a GCT Micromass spectrometer. NMR spectra were recorded on a Bruker AMX-400 MHz apparatus in $CDCl_3$, using TMS as internal standard, with chemical shift values (δ) in ppm and coupling

constants in Hertz (Hz). Optical rotations were measured at 20 °C on an Optical Activity AA-1000 polarimeter at 589 nm.

3.2. General method for preparation of the silyl compounds

Compounds **1**–**9** were prepared based on the literature procedures, with some changes when mentioned (**1**, **2**, **6**–**8**;[3] **3**–**5**,[21] **9**[22]).

3.2.1. Methyl 2,3,4-tri-*O*-acetyl-6-*O*-TBDPS-α-D-glucopyranose (1). Compound **1** (2.62 g) was prepared from methyl α-D-glucopyranose (1 g, 5.15 mmol) in 91% yield, and purified by flash chromatography with hexane/ether 1:4. ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 4H, Ph–H_{ortho}), 7.41 (m, 6H, Ph–$H_{meta,para}$), 5.47 (t, 1H, J=9.8 Hz, H-3), 5.08 (t, 1H, J=9.8 Hz, H-4), 4.97 (d, 1H, J=3.6 Hz, H-1), 4.89 (dd, 1H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=10.2 Hz, H-2), 3.87 (ddd, 1H, $J_{4,5}$=10.1 Hz, $J_{5,6\beta}$=4.8 Hz, $J_{5,6\alpha}$=2.5 Hz, H-5), 3.70 (m, 2H, H-6), 3.41 (s, 1H, OCH_3), 2.084, 2.001, 1.884 (3s, 9H, 3O=C–OCH_3), 1.053 (s, 9H, ^{t}Bu–H) ppm. ^{13}C NMR ($CDCl_3$) δ 170.16 (C=O), 135.62, 135.58 (C–H_{ortho} (Ph)), 133.08 (C (Ph)), 129.68, 129.64 (C–H_{para} (Ph)), 127.64 (C–H_{meta} (Ph)), 96.45 (C-1), 71.00 (C-2), 70.51 (C-3), 69.87 (C-5), 68.89 (C-4), 62.61 (C-6), 55.06 (OCH_3), 26.65 (CH_3 (^{t}Bu)), 20.72, 20.67, 20.51 (CH_3 (Ac)), 19.13 (C (^{t}Bu)) ppm.

3.2.2. Methyl 2,3,4-tri-*O*-acetyl-6-*O*-TBDMS-α-D-glucopyranose (2). Compound **2** (2.20 g) was prepared from methyl α-D-glucopyranose (1 g, 5.15 mmol) in 98% yield, and purified by flash chromatography with hexane/ether 1:4. ^{1}H NMR ($CDCl_3$) δ 5.45 (t, 1H, J=9.8 Hz, H-3), 5.00 (t, 1H, J=9.8 Hz, H-4), 4.92 (d, 1H, J=3.6 Hz, H-1), 4.85 (dd, 1H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=10.2 Hz, H-2), 3.80 (ddd, 1H, $J_{4,5}$=10.1 Hz, $J_{5,6\beta}$=4.8 Hz, $J_{5,6\alpha}$=2.5 Hz, H-5), 3.74 (m, 2H, H-6), 3.385 (s, 1H, OCH_3), 2.06, 2.00, 1.99 (3s, 9H, 3O=C–OCH_3), 0.88 (s, 9H, ^{t}Bu–H), 0.032, −0.017 (Si–$(CH_3)_2$) ppm. ^{13}C NMR ($CDCl_3$) δ 170.22 (C=O), 135.62, 96.48 (C-1), 71.01 (C-2), 70.53 (C-3), 69.88 (C-5), 69.08 (C-4), 62.21 (C-6), 55.11 (OCH_3), 25.83 (CH_3 (^{t}Bu)), 20.71 (CH_3 (Ac)), 18.28 (C (^{t}Bu)), −5.76 (Si–CH_3) ppm.

3.2.3. 1′,2,3,3′,4,4′,6-Hepta-*O*-acetyl-6′-*O*-TBDPS-sucrose (3). Compound **3** (9.36 g) was prepared from sucrose (5 g, 0.015 mol) and 3.8 mL (1 equiv.) of TBDPSCl, followed by conventional acetylation with acetic anhydride, in 73% overall yield. It was purified by flash chromatography with hexane/ethyl acetate 1:1. ^{1}H NMR ($CDCl_3$) δ 7.64 (m, 4H, Ph–H_{ortho}), 7.34 (m, 6H, Ph–$H_{meta,para}$), 5.63 (d, 1H, J=3.6 Hz, H-1), 5.51 (t, 1H, J=5.8 Hz, H-4′), 5.39 (d, 1H, J=5.4 Hz, H-3′), 5.38 (t, 1H, J=8.8 Hz, H-3), 5.01 (t, 1H, J=9.8 Hz, H-4), 4.81 (dd, 1H, $J_{1,2}$=3.7 Hz, $J_{2,3}$=10.3 Hz, H-2), 4.17 (d, 1H, J=12.1 Hz, H-1′α), 4.12 (d, 1H, J=12.4 Hz, H-1′β), 4.16 (m, 3H, H-5,5′,6β), 3.92 (dd, 1H, $J_{5,6\alpha}$=1.4 Hz, $J_{6\alpha,6\beta}$=7.8 Hz, H-6α), 3.85 (dd, 1H, $J_{5',6'\alpha}$=5.1 Hz, $J_{6'\alpha,6'\beta}$=11 Hz, H-6′α), 3.82 (dd, 1H, $J_{5',6'\beta}$=5.6 Hz, $J_{6'\alpha,6'\beta}$=11 Hz, H-6′β), 2.14, 2.10, 2.09, 2.05, 2.01, 1.98, 1.97 (7s, 21H, 7OCH_3), 1.06 (s, 9H, ^{t}Bu–H) ppm. ^{13}C NMR ($CDCl_3$) δ 170.00, 169.76 (C=O), 135.57 (C–H_{ortho} (Ph)), 132.9 (C (Ph)), 129.85 (C–H_{para} (Ph)), 127.78 (C–H_{meta} (Ph)), 103.67 (C-2′), 89.70 (C-1), 81.38 (C-5′), 76.19 (C-3′), 75.11 (C-4′), 70.20 (C-2), 69.78 (C-3), 68.27 (C-5), 68.09 (C-4), 63.83 (C-6′), 62.90 (C-1′), 61.57 (C-6), 26.71 (CH_3 (^{t}Bu)), 20.56 (CH_3 (Ac)), 19.10 (C (^{t}Bu)) ppm.

3.2.4. 1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6,6′-di-*O*-TBDPS-sucrose (4). To a solution of sucrose (5 g, 0.015 mol) in pyridine (90 mL), was added *tert*-butyldiphenyl-chlorosilane (4.2 mL, 1.1 equiv.) in the presence of catalytical amount of DMAP, followed by 4 h heating at 70 °C. After cooling, the same amount of TBDPSCl was added, and the reaction was kept at room temperature for 24 h. Evaporation of the solvent and flash chromatography with ethyl acetate gave 6,6′-di-*O*-TBDPS sucrose (10.05 g) with 84% yield. Acetylation with acetic anhydride followed by column purification with hexane/ethyl acetate 1:1 afforded **4** with 78% of overall yield (12.2 g) ^{1}H NMR ($CDCl_3$) δ 7.63 (m, 8H, Ph–H_{ortho}), 7.35 (m, 12H, Ph–$H_{meta,para}$), 5.65 (d, 1H, J=3.5 Hz, H-1), 5.42 (t, 1H, J=4.6 Hz, H-4′), 5.41 (t, 1H, J=9.6 Hz, H-3), 5.35 (t, 1H, J=9.7 Hz, H-4), 5.31 (d, 1H, J=4.2 Hz, H-3′), 4.82 (dd, 1H, $J_{1,2}$=3.5 Hz, $J_{2,3}$=10 Hz, H-2), 4.30 (d, 1H, J=12.4 Hz, H-1′α), 4.23 (d, 1H, J=12.4 Hz, H-1′β), 4.06 (q, 1H, J=5.6 Hz, H-5′), 4.00 (bd, 1H, J=9.9 Hz, H-5), 3.83 (dd, 1H, $J_{5',6'\alpha}$=5.2 Hz, $J_{6'\alpha,6'\beta}$=10.5 Hz, H-6′α), 3.77 (dd, 1H, $J_{5',6'\beta}$=7 Hz, $J_{6'\alpha,6'\beta}$=10.8 Hz, H-6′β), 3.61 (d, 1H, $J_{5,6\alpha}$=11.2 Hz, H-6α), 3.51 (dd, 1H, $J_{5,6\beta}$=2.4 Hz, $J_{6\alpha,6\beta}$=11.5 Hz, H-6β), 2.11, 2.09, 2.07, 2.04, 2.03, 1.84 (6s, 18H, 6OCH_3), 1.01 (s, 18H, 2^{t}Bu–H) ppm. ^{13}C NMR ($CDCl_3$) δ 170.26, 170.14, 169.63, 169.12 (C=O), 135.65, 135.47 (C–H_{ortho} (Ph)), 133.15, 132.97 (C (Ph)), 129.74, 129.63 (C–H_{para} (Ph)), 127.70, 127.63 (C–H_{meta} (Ph)), 104.56 (C-2′), 90.57 (C-1), 81.93 (C-5′), 76.22 (C-3′), 75.18 (C-4′), 70.65 (C-5), 70.57 (C-3), 70.20 (C-2), 68.02 (C-4), 63.90 (C-6′), 62.22 (C-1′), 61.31 (C-6), 26.69 (CH_3 (^{t}Bu)), 20.75, 20.59, 20.49 (CH_3 (Ac)), 19.14 (C (^{t}Bu)) ppm.

3.2.5. 1′,6,6′-Tri-*O*-TBDPS-2,3,3′,4,4′-penta-*O*-acetyl-sucrose (5). Compound **5** (13.89 g) was prepared from sucrose (5 g, 0.019 mol) in 75% yield, and purified by flash chromatography with hexane/ethyl acetate 2:1. ^{1}H NMR ($CDCl_3$) δ 7.63 (m, 12H, Ph–H_{ortho}), 7.30 (m, 18H, Ph–$H_{meta,para}$), 5.84 (d, 1H, J=6.2 Hz, H-3′), 5.60 (d, 1H, J=3.6 Hz, H-1), 5.39 (t, 1H, J=6.4 Hz, H-4′), 5.37 (t, 1H, J=9.5 Hz, H-4), 5.32 (t, 1H, J=9.6 Hz, H-3), 4.85 (dd, 1H, $J_{1,2}$=3.7 Hz, $J_{2,3}$=9.7 Hz, H-2), 4.12 (q, 1H, J=6.2 Hz, H-5′), 3.98 (bd, 1H, J=9.4 Hz, H-5), 3.84 (dd, 1H, $J_{5',6'\beta}$=5.8 Hz, $J_{6'\alpha,6'\beta}$=11 Hz, H-6′β), 3.75 (dd, 1H, $J_{5',6'\alpha}$=5.1 Hz, $J_{6'\alpha,6'\beta}$=11.3 Hz, H-6′α), 3.78 (d, 1H, J=10.9 Hz, H-1′α), 3.58 (d, 1H, $J_{5,6\alpha}$=11.4 Hz, H-6α), 3.50 (dd, 1H, $J_{5,6\beta}$=2.2 Hz, $J_{6\alpha,6\beta}$=11.6 Hz, H-6β), 3.51 (d, 1H, J=10.8 Hz, H-1′β), 2.02, 1.98, 1.92, 1.85, 1.80 (5s, 15H, 5OCH_3), 1.08, 1.02, 0.99 (3s, 27H, 3^{t}Bu–H) ppm. ^{13}C NMR ($CDCl_3$) δ 170.26, 170.14, 169.63, 169.12 (C=O), 135.65, 135.47 (C–H_{ortho} (Ph)), 133.15, 132.97 (C (Ph)), 129.74, 129.63 (C–H_{para} (Ph)), 127.70, 127.63 (C–H_{meta} (Ph)), 104.56 (C-2′), 90.57 (C-1), 81.93 (C-5′), 76.22 (C-3′), 75.18 (C-4′), 70.65 (C-5), 70.57 (C-3), 70.20 (C-2), 68.02 (C-4), 63.90 (C-6′), 62.22 (C-1′), 61.31 (C-6), 26.69 (CH_3 (^{t}Bu)), 20.75, 20.59, 20.49 (CH_3 (Ac)), 19.14 (C (^{t}Bu)) ppm.

3.2.6. 1′,2,3,3′,4,4′,6-Hepta-*O*-acetyl-6′-*O*-TBDMS-sucrose (6), 1′,2,3,3′,4,4′-hexa-*O*-acetyl-6,6′-di-*O*-TBDMS-sucrose (7) and 1′,6,6′-tri-*O*-TBDMS-2,3,3′,4,4′-penta-*O*-acetyl-sucrose (8). Reaction of sucrose (5 g, 0,019 mol)

with TBDMSCl (0.65 equiv.), followed by acetylation gave, after column chromatography with hexane/ethyl acetate 2:1 and 1:1, compounds **6** (1.21 g, 11%), **7** (4.09 g, 34%) and **8** (4.58 g, 35%). **6**: ^{1}H NMR ($CDCl_3$) δ 5.73 (d, 1H, J=3.6 Hz, H-1), 5.45 (t, 1H, J=5.3 Hz, H-4′), 5.44 (t, 1H, J=9.9 Hz, H-3), 5.41 (d, 1H, J=6.0 Hz, H-3′), 5.07 (t, 1H, J=9.8 Hz, H-4), 4.85 (dd, 1H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=10.4 Hz, H-2), 4.28 (m, 1H, H-5), 4.26 (dd, 1H, $J_{5,6\alpha}$=4.1 Hz, $J_{6\alpha,6\beta}$=11.6 Hz, H-6α), 4.20 (d, 1H, J=12.4 Hz, H-1′α), 4.15 (d, 1H, J=12.6 Hz, H-1′β), 4.12 (dd, 1H, $J_{5,6\beta}$=4.8 Hz, $J_{6\alpha,6\beta}$=12.6 Hz, H-6β), 4.05 (q, 1H, J=5.5 Hz, H-5′), 3.84 (dd, 1H, $J_{5',6'\alpha}$=1.6 Hz, $J_{6'\alpha,6'\beta}$=11 Hz, H-6′α), 3.80 (dd, 1H, $J_{5',6'\beta}$=2.3 Hz, $J_{6'\alpha,6'\beta}$=11.1 Hz, H-6′β), 2.13, 2.09, 2.07, 2.06, 2.02, 2.00 (6s, 21H, 7OCH_3), 0.89 (s, 9H, ^{t}Bu–H), 0.083, 0.077 (2s, 6H, 2Si–$(CH_3)_2$) ppm. ^{13}C NMR ($CDCl_3$) δ 170.68, 170.11 (C=O), 103.80 (C-2′), 89.77 (C-1), 81.52 (C-5′), 76.24 (C-3′), 75.07 (C-4′), 70.26 (C-2), 69.70 (C-3), 68.25 (C-4,5), 63.31 (C-6′), 62.87 (C-1′), 61.68 (C-6), 25.80 (CH_3 (^{t}Bu)), 20.75, 20.64 (CH_3 (Ac)), 18.30 (C (^{t}Bu)), −5.53 (Si–CH_3) ppm. **7**: ^{1}H NMR ($CDCl_3$) δ 5.67 (d, 1H, J=3.5 Hz, H-1), 5.43 (t, 1H, J=10.1 Hz, H-3), 5.40 (t, 1H, J=5.5 Hz, H-4′), 5.38 (d, 1H, J=5.6 Hz, H-3′), 5.17 (t, 1H, J=9.8 Hz, H-4), 4.82 (dd, 1H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=10.4 Hz, H-2), 4.21 (d, 1H, J=12.5 Hz, H-1′α), 4.18 (d, 1H, J=12.5 Hz, H-1′β), 4.11 (m, 1H, H-5), 4.06 (q, 1H, J=5.9 Hz, H-5′), 3.84 (dd, 1H, $J_{5,6\alpha}$=5.6 Hz, $J_{6\alpha,6\beta}$=10.6 Hz, H-6α), 3.78 (dd, 1H, $J_{5,6\beta}$=6.3 Hz, $J_{6\alpha,6\beta}$=10.5 Hz, H-6β), 3.73 (dd, 1H, $J_{5',6'\alpha}$=1.7 Hz, $J_{6'\alpha,6'\beta}$=11.5 Hz, H-6′α), 3.68 (dd, 1H, $J_{5',6'\beta}$=3.3 Hz, $J_{6'\alpha,6'\beta}$=11.5 Hz, H-6′β), 2.12, 2.09, 2.09, 2.03, 2.00 (5s, 18H, 6OCH_3), 0.89, 0.87 (2s, 18H, 2^{t}Bu–H), 0.09, 0.08, 0.02, 0.02 (4s, 12H, 2Si–$(CH_3)_2$) ppm. ^{13}C NMR ($CDCl_3$) δ 170.20, 169.83, 169.21 (C=O), 103.94 (C-2′), 90.17 (C-1), 81.53 (C-5′), 76.41 (C-3′), 75.61 (C-4′), 70.54 (C-5), 70.43 (C-2), 70.20 (C-3), 68.46 (C-4), 63.69 (C-6), 62.85 (C-1′), 61.44 (C-6′), 25.84 (CH_3 (^{t}Bu)), 20.64 (CH_3 (Ac)), 18.32 (C (^{t}Bu)), −5.55 (Si–CH_3) ppm. **8**: ^{1}H NMR ($CDCl_3$) δ 5.68 (d, 1H, J=3.5 Hz, H-1), 5.62 (d, 1H, J=6.6 Hz, H-3′), 5.43 (t, 1H, J=9.8 Hz, H-3), 5.42 (t, 1H, J=6.2 Hz, H-4′), 5.19 (t, 1H, J=9.8 Hz, H-4), 4.84 (dd, 1H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=10.3 Hz, H-2), 4.12 (bd, 1H, J=9.4 Hz, H-5), 3.99 (q, 1H, J=5.4 Hz, H-5′), 3.80 (m, 2H, $J_{5',6'\alpha}$=1.6 Hz, $J_{6'\alpha,6'\beta}$=12.4 Hz, H-6′α,6′β), 3.76 (d, 1H, J=11 Hz, H-1′α), 3.74 (bs, 1H, H-6β), 3.70 (dd, 1H, $J_{5,6\alpha}$=2.5 Hz, $J_{6\alpha,6\beta}$=11.4 Hz, H-6α), 3.50 (d, 1H, J=11 Hz, H-1′β), 2.09, 2.06, 2.03, 2.00 (4s, 15H, 5OCH_3), 0.90, 0.89, 0.88 (3s, 27H, 3^{t}Bu–H), 0.08, 0.07, 0.06, 0.03, 0.02 (5s, 18H, 3Si–$(CH_3)_2$) ppm. ^{13}C NMR ($CDCl_3$) δ 169.97, 169.26 (C=O), 104.98 (C-2′), 89.65 (C-1), 81.02 (C-5′), 75.68 (C-3′), 75.40 (C-4′), 70.57 (C-3), 70.33 (C-2), 70.22 (C-5), 68.62 (C-4), 63.73 (C-1′,6′), 61.52 (C-6), 25.88, 25.82 (CH_3 (^{t}Bu)), 20.67 (CH_3 (Ac)), 18.26 (C (^{t}Bu)), −5.492, −5.543, −5.617 (Si–CH_3) ppm.

3.2.7. 1′-*O*-TBDMS-6,6′-di-*O*-TBDPS-2,3,3′,4,4′-penta-*O*-acetyl-sucrose (9). Compound **9** (1.69 g) was prepared from 6-6′-di-*O*-TBDPS sucrose (1.78 g, 2.17 mmol), followed by acetilation, in 68% yield and purified by flash chromatography with hexane/ethyl acetate 2:1. $[\alpha]_D^{20}$=+58.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.63 (m, 8H, Ph–H_{ortho}), 7.34 (m, 12H, Ph–$H_{meta,para}$), 5.64 (d, 1H, J=3.6 Hz, H-1), 5.57 (d, 1H, J=5.1 Hz, H-3′), 5.44 (t, 1H, J=9.7 Hz, H-3), 5.38 (t, 1H, J=9.2 Hz, H-4), 5.37 (t, 1H, J=5.3 Hz, H-4′), 4.88 (dd, 1H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=9.8 Hz, H-2), 4.10 (m, 1H, J=7.1 Hz, H-5), 3.99 (q, 1H, J=5.5 Hz, H-5′), 3.84 (d, 1H, J=11 Hz, H-1′α), 3.81 (dd, 1H, $J_{5',6'\beta}$=5.6 Hz, $J_{6'\alpha,6'\beta}$=10.9 Hz, H-6′β), 3.76 (dd, 1H, $J_{5',6'\alpha}$=5.4 Hz, $J_{6'\alpha,6'\beta}$=10.9 Hz, H-6′α), 3.69 (dd, 1H, $J_{5,6\alpha}$=1.2 Hz, $J_{6\alpha,6\beta}$=11.7 Hz, H-6α), 3.58 (dd, 1H, $J_{5,6\beta}$=2.4 Hz, $J_{6\alpha,6\beta}$=9.9 Hz, H-6β), 3.55 (d, 1H, J=10.9 Hz, H-1′β), 2.08, 2.02, 2.01, 1.98, 1.84 (5s, 15H, 5OCH_3), 1.02 (s, 18H, 2^{t}Bu–H (TBDPS)), 0.91 (s, 9H, ^{t}Bu–H (TBDMS)), 0.08, 0.07 (d, 6H, Si–$(CH_3)_2$) ppm. ^{13}C NMR ($CDCl_3$) δ 170.09, 169.61 (C=O), 135.66, 135.53 (C–H_{ortho}(Ph)), 133.09 (C (Ph)), 129.68 (C–H_{para}(Ph)), 127.68 (C–H_{meta} (Ph)), 105.53 (C-2′), 90.24 (C-1), 81.43 (C-5′), 76.02, 76.01 (C-3′,4′), 70.57, 70.44, 70.32 (C-3,2,5), 68.18 (C-4), 64.13 (C-6′), 63.36 (C-1′), 61.45 (C-6), 26.70, 25.75 (CH_3 (^{t}Bu)), 20.80, 20.66, 20.56 (CH_3 (Ac)), 19.18 (C (^{t}Bu)), −5.52, −5.63, −5.97 (Si–CH_3) ppm. Anal. Calcd for $C_{60}H_{82}O_{16}Si_3$: C, 63.02; H, 7.23. Found: C, 62.80; H, 7.28.

3.3. General method for Vilsmeier–Haack (V–H) formylation

Freshly distilled phosphorus oxychloride (1.1 equiv.) was dissolved in cold DMF (1 mL) (cooled with an ice bath) and stirred during 30 min at 0–5 °C. The sugar (1 mmol) was dissolved in DMF (2 mL) and cooled in an ice bath. The V–H complex was then added dropwise to the sugar solution and the reaction was stirred at room temperature or at 0–5 °C for the indicated time (see Table 1). Hydrolysis was achieved by adding 30 mL of saturated solution of $NaHCO_3$ at 0–5 °C. The aqueous layer was extracted with ether and washed with water. The combined organic layers were dried over Na_2SO_4 and the solvent was distilled off. The crude was purified by flash chromatography to afford the *O*-formyl derivatives.

3.3.1. Methyl 2,3,4-tri-*O*-acetyl-6-*O*-formyl-α-D-glucopyranose (10). Column chromatography with hexane/ether 1:4 followed by crystallization from ether afforded **10** (296 mg, 85% starting from **1**; 292.6 mg, 84% starting from **2**) as colourless needles; mp 89–90 °C. $[\alpha]_D^{20}$=+136.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.09 (s, 1H, HC=O), 5.49 (t, 1H, J=9.6 Hz, H-3), 5.06 (t, 1H, J=10 Hz, H-4), 4.96 (d, 1H, J=3.6 Hz, H-1), 4.89 (dd, 1H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=10 Hz, H-2), 4.28 (m, 2H, H-6), 4.03 (ddd, 1H, $J_{4,5}$=10.4 Hz, $J_{5,6\beta}$=4.8 Hz, $J_{5,6\alpha}$=2.2 Hz, H-5), 3.43 (s, 1H, OCH_3), 2.08, 2.04, 2.01 (3s, 9H, 3O=C–OCH_3) ppm. ^{13}C NMR ($CDCl_3$) δ 170.04, 169.58 (H_3CC=O), 160.37 (H*C*=O), 96.74 (C-1), 70.72 (C-2), 69.97 (C-3), 68.67 (C-4), 66.94 (C-5), 61.48 (C-6), 55.52 (OCH_3), 20.65 (CH_3 (Ac)) ppm. Anal. Calcd for $C_{14}H_{20}O_{10}$: C, 48.28; H, 5.79. Found: C, 48.33; H, 5.81.

3.3.2. 1′,2,3,3′,4,4′,6-Hepta-*O*-acetyl-6′-*O*-formyl-sucrose (11). Column chromatography with hexane/ethyl acetate 1:1 afforded **11** (584.8 mg, 88% starting from **3**; 544.9 mg, 82% starting from **6**) as colourless oil. $[\alpha]_D^{20}$= +62.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1H, HC=O), 5.65 (d, 1H, J=3.5 Hz, H-1), 5.48 (d, 1H, J=6.5 Hz, H-3′), 5.47 (t, 1H, J=9.6 Hz, H-3), 5.40 (t, 1H, J=6.2 Hz, H-4′), 5.06 (t, 1H, J=9.8 Hz, H-4), 4.88 (dd, 1H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=10.4 Hz, H-2), 4.48 (dd, 1H, $J_{5',6'\alpha}$=3.8 Hz, $J_{6'\alpha,6'\beta}$=

12 Hz, H-6′α), 4.39 (dd, 1H, $J_{5',6'\beta}$=6.5 Hz, $J_{6'\alpha,6'\beta}$= 12 Hz, H-6′β), 4.26 (m, 3H, H-5,5′,6β), 4.22 (d, 1H, J= 12.2 Hz, H-1′α), 4.17 (d, 1H, J=12 Hz, H-1′β), 4.15 (dd, 1H, $J_{5,6\alpha}$=1.4 Hz, $J_{6\alpha,6\beta}$=12 Hz, H-6α), 2.17, 2.12, 2.11, 2.05, 2.02 (6s, 21H, 7OCH$_3$) ppm. ^{13}C NMR (CDCl$_3$) δ 170.66, 170.00, 169.65, 169.49 (H$_3$C*C*=O), 160.45 (H*C*=O), 103.85 (C-2′), 90.21 (C-1), 78.69 (C-5′), 75.62 (C-3′), 74.68 (C-4′), 70.22 (C-2), 69.46 (C-3), 68.46 (C-5), 68.22 (C-4), 62.89 (C-6′), 62.70 (C-6), 61.82 (C-1′), 20.59 (CH$_3$ (Ac)) ppm. Anal. Calcd for $C_{27}H_{36}O_{19}$: C 48.80, H 5.46. Found: C 48.78, H 5.41.

3.3.3. 1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6-*O*-TBDPS-6′-*O*-formyl-sucrose (12), 1′,2,3,3′,4,4′-hexa-*O*-acetyl-6-*O*-formyl-6′-*O*-TBDPS-sucrose (13) and 1′,2,3,3′,4,4′-hexa-*O*-acetyl-6,6′-di-*O*-formyl-sucrose (14). Prepared from **4**. Column chromatography with hexane/ethyl acetate 1:1 afforded **12** (387.4 mg, 45%, colourless oil), **13** (111.9 mg, 13%, colourless oil), **14** (32.5 mg, 5%, colourless needles) and **4** recovered (235.7 mg, 22%). **12**: $[\alpha]_D^{20}$=+67.8 (*c* 1.0, CHCl$_3$). ^{1}H NMR (CDCl$_3$) δ 8.03 (s, 1H, HC=O), 7.65 (m, 4H, Ph–H$_{ortho}$), 7.34 (m, 6H, Ph–H$_{meta,para}$), 5.67 (d, 1H, J=3.5 Hz, H-1), 5.67 (t, 1H, J= 9.9 Hz, H-3), 5.41 (d, 1H, J=5.9 Hz, H-3′), 5.34 (t, 1H, J= 9.8 Hz, H-4), 5.32 (t, 1H, J=6.8 Hz, H-4′), 4.87 (dd, 1H, $J_{1,2}$=3.5 Hz, $J_{2,3}$=10.3 Hz, H-2), 4.37 (dd, 1H, $J_{5',6'\alpha}$= 3.9 Hz, $J_{6'\alpha,6'\beta}$=11.8 Hz, H-6′α), 4.28 (d, 1H, J=12.1 Hz, H-1′α), 4.26 (dd, 1H, $J_{5',6'\beta}$=6.6 Hz, $J_{6'\alpha,6'\beta}$=11.5 Hz, H-6′β), 4.20 (m, 1H, J=5.7 Hz, H-5′), 4.16 (d, 1H, J= 12.3 Hz, H-1′β), 4.09 (bd, 1H, $J_{4,5}$=9.8 Hz, H-5), 3.74 (d, 1H, $J_{6\alpha,6\beta}$=11.8 Hz, H-6α), 3.68 (dd, 1H, $J_{5,6\beta}$=2.9 Hz, $J_{6\alpha,6\beta}$=11.7 Hz, H-6β), 2.12, 2.10, 2.09, 2.08, 2.03, 1.93 (6s, 18H, 6OCH$_3$), 1.04 (s, 9H, ^{t}Bu–H) ppm. ^{13}C NMR (CDCl$_3$) δ 170.28, 170.03, 169.87, 169.70, 169.22 (H$_3$C*C*=O), 160.44 (H*C*=O), 135.72, 135.66 (C–H$_{ortho}$ (Ph)), 133.05, 132.93 (C (Ph)), 129.67 (C–H$_{para}$ (Ph)), 127.66 (C–H$_{meta}$ (Ph)), 104.08 (C-2′), 90.64 (C-1), 78.70 (C-5′), 75.82 (C-3′), 74.92 (C-4′), 70.78 (C-5), 70.55 (C-2), 70.08 (C-3), 68.11 (C-4), 62.76 (C-6′), 62.25 (C-1′), 61.60 (C-6), 26.72 (CH$_3$ (^{t}Bu)), 20.64, 20.48 (CH$_3$ (Ac)), 19.19 (C (^{t}Bu)) ppm. Anal. Calcd for $C_{41}H_{52}O_{18}Si$: C 57.20, H 6.09. Found: C 57.44, H 6.26. **13**: ^{1}H NMR (CDCl$_3$) δ 8.15 (s, 1H, HC=O), 7.69 (m, 4H, Ph–H$_{ortho}$), 7.42 (m, 6H, Ph–H$_{meta,para}$), 5.95 (d, 1H, J=7.3 Hz, H-3′), 5.54 (d, 1H, J= 3.6 Hz, H-1), 5.45 (t, 1H, J=7.4 Hz, H-4′), 5.37 (t, 1H, J= 9.9 Hz, H-3), 5.02 (t, 1H, J=9.7 Hz, H-4), 4.81 (dd, 1H, $J_{1,2}$=3.7 Hz, $J_{2,3}$=10.3 Hz, H-2), 4.46 (dd, 1H, $J_{5,6\alpha}$= 3.2 Hz, $J_{6\alpha,6\beta}$=12.1 Hz, H-6α), 4.35 (dd, 1H, $J_{5,6\beta}$=6 Hz, $J_{6\alpha,6\beta}$=12.1 Hz, H-6β), 4.23 (m, 2H, H-5,5′), 4.12 (dd, 1H, $J_{5',6'\beta}$=4.1 Hz, $J_{6'\alpha,6'\beta}$=14.4 Hz, H-6′β), 4.05 (d, 1H, $J_{6'\alpha,6'\beta}$=11 Hz, H-6′α), 3.76 (d, 1H, J=10.8 Hz, H-1′α), 3.50 (d, 1H, J=10.8 Hz, H-1′β), 2.16, 2.08, 2.05, 2.01, 1.97, 1.71 (6s, 18H, 6OCH$_3$), 1.08 (s, 9H, ^{t}Bu–H) ppm. ^{13}C NMR (CDCl$_3$) δ 170.08, 169.77, 169.94 (H$_3$C*C*=O), 160.54 (H*C*=O), 135.57 (C–H$_{ortho}$ (Ph)), 132.58 (C (Ph)), 129.90 (C–H$_{para}$ (Ph)), 127.79 (C–H$_{meta}$ (Ph)), 104.93 (C-2′), 89.62 (C-1), 77.98 (C-5′), 74.99 (C-3′), 74.50 (C-4′), 69.93 (C-2), 69.81 (C-3), 68.20 (C-4,5), 64.14 (C-1′), 62.86 (C-6), 61.74 (C-66), 26.65 (CH$_3$ (^{t}Bu)), 20.73, 20.61, 20.21 (CH$_3$ (Ac)), 19.20 (C (^{t}Bu)) ppm. *m/z* (CI) 318 (100%, $C_{13}H_{18}O_9$). Found: *M*, 318.0943 requires *M*, 318.0951. *m/z* (CI) 289 (23%, $C_{28}H_{36}O_8Si$–$C_{16}H_{19}Si$). Found: 289.0972 requires 289.0923. **14**: mp 117–118 °C. $[\alpha]_D^{20}$=+71.6 (*c* 1.0, CHCl$_3$). ^{1}H NMR (CDCl$_3$) δ 8.13, 8.11 (2s, 2H, 2HC=O), 5.66 (d, 1H, J=3.6 Hz, H-1), 5.49 (d, 1H, J= 6.4 Hz, H-3′), 5.47 (t, 1H, J=10.7 Hz, H-3), 5.41 (t, 1H, J= 6.4 Hz, H-4′), 5.05 (t, 1H, J=9.8 Hz, H-4), 4.88 (dd, 1H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=10.4 Hz, H-2), 4.47 (dd, 1H, $J_{5',6'\alpha}$= 3.9 Hz, $J_{6'\alpha,6'\beta}$=12.1 Hz, H-6′α), 4.40 (dd, 1H, $J_{5',6'\beta}$= 6.5 Hz, $J_{6'\alpha,6'\beta}$=12.1 Hz, H-6′β), 4.28 (m, 4H, H-5,6α,6β,5′), 4.20 (d, 1H, J=12.3 Hz, H-1′α), 4.14 (d, 1H, J=12.2 Hz, H-1′β), 2.18, 2.12, 2.11, 2.06, 2.02 (5s, 18H, 6OCH$_3$) ppm. ^{13}C NMR (CDCl$_3$) δ 170.02, 169.71 (H$_3$C*C*=O), 160.53, 160.44 (H*C*=O), 103.64 (C-2′), 89.94 (C-1), 78.61 (C-5′), 75.52 (C-3′), 74.50 (C-4′), 70.12 (C-2), 69.40 (C-3), 68.40 (C-4), 68.30 (C-5), 62.92 (C-1′,6′), 61.30 (C-6), 20.60 (CH$_3$ (Ac)) ppm. Anal. Calcd for $C_{26}H_{34}O_{19}$: C 48.00, H 5.27. Found: C 48.22, H 5.32.

3.3.4. 1′,6-Di-*O*-TBDPS-2,3,3′,4,4′-penta-*O*-acetyl-6′-*O*-formyl-sucrose (15) and 1′-*O*-TBDPS-2,3,3′,4,4′-penta-*O*-acetyl-6,6′-di-*O*-formyl-sucrose (16). Prepared from **5**. Column chromatography with hexane/ethyl acetate 2:1 afforded **15** (623.8 mg, 59%, colourless oil), **16** (135.5 mg, 16%, colourless oil) and **5** recovered (266.2 mg, 21%). **15**: $[\alpha]_D^{20}$=+72.0 (*c* 1.0, CHCl$_3$). ^{1}H NMR (CDCl$_3$) δ 8.04 (s, 1H, HC=O), 7.64 (m, 8H, Ph–H$_{ortho}$), 7.36 (m, 12H, Ph–H$_{meta,para}$), 5.90 (d, 1H, J=7 Hz, H-3′), 5.56 (d, 1H, J= 3.6 Hz, H-1), 5.39 (m, 3H, H-4,3,4′), 4.84 (dd, 1H, $J_{1,2}$= 3.7 Hz, $J_{2,3}$=9.5 Hz, H-2), 4.38 (dd, 1H, $J_{5',6'\alpha}$=1.9 Hz, $J_{6'\alpha,6'\beta}$=10.9 Hz, H-6′α), 4.21 (m, 2H, H-5′,6′β), 4.03 (bd, 1H, $J_{4,5}$=8.7 Hz, H-5), 3.77 (d, 1H, J=10.8 Hz, H-1′α), 3.67 (d, 1H, $J_{6\alpha,6\beta}$=11.4 Hz, H-6α), 3.63 (dd, 1H, $J_{5,6\beta}$= 1.9 Hz, $J_{6\alpha,6\beta}$=11.7 Hz, H-6β), 3.49 (d, 1H, J=10.8 Hz, H-1′β), 2.06, 2.03, 1.99, 1.92, 1.76 (5s, 15H, 5OCH$_3$), 1.06, 1.03 (2s, 18H, 2^{t}Bu–H) ppm. ^{13}C NMR (CDCl$_3$) δ 170.42, 169.96, 169.75, 169.15 (H$_3$C*C*=O), 160.47 (H*C*=O), 135.62 (C–H$_{ortho}$ (Ph)), 133.15, 132.97, 132.58 (C (Ph)), 129.92, 129.83, 129.67, 129.58 (C–H$_{para}$ (Ph)), 127.85, 127.74, 127.65, 127.60 (C–H$_{meta}$ (Ph)), 105.13 (C-2′), 90.04 (C-1), 78.03 (C-5′), 75.20 (C-3′), 74.82 (C-4′), 70.48 (C-3), 70.37 (C-5), 70.24 (C-2), 68.09 (C-4), 64.12 (C-1′), 62.80 (C-6′), 61.36 (C-6), 26.72 (CH$_3$ (^{t}Bu)), 20.69, 20.58, 20.33 (CH$_3$ (Ac)), 19.25 (C (^{t}Bu)) ppm. Anal. Calcd for $C_{55}H_{68}O_{17}Si_2$: C 62.48, H 6.48. Found: C 62.27, H 6.56. **16**: $[\alpha]_D^{20}$=+60.2 (*c* 1.0, CHCl$_3$). ^{1}H NMR (CDCl$_3$) δ 8.14, 7.95 (2s, 2H, 2HC=O), 7.68 (m, 4H, Ph–H$_{ortho}$), 7.40 (m, 6H, Ph–H$_{meta,para}$), 5.95 (d, 1H, J=7.5 Hz, H-3′), 5.53 (d, 1H, J=3.7 Hz, H-1), 5.47 (t, 1H, J=7.6 Hz, H-4′), 5.37 (t, 1H, J=9.8 Hz, H-3), 4.97 (t, 1H, J=9.8 Hz, H-4), 4.79 (dd, 1H, $J_{1,2}$=3.7 Hz, $J_{2,3}$=10.3 Hz, H-2), 4.46 (dd, 1H, $J_{5,6\alpha}$= 3.3 Hz, $J_{6\alpha,6\beta}$=12.1 Hz, H-6α), 4.36 (dd, 1H, $J_{5,6\beta}$=6 Hz, $J_{6\alpha,6\beta}$=12.1 Hz, H-6β), 4.26 (m, 3H, H-5,5′,6′α), 4.17 (dd, 1H, $J_{5',6'\beta}$=5.1 Hz, $J_{6'\alpha,6'\beta}$=12.2 Hz, H-6′β), 3.75 (d, 1H, J=10.9 Hz, H-1′α), 3.49 (d, 1H, J=10.8 Hz, H-1′β), 2.15, 2.08, 2.02, 1.96, 1.69 (5s, 15H, 5OCH$_3$), 1.07 (s, 19H, ^{t}Bu–H) ppm. ^{13}C NMR (CDCl$_3$) δ 170.17, 170.04, 169.75, 169.53 (H$_3$C*C*=O), 160.53 (H*C*=O), 135.60 (C–H$_{ortho}$ (Ph)), 132.60 (C (Ph)), 129.96, 129.90 (C–H$_{para}$ (Ph)), 127.86, 127.79 (C–H$_{meta}$ (Ph)), 104.85 (C-2′), 89.43 (C-1), 78.00 (C-5′), 74.92 (C-3′), 74.40 (C-4′), 69.90 (C-2), 69.73 (C-3), 68.57 (C-4), 68.02 (C-5), 64.04 (C-1′), 62.85 (C-6), 61.36 (C-6′), 26.65 (CH$_3$ (^{t}Bu)), 20.71, 20.59, 20.17 (CH$_3$ (Ac)), 19.23 (C (^{t}Bu)) ppm. Anal. Calcd for $C_{40}H_{50}O_{18}Si$: C 56.73, H 5.95. Found: C 56.49, H 5.95.

3.3.5. 1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6-*O*-TBDMS-6′-*O*-formyl-sucrose (17), 1′,2,3,3′,4,4′-hexa-*O*-acetyl-6-*O*-formyl-6′-*O*-TBDMS-sucrose (18). Prepared from **7**. Column chromatography with hexane/ethyl acetate 1:1 afforded **17** (110.5 mg, 15%, colourless oil), **18** (132.6 mg, 18%, colourless oil), **14** (240.7 mg, 37%, colourless needles) and **7** recovered (139.9 mg, 17%). **17**: $[\alpha]_D^{20}=+77.6$ (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.14 (s, 1H, HC═O), 5.63 (d, 1H, $J=3.4$ Hz, H-1), 5.45 (d, 1H, $J=5.6$ Hz, H-3′), 5.44 (t, 1H, $J=8.8$ Hz, H-3), 5.39 (t, 1H, $J=6.1$ Hz, H-4′), 5.15 (t, 1H, $J=9.8$ Hz, H-4), 4.83 (dd, 1H, $J_{1,2}=3.5$ Hz, $J_{2,3}=10.3$ Hz, H-2), 4.45 (dd, 1H, $J_{5',6'\alpha}=4$ Hz, $J_{6'\alpha,6'\beta}=11.9$ Hz, H-6′α), 4.35 (dd, 1H, $J_{5',6'\beta}=6.3$ Hz, $J_{6'\alpha,6'\beta}=11.9$ Hz, H-6′β), 4.24 (d,m, 2H, $J_{1'\alpha,1'\beta}=11.9$ Hz, H-1′α,5′), 4.14 (d, 1H, $J=12.2$ Hz, H-1′β), 4.07 (bd, 1H, $J_{4,5}=9.9$ Hz, H-5), 3.73 (d, 1H, $J_{6\alpha,6\beta}=10.5$ Hz, H-6α), 3.68 (dd, 1H, $J_{5,6\beta}=3.5$ Hz, $J_{6\alpha,6\beta}=11.5$ Hz, H-6β), 2.14, 2.10, 2.01, 2.00 (4s, 18H, $6OCH_3$), 0.87 (s, 9H, ^{t}Bu–H), 0.02, 0.02 (2s, 6H, Si–$(CH_3)_2$) ppm. ^{13}C NMR ($CDCl_3$) δ 170.17 (H_3CC═O), 160.46 (H*C*═O), 103.82 (C-2′), 90.38 (C-1), 78.56 (C-5′), 75.71 (C-3′), 74.78 (C-4′), 70.80 (C-5), 70.38 (C-2), 70.00 (C-3), 68.31 (C-4), 62.90 (C-6′), 62.75 (C-1′), 61.45 (C-6), 25.83 (CH_3 (^{t}Bu)), 20.67, 20.59, 20.48 (CH_3 (Ac)), 18.33 (C (^{t}Bu)) ppm. Anal. Calcd for $C_{31}H_{48}O_{18}Si$: C 50.53, H 6.57. Found: C 50.18, H 6.49. **18**: $[\alpha]_D^{20}=+64$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.08 (s, 1H, HC═O), 5.74 (d, 1H, $J=3.7$ Hz, H-1), 5.47 (t, 1H, $J=6.1$ Hz, H-4′), 5.42 (t, 1H, $J=9.8$ Hz, H-3), 5.42 (d, 1H, $J=6.1$ Hz, H-3′), 5.06 (t, 1H, $J=9.8$ Hz, H-4), 4.85 (dd, 1H, $J_{1,2}=3.7$ Hz, $J_{2,3}=10.4$ Hz, H-2), 4.33 (dt, 1H, $J_{4,5}=10.2$ Hz, $J_{5,6}=3.5$ Hz, H-5), 4.27 (ds, 2H, H-6), 4.18 (d, 1H, $J=12.2$ Hz, H-1′α), 4.14 (d, 1H, $J=12.3$ Hz, H-1′β), 4.05 (q, 1H, $J=5.5$ Hz, H-5′), 3.86 (dd, 1H, $J_{5',6'\alpha}=1.8$ Hz, $J_{6'\alpha,6'\beta}=10.9$ Hz, H-6′α), 3.80 (dd, 1H, $J_{5',6'\beta}=2.1$ Hz, $J_{6'\alpha,6'\beta}=11.1$ Hz, H-6′β), 2.14, 2.10, 2.09, 2.07, 2.04, 2.01 (6s, 18H, $6OCH_3$), 0.89 (s, 9H, ^{t}Bu–H), 0.08, 0.07 (2s, 6H, Si–$(CH_3)_2$) ppm. ^{13}C NMR ($CDCl_3$) δ 170.03 (H_3CC═O), 160.53 (H*C*═O), 103.58 (C-2′), 89.52 (C-1), 81.42 (C-5′), 76.14 (C-3′), 74.86 (C-4′), 70.19 (C-2), 69.64 (C-3), 68.49 (C-4), 68.10 (C-5), 63.28 (C-6′), 63.05 (C-1′), 61.23 (C-6), 25.79 (CH_3 (^{t}Bu)), 20.60 (CH_3 (Ac)), 18.30 (C (^{t}Bu)) ppm. Anal. Calcd for $C_{31}H_{48}O_{18}Si$: C 50.53, H 6.57. Found: C 50.32, H 6.53.

3.3.6. 1′,6-Di-*O*-TBDMS-2,3,3′,4,4′-penta-*O*-acetyl-6′-*O*-formyl-sucrose (19), 1′,6′-di-*O*-TBDMS-2,3,3′,4,4′-penta-*O*-acetyl-6-*O*-formyl-sucrose (20), 1′-*O*-TBDMS-2,3,3′,4,4′-penta-*O*-acetyl-6,6′-di-*O*-formyl-sucrose (21) and 1′,6,6′-tri-*O*-formyl-2,3,3′,4,4′-penta-*O*-acetyl-sucrose (22). Prepared from **8**. Column chromatography with hexane/ethyl acetate 1:1 afforded **19** (80.9 mg, 10%, colourless oil), **20** (105.2 mg, 13%, colourless oil), **21** (224.1 mg, 31%), **22** (31.8 mg, 5%, colourless oil) and **8** recovered (286.5 mg, 32%). **19**: $[\alpha]_D^{20}=+60.8$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.13 (s, 1H, HC═O), 5.56 (d, 1H, $J=6.8$ Hz, H-3′), 5.61 (d, 1H, $J=3.6$ Hz, H-1), 5.43 (t, 1H, $J=9.4$ Hz, H-3), 5.39 (t, 1H, $J=6.8$ Hz, H-4′), 5.17 (t, 1H, $J=9.7$ Hz, H-4), 4.81 (dd, 1H, $J_{1,2}=3.6$ Hz, $J_{2,3}=10.4$ Hz, H-2), 4.41 (d, 1H, $J_{6'\alpha,6'\beta}=11.8$ Hz, H-6′α), 4.30 (dd, 1H, $J_{5',6'\beta}=5.2$ Hz, $J_{6'\alpha,6'\beta}=12$ Hz, H-6′β), 4.15 (bs, 1H, H-5′), 4.08 (bd, 1H, $J_{4,5}=10.3$ Hz, H-5), 3.77 (d, 1H, $J=11.2$ Hz, H-1′α), 3.74 (m, 1H, H-6α), 3.68 (dd, 1H, $J_{5,6\beta}=1.1$ Hz, $J_{6\alpha,6\beta}=11.6$ Hz, H-6β), 3.53 (d, 1H, $J=10.8$ Hz, H-1′β), 2.10, 2.06, 2.04, 2.00 (4s, 15H, $5OCH_3$), 0.89, 0.87 (2s, 18H, 2^{t}Bu–H), 0.07, 0.05, 0.02 (3s, 12H, 2Si–$(CH_3)_2$) ppm. ^{13}C NMR ($CDCl_3$) δ 170.43, 170.05, 169.67, 169.23 (H_3CC═O), 160.60 (H*C*═O), 105.02 (C-2′), 89.96 (C-1), 78.02 (C-5′), 75.31 (C-3′), 74.78 (C-4′), 70.58 (C-5), 70.42 (C-2), 70.31 (C-3), 68.41 (C-4), 63.69 (C-1′), 62.73 (C-6′), 61.41 (C-6), 25.85, 25.73 (CH_3 (^{t}Bu)), 20.70 (CH_3 (Ac)), 18.19 (C (^{t}Bu)) ppm. Anal. Calcd for $C_{35}H_{60}O_{17}Si_2$: C 51.96, H 7.48. Found: C 52.23, H 7.42. **20**: $[\alpha]_D^{20}=+75$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.08 (s, 1H, HC═O), 5.76 (d, 1H, $J=3.7$ Hz, H-1), 5.65 (d, 1H, $J=6.7$ Hz, H-3′), 5.48 (t, 1H, $J=6.9$ Hz, H-4′), 5.45 (t, 1H, $J=10$ Hz, H-3), 5.05 (t, 1H, $J=9.8$ Hz, H-4), 4.86 (dd, 1H, $J_{1,2}=3.8$ Hz, $J_{2,3}=10.3$ Hz, H-2), 4.38 (dt, 1H, $J_{4,5}=10.3$ Hz, $J_{5,6}=3.3$ Hz, H-5), 4.30 (dd, 1H, $J_{5,6b}=3.7$ Hz, $J_{6\alpha,6\beta}=12.4$ Hz, H-6β), 4.26 (dd, 1H, $J_{5,6\alpha}=2.8$ Hz, $J_{6\alpha,6\beta}=11.7$ Hz, H-6α), 4.15 (q, 1H, $J=4.9$ Hz, H-5′), 3.83 (dd, 1H, $J_{5',6'\alpha}=4.3$ Hz, $J_{6'\alpha,6'\beta}=10.8$ Hz, H-6′α), 3.78 (dd, 1H, $J_{5',6'\beta}=4.9$ Hz, $J_{6'\alpha,6'\beta}=10.7$ Hz, H-6′β), 3.73 (d, 1H, $J=11$ Hz, H-1′α), 3.47 (d, 1H, $J=11$ Hz, H-1′β), 2.10, 2.05, 2.03, 2.01 (4s, 15H, $5OCH_3$), 0.90, 0.89 (2s, 18H, 2^{t}Bu–H), 0.07, 0.06, 0.03 (3s, 12H, 2Si–$(CH_3)_2$) ppm. ^{13}C NMR ($CDCl_3$) δ 170.11, 169.99, 169.81, 169.62 (H_3CC═O), 160.55 (H*C*═O), 104.73 (C-2′), 89.07 (C-1), 80.99 (C-5′), 75.35 (C-3′), 74.70 (C-4′), 70.08 (C-2), 69.93 (C-3), 68.58 (C-4), 67.78 (C-5), 63.66 (C-1′), 63.19 (C-6′), 61.32 (C-6), 25.74 (CH_3 (^{t}Bu)), 20.65 (CH_3 (Ac)), 18.21 (C (^{t}Bu)) ppm. Anal. Calcd for $C_{35}H_{60}O_{17}Si_2$: C 51.96, H 7.48. Found: C 52.02, H 7.58. **21**: $[\alpha]_D^{20}=+69.4$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.12, 8.07 (2s, 2H, 2HC═O), 5.66 (d, 1H, $J=6.8$ Hz, H-3′), 5.62 (d, 1H, $J=3.6$ Hz, H-1), 5.44 (t, 1H, $J=9.8$ Hz, H-3), 5.39 (t, 1H, $J=6.9$ Hz, H-4′), 5.02 (t, 1H, $J=9.8$ Hz, H-4), 4.84 (dd, 1H, $J_{1,2}=3.7$ Hz, $J_{2,3}=10.4$ Hz, H-2), 4.43 (dd, 1H, $J_{5',6'\alpha}=3.4$ Hz, $J_{6'\alpha,6'\beta}=12.1$ Hz, H-6′α), 4.32 (dd, 1H, $J_{5',6'\beta}=5.9$ Hz, $J_{6'\alpha,6'\beta}=12$ Hz, H-6′β), 4.29 (m, 1H, H-5), 4.26 (m, 1H, H-6α), 4.22 (dd, 1H, $J_{5,6\beta}=5$ Hz, $J_{6\alpha,6\beta}=12.3$ Hz, H-6β), 4.15 (dt, 1H, $J=6.4$, 3.7 Hz, H-5′), 3.76 (d, 1H, $J=10.9$ Hz, H-1′α), 3.51 (d, 1H, $J=10.9$ Hz, H-1′β), 2.12, 2.06, 2.04, 2.03, 2.00 (5s, 15H, $5OCH_3$), 0.89 (s, 9H, ^{t}Bu–H), 0.07, 0.05 (2s, 6H, Si–$(CH_3)_2$) ppm. ^{13}C NMR ($CDCl_3$) δ 170.09, 169.87, 169.56 (H_3CC═O), 160.52 (H*C*═O), 104.99 (C-2′), 89.70 (C-1), 78.26 (C-5′), 75.17 (C-3′), 74.65 (C-4′), 70.17 (C-2), 69.65 (C-3), 68.54 (C-4), 68.00 (C-5), 63.58 (C-1′), 62.72 (C-6′), 61.37 (C-6), 25.69 (CH_3 (^{t}Bu)), 20.57 (CH_3 (Ac)), 18.18 (C (^{t}Bu)) ppm. Anal. Calcd for $C_{30}H_{46}O_{18}Si$: C 49.85, H 6.42. Found: C 49.77, H 6.45. **22**: $[\alpha]_D^{20}=+62$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.13, 8.12, 8.09 (3s, 3H, 2HC═O), 5.65 (d, 1H, $J=3.3$ Hz, H-1), 5.53 (d, 1H, $J=7.1$ Hz, H-3′), 5.46 (2t, 2H, $J_3=9.5$ Hz, $J_{4'}=7.4$ Hz, H-3,4′), 5.04 (t, 1H, $J=9.8$ Hz, H-4), 4.91 (dd, 1H, $J_{1,2}=3.5$ Hz, $J_{2,3}=10.4$ Hz, H-2), 4.44 (dd, 1H, $J_{5',6'\alpha}=3.2$ Hz, $J_{6'\alpha,6'\beta}=12$ Hz, H-6′α), 4.40 (dd, 1H, $J_{5',6'\beta}=6.4$ Hz, $J_{6'\alpha,6'\beta}=12.1$ Hz, H-6′β), 4.29 (m, 1H, H-5), 4.30 (m, 5H, H-5,1′α,6α,6β,5′), 4.20 (d, 1H, $J=12.1$ Hz, H-1′β), 2.18, 2.11, 2.06, 2.02 (4s, 15H, $5OCH_3$) ppm. ^{13}C NMR ($CDCl_3$) δ 169.98, 169.80, 169.49 (H_3CC═O), 160.50, 160.40, 159.67 (H*C*═O), 103.03 (C-2′), 89.82 (C-1), 78.40 (C-5′), 75.49 (C-3′), 74.06 (C-4′), 69.98 (C-2), 69.44 (C-3), 68.43 (C-4,5), 62.81 (C-6′), 62.54 (C-1′), 61.36 (C-6), 20.53, 20.46 (CH_3 (Ac)) ppm. Anal. Calcd for $C_{25}H_{32}O_{19}$: C 47.17, H 5.07. Found: C 46.99, H 5.07.

3.3.7. 1′-*O*-Formyl-2,3,3′,4,4′-penta-*O*-acetyl-6,6′-di-*O*-TBDPS-sucrose (23) and 1′,6′-di-*O*-formyl-2,3,3′,4,

4′-penta-*O*-acetyl-6-*O*-TBDPS-sucrose (24). Prepared from **9**. Column chromatography with hexane/ethyl acetate 2:1 afforded **23** (729.5 mg, 69%, colourless needles) and **24** (177.8 mg, 21%, colourless oil). **23**: mp 105–106 °C. $[\alpha]_D^{20} = +54$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.05 (s, 1H, HC=O), 7.62 (m, 8H, Ph–H_{ortho}), 7.34 (m, 12H, Ph–$H_{meta,para}$), 5.61 (d, 1H, $J=3.6$ Hz, H-1), 5.45 (t, 1H, $J=5.3$ Hz, H-4′), 5.39 (t, 1H, $J=9.6$ Hz, H-3), 5.36 (d, 1H, $J=5.3$ Hz, H-3′), 5.34 (t, 1H, $J=9.5$ Hz, H-4), 4.86 (dd, 1H, $J_{1,2}=3.6$ Hz, $J_{2,3}=9.8$ Hz, H-2), 4.30 (s, 2H, H-1), 4.08 (q, 1H, $J=5.8$ Hz, H-5′), 3.99 (bd, 2H, $J=9.4$ Hz, H-5), 3.83 (dd, 1H, $J_{5,6'\alpha}=5.7$ Hz, $J_{6'\alpha,6'\beta}=10.8$ Hz, H-6′α), 3.77 (dd, 1H, $J_{5,6'\beta}=6.5$ Hz, $J_{6'\alpha,6'\beta}=10.8$ Hz, H-6′β), 3.62 (d, 1H, $J_{6\alpha,6\beta}=10.5$ Hz, H-6α), 3.53 (dd, 1H, $J_{5,6\beta}=2.7$ Hz, $J_{6\alpha,6\beta}=11.7$ Hz, H-6β), 2.11, 2.06, 2.03, 2.01, 1.87 (5s, 15H, $5OCH_3$), 1.02 (s, 18H, 2^tBu–H) ppm. ^{13}C NMR ($CDCl_3$) δ 170.27, 169.82, 169.65, 169.21 (H_3CC=O), 159.90 (H*C*=O), 135.69, 135.54 (C–H_{ortho} (Ph)), 133.11, 132.92 (C (Ph)), 129.79 (C–H_{para} (Ph)), 127.76 (C–H_{meta} (Ph)), 103.90 (C-2′), 90.52 (C-1), 81.50 (C-5′), 76.56 (C-3′), 75.74 (C-4′), 70.65 (C-5), 70.41 (C-2), 70.30 (C-3), 68.04 (C-4), 64.08 (C-6′), 62.15 (C-1′), 61.36 (C-6), 26.74 (CH_3 (^{t}Bu)), 20.79, 20.69, 20.57 (CH_3 (Ac)), 19.19 (C (^{t}Bu)) ppm. Anal. Calcd for $C_{55}H_{68}O_{17}Si_2$: C 62.48, H 6.48. Found: C 62.67, H 6.59. **24**: $[\alpha]_D^{20} = +75.4$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.06, 8.05 (2s, 2H, 2HC=O), 7.65 (m, 4H, Ph–H_{ortho}), 7.40 (m, 6H, Ph–$H_{meta,para}$), 5.65 (d, 1H, $J=3.6$ Hz, H-1), 5.47 (t, 1H, $J=9.9$ Hz, H-3), 5.46 (d, 1H, $J=6.5$ Hz, H-3′), 5.37 (t, 1H, $J=9.6$ Hz, H-4), 5.37 (t, 1H, $J=6.6$ Hz, H-4′), 4.91 (dd, 1H, $J_{1,2}=3.6$ Hz, $J_{2,3}=10.3$ Hz, H-2), 4.39 (dd, 1H, $J_{5',6'\alpha}=3.5$ Hz, $J_{6'\alpha,6'\beta}=11.9$ Hz, H-6′α), 4.34 (d, 1H, $J=12.1$ Hz, H-1′α), 4.27 (dd, 1H, $J_{5',6'\beta}=6.1$ Hz, $J_{6'\alpha,6'\beta}=11.9$ Hz, H-6′β), 4.22 (d, 1H, $J=11.5$ Hz, H-1′β), 4.22 (m, 1H, H-5′), 4.10 (bd, 1H, $J=10$ Hz, H-5), 3.76 (dd, 1H, $J_{5,6\alpha}=1.6$ Hz, $J_{6\alpha,6\beta}=11.7$ Hz, H-6α), 3.69 (dd, 1H, $J_{5,6\beta}=3.1$ Hz, $J_{6\alpha,6\beta}=11.8$ Hz, H-6β), 2.12, 2.10, 2.07, 2.03, 1.93 (5s, 15H, $5OCH_3$), 1.05 (s, 9H, ^{t}Bu–H) ppm. ^{13}C NMR ($CDCl_3$) δ 170.36, 170.24, 169.84, 169.21 (H_3CC=O), 160.45, 159.72 (H*C*=O), 135.70 (C–H_{ortho} (Ph)), 132.99 (C (Ph)), 129.73 (C–H_{para} (Ph)), 127.68 (C–H_{meta} (Ph)), 103.45 (C-2′), 90.57 (C-1), 78.45 (C-5′), 75.74 (C-3′), 74.40 (C-4′), 70.84 (C-5), 70.37 (C-2), 70.07 (C-3), 68.06 (C-4), 62.64 (C-6′), 62.25 (C-1′), 61.59 (C-6), 26.73 (CH_3 (^{t}Bu)), 20.66 (CH_3 (Ac)), 19.18 (C (^{t}Bu)) ppm. Anal. Calcd for $C_{40}H_{50}O_{18}Si$: C 56.73, H 5.95. Found: C 56.35, H 5.94.

Acknowledgements

The authors are grateful to Fundação para a Ciência e a Tecnologia for financial support (PRAXIS SFRH/BD/878/2000 and POCTI/QUI/47973/2002).

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Synthesis of new 6-substituted purinyl-5′-nor-1′-homocarbanucleosides based on indanol☆

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Received 27 May 2004; revised 15 July 2004; accepted 22 July 2004

Available online 27 August 2004

Abstract—A series of new 6-substituted purinyl-5′-nor-1′-homocarbanucleosides based on indanol were synthesized from (±)-*cis*-3-hydroxymethyl-1-indanol, an appropriately functionalized derivative of which was reacted with 6-chloropurine in the presence of NaH and 18-crown-6 ether to prepare a key intermediate that gave access to the target molecules, purinylcarbanucleosides in which position 6 is occupied by a chloro, hydroxy, methoxy, amino or substituted phenyl group.

1. Introduction

Of the many classes of nucleoside analogues that have been synthesized with a view to clinical applications, one of the most interesting is the class of carbocyclic analogues (CANs), which continues to have great potential for the development of new antitumour and antiviral agents.[2] CANs are compounds in which the furan ring of natural nucleosides has been replaced by a carbocyclic system. This modification endows them with greater biostability than nucleosides by making them more resistant to the hydrolytic action of phosphorylases.[3,4] The anti-AIDS drug carbovir (**I**),[5] which selectively inhibits HIV reverse transcriptase, and its equally potent but less toxic analogue abacavir (**II**),[6] are cyclopentenyl nucleosides CANs in which the sugar ring of natural nucleosides has been replaced with a cyclopentene ring. Variants of carbocyclic nucleosides include 1′-homonucleosides, in which further resistance to enzymatic degradation has been sought by insertion of a methylene group between the heterocyclic base and C-1 of the pseudosugar moiety[7] and a number of nor-compounds in which and improved selectivity index has been achieved by substituting an hydroxyl group for a pseudosugar hydroxymethyl (e.g., the hydroxymethyls on C-5′ of aristeromycin[8] and C-3′ of carbocyclic oxetanocin analogues[9]).

In recent years our research group has prepared a number of cyclopentenyl 1′-homonucleoside derivatives in which the cyclopentene ring is incorporated in an indan system (**III**),[10] our aim being to improve the liposolubility of the compounds and thus facilitate its access to the central nervous system, an important reservoir of the HIV and other viruses.[11] Some of these compounds showed considerable cytostatic activity,[12] particularly the 6-arylpurine derivatives (which is in keeping with reports concerning 6-arylpurinyl ribonucleosides).[13,14]

Here we describe a new series of this kind in which both the variant features mentioned in the previous paragraph have been introduced. Specifically, we report the synthesis and antiviral activity of a series of indanyl 5′-nor-1′-homocarbanucleosides in which position 6 of the purine system bears a Cl (**12**), OH (**13a**), OMe (**13b**), NH_2 (**14a**), cyclopropylamine (**14b**) or –PhR (**16a–d**) group.

☆ See Ref. 1.

Keywords: Synthesis; Antiviral agents; Antineoplastic agents; Indan carbanucleosides; Suzuki–Miyaura cross-coupling reaction.
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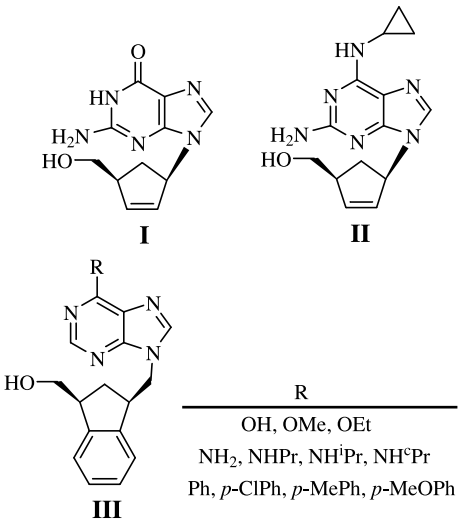
doi:10.1016/j.tet.2004.07.054



2. Results and discussion

Retrosynthetic analysis (Scheme 1) led to the choice of diol *cis*-**4** as starting compound. Appropriate functionalization of *cis*-**4** would allow it to be coupled to 6-chloropurine, and the resulting key intermediate, **9**, would afford purinylcarbanucleosides **12**, **13a–b** and **14a–b** by substitution of the chlorine at position 6 (when necessary) and deprotection, while its Suzuki–Miyaura cross-coupling with appropriate boronic acids would give 6-arylpurinylcarbanucleosides **16a–d**.

Diol **4** was easily obtained from phenylsuccinic anhydride by Friedel–Crafts reaction with aluminium trichloride in 1,2-dichloroethane[15] followed by esterification with methanol in an acidic medium and treatment of the resulting ketoester **3** with lithium borohydride in tetrahydrofuran (Scheme 2). The resulting 83:17 mixture of (±)-*cis*-**4** and (±)-*trans*-**4** was efficiently resolved by chromatography on silica gel.

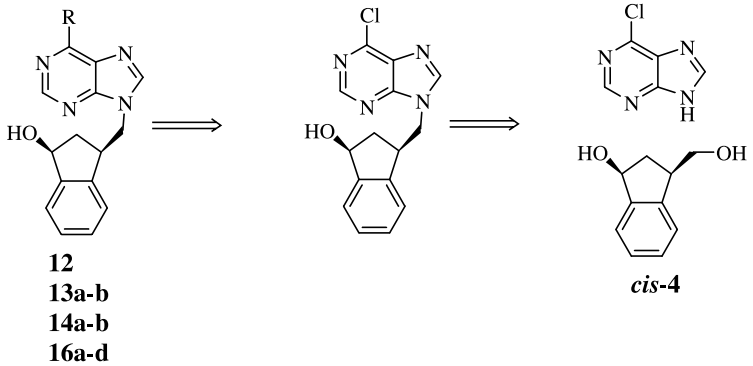
We next acetylated the primary alcohol of *cis*-**4** to prevent its reaction during protection of the secondary alcohol with a group that would subsequently withstand the conditions to be employed for Mitsunobu coupling to 6-chloropurine.[16] Since an attempt at acetylations by reaction with acetic anhydride in pyridine afforded a complex mixture from which the desired acetate **5** was obtained only in unsatisfactory yield and after laborious work-up (accompanied by the diacetate and starting *cis*-**4**), we resorted to lipase-catalysed transesterification from vinyl acetate using *Candida antarctica* lipase (Novozym® 435),[17] which afforded the desired monoacetate **5** as the only product in 93% yield.

The secondary alcohol of **5** was efficiently protected by reaction with *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane,[18] and the primary alcohol of the resulting compound **6**, was then deprotected by treatment with MeONa/MeOH. However, several attempts at Mitsunobu coupling of **7** to 6-chloropurine (addition of DEAD to a mixture of **7**, PPh_3 and 6-chloropurine followed by reaction for times ranging from 12 to 36 h at temperatures ranging from room temperature (rt) to 50 °C) were all unsuccessful, only the starting compound ever being recovered.

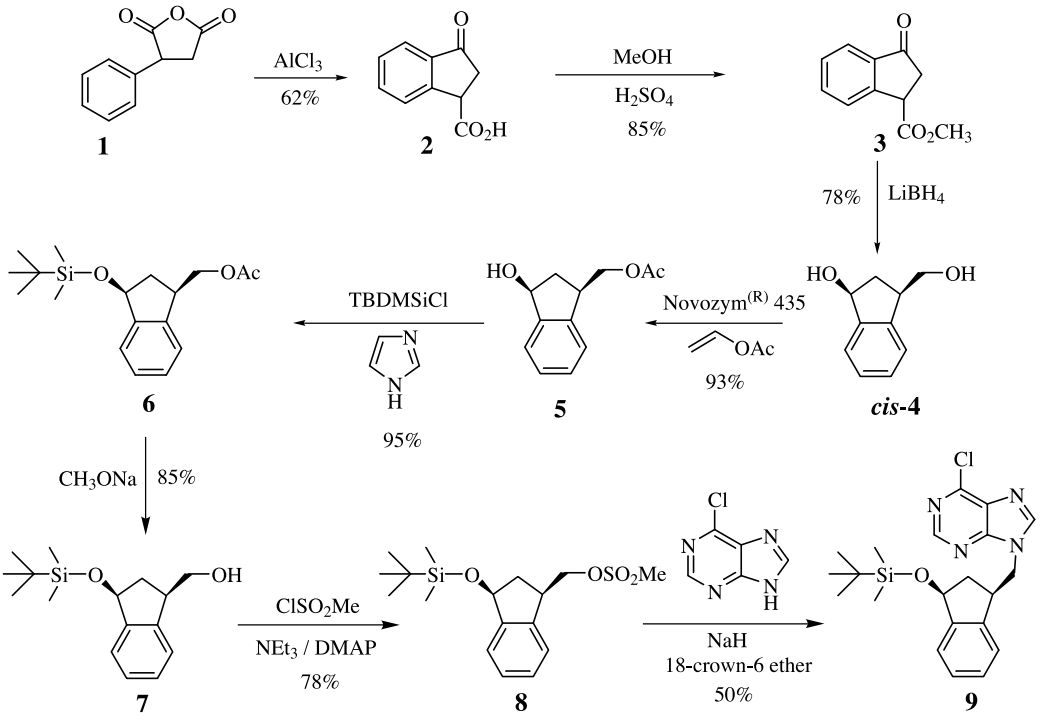
Eventually, the purine was introduced on the diol by a more classical method: treatment of **7** with mesyl chloride provided mesylate **8**, and heating **8** with 6-chloropurine in DMF in the presence of NaH and 18-crown-6 ether[19] afforded a 50% yield of the desired key intermediate **9** by nucleophilic substitution.

To obtain the 6-chloropurinyl carbanucleoside **12**, compound **9** was deprotected by distilling with $FeCl_3$/water (Scheme 3), a method that prevents the OH epimerization that occurs when other deprotecting agents are employed.[20] Treatment of **9** with 0.25 N NaOH in 1,4-dioxane afforded the 6-hydroxypurinyl carbanucleoside **13a** in one step and 75% yield, while treatment with methanol or amine, followed by deprotection with $FeCl_3$/water, gave the 6-methoxy and 6-amino compounds **13b**, **14a** and **14b**.

Finally, following Hocek and co-workers,[21] we introduced substituted phenyls at position 6 of the purine by Suzuki–Miyaura cross coupling reaction of **9** with the appropriate arylboronic acids in dry toluene containing tetrakis(triphenylphosphine)palladium as catalyst, potassium carbonate as base. This procedure gave 50–96% yields of compounds **15a–d**, deprotection of which with $FeCl_3$/water afforded the 6-arylpurinyl carbanucleosides **16a–d** in yields of 71–87%.



Scheme 1.



Scheme 2.

3. Antiviral activity

Compounds **12**, **13a–b**, **14a–b** and **16a–d** were evaluated for antiviral activity[22] against a wide variety of viruses, including herpes simplex virus type 1 (strain KOS), herpes simplex virus type 2 (strain G), vaccinia virus, a thymidine kinase-deficient HSV-1 strain (KOS, ACV^R) and vesicular stomatitis virus (VSV) in HEL cell cultures; respiratory syncytial virus, Coxsackie virus B4 and vesicular stomatitis virus in HeLa cell cultures; and type 3 parainfluenza virus, type 1reovirus, Sindbis virus, Coxsackie virus B4 and Punta Toro virus in Vero cell cultures. None of the compounds showed inhibitory activity against any of the virus strains at 400 μg/mL.

4. Conclusion

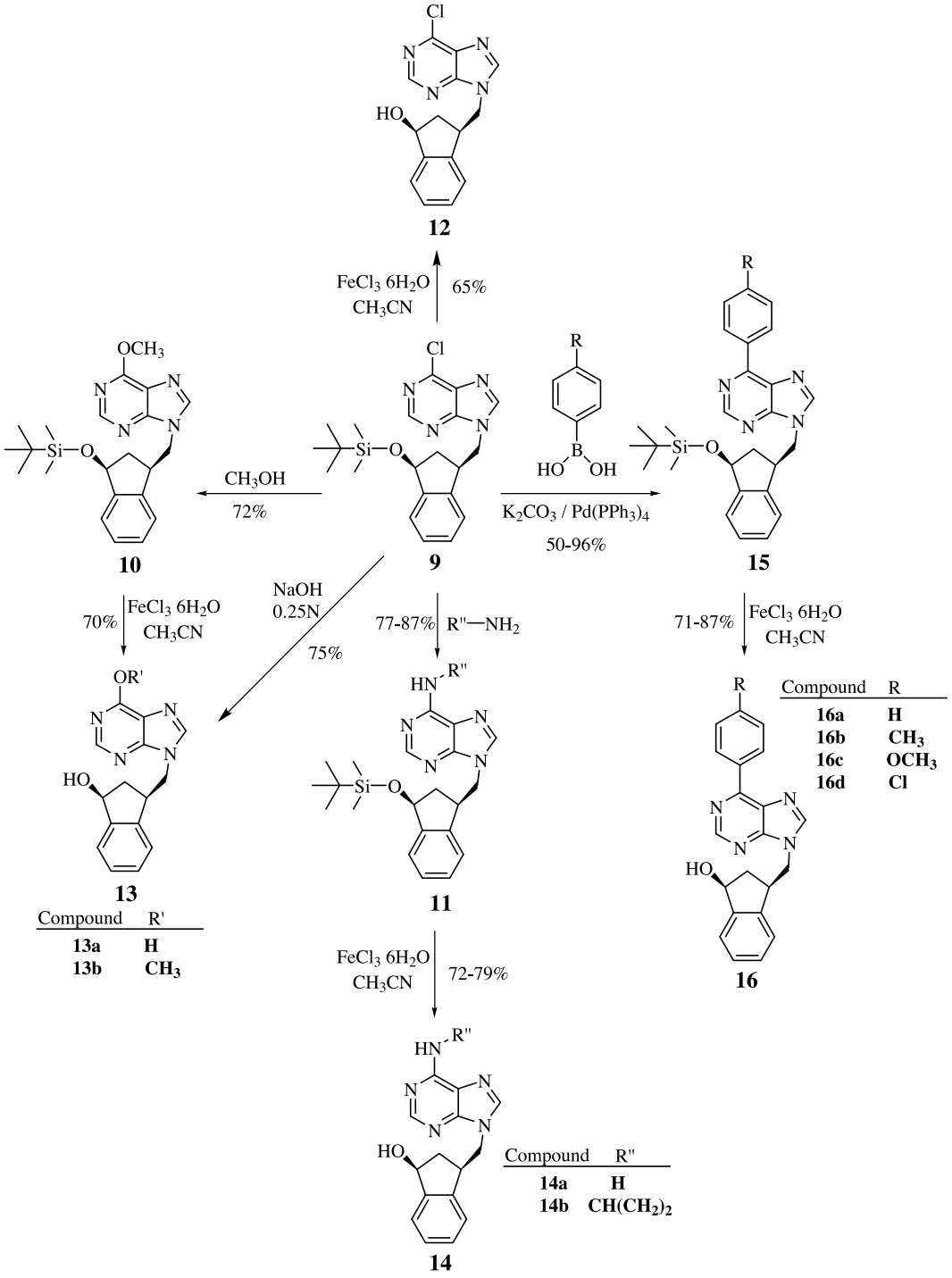
In conclusion, this paper describes a convenient synthetic procedure for the preparation of 6-substituted purinyl-5′-nor-1′-homocarbanucleosides with a pseudosugar based on indanol, **12**, **13a–b**, **14a–b** and **16a–d**, an interesting new template in which the double bond of the cyclopentenyl nucleosides is embedded in a benzene ring. However, none of the members of this family that were synthesized exhibits antiviral activity.

5. Experimental

5.1. General

Silica gel (230 mesh) was purchased from Merck. All other chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. Melting points were determined in a Reichert Kofler Thermopan or in capillary tubes in a Büchi 510 apparatus, and are uncorrected. Infrared spectra were recorded in a Perkin–Elmer 1640-FT spectrometer. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75.47 MHz) were recorded in a Bruker AMX spectrometer, using TMS as internal standard (chemical shifts (δ) in ppm, J in Hz). Elemental analyses were obtained on a Perkin–Elmer 240B microanalyser by the Microanalysis Service of the University of Santiago de Compostela. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TLC on pre-coated silica gel plates (Merck 60 F254, 0.25 mm).

5.1.1. Methyl 3-oxo-1-indanecarboxylate, 3. A solution of phenylsuccinic anhydride (8 g, 45.41 mmol) in 1,2-dichloroethane (65 mL) was added dropwise to a well-stirred suspension of aluminium trichloride (13.6 g, 102 mmol) in 65 mL of the same solvent at 0 °C. The mixture was stirrred for 40 min at rt, quenched with 100 mL of H_2O at 0 °C, and extracted with ethyl ether (3×75 mL). The pooled organic layers were dried (Na_2SO_4), and removal of the solvent under vacuum afforded 3-oxo-1-indanecarboxylic acid, **2**, which was dissolved in MeOH (20 mL) containing 5 drops of sulphuric acid. This solution was refluxed for 16 h, the solvent was removed under vacuum, and the resulting oil was distilled in a Kugelrohr distillation apparatus (185 °C, 0.3 mm Hg), affording **3** (5.75 g, 29.94 mmol, yield 67%) as an oil that crystallized spontaneously as white needles. Mp 40–42 °C. IR (KBr): ν=3009, 2954, 1736, 1715, 1654, 1598, 1342, 1209, 1170, 1049, 762 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=2.83 (d×d, 1H, J_{gem}=19.10 Hz, J_{vic}=8.0 Hz, 2-H), 3.14 (d×d, 1H, J_{gem}=19.1 Hz, J_{vic}=3.6 Hz, 2-H), 3.77 (s, 3H, CO_2CH_3), 4.29 (m, 1H, $J_{3,2}$=8.0 Hz, $J_{3,2}$=3.5 Hz, 1-H), 7.45 (t, 1H, J=7.3 Hz, 5-H), 7.60–7.70 (m, 2H, 4-H and 6-H), 7.76 (d, 1H, $J_{4,5}$=7.6 Hz, 7-H). ^{13}C NMR ($CDCl_3$): δ=39.90, 44.01, 53.08, 124.35, 126.91, 129.21,



Scheme 3.

135.40, 136.75, 151.47, 172.63, 204.49. Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30; found: C, 69.65; H, 5.13.

5.1.2. (±)-*cis*-3-Hydroxymethyl-1-indanol, 4. A solution of **3** (12.48 g, 70.61 mmol) in dry THF was added dropwise under argon to a suspension of $LiBH_4$ (8.09 g, 353.06 mmol) in the same solvent, and after 12 h stirring, 40 mL of saturated NH_4Cl solution was added dropwise at 0 °C. The resulting mixture was filtered through celite, the aqueous and organic phases were separated, the aqueous phase was extracted with AcOEt (3×100 mL), and the pooled organic phases were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Chromatography of the resulting yellow oil on a column of silica gel (295 g) with 40:1 CH_2Cl_2/^{i}PrOH as eluent afforded *cis*-**4** in the early fractions [as an oil that underwent spontaneous solidification; 8.22 g, 50.06 mmol, yield 78%. Mp 78–80 °C (Et_2O/cyclohexane)] and *trans*-**4** in the late fractions (as a yellow oil; 1.76 g, 10.71 mmol, yield 15%). (±)-*cis*-**4**. IR (KBr): ν=3250, 2984, 2933, 1461, 1407, 1379, 1281, 1263, 1211, 1173, 1067, 1051, 1025, 777, 743, 577 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.74–1.81 (m, 1H,

2β-H), 2.20–2.40 (m, 1H, –OH, exchang. with D_2O), 2.49–2.57 (m, 1H, 2α-H), 3.20–3.50 (m, 1H, 3β-H), 3.40–3.50 (b.s., 1H, –OH, exchang. with D_2O), 3.72–3.83 (m, 2H, C*H*$_2$OH), 4.91–5.01 (m, 1H, 1β-H), 7.18–7.35 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ=39.37 (CH_2), 45.63 (CH), 65.60 (CH_2), 74.83 (CH), 124.56, 125.24, 128.02 and 129.17 (CH), 143.77 and 146.43 (C). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.41; H, 7.17. (±)-*trans*-**4**. IR (NaCl): ν=3265, 2922, 1455, 1409, 1372, 1267, 1205, 1169, 1054, 1045, 768, 745, 573 cm^{-1}. ^{1}H RMN ($CDCl_3$): δ=2.02–2.13 (m, 1H, 2β-H), 2.24–2.34 (m, 1H, 2α-H), 3.43–3.50 (m, 1H, 3β-H), 3.68–3.70 (m, 2H, C*H*$_2$OH), 5.22–5.26 (m, 1H, 1α-H), 7.23–7.40 (m, 4H, ArH). ^{13}C RMN ($CDCl_3$): δ=47.06 (CH_2), 52.87 (CH), 73.73 (CH_2), 82.85 (CH), 132.20, 132.38, 135.36 and 136.31 (CH), 151.12 and 153.27 (C). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.36; H, 7.13.

5.1.3. (±)-*cis*-3-Hydroxy-1-indanylmethyl acetate, 5. Vinyl acetate (5.93 mL, 64.37 mmol) was added dropwise under argon to a solution of lipase (Novozym® 435; 2.64 g, 16.36 mmol) and **4** (10.57 g, 64.37 mmol) in 100 mL of dry THF at 0 °C. The mixture was stirred for 4 h at 0 °C and then for 12 h at rt, after which it was filtered through celite. Concentration of the filtrate under reduced pressure afforded a yellow oil that upon chromatography on silica gel (525 g) with 2:1 hexane/AcOEt as eluent gave **5** as a colourless oil that spontaneously crystallized as a white solid (12.39 g, 60.07 mmol, yield 93%). Mp 81–83 °C (Et_2O/cyclohexane). IR (KBr): ν=3351, 3275, 2969, 1728, 1475, 1436, 1394, 1369, 1339, 1276, 1267, 1251, 1229, 1043, 775, 754 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.73–1.81 (dt, 1H, $J_{(t)}$=13.85 Hz, $J_{(d)}$=5.90 Hz, 2β-H), 2.05 (s, 3H, –OC(O)C*H*$_3$), 2.64–2.73 (dt, 1H, $J_{(t)}$=13.82 Hz, $J_{(d)}$=7.10 Hz, 2α-H), 3.36–3.41 (m, 1H, 1β-H), 4.27–4.37 (m, 2H, C*H*$_2$OAc), 5.15–5.21 (m, 1H, 3β-H), 7.26–7.45 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ=21.32 (CH_3), 39.91 (CH_2), 42.05 (CH), 68.06 (CH_2), 75.32 (CH), 124.78, 124.86, 128.81 and 129.01 (CH), 143.07 and 145.80 (C), 171.39 (C). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.04; H, 6.91.

5.1.4. (±)-*cis*-3-(*tert*-Butyldimethylsilyloxy)-1-indanylmethyl acetate, 6. A solution of **5** (12.39 g, 60.07 mmol) in dry CH_2Cl_2 was added at 0 °C under argon to a suspension of *tert*-butyldimethylsilyl chloride (13.7 g, 90.1 mmol) and imidazole (8.18 g, 120.14 mmol) in 80 mL of the same solvent, and the mixture was stirred for 12 h, diluted with 100 mL of CH_2Cl_2, and extracted with 150 mL of saturated $NaHCO_3$ solution. The aqueous phase was in turn extracted with CH_2Cl_2 (3×50 mL), and the pooled organic phases were washed with 100 mL of saturated NH_4Cl solution, dried over anhydrous Na_2SO_4, and concentrated to dryness, affording **6** as a pale yellow oil (18.36 g, 57.28 mmol, yield 95.3%). IR (NaCl): ν=3420, 2954, 2856, 1741, 1604, 1559, 1508, 1463, 1363, 1239, 1107, 1037, 864, 837, 762 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.17 and 0.29 (2s, 6H, 2C*H*$_3$), 0.95 (1s, 9H, –C(C*H*$_3$)$_3$), 1.70–1.80 (m, 1H, 2β-H), 2.10 (s, 3H, –OC(O)C*H*$_3$), 2.50–2.60 (m, 1H, 2α-H), 3.31–3.39 (m, 1H, 1β-H), 4.22–4.28 (part A of an ABM system, 1H, J_{AB}=10.80 Hz, J_{AM}=7.01 Hz, C*H*HOAc), 4.36–4.42 (part B of an ABM system, 1H, J_{BA}=10.80 Hz, J_{BM}=6.39 Hz, CH*H*OAc), 5.18–5.23 (t, 1H, J=6.90 Hz, 3β-H), 7.27–7.34 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ=−4.01 and −4.18 (CH_3), 18.61 (C), 21.41 (CH_3), 26.29 (CH_3), 40.87 (CH_2), 41.53 (CH), 67.94 (CH_2), 75.39 (CH), 124.36, 124.58, 127.88 and 128.88 (CH), 142.34 and 146.44 (C), 171.50 (C). Anal. Calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81. Found: C, 67.19; H, 8.69.

5.1.5. (±)-*cis*-3-(*tert*-Butyldimethylsilyloxy)-1-indanylmethanol, 7. A solution of **6** (0.62 g, 1.93 mmol) and NaOMe (0.22 g, 3.86 mmol) in MeOH (30 mL) was stirred for 4 h at rt, after which concentration of the organic phase under vacuum afforded an oil that upon chromatography on silica gel with 4:1 hexane/AcOEt as eluent gave **7** as a colourless oil (0.46 g, 1.65 mmol, yield 85%). IR (NaCl): ν=3383, 3069, 3026, 2955, 2856, 1740, 1560, 1472, 1458, 1388, 1255, 1111, 1044, 866, 836, 774 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.18 and 0.20 (2s, 6H, 2C*H*$_3$), 0.92 (1s, 9H, –C(C*H*$_3$)$_3$), 1.70–1.80 (m, 1H, 2β-H), 2.10–2.20 (b.s., 1H, –OH exchang. with D_2O), 2.52–2.62 (m, 1H, 2α-H), 3.26–3.34 (m, 1H, 1β-H), 3.79–3.95 (m, 2H, –C*H*$_2$OH), 5.16–5.21 (m, 1H, 3β-H), 7.28–7.36 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ=−4.08 and −1.43 (CH_3), 18.56 (C), 26.24 (CH_3), 40.46 (CH_2), 45.50 (CH), 67.16 (CH_2), 75.46 (CH), 124.50, 124.85, 127.78 and 128.83 (CH), 143.65 and 146.78 (C). Anal. Calcd for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 69.33; H, 9.74.

5.1.6. (±)-*cis*-3-(*tert*-Butyldimethylsilyloxy)-1-indanylmethyl methanesulfonate, 8. Methoxysulphonyl chloride (4 mL, 52.03 mmol) was added dropwise to a solution of **7** (4.83 g, 17.34 mmol), DMAP (catalytic amount) and TEA (7.7 mL) in dry $CHCl_3$, and the mixture was refluxed for 12 h and then poured onto ice. The organic phase was drawn off and washed with 0.5 N NaOH (100 mL) and with saturated NaCl solution, and the pooled aqueous phases were extracted with CH_2Cl_2 (4×100 mL). The pooled organic phases were dried over anhydrous Na_2SO_4 and concentrated to dryness, and chromatography of the residue on silica gel (234 g) with 5:1 hexane/AcOEt as eluent afforded **8** as an oil (4.82 g, 13.52 mmol, yield 78%). IR (NaCl): ν=3075, 3027, 2955, 2928, 2856, 1471, 1361, 1252, 11118, 1103, 1077, 865, 836, 775 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.17 and 0.18 (2s, 6H, 2C*H*$_3$), 0.93 (1s, 9H, –C(C*H*$_3$)$_3$), 1.70–1.80 (m, 1H, 2β-H), 2.52–2.62 (m, 1H, 2α-H), 2.97 (s, 3H, OSO$_2$C*H*$_3$), 3.41–3.51 (m, 1H, 1β-H), 4.34–4.40 (part A of an ABM system, 1H, J_{AB}=9.67 Hz, J_{AM}=7.40 Hz, C*H*HOSO$_2$Me), 4.47–4.53 (part B of an ABM system, 1H, J_{BA}=9.68 Hz, J_{BM}=6.48 Hz, CH*H*OSO$_2$Me), 5.15–5.25 (m, 1H, 1β-H), 7.28–7.35 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ=−4.17 and −4.03 (CH_3), 18.56 (C), 26.26 (CH_3), 37.73 (OSO$_2$C*H*$_3$), 40.12 (CH_2), 42.34 (CH), 73.18 (CH_2), 75.26 (CH), 124.69, 124.99, 128.39 and 128.59 (CH), 141.20 and 146.36 (C). Anal. Calcd for $C_{17}H_{28}O_4SSi$: C, 57.27; H, 7.92. Found: C, 57.46; H, 8.13.

5.1.7. (±)-*cis*-9-[3-(*tert*-Butyldimethylsilyloxy)-1-indanylmethyl]-6-chloro-9*H*-purine, 9. A solution of 6-chloropurine (0.338 g, 2.18 mmol), NaH (0.08 g, 2.18 mmol) and 18-crown-6 ether (0.389 g, 1.45 mmol) in dry DMF was stirred at 70 °C under argon for 1 h and then allowed to cool. A solution of **8** (0.52 g, 1.45 mmol) in dry DMF was slowly added, and stirring was continues at 55 °C for 20 h, after which the resulting solution was concentrated to dryness.

Chromatography of the residue on a column of silica gel (75 g) with 4:1 hexane/AcOEt as eluent afforded **9** as a white solid (0.3 g, 0.72 mmol, yield 50%). Mp 171–173 °C ($CHCl_3$/hexane). IR (KBr): ν=3656, 3281, 2959, 1722, 1708, 1594, 1566, 1497, 1438, 1339, 1240, 1214, 1187, 1068, 771, 655, 564 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.13 and 0.16 (2s, 6H, $2CH_3$), 0.85 (1s, 9H, $-C(CH_3)_3$), 1.72–1.81 (dt, 1H, $J_{(t)}$=13.55 Hz, $J_{(d)}$=8.46 Hz, 2′β-H), 2.40–2.48 (dt, 1H, $J_{(t)}$=13.55 Hz, $J_{(d)}$=6.61 Hz, 2′α-H), 3.70–3.77 (m, 1H, 3′β-H), 4.42–4.49 (part A of an ABM system, 1H, J_{AB}=13.79 Hz, J_{AM}=7.86 Hz, C*H*HN), 4.66–4.73 (part B of an ABM system, 1H, J_{BA}=13.79 Hz, J_{BM}=6.57 Hz, CH*H*N), 5.14–5.18 (m, 1H, 1′β-H), 6.95–6.97 (d, 1H, J=7.12 Hz, ArH), 7.23–7.36 (m, 3H, ArH), 7.89 (s, 1H, 8-H), 8.77 (s, 1H, 2-H). ^{13}C NMR ($CDCl_3$): δ=−4.12 and −4.07 (CH_3), 18.53 (C), 26.25 (CH_3), 40.66 (CH_2), 42.97 (CH), 50.10 (CH_2), 75.26 (CH), 124.44, 125.53, 128.61 and 128.90 (CH), 132.31 (C), 142.23 (C), 146.05 (CH), 146.10 (C), 152.37 (CH). Anal. Calcd for $C_{21}H_{27}ClN_4OSi$: C, 60.78; H, 6.56; N, 13.50. Found: C, 60.44; H, 6.67; N, 13.72.

5.1.8. (±)-*cis*-9-[3-(*tert*-Butyldimethylsilyloxy)-1-indanylmethyl]-6-methoxy-9*H*-purine, 10. A solution of **9** (0.42 g, 1.01 mmol) and NaOMe (0.07 g, 1.23 mmol) in MeOH (10 mL) was stirred at rt under argon for 24 h, and then neutralized with acid resin (Dowex 50×8 (H^+), 80 mg), stirred for a further 15 min., treated with 10 mL of 7:3 MeOH/NH_3, and kept stirring for a further 15 minutes. The resulting solution was filtered and concentrated to dryness, and chromatography of the residue on silica gel (17 g) with 1:1 hexane/AcOEt as eluent afforded **10** as a white solid (0.3 g, 0.75 mmol, yield 72%). Mp 52–54 °C (CH_2Cl_2). IR (KBr): ν=3063, 2929, 2855, 1718, 1599, 1576, 1478, 1405, 1312, 1232, 1111, 1059, 863, 834, 663, 649 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.13 and 0.14 (2s, 6H, $2CH_3$), 0.91 (1s, 9H, $-C(CH_3)_3$), 1.73–1.80 (m, 1H, 2′β-H), 2.40–2.50 (m, 1H, 2′α-H), 3.70–3.80 (m, 1H, 3′β-H), 4.21 (s, 3H, OCH_3), 4.36–4.43 (part A of an ABM system, 1H, J_{AB}=13.76 Hz, J_{AM}=8.00 Hz, C*H*HN), 4.61–4.68 (part B of an ABM system, 1H, J_{BA}=13.76 Hz, J_{BM}=6.93 Hz, CH*H*N), 5.14–5.17 (m, 1H, 1′β-H), 6.90–6.92 (d, 1H, J=7.46 Hz, ArH), 7.22–7.33 (m, 3H, ArH), 7.73 (s, 1H, 8-H), 8.57 (s, 1H, 2-H). ^{13}C NMR ($CDCl_3$): δ=−4.13 and −4.05 (CH_3), 18.54 (C), 26.27 (CH_3), 40.91 (CH_2), 42.81 (CH), 49.85 (CH_2), 54.61 (CH_3), 75.28 (CH), 124.49, 125.29, 128.36 and 128.72 (CH), 142.50 (C), 143.09 (CH), 146.13 (C), 152.39 (C), 152.49 (CH), 161.23 (C). Anal. Calcd for $C_{21}H_{28}N_4O_2Si$: C, 63.60; H, 7.12; N, 14.13. Found: C, 63.84; H, 6.98; N, 14.26.

5.1.9. (±)-*cis*-9-[3-(*tert*-Butyldimethylsilyloxy)-1-indanylmethyl]-6-amino-9*H*-purine, 11a. A solution of **9** (100 mg, 0.24 mmol) and liquid NH_3 (7 mL) in MeOH (3 mL) was heated at 75 °C in a reaction bomb for 60 h. After cooling to rt, removal of the solvent under vacuum left a residue that upon chromatography on silica gel (17 g) with 3:1 hexane/AcOEt followed by 20:1 CH_2Cl_2/MeOH as eluents afforded **11a** as a white solid (83 mg, 0.21 mmol, yield 87%). Mp 178–180 °C ($CHCl_3$/hexane). IR (KBr): ν=3430, 3154, 2928, 1661, 1601, 1475, 1361, 1309, 1246, 1115, 865, 836, 775 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.11 and 0.12 (2s, 6H, $2CH_3$), 0.90 (1s, 9H, $-C(CH_3)_3$), 1.57–1.66 (dt, 1H, $J_{(t)}$=13.22 Hz, $J_{(d)}$=5.17 Hz, 2′β-H), 2.24–2.35 (dt, 1H, $J_{(t)}$=13.22 Hz, $J_{(d)}$=7.28 Hz, 2′α-H), 3.55–3.66 (m, 1H, 3′β-H), 4.17–4.25 (part A of an ABM system, 1H, J_{AB}=13.71 Hz, J_{AM}=8.01 Hz, C*H*HN), 4.44–4.52 (part B of an ABM system, 1H, J_{BA}=13.71 Hz, J_{BM}=6.83 Hz, CH*H*N), 4.99–5.04 (m, 1H, 1′β-H), 6.02 (s, 2H, NH_2, exchang. with D_2O), 6.79–6.82 (d, 1H, J=7.06 Hz, ArH), 7.06–7.22 (m, 3H, ArH), 7.49 (s, 1H, 8-H), 8.25 (s, 1H, 2-H). ^{13}C NMR ($CDCl_3$): δ=−4.52 and −4.44 (CH_3), 7.79 (CH_2), 18.14 (C), 25.87 (CH_3), 40.46 (CH_2), 42.37 (CH), 49.28 (CH_2), 74.87 (CH), 124.10, 124.89, 127.96 and 128.31 (CH), 141.33 (C), 142.15 (C), 145.75 (C), 152.16 (CH), 155.12 (C). Anal. Calcd for $C_{21}H_{29}N_5OSi$: C, 63.76; H, 7.39; N, 17.70. Found: C, 63.92; H, 7.19; N, 17.53.

5.1.10. (±)-*cis*-9-[3-(*tert*-Butyldimethylsilyloxy)-1-indanylmethyl]-6-*N*-cyclopropylamino-9*H*-purine, 11b. A solution of **9** (0.42 g, 1.01 mmol) and *N*-cyclopropylamine (3 mL) in MeOH was heated for 60 h at 75 °C in a reaction bomb that had previously been purged with argon. The resulting solution was concentrated to dryness, and chromatography of the residue on silica gel (20 g) with 20:1 CH_2Cl_2/MeOH as eluent afforded solid **11b** (0.3 g, 0.68 mmol, yield 68%). Mp 60–62 °C ($CHCl_3$/hexane). IR (KBr): ν=3420, 2954, 2926, 1635, 1617, 1577, 1474, 1385, 1355, 1250, 1111, 862, 835, 774 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.13 and 0.14 (2s, 6H, $2CH_3$), 0.69–0.72 (m, 2H, cyclopropyl CH_2), 0.75–0.77 (m, 2H, cyclopropyl CH_2), 0.84 (1s, 9H, $-C(CH_3)_3$), 1.57–1.67 (dt, 1H, $J_{(t)}$=13.16 Hz, $J_{(d)}$=5.06 Hz, 2′β-H), 2.22–2.33 (dt, 1H, $J_{(t)}$=13.16 Hz, $J_{(d)}$=7.23 Hz, 2′α-H), 2.80–2.92 (m, 1H, cyclopropyl CH), 3.55–3.66 (m, 1H, 3′β-H), 4.21–4.29 (part A of an ABM system, 1H, J_{AB}=13.72 Hz, J_{AM}=8.02 Hz, C*H*HN), 4.46–4.54 (part B of an ABM system, 1H, J_{BA}=13.72 Hz, J_{BM}=6.94 Hz, CH*H*N), 4.99–5.04 (m, 1H, 1′β-H), 5.80–5.90 (b.s., 1H, NH, exchang. with D_2O), 6.75–6.78 (d, 1H, J=7.23 Hz, ArH), 7.08–7.22 (m, 3H, ArH), 7.60 (s, 1H, 8-H), 8.44 (s, 1H, 2-H). ^{13}C NMR ($CDCl_3$): δ=−4.13 and −4.04 (CH_3), 7.79 (CH_2), 18.55 (C), 26.28 (CH_3), 40.91 (CH_2), 42.73 (CH), 49.61 (CH_2), 75.30 (CH), 124.53, 125.23, 128.27 and 128.66 (CH), 142.69 (C), 146.16 (C), 153.67 (CH), 155.11 (C). Anal. Calcd for $C_{24}H_{33}N_5OSi$: C, 66.17; H, 7.64; N, 16.08. Found: C, 66.33; H, 7.56; N, 16.21.

5.2. Suzuki–Miyaura coupling of 9 with substituted arylboronic acids. General procedure

A mixture of **9** (0.83 mmol), the appropriate arylboronic acid (0.92 mmol), $Pd(PPh_3)_4$ (0.035 mmol) and K_2CO_3 (1.24 mmol) in toluene (50 mL) was stirred under argon at 100 °C until the starting material has disappeared (TLC monitoring). Once at rt, the solvent was evaporated under reduced pressure anf the residue was chromatographed on silica gel (50 g) using 4:1 hexane–EtOAc as eluent, affording fractions from which the corresponding 6-arylpurine derivative **15** was isolated by evaporation of the solvent and drying.

5.2.1. (±)-*cis*-9-[3-(*tert*-Butyldimethylsilyloxy)-1-indanylmethyl]-6-phenyl-9*H*-purine, 15a. Yield 50%. Mp 133–35 °C ($CHCl_3$/hexane). IR (KBr): ν=3057, 2955, 2927, 2855, 1587, 1567, 1506, 1472, 1460, 1401, 1363, 1333, 1300, 1250, 1212, 1116, 1072, 835, 762, 650 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.14 (1s, 6H, $2CH_3$), 0.91 (1s, 9H,

–C(CH_3)$_3$), 1.61–1.71 (dt, 1H, $J_{(t)}$=13.16 Hz, $J_{(d)}$=5.12 Hz, 2′β-H), 2.26–2.37 (dt, 1H, $J_{(t)}$=13.16 Hz, $J_{(d)}$=7.30 Hz, 2′α-H), 3.70–3.80 (m, 1H, 3′β-H), 4.42–4.49 (part A of an ABM system, 1H, J_{AB}=13.76 Hz, J_{AM}=7.96 Hz, C*H*HN), 4.70–4.77 (part B of an ABM system, 1H, J_{BA}=13.73 Hz, J_{BM}=6.63 Hz, CH*H*N), 5.15–5.20 (m, 1H, 1′β-H), 7.00–7.02 (d, 1H, *J*=7.16 Hz, ArH), 7.25–7.35 (m, 3H, ArH), 7.52–7.60 (m, 3H, ArH), 7.93 (s, 1H, 8-H), 8.78–8.81 (m, 2H, ArH), 9.06 (s, 1H, 2-H). ^{13}C NMR ($CDCl_3$): δ=−4.12 and −4.04 (CH_3), 18.55 (C), 26.28 (CH_3), 40.86 (CH_2), 42.83 (CH), 49.65 (CH_2), 75.32 (CH), 115.80 (CH), 124.53, 125.38, 128.44 and 128.81 (CH), 130.01 and 131.42 (CH), 131.59 (C), 136.06 (CH), 142.52 (CH), 145.28 and 146.16 (C), 152.80 (CH), 152.99 and 155.37 (CH). Anal. Calcd for $C_{27}H_{32}N_4OSi$: C, 71.01; H, 7.06; N, 12.27. Found: C, 70.86; H, 7.24; N, 12.13.

5.2.2. (±)-*cis*-9-[3-(*tert*-Butyldimethylsilyloxy)-1-indanylmethyl]-6-(4′-methyl)phenyl-9*H*-purine, 15b. Yield 96%. Mp 123–25 °C ($CHCl_3$/hexane). IR (KBr): ν=3109, 3030, 2961, 1560, 1515, 1445, 1398, 1358, 1310, 1184, 1110, 1067, 839, 802, 746 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.10 (s, 6H, 2CH_3), 0.77 (s, 9H, C(CH_3)$_3$), 1.62–1.71 (dt, 1H, $J_{(t)}$=13.20 Hz, $J_{(d)}$=4.78 Hz, 2′β-H), 2.29–2.38 (dt, 1H, $J_{(t)}$=13.20 Hz, $J_{(d)}$=6.73 Hz, 2′α-H), 2.31 (s, 3H, CH_3), 3.63–3.68 (m, 1H, 3′β-H), 4.26–4.34 (part A of an ABM system, 1H, J_{AB}=13.78 Hz, J_{AM}=8.06 Hz, C*H*HN), 4.55–4.63 (part B of an ABM system, 1H, J_{BA}=13.78 Hz, J_{BM}=6.60 Hz, CH*H*N), 5.01–5.06 (m, 1H, 1′β-H), 6.86–6.89 (d, 1H, *J*=6.94 Hz, ArH), 7.08–7.25 (m, 5H, ArH), 7.81 (s, 1H, 8-H), 8.56–8.59 (d, 2H, *J*=8.24 Hz, ArH), 8.89 (s, 1H, 2-H). ^{13}C NMR ($CDCl_3$): δ=−4.12 and −4.04 (CH_3), 18.55 (C), 22.02 (CH_3), 26.27 (CH_3), 40.90 (CH_2), 42.81 (CH), 49.61 (CH_2), 75.31 (CH), 124.52, 125.35, 128.41 and 128.79 (CH), 129.85 and 130.15 (CH), 134.11 (C), 134.98 (C), 141.83 (C), 142.54 (C), 144.97 (CH), 146.18 (C) and 152.79 (CH). Anal. Calcd for $C_{28}H_{34}N_4OSi$: C, 71.45; H, 7.28; N, 11.90. Found: C, 71.71; H, 7.11; N, 11.78.

5.2.3. (±)-*cis*-9-[3-(*tert*-Butyldimethylsilyloxy)-1-indanylmethyl]-6-(4′-methoxy)-phenyl-9*H*-purine, 15c. Yield 50%. Mp 165–69 °C ($CHCl_3$/hexane). IR (KBr): ν=3424, 2926, 1604, 1579, 1560, 1513, 1460, 1440, 1301, 1256, 1119, 863, 832, 774 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.14 (s, 6H, 2CH_3), 0.91 (s, 9H, C(CH_3)$_3$), 1.61–1.70 (dt, 1H, $J_{(t)}$=13.10 Hz, $J_{(d)}$=4.95 Hz, 2′β-H), 2.25–2.36 (dt, 1H, $J_{(t)}$=13.10 Hz, $J_{(d)}$=6.97 Hz, 2′α-H), 3.66–3.73 (m, 1H, 3′β-H), 3.89 (s, 3H, OCH_3), 4.39–4.46 (part A of an ABM system, 1H, J_{AB}=13.74 Hz, J_{AM}=8.01 Hz, C*H*HN), 4.68–4.75 (part B of an ABM system, 1H, J_{BA}=13.74 Hz, J_{BM}=6.63 Hz, CH*H*N), 5.15–5.18 (m, 1H, 1′β-H), 6.99–7.02 (d, 1H, *J*=7.25 Hz, ArH), 7.06–7.09 (d, 1H, *J*=9.01 Hz, ArH), 7.24–7.36 (m, 3H, ArH), 7.89 (s, 1H, 8-H), 8.81–8.84 (d, 2H, *J*=9.06 Hz, ArH), 8.99 (s, 1H, 2-H). ^{13}C NMR ($CDCl_3$): δ=−4.12 and −4.04 (CH_3), 18.54 (C), 26.28 (CH_3), 40.88 (CH_2), 42.79 (CH), 49.58 (CH_2), 55.79 (CH_3), 75.31 (CH), 114.49, 115.19 and 116.56 (CH), 124.53, 125.34, 128.39 and 128.78 (CH), 131.01 (C), 131.96 (CH), 142.55 (C), 144.76 (CH), 146.17 (C), 152.75 (CH), 154.97 and 162.44 (C). Anal. Calcd for $C_{28}H_{34}N_4O_2Si$: C, 69.10; H, 7.04; N, 11.51. Found: C, 69.34; H, 6.86; N, 11.41.

5.2.4. (±)-*cis*-9-[3-(*tert*-Butyldimethylsilyloxy)-1-indanylmethyl]-6-(4′-chloro)phenyl-9*H*-purine, 15d. Yield 73%. Mp 167–71 °C ($CHCl_3$/hexane). IR (KBr): ν=3070, 2958, 2927, 1585, 1560, 1500, 1329, 1316, 1250, 1115, 1082, 872, 846, 800, 770 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.13 (s, 6H, 2CH_3), 0.89 (s, 9H, C(CH_3)$_3$), 1.62–1.71 (dt, 1H, $J_{(t)}$=13.25 Hz, $J_{(d)}$=4.83 Hz, 2′β-H), 2.30–2.38 (dt, 1H, $J_{(t)}$=13.30 Hz, $J_{(d)}$=7.25 Hz, 2′α-H), 3.63–3.68 (m, 1H, 3′β-H), 4.28–4.37 (part A of an ABM system, 1H, J_{AB}=13.76 Hz, J_{AM}=7.92 Hz, C*H*HN), 4.57–4.65 (part B of an ABM system, 1H, J_{BA}=13.78 Hz, J_{BM}=6.58 Hz, CH*H*N), 5.02–5.06 (m, 1H, 1′β-H), 6.86–6.89 (d, 1H, *J*=6.90 Hz, ArH), 7.09–7.25 (m, 3H, ArH), 7.38–7.41 (d, 1H, *J*=8.67 Hz, ArH), 7.78 (s, 1H, 8-H), 8.66–8.69 (d, 2H, *J*=8.67 Hz, ArH), 8.90 (s, 1H, 2-H). ^{13}C NMR ($CDCl_3$): δ=−4.12 and −4.05 (CH_3), 18.53 (C), 26.26 (CH_3), 40.80 (CH_2), 42.86 (CH), 49.65 (CH_2), 75.30 (CH), 124.50, 125.42, 128.47 and 128.82 (CH), 129.32 and 131.55 (CH), 134.52 (C), 137.81 (C), 145.34 (CH), 146.13 (C), 152.74 (CH), 152.99 and 154.31 (C). Anal. Calcd for $C_{27}H_{31}ClN_4OSi$: C, 66.03; H, 6.36; N, 11.41. Found: C, 66.19; H, 6.51; N, 11.20.

5.2.5. Cleavage of the *tert*-butyldimethylsilyl group from compounds 15a–d. General procedure. A solution of **15** (0.21 mmol) in CH_3CN was added dropwise with stirring under argon to a solution of $FeCl_3\cdot 6H_2O$ (0.32 mmol) in the same solvent, and stirring was continued for 12 h. H_2O and $CHCl_3$ (100 mL) were added, the aqueous and organic phases were separated, the aqueous phase was extracted with $CHCl_3$ (3×100 mL), and the pooled organic phases were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Chromatography of the residue on silica gel (5 g) with 1:3 hexane/AcOEt as eluent afforded fractions that were concentrated and dried to obtain the corresponding indanol derivative **16**.

5.2.6. (±)-*cis*-3-(6-Phenyl-9*H*-purin-9-ylmethyl)indanol, 16a. Yield 82%. Mp 168–70 °C ($CHCl_3$/hexane). IR (KBr): ν=3300, 3059, 2950, 1582, 1565, 1328, 1207, 1178, 1070, 926, 767, 753, 692, 652, 638 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.73–1.82 (dt, 1H, $J_{(t)}$=13.89 Hz, $J_{(d)}$=3.85 Hz, 2β-H), 2.29–2.31 (d, 1H, *J*=5.02 Hz, OH exchang. with D_2O), 2.49–2.59 (dt, 1H, $J_{(t)}$=13.88 Hz, $J_{(d)}$=6.77 Hz, 2α-H), 3.75–3.85 (m, 1H, 3β-H), 4.51–4.58 (part A of an ABM system, 1H, J_{AB}=13.96 Hz, J_{AM}=7.83 Hz, C*H*HN), 4.66–4.73 (part B of an ABM system, 1H, J_{BA}=13.96 Hz, J_{BM}=6.98 Hz, CH*H*N), 5.18–5.25 (m, 1H, 1β-H), 6.97–7.01 (d, 1H, *J*=7.24 Hz, ArH), 7.25–7.60 (m, 6H, ArH), 7.97 (s, 1H, 8′-H), 8.78–8.81 (m, 2H, ArH), 9.03 (s, 1H, 2′-H). ^{13}C NMR ($CDCl_3$): δ=39.85 (CH_2), 43.52 (CH), 49.61 (CH_2), 75.10 (CH), 124.86, 125.47, 128.75 and 129.12 (CH), 129.35 and 130.22 (CH), 131.49 (C), 136.01 (CH), 143.14 (CH), 145.18 and 145.61 (C), 152.80 (CH), 153.05 and 155.40 (CH). Anal. Calcd for $C_{21}H_{18}N_4O$: C, 73.67; H, 5.30; N, 16.36. Found: C, 73.79; H, 5.45; N, 16.09.

5.2.7. (±)-*cis*-3-[6-(4′-Methyl)phenyl-9*H*-purin-9-ylmethyl)indanol, 16b. Yield 87%. Mp 166–69 °C ($CHCl_3$/hexane). IR (KBr): ν=3416, 3026, 1595, 1397, 1307, 1206, 1185, 783, 758, 639, 625 cm^{-1}. ^{1}H NMR ($CDCl_3$–MeOD): δ=2.48 (s, 3H, CH_3), 2.90–2.96 (d, 1H, *J*=14.93 Hz, 2β-H), 3.20–3.35 (m, 1H, 2α-H), 3.35–3.40 (m, 1H, OH exchang. with D_2O), 4.10–4.20 (m, 1H, 3β-H),

4.95–5.10 (m, 2H, CH_2N), 6.60–6.62 (d, 1H, $J=6.42$ Hz, 1β-H), 7.33–7.63 (m, 4H, ArH), 7.38–7.41 (d, 2H, $J=8.41$ Hz, ArH), 8.58 (s, 1H, 8′-H), 8.82–8.86 (d, 2H, $J=8.41$ Hz, ArH), 9.69 (s, 1H, 2′-H). ^{13}C NMR ($CDCl_3$–MeOD): $\delta=21.36$ (CH_3), 37.66 (CH_2), 40.03 (CH), 57.23 (CH_2), 70.26 (CH), 124.70, 124.83, 129.43 and 129.67 (CH), 131.26 and 131.59 (CH), 133.52 (C), 137.83 (C), 142.69 (CH), 142.80 (C), 142.89 (C), 145.88 (C), 148.31 (CH) and 158.66 (CH). Anal. Calcd for $C_{22}H_{20}N_4O$: C, 74.14; H, 5.66; N, 15.72. Found: C, 73.98; H, 5.83; N, 15.85.

5.2.8. (±)-*cis*-3-[6-(4′-Methoxy)phenyl-9*H*-purin-9-ylmethyl)indanol, 16c. Yield 80%. Mp 142–44 °C ($CHCl_3$/hexane). IR (KBr): $\nu=3648$, 2923, 1654, 1560, 1508, 1458, 1260, 1022, 804 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta=$ 1.75–1.84 (dt, 1H, $J_{(t)}=13.88$ Hz, $J_{(d)}=3.82$ Hz, 2β-H), 2.39–2.48 (m, 1H, 2α-H), 3.69–3.74 (m, 1H, 3β-H), 3.82 (s, 3H, OCH_3), 4.39–4.48 (part A of an ABM system, 1H, $J_{AB}=13.90$ Hz, $J_{AM}=7.86$ Hz, C*H*HN), 4.55–4.63 (part B of an ABM system, 1H, $J_{BA}=13.90$ Hz, $J_{BM}=7.05$ Hz, CH*H*N), 5.11–5.15 (m, 1H, 1β-H), 6.88–6.91 (d, 1H, $J=$ 7.00 Hz, ArH), 6.98–7.02 (d, 2H, $J=8.91$ Hz, ArH), 7.15–7.26 (m, 2H, ArH), 7.36–7.39 (d, 1H, $J=6.92$ Hz, ArH), 7.87 (s, 1H, 8′-H), 8.72–8.75 (d, 2H, $J=8.91$ Hz, ArH), 8.87 (s, 1H, 2′-H). ^{13}C NMR ($CDCl_3$): $\delta=38.42$ (CH_2), 42.05 (CH), 48.11 (CH_2), 54.39 (CH_3), 73.60 (CH), 113.06 (CH), 123.40, 124.01, 127.25 and 127.84 (CH), 129.46 (C), 130.53 (CH), 141.72 (C), 143.26 (CH), 144.23 (C), 151.29 (CH), 153.60 and 161.03 (C). Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.17; H, 5.23; N, 14.87.

5.2.9. (±)-*cis*-3-[6-(4′-Chloro)phenyl-9*H*-purin-9-ylmethyl)indanol, 16d. Yield 71%. Mp 176–78 °C ($CHCl_3$/hexane). IR (KBr): $\nu=3354$, 3079, 2963, 1853, 1561, 1395, 1327, 1252, 1210, 1085, 802, 747, 647 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta=1.23$–1.27 (b.s., 1H, OH exchang. with D_2O), 1.82–1.89 (dt, 1H, $J_{(t)}=13.90$ Hz, $J_{(d)}=$ 3.72 Hz, 2β-H), 2.48–2.57 (dt, 1H, $J_{(t)}=13.89$ Hz, $J_{(d)}=$ 6.75 Hz, 2α-H), 3.75–3.84 (m, 1H, 3β-H), 4.48–4.56 (part A of an ABM system, 1H, $J_{AB}=13.90$ Hz, $J_{AM}=7.79$ Hz, C*H*HN), 4.65–4.71 (part B of an ABM system, 1H, $J_{BA}=$ 13.90 Hz, $J_{BM}=6.92$ Hz, CH*H*N), 5.19–5.22 (m, 1H, 1β-H), 6.97–6.99 (d, 1H, $J=7.14$ Hz, ArH), 7.24–7.34 (m, 2H, ArH), 7.43–7.45 (d, 1H, $J=6.96$ Hz, ArH), 7.51–7.53 (d, 2H, $J=8.62$ Hz, ArH), 7.95 (s, 1H, 8′-H), 8.76–8.79 (d, 2H, $J=8.65$ Hz, ArH), 8.98 (s, 1H, 2′-H). ^{13}C NMR ($CDCl_3$): $\delta=39.82$ (CH_2), 43.51 (CH), 49.61 (CH_2), 75.09 (CH), 124.83, 125.46, 128.78 and 129.35 (CH), 130.93 (C), 131.55 (CH), 134.48 (C), 137.74 (C), 143.09 (CH), 145.30 and 145.61 (C), 152.74 (C), 152.99 and 154.22 (C). Anal. Calcd for $C_{21}H_{17}ClN_4O$: C, 66.93; H, 4.55; N, 14.87. Found: C, 67.12; H, 4.39; N, 14.69.

5.2.10. (±)-*cis*-3-(6-Chloro-9*H*-purin-9-ylmethyl)indanol, 12. Compound **12** was prepared from **9** by the same general procedure as was used to prepare compounds **16** from **15**. Yield 65%. Mp 125–28 °C ($CHCl_3$/hexane). IR (KBr): $\nu=3566$, 3279, 1594, 1560, 1497, 1476, 1398, 1339, 1215, 1187, 1098, 941, 772, 634, 564 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta=1.08$–1.09 (d, 1H, $J=6.11$ Hz, OH exchang. with D_2O), 1.68–1.77 (dt, 1H, $J_{(t)}=13.95$ Hz, $J_{(d)}=$ 7.17 Hz, 2β-H), 2.34–2.42 (dt, 1H, $J_{(t)}=13.95$ Hz, $J_{(d)}=$ 6.93 Hz, 2α-H), 3.62–3.66 (m, 1H, 3β-H), 4.35–4.44 (part A of an ABM system, 1H, $J_{AB}=13.82$ Hz, $J_{AM}=7.63$ Hz, C*H*HN), 4.52–4.60 (part B of an ABM system, 1H, $J_{BA}=$ 13.82 Hz, $J_{BM}=6.82$ Hz, CH*H*N), 5.07–5.11 (m, 1H, 1β-H), 6.83–6.85 (d, 1H, $J=6.75$ Hz, ArH), 7.14–7.31 (m, 2H, ArH), 7.59–7.62 (m, 1H, ArH), 7.79 (s, 1H, 8′-H), 8.63 (s, 1H, 2′-H). ^{13}C NMR ($CDCl_3$): $\delta=39.67$ (CH_2), 43.51 (CH), 50.10 (CH_2), 75.06 (CH), 124.78, 125.48, 128.91 and 129.47 (CH), 132.29 (C), 142.25 (C), 145.99 (CH), 150.15 (C), 152.40 (CH). Anal. Calcd for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; N, 18.63. Found: C, 60.12; H, 4.15; N, 18.44.

5.2.11. (±)-*cis*-9-(3-Hydroxy-1-indanylmethyl)-6-hydroxy-9*H*-purine, 13a. A solution of **9** (100 mg, 0.24 mmol and 0.25 N NaOH (10 mL) in 1,4-dioxane (4 mL) was refluxed for 5 h under argon. Removal of the solvent under vacuum then left a solid (140 mg) that upon chromatography on silica gel (10 g) with 30:1 CH_2Cl_2/MeOH as eluent afforded **13a** as a white solid (51 mg, 0.18 mmol, yield 75%). Mp 138–40 °C (CH_2Cl_2–Et_2O). IR (KBr): $\nu=3352$, 2956, 1697, 1585, 1549, 1458, 1412, 1336, 1212, 1053, 908, 815, 760, 652 cm^{-1}. ^{1}H NMR (MeOH): $\delta=1.58$–1.68 (dt, 1H, $J_{(t)}=13.40$ Hz, $J_{(d)}=5.40$ Hz, 2β-H), 2.30–2.41 (dt, 1H, $J_{(t)}=13.40$ Hz, $J_{(d)}=7.40$ Hz, 2α-H), 3.57–3.63 (m, 1H, 3β-H), 4.27–4.36 (part A of an ABM system, 1H, $J_{AB}=13.73$ Hz, $J_{AM}=8.14$ Hz, C*H*HN), 4.53–4.62 (part B of an ABM system, 1H, $J_{BA}=13.73$ Hz, $J_{BM}=$ 6.40 Hz, CH*H*N), 4.97–5.02 (m, 1H, 1β-H), 6.92–6.95 (d, 1H, $J=6.58$ Hz, ArH), 7.13–7.27 (m, 2H, ArH), 7.29–7.32 (d, 1H, $J=6.60$ Hz, ArH), 7.85 (s, 1H, 8′-H), 7.94 (s, 1H, 2′-H). ^{13}C NMR (MeOH): $\delta=40.99$ (CH_2), 44.34(CH), 50.28 (CH_2), 75.46 (CH), 125.48, 126.34, 129.31 and 129.74 (CH), 142.81 (CH), 144.01 (C), 147.02 (CH), 147.32 (C), 150.89 (C), 159.41 (C). Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 64.03; H, 4.87; N, 19.67.

5.2.12. (±)-*cis*-3-(6-Methoxy-9*H*-purin-9-ylmethyl)indanol, 13b. Compound **13b** was prepared from **10b** by the same general procedure as was used to prepare compounds **16** from **15**. Yield 70%. Mp 152–156 °C (CH_2Cl_2–Et_2O). IR (KBr): $\nu=3567$, 3387, 2954, 2883, 1654, 1600, 1576, 1478, 1405, 1312, 1250, 1111, 863, 835, 774, 649 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta=1.18$ (s, 1H, OH exchang. with D_2O), 1.78–1.85 (dt, 1H, $J_{(t)}=13.86$ Hz, $J_{(d)}=7.80$ Hz, 2β-H), 2.41–2.51 (dt, 1H, $J_{(t)}=13.81$ Hz, $J_{(d)}=7.22$ Hz, 2α-H), 3.69–3.76 (m, 1H, 3β-H), 4.17 (s, 3H, OCH_3), 4.39–4.46 (part A of an ABM system, 1H, $J_{AB}=13.91$ Hz, $J_{AM}=8.03$ Hz, C*H*HN), 4.56–4.63 (part B of an ABM system, 1H, $J_{BA}=$ 13.91 Hz, $J_{BM}=7.05$ Hz, CH*H*N), 5.15–5.18 (m, 1H, 1β-H), 6.88–6.91 (d, 1H, $J=7.25$ Hz, ArH), 7.18–7.29 (m, 2H, ArH), 7.40–7.43 (d, 1H, $J=7.17$ Hz, ArH), 7.74 (s, 1H, 8′-H), 8.49 (s, 1H, 2′-H). ^{13}C NMR ($CDCl_3$): $\delta=38.29$ (CH_2), 42.08(CH), 48.28 (CH_2), 53.26 (CH_3), 73.46 (CH), 120.38 (C), 123.32, 124.03, 127.18 and 127.75 (CH), 141.59 (C), 144.31 (CH), 151.06 (CH), 160.11 (C). Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.77; H, 5.71; N, 19.01.

5.2.13. (±)-*cis*-3-(6-Amino-9*H*-purin-9-ylmethyl)indanol, 14a. Compound **14a** was prepared from **11a** by the same general procedure as was used to prepare compounds **16** from **15**. Yield 79%. Mp 214–16 °C (CH_3OH). IR (KBr): $\nu=3293$, 3146, 2943, 2880, 1693, 1606, 1572, 1424, 1338,

1300, 1223, 1077, 1012, 756, 744, 645 cm^{-1}. ^1H NMR (DMSO): $\delta=1.43$–1.54 (dt, 1H, $J_{(t)}=12.69$ Hz, $J_{(d)}=5.52$ Hz, 2β-H), 2.12–2.23 (dt, 1H, $J_{(t)}=12.69$ Hz, $J_{(d)}=7.18$ Hz, 2α-H), 2.39 (s., 2H, NH_2, exchang. with D_2O), 3.48–3.60 (m, 1H, 3β-H), 4.12–4.21 (part A of an ABM system, 1H, $J_{AB}=13.60$ Hz, $J_{AM}=8.52$ Hz, C*H*HN), 4.50–4.58 (part B of an ABM system, 1H, $J_{BA}=13.60$ Hz, $J_{BM}=5.87$ Hz, CH*H*N), 4.83–4.90 (q, 1H, $J=12.63$, 6.52 Hz, 1β-H), 5.27–5.29 (d, 1H, $J=5.57$ Hz, OH), 6.99–7.02 (d, 1H, $J=6.16$ Hz, ArH), 7.09–7.26 (m, 3H, ArH), 8.00 (s, 1H, 8′-H), 8.05 (s, 1H, 2′-H). ^{13}C NMR (DMSO): $\delta=40.60$ (CH_2), 41.89 (CH), 47.65 (CH_2), 73.03 (CH), 119.04 (C), 123.89, 124.71, 127.50 and 127.85 (CH), 141.34 (CH), 142.52 (C), 147.21 (C), 150.10 (CH), 152.81 (CH), 156.33 (C). Anal. Calcd for $C_{15}H_{15}N_4O_2$: C, 64.04; H, 5.37; N, 24.90. Found: C, 64.24; H, 5.15; N, 25.03.

5.2.14. (±)-*cis*-3-(6-*N*-Cyclopropylamino-9*H*-purin-9-ylmethyl)indanol, 14b. Compound **14b** was prepared from **11b** by the same general procedure as was used to prepare compounds **16** from **15**. Yield 72%. Mp 95–98 °C (CH_3OH). IR (KBr): $\nu=3566$, 3184, 2951, 1626, 1585, 1542, 1478, 1448, 1331, 1305, 1233, 1046, 1020, 796, 764, 647 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=0.64$–0.67 (m, 2H, cyclopropyl CH_2), 0.89–0.92 (m, 2H, cyclopropyl CH_2), 1.78–1.86 (dt, 1H, $J_{(t)}=13.80$ Hz, $J_{(d)}=3.94$ Hz, 2β-H), 2.43–2.54 (dt, 1H, $J_{(t)}=13.80$ Hz, $J_{(d)}=7.57$ Hz, 2α-H), 2.98–3.05 (m, 1H, cyclopropyl CH), 3.67–3.65 (m, 1H, 3β-H), 4.34–4.43 (part A of an ABM system, 1H, $J_{AB}=13.92$ Hz, $J_{AM}=7.94$ Hz, C*H*HN), 4.52–4.60 (part B of an ABM system, 1H, $J_{BA}=13.92$ Hz, $J_{BM}=6.87$ Hz, CH*H*N), 5.17–5.21 (m, 1H, 1β-H), 6.25–6.35 (b.s., 1H, NH, exchang. with D_2O), 6.97–7.01 (d, 1H, $J=6.64$ Hz, ArH), 7.21–7.46 (m, 3H, ArH), 7.54 (s, 1H, 8′-H), 8.43 (s, 1H, 2′-H). ^{13}C NMR ($CDCl_3$): $\delta=7.27$ (CH_2), 23.69 (CH), 39.20 (CH_2), 43.19 (CH), 48.91 (CH_2), 74.45 (CH), 119.62 (C), 124.33, 125.01, 128.11 and 128.69 (CH), 140.12 (C), 142.74 (C), 145.38 (C), 149.23 (CH), 153.29 (CH), 155.78 (C). Anal. Calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.05; H, 5.89; N, 21.99.

Acknowledgements

The authors thank the Xunta de Galicia for financial support of this work under projects PGIDT01PXI20302PR and PGIDT02BTF2030SPR.

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Coloured products from thiophene and aromatic 1,2-diketones

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Received 12 May 2004; revised 5 July 2004; accepted 22 July 2004

Available online 26 August 2004

Abstract—Thiophene and phenanthrene-9,10-quinone react in acidic solution to produce the deep blue extended quinone (*Z*,*Z*)-2,5-di(9-oxo-9,10-dihydro-10-phenanthrylidene)-2,5-dihydrothiophene the structure of which is confirmed by X-ray crystallography. Other aromatic 1,2-diketones give rise to related products.

1. Introduction

Meyer reported[1] in 1883 that phenanthrenequinone reacted with thiophene in a mixture of sulphuric and acetic acids to give a 'dunkelgrune Farbstoffe' of unknown constitution. Many years later Hartough[2] suggested that this might have the structure **1** by analogy with that proposed[3] for the isatin-thiophene product 'indophenine'. We were surprised to find that no attempt has apparently been made to isolate and characterise the substance responsible for the intense colour and we have therefore re-examined Meyer's reaction.

2. Discussion

Repetition of the phenanthrenequinone–thiophene reaction[1] using equimolecular amounts of the reactants[4] and purification of the product by PLC gave a deep blue compound, $C_{32}H_{20}O_2S$, in 47% yield that crystallised from chloroform as its 1:1 solvate. The presence of chloroform in the crystal accounts for the characteristic $CHCl_2^+$ ions seen in the mass spectrum (at *m/z* 83 and 85) and for the chloroform proton signal observed when the NMR spectrum is measured in $(CD_3)_2SO$. We formulate the solvent-free compound as the extended quinone **2**. The carbonyl absorption in the IR at 1630 cm^{-1} is typical[5] of such a system as is the intense absorption in the visible at 582 nm. As with many other quinones[6] the base peak in the mass spectrum corresponds to the $(M+2H)^+$ ion. In the ^1H NMR spectrum the two low-field 2H doublets centred at δ 8.36 can be assigned to H-8 and -8[1] *peri* to the carbonyl groups while the 4H multiplet at δ 8.08–8.12 corresponds to the 'bay' protons H-4, -4[1], -5 and -5[1]. The 2H singlet at δ 7.83 must result from the protons H-12 and -12[1] of the thiophenoid unit. The absence of coupling between these protons indicates that they have the same chemical shift and consequently that in solution the molecule is symmetrical. The ^{13}C NMR spectrum provides further support for this, showing signals corresponding to only one type of carbonyl, one type of tertiary sulphide, five types of quaternary, and nine types of methine carbon atoms.

Catalin models indicate that in order to maximise the conjugation in the extended quinone both the double bonds between the ring systems should have the (*Z*)-configuration as shown in structure **2**; the alternative (*E*,*Z*)- and (*E*,*E*)-arrangements result in much increased distortion of the π-electron system. The chemical shift (δ 7.83) of the thiophenoid protons provides support for the (*Z*,*Z*)-configuration, the protons being only weakly de-shielded by the adjacent aromatic rings of the phenanthronoid groups. They would of course be strongly de-shielded in the (*E*,*E*)-arrangement where they would be close to the carbonyl groups; the comparable protons in the related ninhydrin-thiophene product **20** for example give rise to a singlet at δ 8.84. A selective NOE experiment gave further support for the (*Z*,*Z*) configuration, irradiation at δ_H 7.83 producing a strong NOE at δ_H 7.78 (H-1 and -1[1]).

An X-ray crystallographic examination established the structure (Fig. 1) of the solvated quinone (**2**, $CHCl_3$) and so confirmed the proposed structure **2** for the solvent-free compound. The geometrical parameters for (**2**, $CHCl_3$) are those expected for such conjugated systems albeit with rather larger standard uncertainties. Within each asymmetric molecule the benzenoid and thiophenoid rings are essentially planar but the *o*-quinonoid rings are significantly distorted. The three component ring systems are far from coplanar (Fig. 2), the considerable twisting about both of the inter-ring bonds being a consequence of the steric repulsion

Keywords: Thiophene; Diketones; Quinone; X-ray crystal structure.
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doi:10.1016/j.tet.2004.07.066

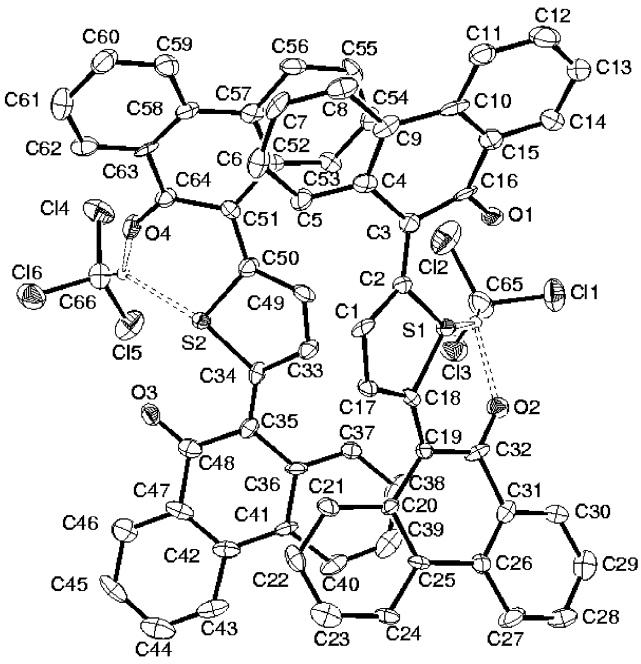


Figure 1. Asymmetric unit containing two molecules of (**2**, $CHCl_3$) (50% thermal ellipsoids). All hydrogen atoms except those of chloroform are omitted for clarity. Weak interactions (see Table 1) are indicated by dashed lines. Selected geometrical data (Å, °): S1–C18 1.781 (9), S1–C2 1.781 (11), S2–C34 1.773 (10), S2–C50 1.790 (11), O1–C16 1.220 (13), O2–C32 1.230 (13), O3–C48 1.232 (14), O4–C64 1.225 (13), O1–C16–C3–C2 25.7 (15), C16–C3–C2–S1 −16.3 (14), C3–C2–S1–C18 177.4 (10), C2–S1–C18–C19 179.1 (8), S1–C18–C19–C32 13.7 (13), C18–C19–C32–O2 −25.0 (15), C1–C2–C3–C4 −16.4 (17), C17–C18–C19–C20 8.3 (15).

between the thiophenoid hydrogens and the adjacent phenanthronoid hydrogens. Because of the presence of the molecule of chloroform the structure is asymmetric and possesses only approximate C_s symmetry. The chloroform is attached to its $C_{32}H_{18}O_2S$ partner (Fig. 1) by an unusual bifurcated[7a] C–H···(O,S) interaction (Table 1). Short Cl_3C–H···O interactions have been observed previously[7b] as a consequence[8] of the 'activation' of the hydrogen atom of chloroform by the electron-withdrawing effects of the chlorine atoms. The molecules of (**2**, $CHCl_3$) interact with each other not only by van der Waals' forces but also by way of π···π stacking, several ring centroid···ring centroid contacts being less than 4.0 Å (Table 1).

Reductive acetylation of the blue quinone **2** using zinc dust, acetic anhydride and triethylamine gave the leucoacetate **5** which shows carbonyl absorption in the IR at 1759 cm^{-1} typical of an aryl acetate while the UV absorption[9] and NMR signals are characteristic of a 9,10-disubstituted phenanthrene system. The NMR signals also include a 2H singlet at δ 7.27 which we attribute to the protons of the diaryl-substituted thiophene group.

With the object of obtaining the corresponding quinone **3** containing two thiophene units we treated phenanthrenequinone with 2 equiv. of thiophene in aqueous 75% v/v sulphuric acid. Under these more vigorous conditions the products were the extended quinone **2** containing one thiophene unit, a mixture of two related quinones containing two and three thiophene units respectively, and the thienylphenanthrol **9**. The last of these shows UV absorption and NMR signals typical[9,10] of a phenanthren-9-ol while the three protons of the thienyl group give rise to a multiplet centred at δ 6.92. We were unable to separate the mixed quinones by PLC but confirmed the presence of the quinone **3** by repeating the reaction and reductively acetylating the quinone fractions. The products were the hydroxyacetate **4**, the corresponding diacetate **5**, and the diacetoxybithienyl derivative **6**. The NMR signals of the last of these include a 6H singlet at δ 2.37 from the aryl acetate protons and a 4H AB pair of doublets centred at δ 7.09 and 7.35 from the bithienyl unit which indicate the formation of the symmetrical bithienylquinone in the original reaction. However we were unable to isolate the leucoacetate corresponding to the terthienylquinone, the minor component of the mixture.

The formation of the extended quinone **2** must involve the addition of thiophene to a protonated carbonyl group of phenanthrenequinone as in Scheme 1 to give first the ketol **7** and thence the positive ion **8**. The reduction of the latter would produce the phenanthrenol **9** (which we isolated from the reaction in aqueous sulphuric acid) that could react with a second molecule of phenanthrenequinone to form the diol **10** which would undergo dehydration to give the extended quinone **2**. The reducing agent required in this reaction must be derived from thiophene which is known[11] to undergo polymerisation on treatment with acid probably via the thienyldihydrothiophene **11**. The latter could clearly act as a hydride-source being itself converted into 2,3-bithienyl in

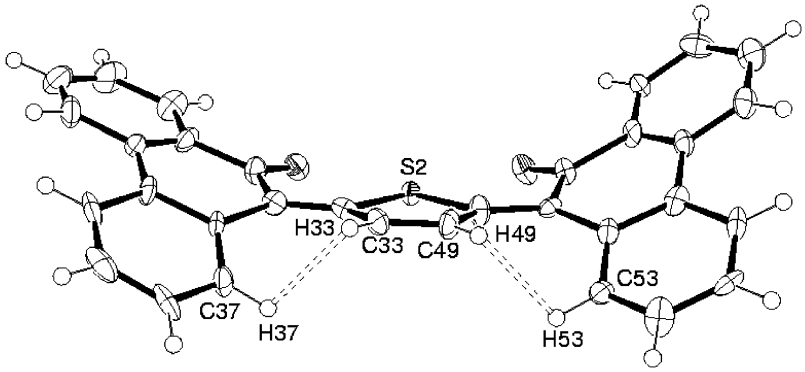


Figure 2. Edge-on view of the S2-containing molecule of (**2**, $CHCl_3$), showing the twisting about the inter-ring bonds caused by steric repulsions between the thiophenoid and phenanthronoid H atoms indicated by dashed lines [*d*(H33···H37)=2.16 Å, *d*(H49···H53)=2.17 Å]. The situation involving the S1 molecule is very similar. For clarity the $CHCl_3$ molecule has been omitted.

Table 1. Weak intermolecular interactions in (**2**, $CHCl_3$)

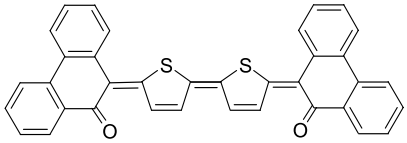
C29–H29···O3^{i}	0.95	2.58	3.428(14)	150
C62–H62···O2^{ii}	0.95	2.55	3.405(15)	150
C65–H65···S1	1.00	2.83	3.770(15)	157
C65–H65···O2	1.00	2.34	3.184(15)	142
C66–H66···S2^{i}	1.00	2.80	3.709(12)	152
C66–H66···O4^{i}	1.00	2.35	3.214(14)	144

The four numerical columns refer to the C–H, H···A, C···A distances (Å) and C–H···A angle (°), respectively (A = acceptor atom). Symmetry codes: (i) $x, y-1, z$; (ii) $x, y+1, z$. The donor(C)/acceptor(O,S) bond-angle sums about H65 and H66 are 359 and 358°, respectively

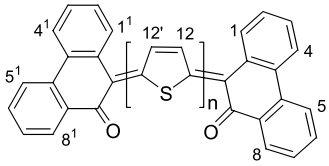
π1···π2	3.832 (7)	5.9
π1···π2^{iii}	3.773 (7)	5.9
π3···π4	3.780 (7)	2.1
π3···π4^{iii}	3.792 (7)	2.1

The two numerical columns refer to the *Cg*···*Cg* separation (Å) and the dihedral angle between ring planes (°) respectively. π1 = centroid (*Cg*) of atoms C4–C9; π2 = centroid of atoms C52–C57; π3 = centroid of atoms C20–C25; π4 = centroid of atoms C36–C41. Symmetry code: (iii) $x+1, y, z$

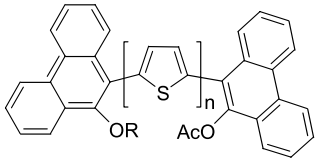
the process. The formation of the bithienylquinone **3** does not require such a reduction step. In this case the ion **8** presumably reacts with the ketol **7** as in Scheme 2 to give a second ketol **12** which then undergoes dehydration to form the bithienylquinone **3**.



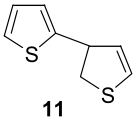
1



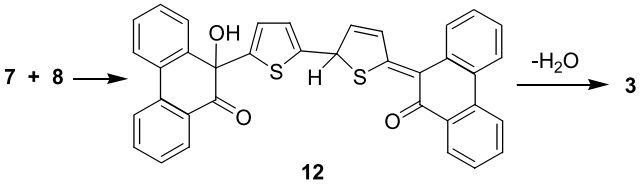
2; n = 1
3; n = 2



4; n = 1; R = H
5; n = 1; R = Ac
6; n = 2; R = Ac



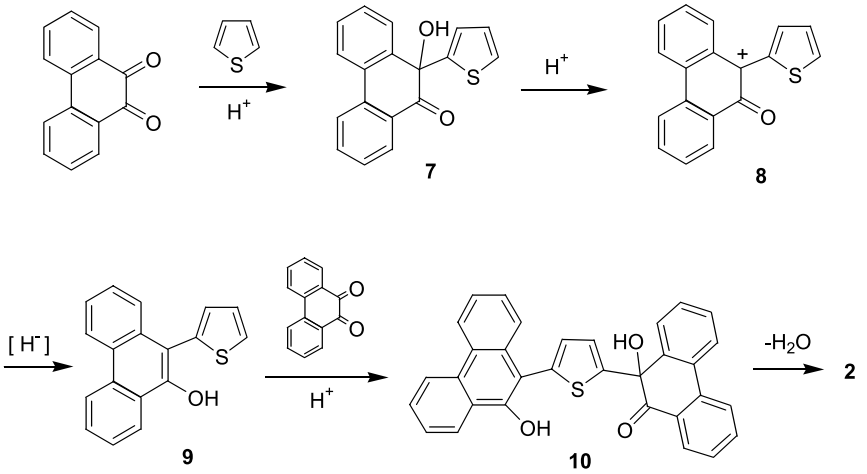
11



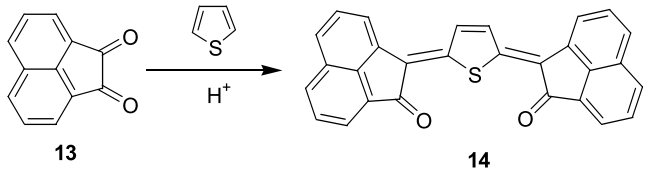
12

Scheme 2.

The two carbonyl groups of phenanthrenequinone are present in a six-membered ring and to ascertain the importance of ring size we investigated similar reactions between thiophene and compounds containing two or three carbonyl groups in five-membered rings. Acenaphthene-1,2-dione (acenaphthenequinone) **13** gave as the sole product a red compound to which we ascribe the structure **14** (Scheme 3). Although this bears a formal resemblance to the thiophene-phenanthrenequinone product **2** the properties of the two compounds are significantly different, compound **2** behaving as a quinone while compound **14** has the properties of an unsaturated ketone. Thus compound **14** shows carbonyl absorption in the IR at a much higher frequency (1679 cm^{-1}) than that (1630 cm^{-1}) of the corresponding groups in **2** while its UV–VIS absorption is significantly weaker and at a shorter wavelength than that of **2**. The mass spectrum of **2** shows the abundant (M+2) ion typical[6] of many quinones while compound **14** provides only the normal molecular ion. The two compounds also

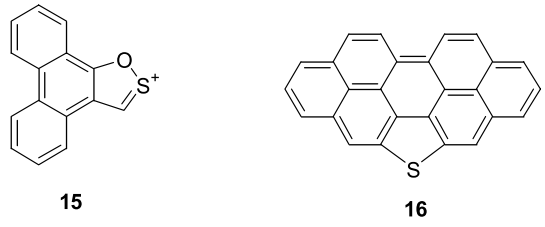


Scheme 1.



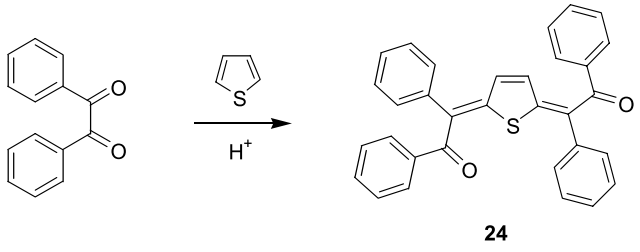
Scheme 3.

undergo fragmentation in the mass spectrometer by different pathways. Compound **2** provides numerous relatively abundant fragment ions most of which can be formulated as derivatives of phenanthrene. For example the fragment ion *m*/*z* 237 has the molecular formula $C_{15}H_9OS$ and may be represented by the aromatic structure **15**. In contrast the molecular ion of **14** loses two formyl radicals to give ions *m*/*z* 356 and 178 which we suggest are derived from the polycyclic thiophene derivative **16**.

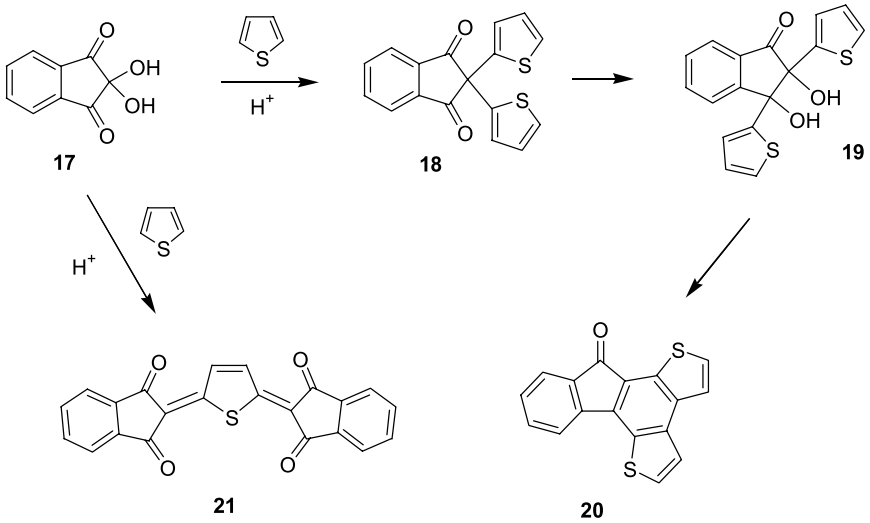


Ninhydrin **17** behaves chemically as a five-membered ring triketone the middle carbonyl group of which is the more reactive. With thiophene in aqueous 75% v/v sulphuric acid it gave low yields of three products. The typical reaction[12] of a ketone with thiophene produced a little of the dithienyldiketone **18** which, by acid-induced rearrangement to the diol **19** and dehydration[13] of this, gave the pentacyclic ketone **20**. The UV absorption of the latter resembles that[14] of its benzenoid analogue **23** and so provides support for the polycyclic aromatic structure. The third, major product was the tetraketone **21**. The ^{1}H NMR signals for this are particularly simple, the benzenoid protons giving rise to an AA^{1}BB^1 system while those of the thiophene unit, which are deshielded by the adjacent carbonyl groups, produce a singlet signal at δ 8.84. In the mass spectrometer the molecular ion of the tetraketone undergoes successive loss of four molecules of carbon monoxide to give a fragment ion *m*/*z* 258 which may be represented as the polycyclic ion **22** (Scheme 4).

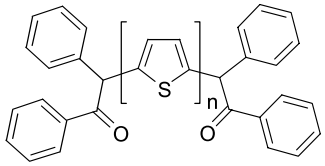
Finally, we examined the reaction between thiophene and the acyclic diketone benzil (Scheme 5). This gave an orange product and a blue mixture. We formulate the former as the polyunsaturated diketone **24** because its UV–visible light absorption indicates the presence of an extended conjugated system. The two thiophenoid protons are not equivalent giving rise to an AB pair of doublets in the NMR spectrum which establishes that the molecule cannot be symmetrical and must have the (*E*,*Z*)-configuration about the exocyclic double bonds. This receives support from the ^{13}C NMR spectrum which shows 24 signals corresponding to the two carbonyl, the two tertiary sulphide, the six quaternary, and the fourteen different types of methine carbon atoms.



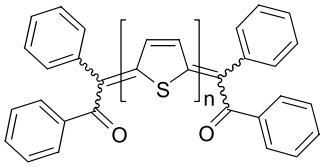
Scheme 5.



Scheme 4.



25; n = 2
26; n = 3



27; n = 2
28; n = 3

We were unable to separate the blue mixture into its components by PLC and therefore subjected it to the reductive acetylation procedure which we had used earlier with the mixed quinones from the phenanthrenequinone–thiophene reaction. The two colourless products proved to be not the expected enol acetates but the bi- and the terthienyl diketones **25** and **26**. The NMR spectrum of the former shows a 2H singlet at δ 6.14 for the α-keto-methine protons and a 4H AB pair of doublets centred at δ 6.74 and 6.92 for the protons of the bithienyl unit. The terthienyl diketone **26** shows similar signals, a 2H singlet at δ 6.17 for the α-ketomethine protons and two 2H broad singlets at δ 6.71 and 6.86 for the protons of the flanking thiophene units, plus a 2H singlet at δ 6.63 for the protons of the central thiophene group. The formation of the diketones **25** and **26** by a reduction process indicates that the blue reaction product was a mixture of the unsaturated diketones **27** and **28**.

The colourless diketone **25** had been prepared previously by a different route[15] but the mp then recorded (219.5–220.5 °C) is quite different to that (108–110 °C) of our product. The formation in the earlier work of a blue substance during the heating process suggests that aerial oxidation had occurred producing the unsaturated diketone **27**.

3. Experimental

FTIR spectra were measured with an ATI Mattson Genesis spectrophotometer for KBr discs and UV absorptions with a Perkin–Elmer Lambda 15 instrument for methanolic solutions unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions at 250 MHz on an A. C. Bruker 250 instrument or at 400 MHz on a Varian Unity Inova using respectively Me_4Si and residual $CHCl_3$ (7.25 ppm) as internal standards. Mass spectra were obtained using EI at 70 eV with an AEI MS30 spectrometer. PLC was performed on Merck Kieselgel GF_{254} or, for the more polar compounds, on silica gel which had previously been treated with aqueous 3% oxalic acid; 'light petroleum' refers to the fraction bp 60–80 °C. Yields are based on the initial weights of the diketones used, no account being taken of the weights of the starting materials that were recovered from the reactions.

Reductive acetylation was effected by boiling a mixture of the compound (100 mg), acetic anhydride (100 ml), zinc dust (500 mg) and triethylamine (0.2 ml) under reflux for 45 min.

3.1. Reactions of thiophene with phenanthrene-9,10-quinone

3.1.1. In acetic acid–sulphuric acid. Concentrated sulphuric acid (25 ml) was added dropwise during 30 min to a stirred mixture of thiophene (2.1 g, 25.0 mmol), phenanthrenequinone (5.2 g, 25.0 mmol) and acetic acid (100 ml). After being stirred for 4 h at room temperature the mixture was poured into water (2 l). The resulting dark solid on being subjected to PLC on silica gel using chloroform gave (*Z*,*Z*)-2,5-di(9-oxo-9,10-dihydro-10-phenanthrylidene)-2,5-dihydrothiophene **2** (3.44 g, 5.87 mmol, 47%) which crystallised from chloroform as the 1:1 solvate with chloroform in deep blue needles, mp 272–274 °C [Found: $(M+2H)^+$, 468.1189. $C_{32}H_{20}O_2S$ requires: *M*, 468.1184]; *m/z* 468 [100%, $(M+2H)^+$], 466 (19, M^+), 437 (12, M−CHO), 435 (12, 437−2H), 250 (23, $C_{16}H_{10}OS$), 247 (12, $C_{17}H_{11}S$), 237 (17, $C_{15}H_9OS$), 231 (17, $C_{17}H_{11}O$), 218 (15, $C_{16}H_{10}O$), 189 (13, $C_{15}H_9$), 165 (12, $C_{13}H_9$), 85 (12, $CH^{35}Cl^{37}Cl$) and 83 (24, $CH^{35}Cl_2$); λ_{max}/nm 241 infl (log ε 4.58), 260 (4.66), 340 infl (3.71) and 582 (4.25); ν_{max}/cm^{-1} 1630 (quinone C=O), 1596 (aromatic C=C), and 756 (4 adjacent ArH); δ_H 7.41–7.51 (6H, m, H-3, -3^1, -6, -6^1, -7, -7^1), 7.665 (2H, ddd, *J*=8, 8, 1.5 Hz, H-2 and -2^1), 7.78 (2H, dd, *J*=8, 1.5 Hz, H-1 and -1^1), 7.83 (2H,s, thiophenoid CH=CH), 8.08–8.12 (4H, m, H-4, -4^1, -5 and -5^1) and 8.36 (2H, dd, *J*=8, 1.2 Hz, H-8 and -8^1); δ_C 185.67 (CO); 157.29 (C–S); 135.79, 131.72, 130.08, 129.92 and 123.11 (quaternary C); 139.20, 133.52, 130.82, 128.76, 128.41, 128.13, 127.95, 124.37 and 122.81 (C–H).

The leucoacetate **5** crystallised from chloroform–ethanol as yellow needles mp 170–171 °C (Found: M^+, 552.1401. $C_{36}H_{24}O_4S$ requires *M*, 552.1395); *m/z* 552 (11%, M^+), 510 (32, $M-CH_2CO$), 468 (100, $510-CH_2CO$), 434 (18, $468-H_2S$), 250 (9, $C_{16}H_{10}OS$), 247 (7, $C_{17}H_9S$), 231 (11, $C_{17}H_{11}O$), 218 (17, $C_{16}H_{10}O$), 189 (9, $C_{15}H_9$), 165 (8, $C_{13}H_9$) and 91 (11, C_7H_7); λ_{max}/nm 257 (log ε 4.88), 273 infl (4.64), 277 infl (4.53), 293 (4.37) and 303 (4.41); ν_{max}/cm^{-1} 1759 (aryl acetate C=O), 1603 (aromatic C=C), 759 and 751 (4 adjacent ArH); δ_H 2.39 (6H, s, CH_3CO_2Ar), 7.27 (2H, s, thienylene H), 7.58–7.80 (8H, m, H-2, -3, -6, and -7), 7.91–8.05 (4H, m, H-1 and -8) and 8.72–8.80 (4H, m, H-4 and -5).

3.1.2. In aqueous 75% v/v sulphuric acid. A mixture of phenanthrenequinone (2.08 g, 10.0 mmol), thiophene (1.68 g, 20.0 mmol) and aqueous 75% v/v sulphuric acid (50 ml) was stirred at room temperature for 24 h and poured into water. The resulting solid was subjected to PLC on oxalic acid-washed silica gel using light petroleum–chloroform (1:1) giving three products. The first, a glassy solid, was 10-(2-thienyl) phenanthren-9-ol **9** (375 mg, 3.62 mmol, 14%) (Found: M^+, 276.0616. $C_{18}H_{12}OS$ requires *M*,

276.0609); *m/z* 276 (100%, M^+), 247 (40, M−CHO), 231 (14, M−CHS), 215 (10, 247−S), 202 (8, 247−CHS), 97 (10, C_5H_5S) and 83 (15, C_4H_3S); λ_{max}/nm 245 (log ε 4.26), 253 infl (4.18), 276 infl (3.67), 307 (3.41), 341 (2.94) and 358 (2.76); ν_{max}/cm^{-1} 3340 (phenolic OH), 1592 (aromatic C=C) and 755 (4 adjacent ArH); δ_H 5.85 (1H, br.s, ArOH), 6.81–7.07 (3H, m, thienyl H), 7.10–7.76 (5H, m, ArH), 8.36–8.42 (1H, m, H-8) and 8.55–8.71 (2H, m, H-4 and -5).

Next came an inseparable mixture, mp 242–243 °C, of 2,5^1-di(9-oxo-9,10-dihydro-10-phenanthrylidene)-5,5^1-dihydro-2,2^1-bithienyl **3** [Found: $(M+2H)^+$, *m/z* 550 (100%). Calcd for $C_{36}H_{22}O_2S_2$: *M*, 550] and the corresponding terthienylquinone [Found: $(M+2H)^+$, *m/z* 632 (38%). Calcd for $C_{40}H_{24}O_2S_3$: *M*, 632]. The final product was the diphenanthrylidenedihydrothiophene **2** (756 mg, 1.62 mmol, 32%).

Repetition of the reaction followed by reductive acetylation of the quinonoid components and their separation by PLC as before gave three fractions. The first was 2-(9-hydroxy-10-phenanthryl)-5-(9-acetoxy-10-phenanthryl)thiophene **4** (264 mg, 0.52 mmol, 10%), mp190–192 °C (Found: M^+, 510.1297. $C_{34}H_{22}O_3S$ requires *M*, 510.1290); *m/z* 510 (32%, M^+), 468 (100, M−CH_2CO), 433 (15, 468−H_2O–OH), 274 (9, $C_{18}H_{10}OS$), 250 (14, $C_{16}H_{10}OS$), 247 (9, $C_{17}H_9S$), 231 (18, $C_{17}H_{11}O$), 218 (23, $C_{16}H_{10}O$), 189 (16, $C_{15}H_9$) and 165 ($C_{13}H_9$); λ_{max}/nm 250 (log ε 4.76), 274 infl (4.40), 303 (4.20), 336 infl (3.73) and 350 (3.50); ν_{max}/cm^{-1} 3450 (phenolic OH), 1745 (aryl acetate C=O), 1596 (aromatic C=C) and 758 (4 adjacent ArH); δ_H 2.40 (3H, s, CH_3CO_2Ar), 6.07 (1H, s, ArOH), 7.33 (2H, br.s, thienylene H), 7.48–7.82 (8H, m, ArH), 7.86–8.07 (3H, m, H-1, -1^1, and -8^1), 8.39–8.47 (1H, m, H-8), and 8.62–8.83 (4H, m, H-4, -5, -4^1, and -5^1).

The next fraction was 5,5^1-di(9-acetoxy-10-phenanthryl)-2.2^1-bithienyl **6** (1.41 g, 2.22 mmol, 45%) which crystallised from chloroform–methanol in yellow–orange needles mp 290–291 °C (Found: M^+, 634.1268. $C_{40}H_{26}O_4S_2$ requires *M*, 634.1273); *m/z* 634 (32%, M^+), 592 (32, M−CH_2CO), 550 (100, 592−CH_2CO), 521 (14, 550−CHO), 275 (18, 550^{2+}) and 231 (24, $C_{17}H_{11}O$); λ_{max}/nm 251 (log ε 4.97), 291 (4.36), 301 (4.42) and 332 (4.45); ν_{max}/cm^{-1} 1758 (aryl acetate CO), 1600 (aromatic C=C) and 756 (4 adjacent ArH); δ_H 2.37 (6H, s, CH_3CO_2Ar), 7.09 and 7.35 (each 2H, d, *J*=3.5 Hz, thienylene H), 7.54–7.81 (8H, m, ArH), 7.90–8.01 (4H, m, H-1 and -8) and 8.67–8.82 (4H, m, H-4 and -5).

The final fraction was the diphenanthrylthiophene **5** (843 mg, 1.53 mmol, 31%).

3.1.3. Reaction of thiophene with acenaphthene-1,2-dione. Concentrated sulphuric acid (100 ml) was added dropwise during 8 h to a stirred mixture of thiophene (1.5 g, 17.86 mmol), acenaphthene-1,2-dione (2.44 g, 13.41 mmol) and acetic acid (120 ml) After being stirred for 16 h the mixture was poured into water and the resulting solid was subjected to PLC using chloroform–light petroleum (1:1) which removed the unchanged diketone (0.95 g). The sole product was 2,5-di(2-oxo-1-acenaphthenylidene)-2,5-dihydrothiophene **14** (0.53 g, 1.28 mmol, 19%) which crystallised from chloroform–light petroleum as red microcrystals mp >300 °C (Found: M^+, 414.0710. $C_{28}H_{14}O_2S$ requires M, 414.0714); *m/z* 414 (100%, M^+), 385 (7, M−CHO), 356 (6, 385−CHO), 207 (13, M^{2+}) and 178 (13, 356^{2+}); λ_{max}/nm ($CHCl_3$) 326 (log ε 3.77), 358 infl (3.56), 511 (3.08) and 546 (3.14); ν_{max}/cm^{-1} 1679 (unsaturated C=O), 1601 (aromatic C=C) and 779 (3 adjacent ArH); δ_H 7.04–8.57 (14H, m, ArH and CH=CH).

3.1.4. Reaction of thiophene with ninhydrin. A mixture of ninhydrin **17** (1,78 g, 10.0 mmol), thiophene (1.68 g, 20.0 mmol) and aqueous 75% v/v sulphuric acid (50 ml) was stirred at room temperature for 12 h, poured into water and extracted with chloroform. PLC of the product using chloroform gave two fractions. The first crystallised from chloroform–light petroleum to give 11-oxofluoreno[1,2-*b*:4,3-*b*^{1}]dithiophene **20** (15 mg, 0.05 mmol, 0.5%) as orange needles mp 194–195 °C (Found: M^+, 292.0017. $C_{17}H_8OS_2$ requires *M*, 292.0014); *m/z* 292 (100%, M^+), 264 (15, M−CO), 263 (38, M−CHO), 219 (7, 264−CHS) and 132 (13, 264^{2+}); λ_{max}/nm 230 (log ε 4.30), 255 (4.40), 279 (4.31), 304 (4.19), 317 (4.08) and 390 (3.34); ν_{max}/cm^{-1} 1701 (aromatic ketone C=O), 1603 (aromatic C=C) and 768 (4 adjacent ArH); δ_H 6.96 and 7.09 (each 1H, d, *J*=4 Hz, SCH=CH), 7.23–8.18 (6H, m, ArH and SCH=CH).

Addition of light petroleum to the mother-liquor gave 2,2-di(2-thienyl)indane-1.3-dione **18** (26 mg, 0.082 mmol, 0.8%) which crystallised from chloroform–light petroleum in plates mp 135–137 °C (Found: M^+, 310.0120. $C_{17}H_{10}O_2S_2$ requires *M*, 310.0122); *m/z* 310 (100%, M^+), 282 (6, M−CO), 281 (6, M−CHO), 277 (6, M−SH), 253 (55, 281−CO), 221 (18, 253−S), 208 (7, 253−CHS), 104 (6, C_6H_4CO) and 76 (15, C_6H_4); λ_{max}/nm 249 infl (log ε 4.34), 304 (3.70) and 366 (3.84); ν_{max}/cm^{-1}, 1736 and 1702 (indane-1,3-dione C=O), 1586 (aromatic C=C) and 766 (4 adjacent ArH); δ_H 6.95 (2H, dd, *J*=3, 5 Hz, thienyl H-4), 7.09 (2H, d, *J*=3 Hz, thienyl H-3), 7.28 (2H, d, *J*=5 Hz, thienyl H-5), 7.87–8.00 and 8.04–8.19 (4H, AA^{1}BB^1 m, ArH).

The second fraction from the PLC separation crystallised from chloroform–light petroleum to give 2,5-di(1,3-dioxoindan-2-ylidene)-2,5-dihydrothiophene **21** (135 mg, 0.36 mmol, 7%) as brown needles mp >300 °C (Found: M^+, 370.0299. $C_{22}H_{10}O_4S$ requires *M*, 370.0300); *m/z* 370 (100%, M^+), 342 (4, M−CO), 314 (9, 342−CO), 286 (8, 314−CO), 258 (12, 286−CO), 213 (5, 258−CHS), 185 (7, M^{2+}), 129 (7, 258^{2+}), 104 (8, C_6H_4CO) and 76 (18, C_6H_4); λ_{max}/nm ($CHCl_3$) 275 infl (log ε 3.92), 306 infl (3.79), 336 infl (3.62) and 482 (3.16); ν_{max}/cm^{-1} 1678 ($\alpha\beta$-unsaturated C=O), 1593 (aromatic C=C) and 735 (4 adjacent ArH); δ_H 7.78–8.04 (8H, AA^{1}BB^1 m, ArH) and 8.84 (2H, s, thiophenoid CH=CH).

3.1.5. Reaction of thiophene with benzil. Concentrated sulphuric acid (200 ml) was added dropwise during 3 h to a stirred mixture of thiophene (3.5 g, 41.67 mmol), benzil (5.2 g, 24.76 mmol) and acetic acid (200 ml) at 0 °C. After being stirred for 3 h the mixture was added to water. The resulting solid was subjected to PLC on oxalic acid-washed silica gel using chloroform–light petroleum (1:1) which removed unreacted benzil (3.21 g) and gave two products.

The first was (*E*,*Z*)-2,5-di(1-benzoylbenzylidene)-2,5-dihydrothiophene **24** (665 mg, 1.42 mmol, 11%) which crystallised from diethyl ether–light petroleum in orange needles mp 105–106.5 °C (Found: M^+, 470.1337. $C_{32}H_{22}O_2S$ requires *M*, 470.1340); *m/z* 472 (10%, M+2H), 470 (77, M^+), 442 (4, M−CO), 441 (2, M−CHO), 367 (6, 472−PhCO), 365 (15, M−PhCO), 333 (4, 365−S), 260 (4, 365−PhCO), 258 (5, 367−Ph–S), 105 (100, PhCO) and 77 (77, Ph); λ_{max}/nm 245 (log ε 4.20), 282 infl (4.11) and 449 (4.42); ν_{max}/cm^{-1} 1640 (C=O), 1594 (aromatic C=C), 760 and 695 (5 adjacent ArH); δ_H 6.86 and 7.03 (each 1H, d, J=6.4 Hz, thiophenoid CH=CH), 7.10–7.55 (16H, m, ArH), 7.55–7.60 and 7.84–7.88 (each 2H, m, *o*-H of PhCOR); δ_C 194.96 and 193.04 (C=O); 157.16 and 149.73 (C–S); 139.24. 137.90, 137.42, 137.31, 136.56, and 128.75 (quaternary C); 136.66. 135.38, 133.39, 130.90, 130.86, 130.08, 129.10, 129.09, 128.99. 128.31, 128.60, 128.42, 127.71, and 127.59 (C–H).

The second fraction (2.10 g) from the PLC separation on being subjected to the reductive acetylation conditions followed by PLC using chloroform–light petroleum gave two products. The first was 5,5[1]-di(2-oxo-1,2-diphenylethyl)-2,2[1]-bithienyl **25** (210 mg, 0.38 mmol, 3%) which crystallised from chloroform–light petroleum in needles mp108–110 °C [Found: $(M-PhCO)^+$, 449.1034. $C_{29}H_{21}OS_2$ requires *M*, 449.1032]; *m/z* 554 (8%, M^+), 449 (100, M−PhCO), 344 (85, 449−PhCO), 105 (52, PhCO) and 77 (30, Ph); λ_{max}/nm 250 (log ε 4.25), 302 infl (3.87) and 344 (3.74); ν_{max}/cm^{-1} 1677 (aryl ketone C=O), 1593 and 1578 (aromatic C=C), 760 and 699 (5 adjacent ArH); δ_H 6.13 (2H, s, CHCO), 6.74 and 6.92 (each 2H, d, J=3 Hz, thienylene CHCH), 7.20–7.57 (16H, m, ArH), and 7.93–8.04 (4H, m, *o*-H of PhCOR).

The second product was 5,5[11]-di(2-oxo-1,2-diphenylethyl)-2,2[1]:5[1],2[11]-terthienyl **26** (147 mg, 0.23 mmol, 2%) which crystallised from light petroleum as needles mp180–182 °C (Found: M^+, 636.1435. $C_{40}H_{28}O_4S_2$ requires *M*, 636.1429); *m/z* 636 (3%, M^+), 531 (22, M−PhCO), 441 (13, M−$C_{14}H_{11}O$), 426 (17, 531−PhCO), 337, (11, 426−C_7H_5), 105 (100, PhCO) and 77 (60, Ph); λ_{max}/nm 248 (log ε 4.34) and 305 infl (3.99); ν_{max}/cm^{-1} 1675 (aryl ketone C=O) 1592 (aromatic C=C), 789 and 697 (5 adjacent ArH); δ_H 6.17 (2H, s, CHC=O), 6.63 (2H, s, thienylene CHCH), 6.71 and 6.86 (each 2H, br.s, thienylene CHCH), 7.08–7.63 (16H, m, ArH) and 7.97–8.13 (4H, m, *o*-H of PhCOR).

3.2. Crystal structure analysis

Intensity data for an intense blue rod of the chloroform solvate (**2**, $CHCl_3$) were collected using an Enraf Nonius KappaCCD diffractometer (graphite monochromated Mo K_α radiation, λ=0.71073 Å, T=120 K) with the aid of the COLLECT[16] program to a maximum 2θ value of 52°. The triclinic cell dimensions of a=7.4848 (2) Å, b=13.0210 (3) Å, c=14.9361 (5) Å, α=66.3457 (10)°, β=86.1472 (11)° and γ=76.2000 (17)° [V=1294.21 (6) Å^3] were refined using 24556 reflections measured in the 2θ range 5.8–52.0°. After merging of symmetry-equivalent and multiply measured data, 9842 independent reflections (R_{int}=0.179) were retrieved from the 24254 measured and used for structure determination and refinement. The structure of (**2**, $CHCl_3$) was solved by direct methods in space group *P*1 (No. 1) using SHELXS-97[17] which located most of the non-hydrogen atoms. The remaining non-H atoms were routinely located in difference maps during the full-matrix nonlinear least squares refinement on $|F^2|$, carried out with SHELXL-97.[17] All the H atoms were placed in idealized positions and refined by riding on their carrier atoms with the constraint U_{iso}(H)=1.2U_{eq} (carrier atom) applied in all cases, resulting in final $R(F)$ and $\omega R(F^2)$ values of 0.128 and 0.348, respectively. Diffraction quality was poor, which probably correlates with the high value of R_{Int}, the relatively large standard uncertainties on the derived geometrical parameters and the very high *R* factors. However, the atomic connectivity revealed for (**2**, $CHCl_3$) is unambiguous. The situation of space group *P*1 (No. 1) with Z=2 for $C_{32}H_{18}O_2S\cdot CHCl_3$ is a 'suspicious' one, and careful checks were made for missed crystal symmetry.[18] However, none could be found and no reasonable models could be established in space group $P\bar{1}$ (No. 2). The Flack absolute structure parameter[19] refined to 0.10 (15) [i.e., the absolute structure of (**2**, $CHCl_3$) is well defined and is not a racemic twin] which offers support for the choice of *P*1 as space group.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 236209 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).

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Tetrahedron 60 (2004) 9263–9272
Tetrahedron

Chiral thiazoline ligands: application in Pd-catalysed allylic substitution

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Received 7 May 2004; revised 1 July 2004; accepted 22 July 2004

Available online 26 August 2004

Abstract—A series of thiazoline ligands, analogues of well-known oxazolines, easily prepared from chiral aminoalcohols and appropriate dithioesters, was tested in the Pd-catalysed allylic substitution. A systematic comparison with the corresponding oxazolines (using literature data or our own tests) has been made for each case. Some important differences (between their catalytic activity and enantioselectivity) were noted for the two types of ligands, especially in the case of bis(thiazolines) and bis(oxazolines).

1. Introduction

In comparison with the widely applied oxazolines ligands in asymmetric catalysis[1], their sulfur analogues, the thiazolines, are less known and have been rarely used for this purpose. However, since the first example published by Helmchen[2] and which concerned the use of metal-complexes of chiral bis(thiazolines) as catalysts, the interest in thiazoline ligands seem to increase and other authors reported the syntheses and applications of new structures of these compounds.[3,4] Comparative studies,[2,4e] in some well known metal-catalysed asymmetric reactions between oxazolines and thiazolines, appear necessary for further development of the latter, bringing out the different behaviors of the two heterocycles towards metal chelation. However, studies related to the thiazoline ligands were limited so far by the difficult access to a large variety of enantiopure structures. In our previous work,[3] we described a versatile method to prepare thiazolines as easily as oxazolines by using chiral aminoalcohols and appropriate dithioesters (Scheme 1) together with a preliminary test using one of them in Pd-catalysed allylic substitution. We report here our full study on the efficiency, as ligands in this model reaction, of all the synthesized thiazolines (Fig. 1). A systematic comparison with the corresponding already known oxazolines has been made for each case.

Keywords: Thiazolines; Oxazolines; Chiral ligands; Asymmetric catalysis; Allylic substitution.

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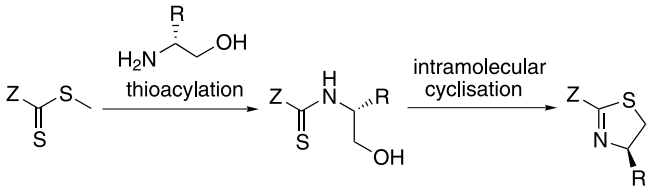
doi:10.1016/j.tet.2004.07.048

2. Results and discussion

2.1. Synthesis of thiazolines

The general syntheses of thiazolines **1**, **2**, **3**, **4** and **12** are already described in our previous paper,[3] starting from the corresponding dithioesters and commercial enantiopure aminoalcohols. The synthetic pathways used five steps (from the isopropyl or cyclohexyl dithioester) for the bis(thiazolines) **1** and **2** and two steps (from pyridyl or quinolyl dithioester) for the thiazolines **3**, **4** and **12**.[5] Two new types of structures have been added to the thiazoline ligand family and are reported here: the 8-quinolyl thiazolines **5** (Scheme 2), analogues of the reported 8-quinolyl oxazolines[6] and the phosphine-thiazoline **9b** (Scheme 3), analogue of the widely known phosphine-oxazoline.[7]

Similarly to the 2-quinolyl thiazolines, 8-quinolyl thiazolines **5** were prepared in two steps (with 81-86% overall yield) starting from the 8-quinolyl dithioester **13**[8] via the corresponding thioamides **14** (Scheme 2).



a: R = Et, **b**,**c**: R = iPr, **d**: R = tBu, **e**: R = Bn, **f**: R = Ph

Scheme 1.

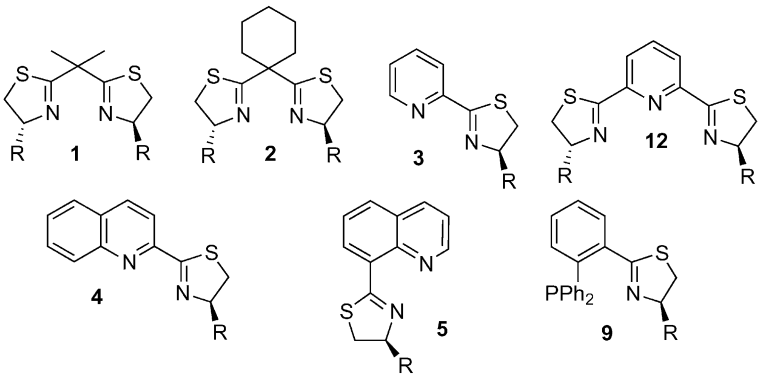
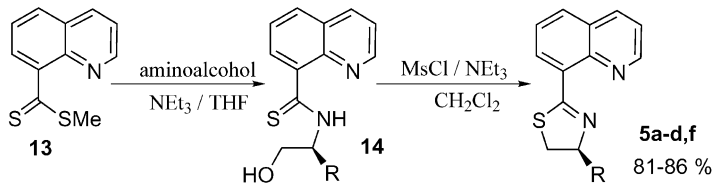
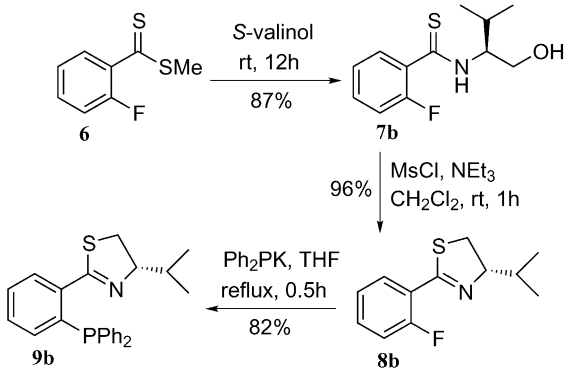


Figure 1.



Scheme 2.

Phosphine-thiazoline **9b** was prepared starting from the 2-fluoro-phenylthiazoline **8b** by reaction with potassium diphenylphosphide.[9] Thiazoline **8b** was obtained in two steps (thioacylation, then cyclization of **7b**) from 2-fluoro-benzene dithioester **6**[8] and *S*-valinol. The overall yield for the three steps was 68% (Scheme 3).

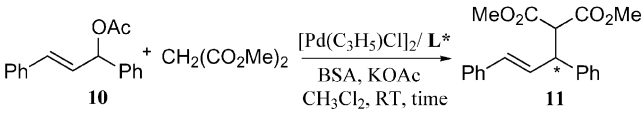


Scheme 3.

It should be noted that we recently reported a new high yielding method to synthesize all required aromatic and heteroaromatic dithioesters, precursors of thiazolines **3**, **4**, **5**, **8** and **12**[8] (Scheme 4).

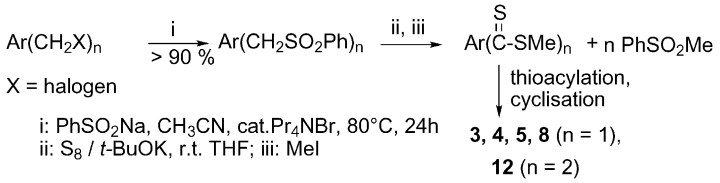
2.2. Pd-catalysed allylic substitution using thiazolines and comparison with oxazolines

We chose as a model reaction the version of the Pd-catalysed allylic substitution which is often used to test new ligands[10] the enantioselective substitution of the acetyloxy group of the racemic 1,3-diphenylpropenyl acetate **10** by the carbanion of the dimethyl malonate. The latter is generated using the couple bis(trimethylsilyl)-acetamide (BSA)/potassium acetate (KOAc), in presence of allylpalladium dimer. This affords the (*E*)-2-methoxycarbonyl-3,5-diphenylpent-4-enoate **11** (Scheme 5).



Scheme 5.

First, the effects of solvent (Et_2O, THF, CH_2Cl_2, toluene, CH_3CN), temperature (20, 0 °C, reflux of toluene or CH_2Cl_2) and amounts of reagents and catalyst were examined for each type of thiazoline ligand.[11] We selected and summarized here the results obtained under optimal conditions (CH_2Cl_2 at room temperature, see Section 3). The comparison with the corresponding oxazolines has



Scheme 4.

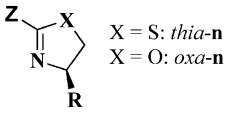


Figure 2.

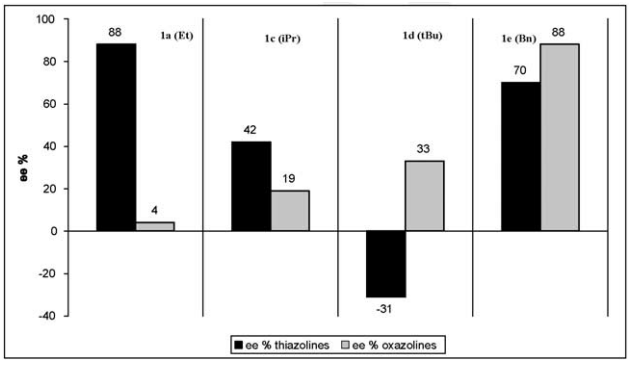
been made using literature data or our own experimental results.

In order to make easier the analysis of the following results, prefixes thia and oxa will be employed respectively for thiazolines and oxazolines ligands, the same number *n* indicating the analogy of their structures (Fig. 2).

Graphs 1 and 2 facilitate the comparison between the enantiomeric excesses obtained with the different ligands.

2.2.1. Bis(thiazolines) 1 and 2. In this series, all catalytic tests were done in our laboratory, except for oxa-**1e**, for which data were extracted from the literature.[12]

The analysis of Table 1 and Graph 1 discloses some amazing differences between the two types of ligands.

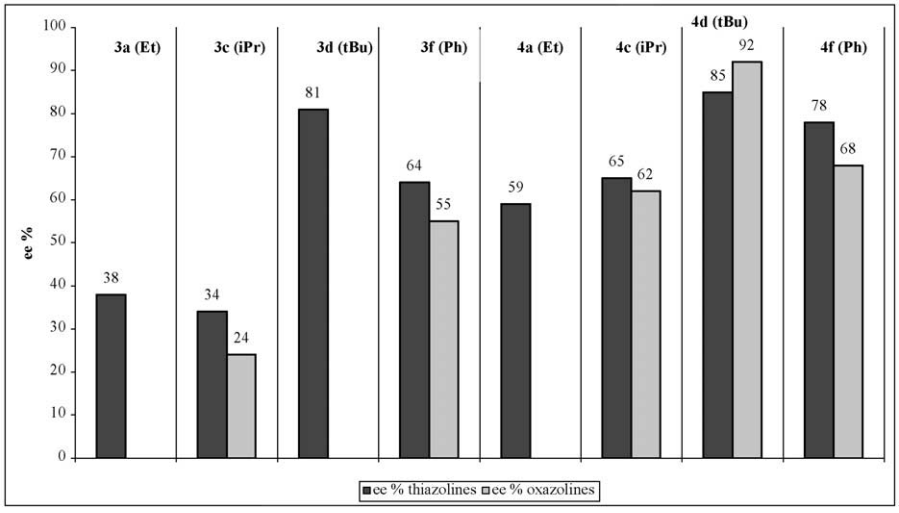


Graph 1. Comparative graph: ee % of **11** with ligands **1** (Table 1, entries 1, 2, 4–9); (*R*)-**11** ee % are given in positive values and (*S*)-**11** ee % in negative values; for an easier reading of the graph we extrapolated the data for the (*S,S*) ligands oxa and thia-**1d** and **1e** and considered them of (*R,R*) configuration).

Generally, bis(thiazolines) (Table 1, entries 1–4, 6–8) had better catalytic activity (see the reaction time) than the corresponding bis(oxazolines) and gave higher ee % for **11**. The only exception was found for the benzyl substituted ligand **1e** for which the results were nearly comparable, but favourable to oxa-**1e** (Table 1, entries 5 and 9). For most cases, enantiomer (*R*)-**11** was the major enantiomer obtained using ligands **1**[13] or **2** with (*R,R*) configuration, while (*S*)-**11** comes from (*S,S*) ligands **1** or **2**. One exception emerged for thia-**1d** with (*S,S*) configuration, which led to (*R*)-**11**. Moreover, in the case of bis(thiazolines), the enantiomeric excess of **11** decreases from thia-**1a** to thia-**1b**, with the increase of the steric hindrance of the substituent R on the heterocycle, leading even to an inversion of configuration in the case of thia-**1d**, when R = *t*Bu, in contrast to the bis(oxazolines) series (Graph 1).

A possible explanation for this specific behavior of bis(thiazolines) could be a competition between nitrogen and sulfur in the chelation of palladium.[4e] Indeed, compared to oxygen, sulfur, due to its voluminous HOMO orbital, is able to coordinate soft metals like Pd. Based on already described models,[12,14] we suggest the co-existence of three π-allylic palladium complexes (intermediates in the reaction mixture): the complex **A**-(**N,N**), in which Pd is chelated by the two nitrogen atoms and the two diastereomeric complexes **B1**-(**N,S**) *syn–syn* (*endo*) and **B2**-(**N,S**) *syn–syn* (*exo*), in which Pd is chelated by one nitrogen and one sulfur atoms (Scheme 6).

The reaction involving the complex **A**-(**N,N**) should proceed as for bis(oxazolines).[12,14] In this case, a strong interaction between the substituent R of one heterocycle and one phenyl group of the allylic substrate, directs the attack of the nucleophile preferentially on the more sterically congested carbon center (C^1 in Scheme 6) leading to a major (*R*) product for a (*R,R*) configuration of the ligand. It is possible that an important increase of the steric interaction in **A**-(**N,N**) (with a more bulky R substituent), causes a rotation of one of the thiazoline cycles, releasing the constraint and allowing the Pd-chelation by one sulfur atom to give **B1**-(**N,S**) complex. The C_2 symmetric bis(thiazoline)

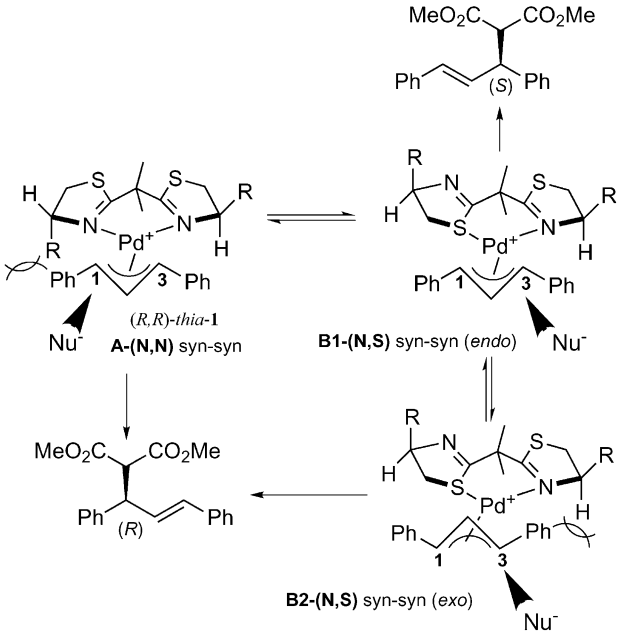


Graph 2. Comparative graph: ee% of **11** with ligands **3** (Table 2, entries 1, 2, 4–7) and **4** (Table 3, entries 1, 2, 4–8); (*R*)-**11** ee % are given in positive value) and for an easier reading of the graph we extrapolated the data for the (*S*) ligands and considered them of (*R,R*) configuration.

Table 1. Pd-catalysed asymmetric allylic substitution with bis(thiazolines) thia-**1** and **2** and bis(oxazolines) oxa-**1**

Entry	Ligand	Config. of the ligand	R	Time (h)	Conv. %	ee %	Config. of **11**
1	thia-**1a**	(*R*,*R*)	Et	30	95	88	(*R*)
2	thia-**1b**	(*S*,*S*)	*i*Pr	42	95	42	(*S*)
3	thia-**1c**	(*R*,*R*)	*i*Pr	42	95	42	(*R*)
4	thia-**1d**	(*S*,*S*)	*t*Bu	30	90	31	(*R*)
5	thia-**1e**	(*S*,*S*)	Bn	72	94	70	(*S*)
6	oxa-**1a**	(*R*,*R*)	Et	168	7	4	(*R*)
7	oxa-**1b**	(*S*,*S*)	*i*Pr	168	8	19	(*S*)
8	oxa-**1d**	(*S*,*S*)	*t*Bu	168	20	33	(*S*)
9[a]	oxa-**1e**	(*S*,*S*)	Bn	68	97	88	(*S*)
10	thia-**2a**	(*R*,*R*)	Et	48	95	51	(*R*)
11	thia-**2c**	(*R*,*R*)	*i*Pr	72	95	41	(*R*)

[a] Literature data.



Scheme 6.

could now behave as a heterofunctinal hemilabile N,S-ligand.[15] In this case, the Pd-complex could exist in two diastereomeric forms in equilibrium, **B1**-(**N**,**S**) *syn–syn* (*endo*) and **B2**-(**N**,**S**) *syn–syn* (*exo*), the selectivity of the nucleophilic attack being dependent upon the difference between their reactivities.[7d,16] Therefore, the ligand can be considered relatively similar to the α-sulfanyl oxazolines ligands reported by Williams[17,18] for which, on the π-allylic intermediate complexes, an attack *trans* to the sulfur atom (C^3 in Scheme 6) is observed. Thus, complex **B1**-(**N**,**S**) would lead to (*S*)-**11**, while **A**-(**N**,**N**) and **B2**-(**N**,**S**) to (*R*)-**11**, explaining the decrease of the enantiomeric excess, as well as the inversion of the enantioselection, with a bulkier R substituent. The possibility of the metal-chelation by two sulfur atoms cannot be completely excluded, but in that case, the chiral effect around the sulfur would be probably too small to generate enantioselectivity.

In order to examine the Pd-chelation with bis(thiazolines) and to rationalize the experimental results, we have undertaken to analyse some Pd-complexes with bis(thiazolines) and tried to obtain crystallographic analyses. First, we attempted to prepare the postulated reaction intermediates

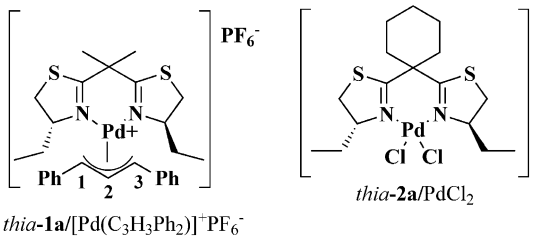


Figure 3.

thia-**1a**–**d**/$[Pd(C_3H_3Ph_2)]^+PF_6^-$ but, unfortunately, the complexes had low stability and crystals could not be isolated. However, one of them, the complex thia-**1a**/$[Pd(C_3H_3Ph_2)]^+PF_6^-$ (Fig. 3) could be characterized by ^1H NMR (see Section 3). The highest chemical shifts of the CH–N protons let supposed in this case the chelation of Pd by the two nitrogen atoms. The lack of the ^{13}C NMR did not allow us to have the $\Delta\delta(^{13}C)$ between the signals of C^1 and C^3, indicating the electronic difference around these atoms coordinated to Pd.[12a]

On the other hand, we succeeded in the isolation of a single crystal of the complex thia-**2a**/$PdCl_2$ (Fig. 3) and determined its structure by X-ray diffraction analysis.

The structure showed in Figure 4, clearly discloses the N,N coordination. However, this complex is not the real reaction intermediate, so it does not exclude our previous hypotheses related to the participation of sulfur in the chelation of the π-allylic palladium complex.

2.2.2. Pyridyl thiazolines 3. In this series, we have tested the thiazolines ligands and compared two of them with the corresponding oxazolines for which data have been already reported in the literature.[19]

The analysis of Table 2 shows that the catalytic activity of pyridyl oxazolines oxa-**3b**,**f** is better than that of their analogues thiazolines thia-**3b**,**f**. About 2 h are needed for the formers to give a good conversion, while 3–4 days are needed using the latters. Enantiomeric excesses are nearly similar, with a small superiority for the thiazolines (Table 2, Graph 2). The best result in the thiazolines series is 81% ee, obtained with thia-**3d** (R = *t*Bu).

The enantioselection was the same for both oxazolines and

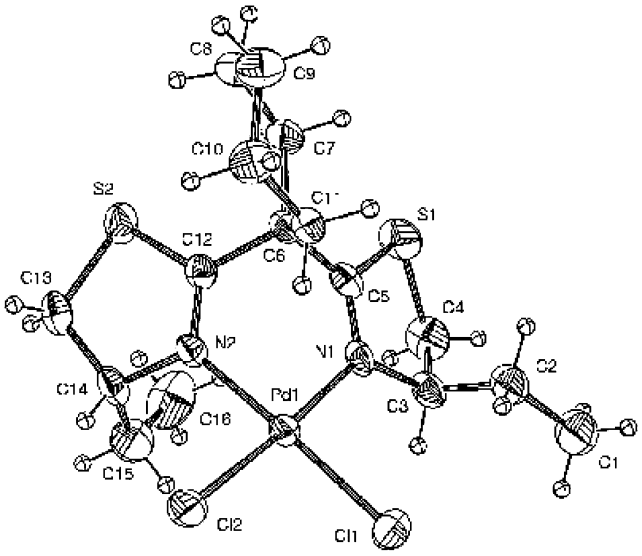
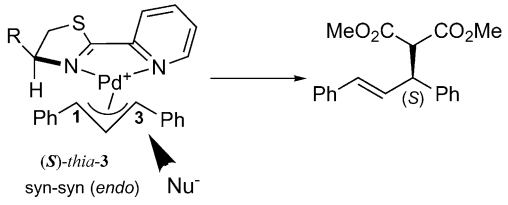


Figure 4.

thiazolines: the enantiomer (*R*)-**11** was obtained using ligands (*R*)-**3**, while (*S*)-**11** comes from (*S*)-**3**. This suggests that the reaction intermediates with thiazolines are similar to those proposed for the pyridyl oxazolines,[19] the Pd being complexed by the two nitrogen atoms of the pyridine and thiazoline heterocycles. Thus, the attack of the nucleophile should take place preferentially on the terminal carbon C[3] *trans* to the thiazoline nitrogen of the π-allylic Pd-complex *syn–syn endo*, for an *S* configuration of the ligand (Scheme 7).



Scheme 7.

2.2.3. 2,6-Pyridyl bis(thiazolines) 12. Only the (*S*,*S*)-2,6-pyridyl bis(thiazoline) **12b** (with R = *i*Pr) has been tested in this series. Whatever the conditions tested (different solvents and temperatures), the catalyst with this ligand proved to be completely inefficient in this reaction. The corresponding oxazoline (the Pybox) has been described giving 80% conversion after 2 days in refluxing dichloromethane and only 26% ee.[20] Besides, it is interesting to note that both oxazolines[21] and thiazolines[22] of this series have been successfully used as ligands in the cyclopropanation with diazoesters catalysed by ruthenium.

2.2.4. 2- and 8-Quinolyl thiazolines 4 and 5. The behavior of the 2-quinolyl thiazolines **4** as ligands in the allylic substitution was found to be very similar to that of the pyridyl thiazolines **3**. Their catalytic activity was found lower than the one of the pyridyl oxazolines reported in the literature.[19] Thus, about 72 to 144 h (Table 3, entries 1–5) are necessary for a good conversion using thiazolines, compared to 5 to 17 h (Table 3, entries 6–8) with the oxazoline analogues. Analysis of the results indicated in Table 3 (entries 1–8) and Graph 2 shows that the enantiomeric excesses are nearly similar and grow in this series with the steric hindrance of the R substituent. The best result was obtained in both cases with the most bulky substituent (R = *t*Bu), 85% ee with thia-**4d** and 92% ee with oxa-**4d**. The enantioselection for thia-**4d** was close to that observed for the corresponding pyridyl thiazoline thia-**3d** and let suppose a reaction intermediate similar in both cases (Scheme 7).

In a second series of experiments, we compared the 2-quinolyl thiazolines thia-**4** (Table 3, entries 1–5) and the 8-quinolyl thiazolines thia-**5** (Table 3, entries 9–12), which could form respectively with the Pd, a five- or a six-membered chelate ring. Then, the 8-quinolyl thiazolines thia-**5** were compared with the corresponding oxazolines[6]. The literature data show that for the quinolyl oxazolines, the 8-substituted derivatives oxa-**5** (Table 3, entries 13–15) are more reactive than the 2-substituted ones oxa-**4** (Table 3, entries 6–8). Compared to both 2-quinolyl thiazolines thia-**4** and their oxygenated analogues oxa-**5**, the 8-quinolyl thiazolines thia-**5** have been found to be rather inefficient, giving only 8–20% conversion after 10 days and 13–48% enantiomeric excesses.

2.2.5. 2-Diphenylphosphino-phenylthiazoline 9. Unlike the phosphine-oxazoline analogue, well known for its high efficiency as ligand in the Pd-catalysed allylic substitution,[7] thia-**9b** (R = *i*Pr) showed very disappointing results. Testing the two ligands in our reaction conditions (in dichloromethane at room temperature), a total conversion after 48 h and 93% ee were observed with the commercial oxa-**9b**, while only 8% conversion and 24% ee were obtained with thia-**9b**. Moreover, the enantioselection was reversed, the major enantiomer (*S*)-**11** being produced with (*S*)-oxa-**9b**, while (*R*)-**11** was preferentially obtained with (*S*)-thia-**9b** ligand.

In conclusion, a new family of ligands, the thiazolines, has

Table 2. Pd-catalysed asymmetric allylic substitution with pyridyl -thiazolines and -oxazolines **3**

Entry	Ligand	Config. of the ligand	R	Time (h)	Conv. %	ee %	Config. of **11**
1	thia-**3a**	(*R*)	Et	96	95	38	(*R*)
2	thia-**3b**	(*S*)	*i*Pr	96	95	34	(*S*)
3	thia-**3c**	(*R*)	*i*Pr	42	95	42	(*R*)
4	thia-**3d**	(*S*)	*t*Bu	30	90	81	(*S*)
5	thia-**3f**	(*R*)	Ph	72	94	64	(*R*)
6[a]	oxa-**3b**	(*S*)	*i*Pr	1	84	24	(*S*)
7[a]	oxa-**3f**	(*R*)	Ph	1.5	86	55	(*R*)

[a] Literature data.

Table 3. Pd-catalysed asymmetric allylic substitution with 2- and 8-quinolyl- thiazolines and oxazolines **4** and **5**

Entry	Ligand	Config. of the ligand	R	Time (h)	Conv. %	ee %	Config. of **11**
1	thia-**4a**	(*R*)	Et	144	95	59	(*R*)
2	thia-**4b**	(*S*)	*i*Pr	144	95	65	(*S*)
3	thia-**4c**	(*R*)	*i*Pr	96	95	66	(*R*)
4	thia-**4d**	(*S*)	*t*Bu	144	70	85	(*S*)
5	thia-**4f**	(*R*)	Ph	72	53	78	(*R*)
6[a]	oxa-**4b**	(*S*)	*i*Pr	4.5	88	62	(*S*)
7[a]	oxa-**4d**	(*S*)	*t*Bu	15	85	92	(*S*)
8[a]	oxa-**4f**	(*R*)	Ph	17	93	68	(*R*)
9	thia-**5a**	(*R*)	Et	240	19	13	(*R*)
10	thia-**5b**	(*S*)	*i*Pr	240	20	21	(*S*)
11	thia-**5d**	(*S*)	*t*Bu	240	15	22	(*S*)
12	thia-**5f**	(*R*)	Ph	240	8	48	(*R*)
13[a]	oxa-**5b**	(*S*)	*i*Pr	0.5	96	42	(*S*)
14[a]	oxa-**5d**	(*S*)	*t*Bu	1	88	77	(*S*)
15[a]	oxa-**5f**	(*R*)	Ph	2	94	59	(*R*)

[a] Literature data.

been tested in Pd-catalysed allylic substitution and the results were compared with those of the known oxazolines analogues. In several cases, the behavior of the two types of ligands was very different, as far as catalytic activities and enantiomeric excesses are concerned. Bis(thiazolines) were found to be globally more active than bis(oxazolines) and furnished good enantioselectivity (up to 88%). Pyridyl- and quinolyl-thiazolines were found to behave quite similarly to the corresponding oxazolines concerning the enantioselective induction, but were less active. Lastly, while the phosphine-oxazoline is one of the best ligands for this reaction, the phosphine-thiazoline was inefficient. In some cases, a competition between nitrogen and sulfur in the palladium chelation is suspected but further studies are still needed to confirm this hypothesis. Investigations related to other metal-catalyzed reactions are in progress, in our laboratory or in collaboration with other research groups, in order to expand the application scope of these thiazolines chiral ligands in asymmetric catalysis.

3. Experimental

3.1. General remarks

Most of the reactions were carried out under nitrogen atmosphere with magnetic stirring, unless otherwise specified and monitored by TLC using silica plates. Synthesized products were purified by flash column chromatography on silica gel or recrystallised if needed. Solvents were dried by distillation prior to use. The NMR spectra were recorded in $CDCl_3$, with a 'Brucker AC 250' or a 'Brucker AC 400' spectrometer. The chemical shifts δ are expressed in ppm, conventional abbreviations are used. Optical rotation values were measured on a Perkin–Elmer-241 polarimeter for the sodium D line at 20 °C. Melting points are uncorrected. The infrared spectra were recorded with a Perkin–Elmer 16 PC spectrometer, $\nu(cm^{-1})$ are given. Mass spectra were recorded with a Nermag R 10 10H spectrometer in electronic impact at 70 eV, *m*/*z* and relative abundance are given. HRMS were obtained with a JEOL JMS-AX 500 mass spectrometer. Elemental microanalyses were performed at Caen with an automatic apparatus CHNS-O ThermoQuest.

Compounds **1a**,**c** (**1b** is the enantiomer of **1c**); **2a**,**c**; **3a**,**c**,**f**; **4a**,**c**,**d**,**f** and **12d**,**f** have been already synthesized and characterized.[3]

3.2. Preparation of bis(thiazolines) 1d and 1e

Bis(thiazolines) **1d** and **1e** have been prepared using the general procedure described for bis(thiazolines),[3] in five steps, starting from isopropyl methyldithioester and the corresponding aminoalcohol (*S*-(+)-*tert*-leucinol and respectively *S*-(+)-phenylalaninol). They were purified by silica gel flash chromatography (pentane/diethyl ether: 70/30).

3.2.1. (*S*,*S*)-2,2′-(1-Methylethylidene)-bis[4,5-dihydro-4-*tert*-butylthiazole] 1d. Viscous yellow oil, $[\alpha]_D^{20} = -29$ (*c* 1, acetone), overall yield = 62%. ^{1}H NMR (400 MHz, $CDCl_3$): 0.98 (s, 18H, 2×$(CH_3)_3C$), 1.52 (s, 6H, $C(CH_3)_2$), 3.10–3.16 (m, 4H, 2×CH_2S), 4.16 (t, 2H, *J* = 9.0 Hz, 2×CHN). ^{13}C NMR (62.9 MHz, $CDCl_3$): 26.3 (2×CH_3), 27.0 (2×CH_3), 27.1 (2×CH_3), 30.1 (2×$(CH_3)_3C$), 34.6 ($(CH_3)_2C$), 34.6 (2×CH_2), 47.8 ($C(CH_3)_2$), 87.3 (2×CHN), 173.1 (2×C=N). IR (NaCl): 2960, 2920, 2870, 1620 ($\nu_{C=N}$), 1450, 1370. Mass *m*/*z*: 326 (M^+, 15) 269 (100), 255 (17), 211 (8), 187 (6), 153 (41), 126 (13), 41 (12). Anal. Calcd for $C_{17}H_{30}N_2S_2$: C, 62.52; H, 9.26; N, 8.58. Found: C, 62.67; H, 9.45; N, 8.15.

3.2.2. (*S*,*S*)-2,2′-(1-Methylethylidene)bis[4,5-dihydro-4-benzylthiazole] 1e. yellow oil, overall yield = 58%. ^{1}H NMR (400 MHz, $CDCl_3$):1.58 (s, 6H, $C(CH_3)_2$), 2.73 (dd, 2H, *J* = 13.6, 9.3 Hz, 2×C*H*HPh), 3.06 (dd, 2H, *J* = 11.8, 5.4 Hz, 2×C*H*HS), 3.19 (dd, 2H, *J* = 13.6, 5.0 Hz, 2×CH*H*Ph), 3.22 (dd, 2H, *J* = 11.8, 6.0 Hz, 2×CH*H*S), 4.73–4.80 (m, 2H, 2×CHN), 7.22–7.34 (m, 10H, H^{arom}). ^{13}C NMR (62.9 MHz, $CDCl_3$): 26.9 ($C(CH_3)_2$), 37.8 (2×H_2C–Ph), 40.1 (2×CH_2S), 47.9 ($C(CH_3)_2$), 78.3 (2×CHN), 126.8 (2×CH^{arom}), 128.9 (2×CH^{arom}), 129.8 (2×CH^{arom}), 138.9 (2×C^{arom}), 174.9 (2×C=N). IR (NaCl): 3010, 2960, 2920, 1600 ($\nu_{C=N}$), 1450, 1350. Mass *m*/*z*: 394 (M^+, 18), 303 (100), 245 (2), 218 (2), 153 (45), 126 (12), 91 (25), 65 (7). Anal. Calcd for $C_{23}H_{26}N_2S_2$: C, 70.01; H, 6.64; N, 7.10. Found: C, 69.71; H, 6.32; N, 6.95.

3.3. Preparation of 2-pyridyl thiazoline 3d

Thiazoline **3d** has been prepared using the general procedure described for the 2-pyridyl thiazolines,[3] in two steps, starting from methyl pyridine-2-dithiocarboxylate[8] and *S*-*tert*-leucinol. It was purified by silica gel flash chromatography (pentane/diethyl ether: 70/30).

3.3.1. 2-[(*S*)-4,5-dihydro-4-*tert*-butyl-2-thiazolyl]pyridine 3d. Yellow solid, mp 44 °C, $[\alpha]_D^{20}=-51$ (*c* 1, acetone), overall yield=81%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.08 (s, 9H, $(CH_3)_3C$), 3.21 (dd, 1H, *J*=11.0, 10.4 Hz, C*H*HS), 3.33 (dd, 1H, *J*=11.0, 9.3 Hz, CH*H*S), 4.46 (dd, 1H, *J*=10.4, 9.3 Hz, CHN), 7.37 (dd, 1H, *J*=7.7, 4.9 Hz, H_4), 7.77 (dt, 1H, *J*=7.7, 1.4 Hz, H_5), 8.13 (d, 1H, *J*=7.7 Hz, H_6), 8.65 (dd, 1H, ^3J=4.9, 1.4 Hz, H_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): 27.2 ($(CH_3)_3C$), 33.4 (CH_2S), 35.8 ($(CH_3)_3C$), 88.8 (CHN), 122.0, 125.6, 136.7, 149.6, 151.8, 177.9 (SC=N) IR (NaCl): 2950, 2870, 1610 ($\nu_{C=N}$), 1460, 1380, 1270. Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.71; S, 14.55. Found: C, 65.08; H, 7.40; N, 12.42; S, 14.33.

3.4. Preparation of pyridine-2,6-bis(thiazoline) 12b

Thiazoline **12b** has been prepared using the general method already described for analogous compounds with R=*t*Bu, Ph,[3] in two steps, starting from dimethyl 2,6-pyridine bis(dithiocarboxylate)[8] and two equivalents of *S*-valinol. It was purified by silica gel flash chromatography (pentane/diethyl ether).

3.4.1. 2,6-Bis[(*S*)-4,5-dihydro-4-isopropyl-2-thiazolyl]-pyridine 12b. Yellow solid, mp 190 °C, $[\alpha]_D^{20}=-125$ (*c* 1, acetone), overall yield=61%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.08 (t, 12H, *J*=6.7, Hz, 2×$CH(CH_3)_2$), 2.13 (oct, 2H, *J*=6.7 Hz, 2×C*H*$(CH_3)_2$), 3.11 (t, 2H, *J*=10.4 Hz, 2×C*H*HS), 3.38 (dd, 2H, *J*=10.4, 9.3 Hz, 2×C*H*HS), 4.53 (ddd, 2H, *J*=10.4, 9.3, 6.7 Hz, 2×C*H*N), 7.83 (t, 1H, *J*=7.7 Hz, H_4), 8.16 (d, 2H, *J*=7.7 Hz, H_4 and H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): 19.4 and 19.7 (2×$(CH_3)_2CH$), 33.4 (2×*C*H$(CH_3)_2$), 34.1 (2×CH_2S), 84.0 (2×CHN), 122.7, 136.9, 150.6, 167.9 (S–C=N). IR (KBr): 2960, 2870, 1600 ($\nu_{S-C=N}$), 1450, 1360, 1310, 1020. Calcd for $C_{17}H_{23}N_3S_2$: C, 61.22; H, 6.95; N, 12.60. Found: C, 60.91; H, 6.92; N, 12.78.

3.5. Preparation of 8-quinolyl thiazolines 5

The 8-quinolyl thiazolines **5a**,**b**,**d**,**f** have been prepared using the general procedure described for the 2-quinolyl thiazolines **4**[3], in two steps, starting from dithioester **13**[8] and the corresponding aminoalcohol (*R*-2-aminobutanol, *S*-valinol, *S*-*tert*-leucinol and, respectively, *R*-phenylglycinol). They were purified by silica gel flash chromatography (pentane/diethyl ether: 70/30).

3.5.1. 8-[(*R*)-4,5-Dihydro-4-ethyl-2-thiazolyl]quinoline 5a. Viscous dark red oil, $[\alpha]_D^{20}=+138$ (*c* 1, acetone), overall yield=79%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.13 (t, 3H, *J*=7.3 Hz, C*H*$_3$CH$_2$), 1.74 (m, 1H, C*H*$_2$CH$_3$), 1.92 (m, 1H, C*H*$_2$CH$_3$), 3.07 (dd, 1H, *J*=10.8, 9.0 Hz, C*H*HS), 3.48 (dd, 1H, *J*=10.8, 8.5 Hz, CH*H*S), 4.56 (dt, 1H, *J*=8.5, 7.3 Hz, CHN), 7.31 (dd, 1H, *J*=8.3, 4.2 Hz, H_3), 7.57 (dd, 1H, *J*=8.1, 7.5 Hz, H_6), 7.77 (d, 1H, *J*=8.1 Hz, H_5), 8.04 (dd, 1H, *J*=8.3, 1.7 Hz, H_4), 8.25 (d, 1H, *J*=7.4 Hz, H_7), 8.90 (dd, 1H, *J*=4.2, 1.7 Hz, H_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): 11.5 (*C*H$_3$CH$_2$), 28.4 (*C*H$_2$CH$_3$), 38.6 (CH_2S), 77.9 (CHN), 121.7, 126.4, 128.6, 130.8, 130.8, 133.0, 136.7, 145.9, 150.1, 165.5 (S–C=N). IR (KBr): 2960, 2920, 1650 ($\nu_{C=N}$), 1570, 1490, 1460, 1380, 1310, 1250. Calcd for $C_{14}H_{14}N_2S$: C, 69.39; H, 5.82; N, 11.56. Found: C, 69.93; H, 5.52; N, 11.17.

3.5.2. 8-[(*S*)-4,5-Dihydro-4-isopropyl-2-thiazolyl]quinoline 5b. Brown solid, mp 55 °C, $[\alpha]_D^{20}=-141$ (*c* 1, acetone), overall yield=81%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.15 (d, 6H, *J*=6.8 Hz, $CH(CH_3)_2$), 2.22 (sept, 1H, *J*=6.8 Hz, C*H*$(CH_3)_2$), 3.14 (t, 1H, *J*=10.7 Hz, C*H*HS), 4.43 (dd, 1H, *J*=10.7, 8.6 Hz, CH*H*S), 4.45 (ddd, 1H, *J*=10.4, 8.6, 6.8 Hz, CH=N), 7.46 (dd, 1H, *J*=8.3, 4.2 Hz, H_3), 7.60 (dd, 1H, *J*=8.1, 7.3 Hz, H_6), 7.92 (d, 1H, *J*=8.1, 1.4 Hz, H_5), 8.21 (dd, 1H, *J*=8.3, 1.8 Hz, H_4), 8.38 (dd, 1H, *J*=7.3, 1.4 Hz, H_7), 9.03 (dd, 1H, *J*=4.2, 1.8 Hz, H_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): 19.4, 20.3 ($(CH_3)_2CH$), 33.6 (CH_2S), 36.3 (*C*H$(CH_3)_2$), 82.2 (CHN), 121.7, 126.5, 128.6, 130.7, 130.7, 133.2, 136.6, 146.0, 150.1, 165.5 (S–C=N). IR (KBr): 2970, 2850, 1610 ($\nu_{S-C=N}$), 1550, 1490, 1460, 1380, 1310, 1250. Calcd for $C_{15}H_{16}N_2S$: C, 70.27; H, 6.29; N, 10.93. Found: C, 70.32; H, 6.29; N, 11.12.

3.5.3. 8-[(*S*)-4,5-Dihydro-4-*tert*-butyl-2-thiazolyl]quinoline 5d. Brown solid, mp 75 °C, $[\alpha]_D^{20}=-157$ (*c* 1, acetone), overall yield=85%. ^{1}H NMR (400 M^{1}H NMR (400 MHz, $CDCl_3$): 1.12 (s, 9H, $(CH_3)_3C$), 3.11 (t, 1H, *J*=11.5 Hz, C*H*HS), 3.34 (dd, 1H, *J*=11.5, 8.7 Hz, CH*H*S), 4.34 (dd, 1H, *J*=11.5, 8.7 Hz, CHN), 7.43 (dd, 1H, *J*=8.3, 4.2 Hz, H_3), 7.57 (dd, 1H, *J*=8.1, 7.4 Hz, H_6), 7.89 (dd, 1H, *J*=8.1, 1.2 Hz, H_5), 8.16 (dd, 1H, *J*=8.3, 1.7 Hz, H_4), 8.38 (dd, 1H, *J*=7.4, 1.2 Hz, H_7), 8.99 (dd, 1H, *J*=4.2, 1.7 Hz, H_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): 27.5 ($(CH_3)_3C$), 35.1 (CH_2S), 35.6 ($C(CH_3)_3$), 85.8 (CHN), 121.7, 126.5, 128.6, 130.8, 130.7, 133.2, 136.7, 146.0, 150.0, 165.2 (S–C=N). IR (KBr): 2970, 2850, 1610 ($\nu_{S-C=N}$), 1520, 1490, 1380, 1310, 1250. Mass *m*/*z*: 270 (M^+, 6), 213 (100), 155 (16), 128 (7), 101 (5), 59 (8). Calcd for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.71; N, 10.36; S, 11.86. Found: C, 70.76; H, 6.89; N, 10.10; S, 11.49.

3.5.4. 8-[(*R*)-4,5-Dihydro-4-phenyl-2-thiazolyl]quinoline 5f. Orange solid, mp 62 °C, $[\alpha]_D^{20}=-3.1$ (*c* 1, acetone), overall yield=82%. ^{1}H NMR (400 MHz, $CDCl_3$): 3.29 (t, 1H, *J*=10.9 Hz, C*H*HS), 3.81 (dd, 1H, *J*=10.9, 8.7 Hz, CH*H*S), 5.70 (dd, 1H, *J*=10.9, 8.7 Hz, CHN), 7.24–7.54 (m, 6H, H_3 and C_6H_5), 7.62 (dd, 1H, *J*=8.0, 7.4 Hz, H_6), 7.94 (dd, 1H, *J*=8.0, 1.3 Hz, H_5), 8.21 (dd, 1H, *J*=8.3, 1.7 Hz, H_4), 8.52 (dd, 1H, *J*=7.4, 1.3 Hz, H_7), 9.03 (dd, 1H, *J*=4.2, 1.7 Hz, H_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): 42.0 (CH_2S), 78.7 (CHN), 121.8, 126.5, 127.2, 127.8, 128.7, 129.0, 131.0, 131.1, 132.6, 136.8, 142.9, 145.9, 150.1, 167.6 (C=N). IR (KBr): 1650 ($\nu_{S-C=N}$), 1610, 1510, 1490, 1380, 1310, 1250. HRMS (MH^+) calcd for $C_{18}H_{15}N_2S$: 291.0956. Found: 291.0951. Calcd for $C_{18}H_{14}N_2S$: C, 74.45; H, 4.86; N, 9.65; S, 11.04. Found: C, 73.73; H, 4.75; N, 9.60; S, 11.04.

3.6. Synthesis of (*S*)-(2-fluoro-phenyl)-4-isopropyl 4,5-dihydro-thiazole 8b

A mixture of dithioester **6**[8] (1.5 mmol) and *S*-valinol (1.5 mmol) was stirred at room temperature for 12 h. Then, the mixture was concentrated under reduced pressure, providing thioamide **7b** which was sufficiently pure according to ^{1}H NMR to be used without purification in the next step.

3.6.1. 2-Fluorobenzenethioamide 7b. Crude product: viscous green-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): 1.07 and 1.09 (2d, 6H, J=6.7 Hz, CH(CH_3)$_2$), 1.99 (s, 1H, OH), 2.17 (sept, 1H, J=6.7 Hz, CH(CH$_3$)$_2$), 3.87 (dd, 1H, J=11.1, 4.4 Hz, CHHOH), 3.94 (dd, 1H, J=11.1, 2.1 Hz, CHHOH), 4.76 (m, 1H, CHNH), 7.09 (ddd, 1H, J=11.8, 8.3, 1.2 Hz, H$_3$), 7.22 (dt, 1H, J=7.6, 1.2 Hz, H$_5$), 7.42 (m, 1H, H$_4$), 8.08 (dd, 1H, J=1.8 Hz, J=7.6 Hz, H$_6$), 8.11 (s, 1H, NH).

To crude **7b** diluted in 10 mL of THF, mesylchloride (2 mmol) was added. Then, NEt_3 (4 mmol) was added dropwise, at room temperature. Stirring was maintained for 10 min then water (10 mL) was added and the mixture extracted with dichloromethane (2×10 mL). The organic phase was dried ($MgSO_4$), solvents were evaporated and the residual oil was purified by flash chromatography on silica gel (pentane/diethyl ether: 80/20) to provide 2-fluorobenzene thiazoline **8b**.

Compound **8b**. Yellow oil, yield=78%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.05 and 1.13 (2d, 6H, J=6.7 Hz, CH(CH_3)$_2$), 2.14 (sept, 1H, J=6.7 Hz, CH(CH$_3$)$_2$), 3.17 (dd, 1H, J=10.9, 9.7 Hz, CHHS), 4.14 (dd, 1H, J=10.9, 9.1 Hz, CHHS), 4.83 (m, 1H, CHN), 7.11 (ddd, J=10.6, 8.1, 0.8 Hz, H^{arom}), 7.19 (dt, 1H, J=7.8, 0.8 Hz, H^{arom}), 7.42 (m, 1H, Ar–H^{arom}), 7.88 (dd, 1H, J=7.8, 1.7 Hz, H^{arom}). ^{19}F NMR (235.3 MHz, $CDCl_3$): −111.94 (m). ^{13}C NMR (62.9 MHz, $CDCl_3$): 19.9 and 19.7 ((CH_3)$_2$CH), 33.1 ((CH$_3$)$_2$CH), 35.3 (d, J=3.3 Hz, CH_2S), 83.0 (CHN), 116.3 (d, J=22.0 Hz, C$_3$), 121.7 (d, J=11.4 Hz, C^{arom}), 124.0 (d, J=3.6 Hz, C^{arom}), 130.6 (d, J=2.5 Hz, C^{arom}), 132.1 (d, J=8.6 Hz, C^{arom}), 160.5 (d, J=254.5 Hz, FC^{arom}), 161.1 (d, J=4.9 Hz, S–C=N). IR (KBr): 2960, 2870, 1600 ($\nu_{S-C=N}$), 1590, 1480, 1450, 1380, 1270.

3.7. Synthesis of (*S*)-(2-diphenylphosphino-phenyl)-4-isopropyl 4,5-dihydro-thiazole 9b

A commercial 0.5 M solution of Ph_2PK in THF (1.1 mmol, 2.16 mL) was diluted with THF (4 mL) and refluxed under nitrogen. A solution of **8b** in 3 mL of THF was added dropwise and the mixture refluxed for 20 min. After cooling down to room temperature, hydrolysis with water and extraction with dichloromethane, the solution was dried with $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography on silica gel with pentane, affording pure compound **9b**.

Yellow solid, mp 94 °C, $[\alpha]_D^{20}$=−42 (*c* 1, acetone), overall yield=82%. ^{1}H NMR (400 MHz, $CDCl_3$): 0.81 and 0.89 (2d, 6H, J=6.7 Hz, CH(CH_3)$_2$), 1.79 (oct, 1H, J=6.7 Hz, CH(CH$_3$)$_2$), 2.99 (t, 1H, J=10.6 Hz, CHHS), 3.27 (dd, 1H, J=10.6, 8.4 Hz, CHHS), 4.83 (ddd, 1H, J=10.6, 8.4, 6.8 Hz, CHN), 6.92 (ddd, 1H, J=3.8, 7.6, 1.2 Hz, H^{arom}), 7.19 (dt, 1H, J=7.6, 1.3 Hz, H^{arom}), 7.23–7.34 (m, 10H, H^{arom}), 7.39 (m, 1H, H^{arom}), 7.73 (ddd, 1H, J=7.8, 3.6, 1.3 Hz, H^{arom}). ^{31}P NMR (101.2 MHz, $CDCl_3$): −6.95. ^{13}C NMR (62.9 MHz, $CDCl_3$): 19.6 and 20.4 ((CH_3)$_2$CH), 33.6 ((CH$_3$)$_2$CH), 36.7 (CH_2S), 85.3 (CHN), 128.5 (d, J=1.9 Hz, C^{arom}), 128.63, 128.64, 128.68, 128.7, 130.2, 130.6 (d, J=3.1 Hz, C^{arom}), 134.2 (d, J=10.1 Hz, C^{arom}), 134.5 (d, J=10.7 Hz, C^{arom}), 134.9, 138.2 (d, J=20.1 Hz, C^{arom}), 138.3 (d, J=23.7 Hz, C^{arom}), 139.1 (d, J=24.5 Hz, C^{arom}), 139.2 (d, J=1.9 Hz, C^{arom}), 165.4 (S–C=N). IR (KBr): 3050, 2960, 2910, 2870, 1600 ($\nu_{S-C=N}$), 1550, 1460, 1430, 1380, 1360, 1260. Calcd for $C_{24}H_{24}NPS$: C, 74.01; H, 6.21; N, 3.60; S, 8.23. Found: C, 73.72; H, 6.32; N, 3.54; S, 7.78.

3.8. Synthesis of complex thia-1a/[Pd($C_3H_3Ph_2$)]$^+PF_6^-$

The same procedure as described in the literature for a bis(oxazolines) was used.[12] From [Pd(1,3-diphenylallyl)Cl]$_2$ (0.1 mmol), $AgPF_6$ (0.2 mmol) and thia-**1a** (0.2 mmol), the complex thia-**1a**/[Pd($C_3H_3Ph_2$)]$^+PF_6$ was obtained in 66% yield, as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$), δ 0.89 (t, 6H, J=6.7, Hz, 2× CH_3CH$_2$), 1.56 (s, 6H, (CH_3)$_2$C), 2.13–2.42 (m, 4H, 2× CH$_3$CH_2), 3.14 (dd, 1H, J=6.3, 11.3, Hz, CHHS), 3.48 (dd, 1H, J=9.5, 11.3, Hz, CHHS), 4.84 (d, 1H, J=11.4 Hz, CH), 4.92 (m, 1H, NCH), 5.24 (d, 1H, J=11.4 Hz, CH), 6.35 (t, 1H, J=11.4 Hz, CH), 7.34–7.45 (m, 4H, H^{arom}), 7.63–7.73 (m, 6H, H^{arom}).

3.9. Synthesis of complex thia-2a/$PdCl_2$ and crystal structure determination

1.5 g of $(PdCl_2)_n$ were stirred with 40 mL of acetonitrile, at room temperature, for 24 h, under nitrogen. The orange solid was filtered, washed with diethyl ether and dried. Pd[Cl_2(CH_3CN)$_2$] was obtained as an orange solid in 91% yield (2 g). A mixture of Pd[Cl_2(CH_3CN)$_2$] (0.5 mmol) and ligand thia-**2a** (0.5 mmol) in dichloromethane (5 mL) was stirred at room temperature, for 24 h, under nitrogen. After evaporation of the solvent the crude thia-**2a**/$PdCl_2$, an orange solid, was characterized in ^{1}H NMR. Then, the complex was crystallized and one monocrystal was analysed by X-ray diffraction.

3.9.1. (*R*,*R*)-2,2′-Cyclohexylidene bis[4-ethyl-4,5-dihydrothiazoline]/$PdCl_2$ (thia-2a/$PdCl_2$). ^{1}H NMR (250 MHz, $CDCl_3$): 0.94 (t, 6H, J=7.4 Hz, 2×CH_3CH$_2$), 1.52–1.95 (m, 10H, (CH$_2$)$_5$), 2.15 (m, 2H, CH$_3$CHH), 2.45 (m, 2H, CH$_3$CHH), 3.22 (dd, 2H, J=11.4, 11.3 Hz, 2× CHHS), 3.35 (dd, 2H, J_1=11.3, 11.2 Hz, 2×CHHS), 4.95–5.20 (m, 2H, 2×CHN).

The crystal structure of thia-**2a**/$PdCl_2$ has been registered at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 236476.

$C_{16}H_{26}Cl_2N_2PdS_2$, Fw=487.81, orthorhombic, space group $P2_12_12_1$, a=10.361 (2) Å, b=13.425 (8) Å, c=14.655 (7) Å, V=2038.5(2) Å^{-3}. Z=4, D_x=1.589 Mg/m^3, λ(Mo Kα)=0.71073 Å, μ=13.77 cm^{-1}, F(000)=992, T=293 K. The sample (0.35×0.32×0.27 mm^3) was

studied on an automatic diffractometer CAD4 NONIUS with graphite monochromated Mo Kα radiation. The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}=54°$, scan $\omega/2\theta=1$, $t_{max}=60$ s, range *HKL*: *h* 0,13; *k* −3,17; *l* −4,18) gives 4061 unique reflections from which 3110 with $I>2.0\sigma(I)$. After Lorenz and polarization corrections, the structure was solved with SIR-97, which reveals the non-hydrogen atoms of the compound. The whole structure was refined with SHELXL97 by the full-matrix least-square techniques (use of *F* square magnitude; *x*, *y*, *z*, β_{ij} for Pd, S, Cl, C and N atoms, *x*, *y*, *z* in riding mode for H atoms; 209 variables and 3110 observations; calcd $w=1/[\sigma^2(F_o^2)+(0.21P)^2]$ where $P=(F_o^2+2F_c^2)/3$ with the resulting $R=0.029$, $R_w=0.073$ and $S_w=01.127$ (residual $\Delta\rho\leq 0.67$ e Å^{-3}). The absolute configuration was unambiguously confirmed by the Flack parameter (0.02(4)).

3.10. Typical procedure for the Pd-catalysed allylic substitution

Under a nitrogen atmosphere, allylpalladium chloride dimer (0.012 mmol), the ligand (0.03 mmol) and solid potassium acetate (0.025 mmol) were mixed in 2 mL of dichloromethane for 30 min. Diphenylpropenyl acetate **10** (0.5 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (1.5 mmol) and the dimethyl malonate (1.5 mmol) were then successively added. The reaction mixture was stirred at 20 °C and monitored by TLC (pentane/diethyl ether: 80/20). The solvent was removed and the residue directly analysed by HPLC, using a Chiralpak AD analytical column Daicel (90/10 *n*-heptane/2-propanol, flow rate 1 mL/min, 252.1 nm). Conversions have been calculated from the integration of the corresponding peaks of **10** ($t=7.2$ min) and **11**. Enantiomeric excesses of (*E*)-methyl 2-methoxycarbonyl-3,5-diphenylpent-4-enoate **11** have been measured by HPLC; the separation of the two enantiomers was calibrated using racemic product: (*R*)-(+)-**11**, $t_1=$ 14.3 min; (*S*)-(−)-**11**, $t_2=20.1$ min).

Acknowledgements

The authors thank Pr. A. Pfaltz (University of Basel) for helpful information. Dr. L. Toupet (University of Rennes) is gratefully acknowledged for the X-ray crystal diffraction analysis. We also thank M. Lemarié for her precious assistance in HPLC analyses. This work has been performed within the 'PUNCHOrga' interregional network (Pôle Universitaire Normand de Chimie Organique). We gratefully acknowledge the 'Ministère de la Recherche et des Nouvelles Technologies', CNRS (Centre National de la Recherche Scientifique), the 'Région Basse-Normandie' and the European Union (FEDER funding) for financial support.

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Chemical synthesis of an artificially branched hairpin ribozyme variant with RNA cleavage activity

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Received 22 April 2004; revised 12 July 2004; accepted 22 July 2004

Available online 25 August 2004

Abstract—Due to the development in the field of RNA synthesis over the past decade of years, preparation of RNA oligonucleotides longer than 50 nucleotides is possible today. In this report, we describe the chemical preparation of a branched RNA molecule with RNA cleavage activity consisting of 81 nucleotides. It is derived from the hairpin ribozyme, a small catalytic RNA occurring in nature. The hairpin ribozyme consists of two separately folded domains (loop A and loop B domain), which can be joined in a number of different ways without loss of activity. In the construct presented here, 2′-deoxy-*N*4-(6-hydroxyhexyl)-5-methylcytidine was introduced to connect the loop B domain with the loop A domain via an artificial branch. The synthesized branched RNA is able to catalyze the cleavage of a number of suitable substrates. Compared with the corresponding non-branched reverse-joined ribozyme it cleaves its substrates only 5-fold slower. Surprisingly, no ligation activity could be detected.

1. Introduction

The past few decades of research have revealed that RNA can catalyze an amazing number of chemical reactions. The structure of a number of ribozymes is known and mechanistic details of RNA catalysis have been elucidated. We can now begin to understand ribozymes well enough to turn them into useful tools. The development of ribozymes for site-directed alteration of an RNA sequence has been a major goal in our laboratory. We have studied the ability of the hairpin ribozyme[1,2] to carry out RNA cleavage and ligation and have combined two hairpin ribozymes into one molecule henceforth dubbed twin ribozyme.[3,4] A twin ribozyme that was engineered by combination of two conventional hairpin ribozymes mediates the removal of a specific fragment from the parent RNA, followed by ligation of a separately added repair oligonucleotide into the resulting gap with 30% yield.[4]

In addition to the conventional hairpin ribozyme, we also used reverse-joined hairpin ribozymes,[5,6] for twin ribozyme engineering (Fig. 1).[3]

Even though these twin ribozymes catalyze the cleavage of an RNA substrate at two specific sites (upper part of Fig. 1), the desired sequence exchange reaction (lower part of Fig. 1) turned out being less efficient (K. Bossmann, S. Müller, unpublished results). The low efficiency may be attributed to the specific structure of the reverse-joined hairpin ribozyme unit in the twin ribozyme. Due to a single stranded linker connecting the loop A domain with the loop B domain (Figs. 1 and 2) the length of the substrate ribozyme duplex on the left of the cleavage site is limited to six base pairs. Upon cleavage the resulting product can easily dissociate making ligation at this site less efficient. We, therefore, re-designed the structure of the so far used reverse-joined hairpin ribozyme HP-RJWTC6 into HP-RJTLB that consists of the loop B domain linked to the loop A domain via a non-natural branch (Fig. 2). In comparison to HP-RJWTC6 that due to its specific structure can form only six base pairs with the 3′-end of its substrate, the branched ribozyme HP-RJTLB is able to bind substrates of any length just by adaptation of the binding arm lengths. Thus, fragments can be more strongly bound and consequently ligated. In this paper, we describe the synthesis and functional characterization of the artificially branched ribozyme.

2. Results and discussion

2.1. Ribozyme design

In the branched ribozyme HP-RJTLB the loop A domain and the loop B domain are joined via a cytidine analogue

Keywords: RNA synthesis; Branched RNA; Reverse-joined hairpin ribozyme.
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doi:10.1016/j.tet.2004.07.055

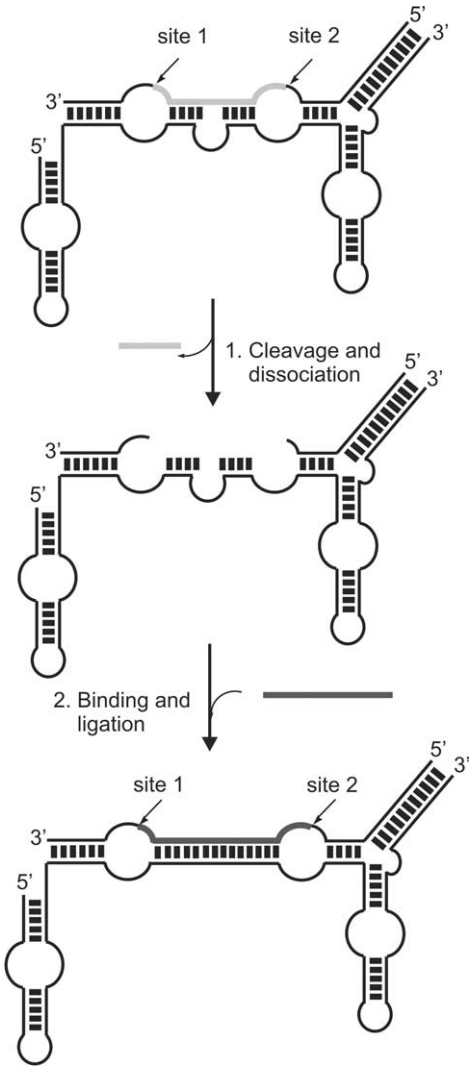

Figure 1. Schematic presentation of site-directed alteration of RNA sequence by an engineered twin ribozyme involving a reverse-joined hairpin ribozyme unit. The twin ribozyme is designed to first cleave the input substrate at two positions to remove the sequence fragment marked in light grey (top). In the second step, a new RNA fragment (dark grey) is bound in the gap left behind and ligated to the remaining fragments of the substrate RNA. For validity of this concept see Ref. 4.

serving as branch point (Fig. 2). The cytidine analogue is modified at C-4 with a linker providing an OH group to be used for assembly of a third RNA chain. The exocyclic amino group at C-4 of cytidine points into the major groove of a double stranded RNA,[7] such that sterical interfering of RNA chains in the branch point is likely to be minimal. Furthermore, the Watson-Crick face of the modified nucleoside is free for base pairing with the opposite guanosine in the substrate strand (Fig. 2). Since the overall structure of an RNA duplex is not affected by a single 2′-deoxy substitution,[8] we decided to use a 2′-deoxy nucleotide instead of the natural ribonucleoside at the branch point to keep preparation and handling of the modified building block as facile as possible. The 2′-deoxy analogue is not located within a conserved sequence and hence will not interfere with ribozyme activity.

2.2. Synthesis of the branched ribozyme

Our first attempts towards the synthesis of a branched RNA employed the strategy shown in Figure 3, route A. The phosphoramidite building block of thymidine was transformed into the corresponding 4-triazolide **2** following a strategy first introduced by Sung et al.[9] The further strategy involved standard RNA synthesis followed by treatment of the protected RNA on the polymer with hexanolamine to substitute the triazole moiety and to introduce the required functionality for branching.

To evaluate this strategy, we first prepared a short model oligoribonucleotide SI-SLA5 (for sequence details refer to Section 4). After assembly of eight building blocks including the modified monomer **2**, the terminal 5′-OH group was acetylated and the polymer bound protected oligomer was treated with aminohexanol/CH_3CN to substitute the triazole residue at the branching nucleotide. Then, synthesis was continued with stepwise coupling of five more adenosine units at the OH group of the amino hexanol linker to yield the branched oligoribonucleotide. Analysis of SI-SLA5 by enzymatic digestion, however, showed that the oligomer had not the expected nucleoside composition (data not shown). While less cytidines than expected could be identified, the amount of detected adenosine residues was to high. The most plausible explanation for this observation is a side reaction during aminohexanol treatment. Position C-4 of cytidine residues is easy accessible for substitution reactions.[10] Thus, also the natural phenoxyacetyl protected cytidine residue within the synthesized RNA chain may have undergone partial transamination during hexanolamine treatment, such that additional adenosine residues could be attached also at this site. An alternative explanation might be partial removal of the acetyl group at the 5′-terminus of the first synthesised chain during aminohexanol treatment. This however, could be ruled out by further experiments (see below).

In order to circumvent this problem, we applied an alternative strategy focussing on the synthesis of an aminohexanol modified monomer and its incorporation into RNA. For the synthesis of the modified monomer building block **3** (Fig. 3, route B) we basically followed the methodology introduced by Horn and co-workers for synthesis of comb-type oligodeoxyribonucleotides.[11] Briefly, the 5′- and 3′-hydroxyl groups of the sugar moiety were protected with dimethoxytrityl- and *tert*-butyldimethylsilyl functionalities, respectively, following standard procedures.[12–14] The compound was transferred into the 4-triazolo derivative and the triazole group was substituted with hexanolamine. The alcohol group at the linker was converted into a levulinic acid ester followed by removal of the 3′-*O*-TBDMS group. Finally the phosphoramidite was prepared following the standard protocol.[15,16] As demonstrated before, the levulinic acid residue is stable under the conditions of oligonucleotide synthesis.[13,17,18] Vice versa, it can be quantitatively removed with hydrazine hydrate in pyridine/acetic acid, leaving the 2′-*O*-*tert*-butyldimethylsilyl protecting group and the succinyl linker attaching the oligonucleotide to the solid support intact.[19,20] However, the routinely used and easily removable phenoxyacetyl (PAC) groups for N-protection[21] turned out to be too labile under

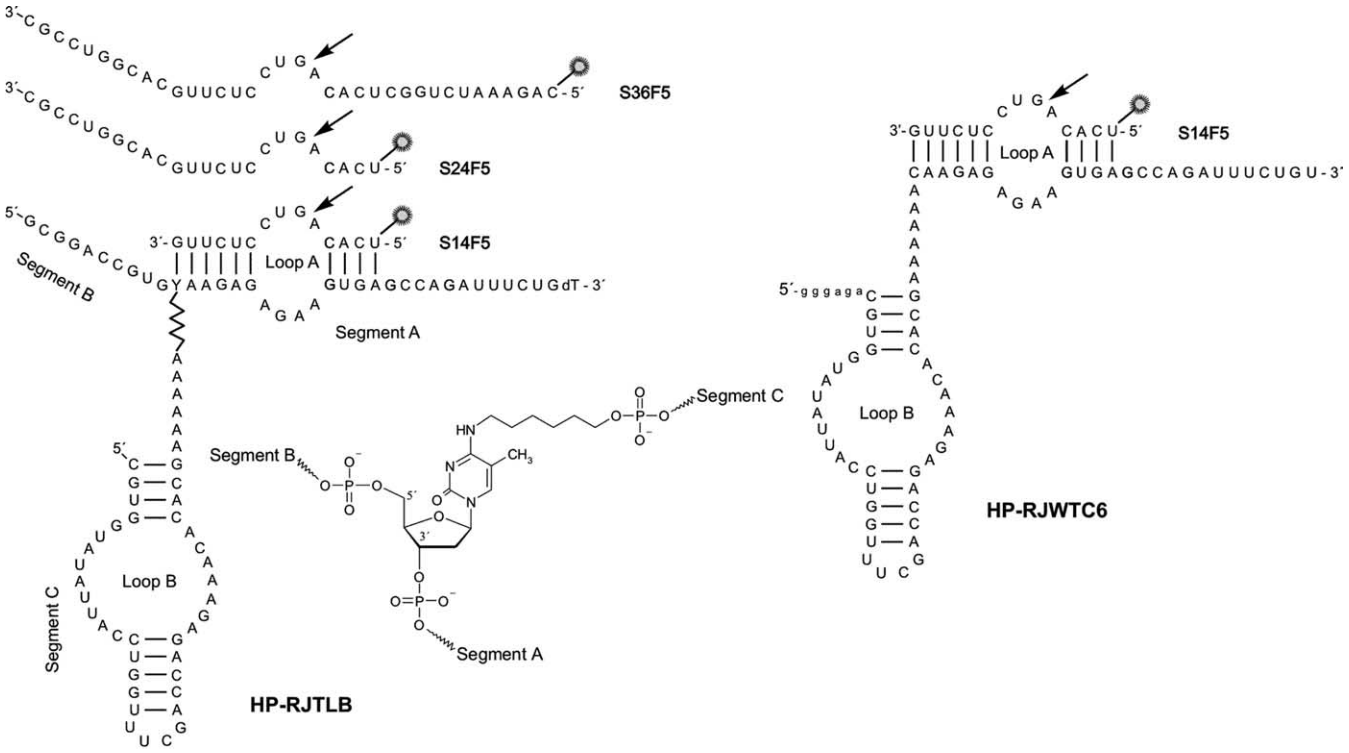

Figure 2. Secondary structure of the branched ribozyme HP-RJTLB with three substrates S14F5, S24F5, S36F5, and of the reverse-joined hairpin ribozyme HP-RJWTC6 with substrate S14F5. All substrates are 5′-end labelled with fluorescein; arrows denote the cleavage site. The structure of the nucleoside at the branch point (marked as Y in HP-RJTLB) is separately shown.

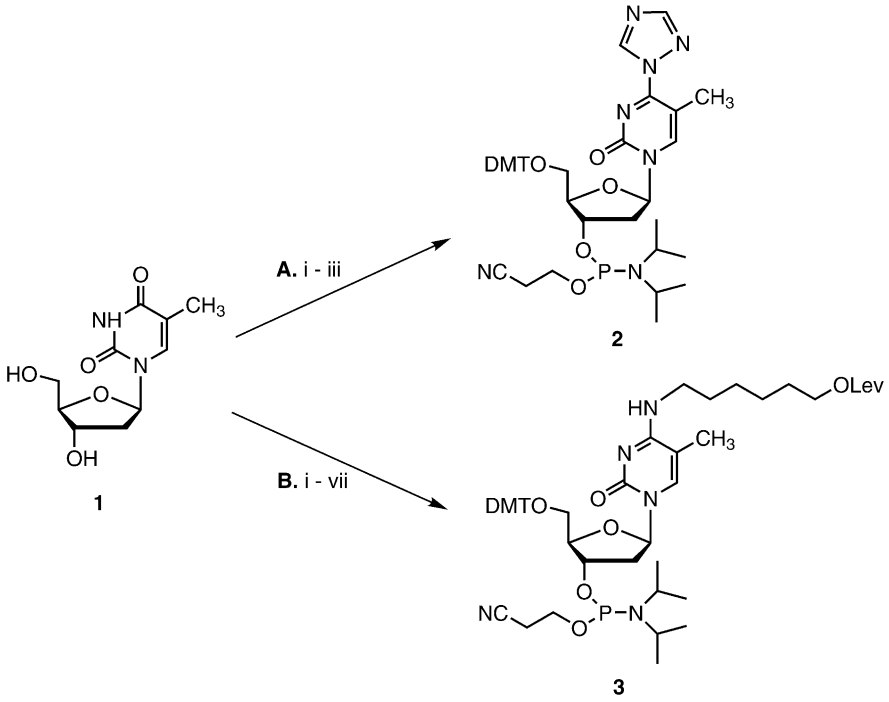

Figure 3. Synthesis of alternative phosphoramidite building blocks **2** and **3** for synthesis of the branched RNA. Route A: (i) DMTCl, DMAP, pyridine, 1.5 h, rt; (ii) chloro-(2-cyanoethoxy)-diisopropylaminophosphine, EtN(*iso*-Pr)$_2$, THF, 2 h, rt; (iii) 1,2,4-triazole, $POCl_3$, Et_3N, CH_3CN, 1 h, 0 °C→rt. Route B: (i) DMTCl, DMAP, pyridine, 1.5 h, rt; (ii) TBDMSCl, imidazole, DMF, 12 h, rt; (iii) 1,2,4-triazole, $POCl_3$, Et_3N, CH_3CN, 1 h, 0 °C→rt; (iv) H_2N–$(CH_2)_6$–OH, CH_3CN, 1 h, rt; (v) (a) levulinic acid, DCC, pyridine, 5 h, rt, levulinic anhydride, DMAP, pyridine, 1.5 h, rt; (vi) TBAF–$3H_2O$, THF, 15 min, rt; (vii) chloro-(2-cyanoethoxy)-diisopropylaminophosphine, EtN(*iso*-Pr)$_2$, THF, 2 h, rt.

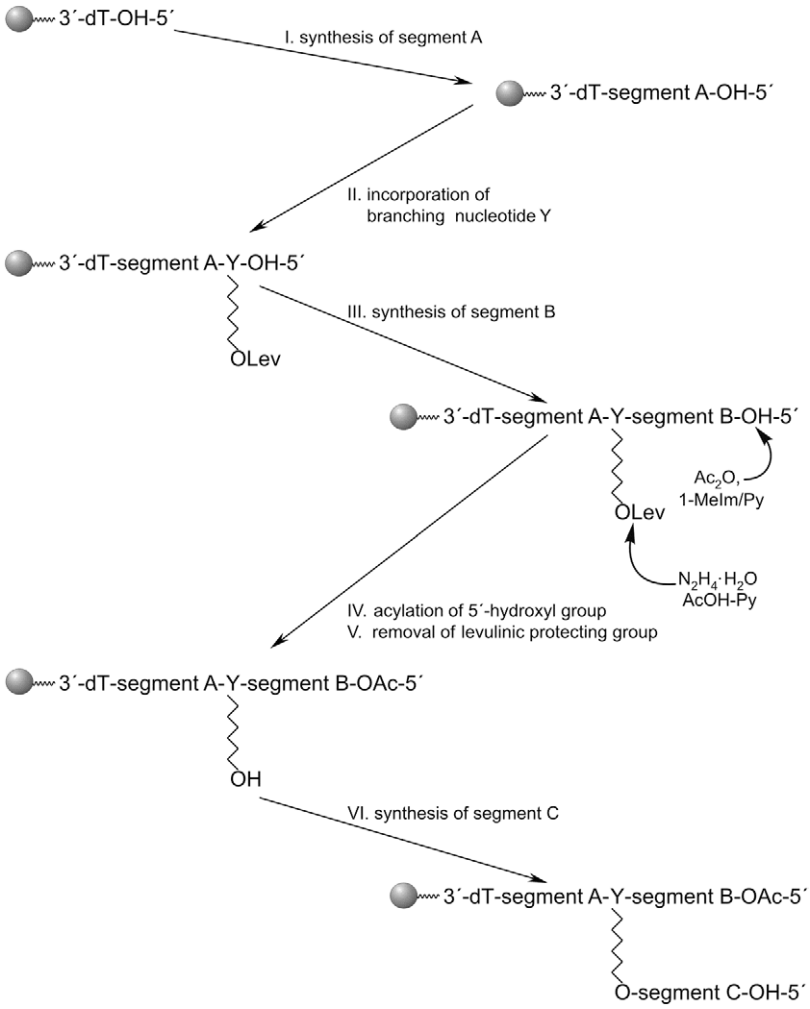

Figure 4. Synthesis scheme of the branched RNA HP-RJTLB. Sequences of segments A, B and C as well as the structure of Y are shown in Figure 2. Details of synthesis are given in the text.

the conditions of hydrazinolysis. Therefore, more stable N-protecting groups were used: benzoyl for A and C,[17] and dimethylformamidine for G.[21,22] The half life of *N*-benzoyl protected adenosine and cytidine under the conditions of hydrazinolysis was determined to be about 3 and 5 h, respectively, while the dimethylformamidine group was stable for the time of observation. Removal of the levulinyl group by hydrazinolysis takes about 5 min, hence leaving the major part of the N-protected nucleobases intact.

Chain assembly was carried out as shown in Figure 4. We used a 1000 Å CPG support (instead of the routinely used 500 Å), to avoid sterical hindrance of reaction sites by growing branched oligonucleotide chains.

Synthesis of segment A (Fig. 4, step I) was performed using the standard procedure of automated RNA synthesis. The branching nucleotide was incorporated with small changes to the standard protocol. A higher excess of **3** and an extended coupling time ensured 99.5% coupling efficiency (Fig. 4, step II, for details refer to Section 4). Synthesis was continued to assemble segment B, as before following the standard protocol (Fig. 4, step III). Next, the 5′-OH group at the end of segment B was capped with an acetyl group to prevent further reaction (Fig. 4, step IV). To initiate the synthesis of segment C, the levulinic acid group at the modified cytidine base was removed (Fig. 4, step V) followed by assembly of segment C (Fig. 4, step VI). Synthesis of all three segments of the branched oligonucleotide was achieved with yields as usual for completely unmodified non-branched oligoribonucleotides.

2.3. Deprotection, purification and characterization

Removal of base protecting groups and β-cyanoethyl groups at the phosphates as well as cleavage from the polymer support was accomplished using saturated methanolic ammonia, followed by treatment with TEA-3HF/DMF (3:1) to remove silyl groups at the 2′-OH.[23] In order to avoid exposure of the branched RNA to long heating in ammonia, the first of these two steps was carried out at ambient temperature, however, for prolonged time. The deprotected oligonucleotide was precipitated from *n*-butanol and purified by electrophoresis through a 20% denaturing polyacrylamide gel at 60 °C. We evaluated these conditions as being essential to achieve sufficient resolution of the desired product band (Fig. 5).

Due to the presence of branched and non-branched species it was not possible to predict the migration properties of the

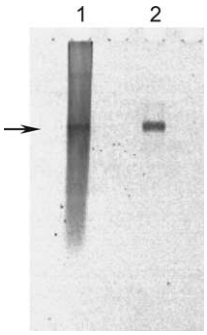

Figure 5. Gel electrophoretic analysis (20% polyacrylamide) of HP-RJTLB. Lane 1: crude product of HP-RJTLB synthesis. The arrow denotes the product band. Lane 2: HP-RJTLB after purification and reloading onto the gel.

product RNA. Therefore, the strongest band was cut out and the RNA was eluted from the gel. In order to prove the identity of the product, the obtained RNA was subjected to nucleoside composition analysis. For this purpose samples were digested with both nuclease P1 and alkaline phosphatase and the resulting nucleosides were separated and identified by HPLC (Fig. 6). In the presence of nuclease P1 the phosphodiester bond between the aminolinker hydroxyl group and the neighbouring nucleoside was totally hydrolyzed. We found snake venom phosphodiesterase being less efficient in catalyzing this reaction (data not shown). 2′-Deoxy-*N*4-(6-hydroxyhexyl)-5-methylcytidine could be identified in the digestion mixture (marked as Y in Fig. 6), which confirms successful incorporation of this modified nucleoside into the analyzed oligonucleotide. Integration of peak areas normalized to specific extinction coefficients revealed a nucleoside composition which agrees very well with theoretically calculated values, demonstrating the superior quality of the synthesized branched RNA.

2.4. Cleavage experiments and kinetic characterization

Since HP-RJTLB is derived from a catalytic RNA structure we next asked if activity has been preserved in the branched ribozyme. To this end, we studied the ability of HP-RJTLB to cleave three substrates of different length: S14F5, S24F5 and S36F5 (Fig. 2), and compared the results with the non-branched reverse-joined hairpin ribozyme HP-RJWTC6. All three substrates carry a fluorescein label at the 5′-end to allow for reaction analysis with an automated DNA sequencer as demonstrated previously.[3] Reactions were carried out in the presence of 2 mM spermine, since we have found previously that activity of reverse-joined hairpin ribozymes is considerably improved in the presence of the polyamine.[24] All substrates are cleaved by HP-RJTLB with the same specificity as observed for HP-RJWTC6. The results are summarized in Table 1.

The short substrate S14F5 as well as S24F5 that extends over the branch point are cleaved by HP-RJTLB with only about 5-fold lower rates than observed with the non-branched ribozyme HP-RJWTC6. Interestingly, cleavage of the substrate S36F5 that is fully paired with the ribozyme proceeds with rather slow rate, k_{react} for HP-RJTLB is another 5-fold down compared with the other two substrates S14F5 and S24F5. A similar result has been obtained with HP-RJWTC6: S36F5 is cleaved 3-fold slower than the two shorter substrates. Also, the end-point of the reaction is rather low. Only 7% of the total S36F5 substrate is cleaved by HP-RJTLB, 45% by HP-RJWTC6. This result might be attributed to an increased ligation activity of both ribozymes with the long substrate. The 5′-terminus of S36F5 forms a contiguous 16 base pair helix with the 3′-terminus of the ribozyme. As mentioned above the natural hairpin ribozyme is also an efficient ligase and it has been shown earlier that structural stabilisation shifts the cleavage/ligation equilibrium towards ligation. Fedor and co-workers have

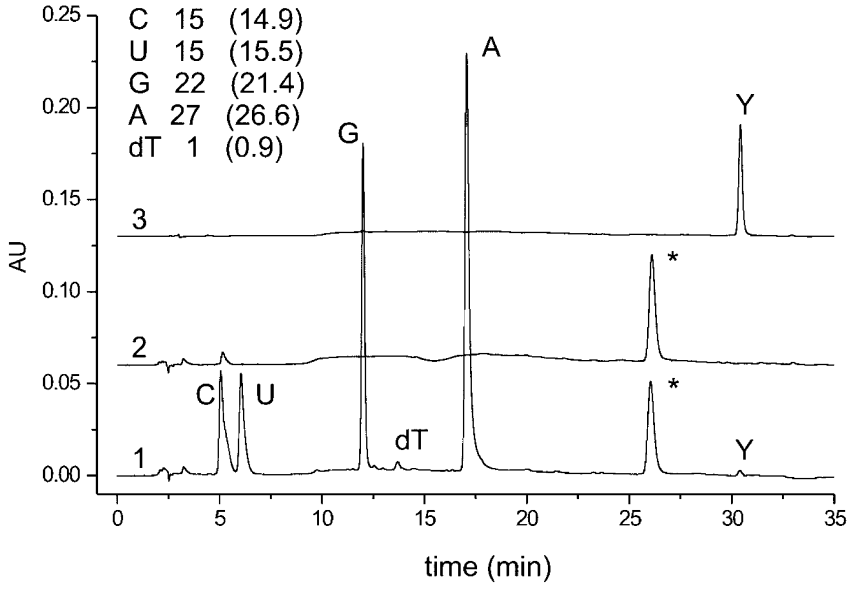

Figure 6. Nucleoside composition analysis of HP-RJTLB by reverse phase HPLC. Lane 1: digestion mixture of synthesized HP-RJTLB. The peak marked with an asterisk results from a component of the digestion buffer or the enzyme (see also lane 2). Lane 2: enzymatic digestion mixture without RNA as control. Lane 3: marker nucleoside Y: 2′-deoxy-N4-(6-hydroxyhexyl)-5-methylcytidine. The calculated and experimentally found (in parenthesis, data results from three independent digestion experiments) base composition for HP-RJTLB is shown.

Table 1. Kinetic constants for cleavage reactions of HP-RJTLB and HP-RJWTC6

Substrate	HP-RJTLB			HP-RJWTC6		
	K_1, nM	$k_{react}\times10^2$ min^{-1}	End-point of reaction (%)	K_1, nM	$k_{react}\times10^2$ min^{-1}	End-point of reaction (%)
S14F5	71.0±10.3	2.4±0.1	80	12.8±2.4	13.0±0.4	95
S24F5	84.3±11.5	2.3±0.1	70	93.0±15.6	12.4±0.7	90
S36F5	152.7±31.2	0.044±0.004	7	46.5±11.9	3.8±0.2	45

demonstrated that cleavage takes place rapidly only when cleavage products dissociate rapidly and that cleavage rates fall when cleavage products remain bound in stable base paired helices. This was taken as evidence that bound products are re-ligated.[25–28] What holds for the conventional hairpin ribozyme also applies to reverse-joined hairpin ribozymes, ligation activity increases with the length of duplexes (S. Ivanov, S. Müller, unpublished observations). Therefore, the observed slow cleavage of S36F5 by HP-RJTLB and HP-RJWTC6 might be interpreted as enhanced ligation due to stable bound cleavage products and in consequence re-ligation. This interpretation gains further support by the observation, that both ribozymes cleave only a fraction of the long substrate, while cleavage of short substrates went on further (Table 1). To additionally support this result we carried out ligation experiments with both ribozymes providing the two cleavage fragments as substrates (Fig. 7).

Whereas as expected, the reverse-joined ribozyme HP-RJWTC6 readily ligated the two fragments (yield: 11%), very surprisingly no ligation activity could be detected for HP-RJTLB. The ligation reaction has been carried out several times with varied concentrations of the two fragments and of the ribozyme as well as under differing reaction conditions. However, in no case ligation activity could be detected. Obviously, the low activity of the branched ribozyme HP-RJTLB for cleavage of the long substrate S36F5 is not the result of re-ligation. Comparison of HP-RJTLB with HP-RJWTC6 shows that the branched ribozyme HP-RJTLB cleaves all three substrates to a smaller extent than HP-RJWTC6 and the cleaved fraction decreases with the length of substrates (Table 1). This might imply that a fraction of HP-RJTLB is trapped in inactive conformations. With increasing length of the substrate the ability to fold into the required active structure may be decreased, such that only a small fraction of the substrate can be cleaved. Accordingly, also ligation would be hampered with long substrates. Strikingly, cleavage might occur only from temporarily folded species that are insufficiently stable to allow for ligation. Extending the linker that connects the two domains in the branch point might help to improve ribozyme folding in a way that the two domains have more conformational freedom to be

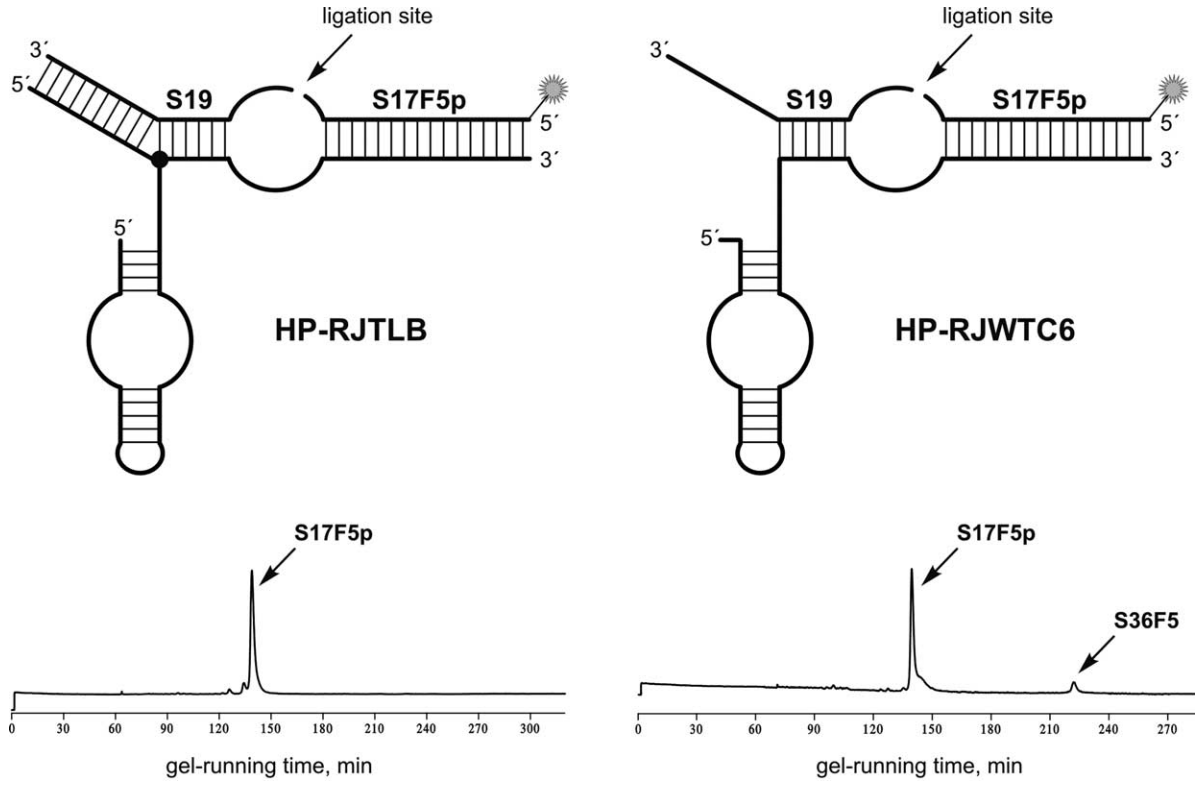

Figure 7. Schematic presentation of the ligation assay and data analysis. The substrate S17F5p carries a 2′,3′-cyclic phosphate and is ligated with S19 to yield the product S36F5.

positioned in an optimal orientation to each other and to interact via a specific net of hydrogen bonds that is known to stabilize the three-dimensional complex.[29]

3. Conclusion

A ribozyme 81 nucleotides in length was prepared by chemical synthesis and the modified nucleoside 2′-deoxy-*N*4-(6-hydroxyhexyl)-5-methylcytidine was introduced in order to create an artificial branch at a pre-defined position of the RNA chain. The branched ribozyme is functional: cleavage rates were only 5-fold lower compared with the corresponding non-branched ribozyme. To the best of our knowledge, HP-RJTLB is the first example of a chemically synthesised artificially branched catalytic RNA. Even though, HP-RJTLB in its present form does not catalyze ligation of RNA fragments and, therefore, is not suitable to be used as building block of a twin ribozyme for RNA repair,[4] the herein presented results demonstrate, that the existing strategies for chemical preparation of RNA allow for the development of new catalytic structures that cannot be prepared enzymatically. This considerably increases the range of structural modification for analysis and functional design of RNA molecules. We expect our results to greatly enhance the prospects of synthetic RNA molecules in molecular biology and biochemistry studies. Further investigations into optimization of the structure of reverse-joined hairpin ribozymes for the twin ribozyme approach[4] are in progress.

4. Experimental

4.1. General methods

NMR studies were carried out on a Bruker AM 300 NMR spectrometer at 300 K using approx. 30 mM sample solutions in $CDCl_3$. ^1H, ^{13}C and ^{31}P NMR spectra were recorded at 300, 75 and 121 MHz, respectively. Chemical shifts were measured in relation to tetramethylsilane ($\delta=0$ ppm) for ^1H NMR and ^{13}C NMR spectra and 85% phosphoric acid ($\delta=0$ ppm) for ^{31}P NMR spectra. Mass spectra (FAB or ESI) of compounds were taken with a Quadrupole Mass Spectrometer HP 5995 A. Analytical HPLC was performed using an Eurospher 100 C18 column (4.6×250 mm, 5 μm) (Knauer GmbH, Germany). Gravity chromatography was performed on a 2.5×15 cm column packed with silica gel 60 (0.063–0.200 mm, Merck, Germany) with an appropriate solvent as eluent. Thin-layer chromatography (TLC) of reaction mixtures and purified compounds was carried out using pre-coated silica gel 60 F_{254} plates (Merck).

4.2. Reagents and solvents

Reagents and solvents for preparation of modified phosphoramidites were purchased from Sigma-Aldrich Chemie GmbH (Germany) and Merck (Germany), fully protected ribonucleoside phosphoramidites and long-chain alkylamine CPG-columns for RNA-synthesis were purchased from Glen Research (USA). Substrate RNAs were 5′-end labelled using 'fluoreprime' fluorescein amidite (Amersham Pharmacia Biotech). Buffers for ribozyme digestion and substrate cleavage were prepared using autoclaved deionized water, filtered through a sterile 0.2 μm pore filter, and stored at −20 °C prior to use.

4.2.1. Preparation of modified phosphoramidite building blocks 5′-*O*-(4,4′-dimethoxytrityl)-4-(1,2,4-triazolyl)-thymidine-3′-*O*-(2-cyanoethyl-*N*,*N*-diisopropylphosphoramidite) 2. 1,2,4-Triazole (780 mg, 11.29 mmol) was suspended in dry CH_3CN (15 ml), with intensive stirring, in an ice bath. Dry triethylamine (1.8 ml, 12.95 mmol) was added followed by dropwise addition of $POCl_3$ (0.24 ml, 2.70 mmol). The mixture was left to react for 45 min and then filtered through cellulose into a solution of 5′-*O*-(4,4′-dimethoxytrityl)-thymidine-3′-*O*-(2-cyanoethyl-*N*,*N*-diisopropylphosphoramidite) (447 mg, 0.60 mmol) in dry CH_3CN (1 ml). After 1 h at room temperature quantitative conversion of the educt into product (TLC analysis) was observed. Ethylacetate (100 ml) was added to the reaction mixture and the organic layer was washed with an equal volume of 10% aqueous $NaHCO_3$ followed by brine. The aqueous solution was back-extracted with ethylacetate. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to dryness in vacuo resulting in yellow oil. The viscous material was purified on a silica gel column under isocratic conditions using $Et_3N/CHCl_3$ (0.5:99.5, v/v) as eluent. The desired fractions were pooled and evaporated to obtain **2** as white foam (392 mg, 82.0%). TLC analysis: R_f (**2**)=0.73 (both isomers) ($AcOEt/Et_3N/CH_2Cl_2$, 34:8:58, v/v). ^1H NMR ($CDCl_3$): $\delta=9.21$ (s, 1H, H-triazolyl), 8.29 (d, 1H, H–C6), 8.01 (d, 1H, H-triazolyl), 7.35–7.20 (m, 9H, H-phenyl), 6.76 (d, 4H, H-phenyl), 6.27 (q, 1H, H–C1′), 4.61 (m, 1H, H–C3′), 4.05 (m, 1H, H–C4′), 3.72 (s, 6H, CH_3O), 3.62–3.45 (m, 1H, H_a-C5′; 2H CH_2OP; 2H H–C *i*-Pr), 3.29 (m, 1H, H_b-C5′), 2.77 (m, 1H, H_a-C2′), 2.56 (t, 1H, H–CHCN), 2.35 (m, 1H, H_b-C2′; 1H, H–CHCN), 1.87, 1.86 (ss, 3H, CH_3–C5), 1.18–0.97 (m, 12H, CH_3 *i*-Pr). ^{13}C NMR ($CDCl_3$): $\delta=158.7$ (C phenyl), 158.1 (C4), 153.9 (C2), 153.3, 146.7 (C triazolyl), 145.0 (C phenyl), 144.2 (C6), 135.2 (C phenyl), 130.2–127.2 (CH phenyl), 117.4 (CH_2CN), 113.4–113.3 (CH phenyl), 105.8 (C5), 87.5, 87.4, 86.9 (Cq, C1′,C4′), 72.1 (C3′), 62.3 (C5′), 58.0 (CH_2OP), 55.2 (OCH_3), 41.2 (C2′), 43.2 (CH_2CN), 24.6 (CH-*i*Pr), 20.2 ($(CH_3)_2$*i*Pr), 16.4 (CH_3–C5). ^{31}P NMR ($CDCl_3$): $\delta=$ 150.6, 150.0. FAB-MS, *m*/*z*: Calcd ($M+Na^+$) 818.87, found 818.40 ($M=C_{42}H_{50}O_7N_7P$).

4.2.2. 2′-Deoxy-5′-*O*-(4,4′-dimethoxytrityl)-*N*4-(6-hydroxyhexyl-(*O*-levulinyl))-5-methyl-cytidine 3′-*O*-(2-cyanoethyl-*N*,*N*-diisopropylphosphoramidite) 3. The modified nucleoside was prepared mainly as described by Horn et al.[11] and converted into the phosphoramidite building block. Briefly, the procedure involved protection of 5′- and 3′-hydroxyl groups of 2′-deoxyuridine followed by conversion of the base into the 4-triazolo derivative. Next, the triazolo group was substituted with 6-amino-hexanol and the alcohol group at the linker was converted into a levulinic acid ester. Finally the 3′-*O*-TBDMS group was removed for preparation of the 3′-*O*-phosphoramidite. 2′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-*N*4-(6-hydroxyhexyl-(*O*-levulinyl))-5-methyl-cytidine 3′-*O*-(2-cyanoethyl-*N*,*N*-diisopropylphosphoramidite) **3** was obtained as light yellow foam (392 mg, 83.2%). TLC analysis: R_f (**3**)=0.66, 0.75

(both isomers) (n-C_6H_{14}/AcOEt/Et_3N, 5:25:2.4, v/v). ^{1}H NMR ($CDCl_3$): δ=7.58 (s, 1H, H–C6), 7.33–7.15 (m, 9H, H-phenyl), 6.75 (d, 4H, H-phenyl), 6.39 (m, 1H, H–C1′), 4.52 (m, 1H, H–C3′), 4.02 (m, 1H, H–C4′), 3.99 (t, 2H, CH_2-Lev), 3.73, 3.72 (ss, 6H, CH_3O), 3.51–3.42 (m, 4H, CH_2; 2H, CH_2OP, 2H H–C i-Pr), 3.22 (m, 2H, H–C5′), 2.70–2.66 (m, 2H, CH_2-Lev), 2.56–2.47 (m, 1H, H_a-C2′; 1H, H–CHCN), 2.31 (t, 1H, H–CHCN), 2.18 (m, 1H, H_b-C2′), 2.12 (s, 3H, CH_3-Lev), 1.55 (m, 4H, CH_2), 1.37 (s, 3H, CH_3-C5), 1.30 (m, 4H, CH_2), 1.22–0.93 (m, 12H, CH_3 i-Pr). ^{13}C NMR ($CDCl_3$): δ=206.8 (Me–CO), 172.8 (O–CO), 163.1 (C4), 158.6 (C phenyl), 156.2 (C2), 144.4 (C phenyl), 137.1 (C6), 135.5 (C phenyl), 130.2–127.0 (CH phenyl), 117.6 (CH_2CN), 113.3–113.2 (CH phenyl), 101.7 (C5), 86.6, 85.5 (Cq, C1′,C4′), 72.1 (C3′), 64.5 (C5′), 58.1 (CH_2OP), 55.3 (OCH_3), 46.9 (C2′), 45.7 (CH_2-linker), 43.2 (CH_2CN), 40.9 (CH_2-linker), 37.9 (CH_2-Lev), 29.9, 29.2 (CH_2-linker), 28.5 (CH_3-Lev), 28.0 (CH_2-Lev), 26.4, 25.6 ($2CH_2$-linker), 24.7–24.5 (CH-iPr), 20.1–19.4 ((CH_3)$_2$iPr), 12.4 (CH_3–C5). ^{31}P NMR ($CDCl_3$): δ=150.1, 149.5. FAB-MS, m/z: Calcd ($M+Na^+$) 965.10, found 965.03 ($M=C_{51}H_{68}O_{10}N_5P$).

4.3. RNA synthesis

Oligoribonucleotides were synthesized by the phosphoramidite method essentially as described previously.[3,30] An automated DNA/RNA synthesizer (Gene Assembler Special, Pharmacia) was used for chain assembly at a 1 μmol scale.

The model oligoribonucleotide SI-SLA5 ($^{AAAAA-}_{CGUG-}$XAA(dT) with X=4-triazolo-dT), was synthesized on a 500 Å CPG support. The modified phosphoramidite **2** was dissolved in dry acetonitrile to give a 0.12 M concentration and filtered through 0.45 μm Teflon filters prior to use. Synthesis was performed 'trityl off'. Phenoxyacetyl groups were used for protection of the amino functions of adenine, cytosine and guanine. Unmodified phosphoramidites were coupled using the standard protocol.[30] The coupling time for **2** was extended from 5 min (standard protocol) to 10 min. The following nucleotides CGUG were coupled without changes to the standard protocol. Prior to synthesis of the side-chain (A)5, the terminal 5′-OH group of the main-chain was acetylated by manually treating the polymer support five times with 100 μl Capping A solution (Ac_2O in pyridine) and 100 μl Capping B solution (1-methylimidazole in pyridine), each turn taking 10 s. The column was washed thoroughly with acetonitrile (5 ml), then removed from the synthesizer and treated with 10 ml of a freshly prepared solution of 0.33 M aminohexanol in acetonitrile for 45 min (solution was slowly passed through the column using a syringe). The column again was washed thoroughly with anhydrous acetonitrile (10 ml), transferred back to the synthesizer and washed again with anhydrous acetonitrile (5 ml). Assembly of the side-chain was carried out following the standard protocol.

For synthesis of the branched ribozyme HP-RJTLB, CPG with a pore size of 1000 Å was used. The branching nucleotide building block **3** was dissolved in dry acetonitrile at a concentration of 0.2 M and filtered through 0.45 μm Teflon filters prior to use. Synthesis was performed 'trityl off'. Benzoyl was used for N-protection with adenine and cytosine, dimethylformamidine with guanine. Unmodified phosphoramidites were coupled using the standard protocol.[30] For coupling of the branching nucleotide the following changes to the protocol were made: a 40-fold excess of phosphoramidite over the solid phase was used and the coupling time was extended from 5 to 24 min. The coupling reaction was carried out in two steps: first, 100 μl of the 0.2 M phosphoramidite solution were cycled over the column and coupling was allowed to proceed for 12 min. Immediately after this, the same amount of fresh phosphoramidite solution was transferred to the column and the coupling reaction was extended for another 12 min. The following nucleotides (segment B) were coupled without changes to the standard protocol. Prior to synthesis of segment C (see Figs. 2 and 4), the terminal 5′-OH group of segment B was acetylated by treating the polymer support manually five times with 100 μl Capping A solution (Ac_2O in pyridine) and 100 μl Capping B solution (1-methylimidazole in pyridine), each turn taking 3 s. The column was washed thoroughly with acetonitrile (5 ml), then removed from the synthesizer and treated with 6 ml of a freshly prepared solution of 0.5 M hydrazine hydrate in pyridine/acetic acid (4:1, v/v) for 5 min (solution was slowly passed through the column using a syringe). The column again was washed thoroughly with anhydrous acetonitrile (7 ml) and transferred back to the synthesizer. Assembly of segment C was carried out again following the standard protocol.

Fluorescein labelled RNA substrates (S14F5, S24F5 and S36F5) were synthesized on CPG 500 Å, as described.[30]

Deblocking was performed using saturated methanolic ammonia for 22 h at 25 °C with the branched RNAs SI-SLA5 and HP-RJTLB or over 12 h at ambient temperature with substrate RNAs S14F5, S24F5 and S36F5. Removal of the 2′-O-silyl-protecting groups was achieved by treating the samples with triethylamine trihydrofluoride in DMF (3:1, v/v, 0.8 ml) for 1.5 h at 55 °C. The reaction was quenched by addition of water (0.2 ml) and the RNA chains were precipitated from n-butanol.

The branched RNAs were purified by 20% denaturing (7 M urea) PAGE (acrylamide/bis-acrylamide 19:1) on 8×10 cm glass plates at 60 °C in TBE buffer at 100 V. The gel was soaked in ethidium bromide solution; visualization of RNA was achieved by irradiation with UV-light (254 nm). The band corresponding to the desired product was excised from the gel and eluted with 2 M $LiClO_4$ overnight at room temperature. The oligonucleotide then was precipitated from acetone. Fluorescein labelled RNA substrates were purified using 20% denaturing polyacrylamide gels. Bands corresponding to the desired products were visualized both at 254 and 366 nm, excised from the gel and treated as described above.

4.4. Nucleoside composition analysis

Oligoribonucleotides (0.08 O.D.$_{260}$) were dissolved in 10 μl of nuclease P1 buffer (40 mM AcONa, 2 mM $(AcO)_2Zn$ pH 5.3) and a freshly prepared solution of nuclease P1 from Penicillium citrinum in the same buffer (10 μl, 10 μg/ml) was added. After incubation at 37 °C for 12 h, 10× dephosphorylation buffer (4 μl), alkaline phosphatase from

calf intestine (3 μl, 3 U) and water (13 μl) were added to obtain a final volume of 40 μl. Reaction was allowed to proceed for 3 h at 37 °C. Individual reaction mixtures were analysed by HPLC using a RP-18 column with buffer A (0.1 M ammonium acetate, pH 6.5), and a gradient of buffer B (0.1 M ammonium acetate, pH 6.5, 60% CH_3CN): 0–15% B over 20 min, 15–40% B over 30 min and 40–100% over 2 min at 37 °C and a flow rate of 1 ml/min.

Peak areas in conjunction with extinction coefficients at 260 nm (C: 7.4, U: 9.9, G: 11.5, A: 15.4, d*T*: 8.7, in l/mmol cm) were used to calculate relative concentrations of monomers.

4.5. Cleavage reactions

Cleavage reactions were performed under single-turnover conditions and each experiment was repeated at least once. A mixture of ribozyme (20–220 nM) and substrate (10 nM) in Tris–HCl buffer (15 mM, pH 7.5) was heated at 90 °C for 1 min followed by incubation at 32 °C for 15 min. Magnesium chloride was added to a concentration of 10 mM and the mixture was left at 32 °C for another 10 min. The cleavage reaction was started by addition of spermine (pH 7.5, final concentration 2 mM). The final volume of the reaction mixture was 20 μl. Aliquotes (3 μl) were removed at six suitable time intervals and the reaction was quenched by addition to 3 μl of stop-mix (10 mM EDTA in 90% formamide). Samples were heated to 90 °C for 1 min, then immediately cooled on ice and subsequently subjected onto a 15% denaturing gel (7 M urea) using an ALF DNA sequencer as described previously.[3] Initial rates of reactions were obtained from a plot of product formation against time within the linear phase of reaction. Kinetic parameters were determined from linear curve fitting using Eaddie–Hofstee plots.

4.6. Ligation reactions

For ligation the two following substrates were used: GUC CUC UUG CAC GGU CCG C (S19) and 5′-fluorescein labelled Φ-CAG AAA UCU GGC UCA CAcp (S17F5p), which carries a 2′, 3′-cyclic-phosphate group. Ligation was performed with equimolar concentrations of substrates and ribozyme (200 nM). A mixture of ribozyme and 19-mer in Tris–HCl buffer (15 mM, pH 7.5) was heated at 90 °C for 1 min followed by incubation at 32 °C for 15 min. Then the 17-mer and $MgCl_2$ (final concentration of $MgCl_2$ 10 mM) were added and incubated at 32 °C for another 10 min. The reaction was started by addition of spermine (pH 7.5) to a concentration of 2 mM. The final volume of the reaction mixture was 20 μl. Aliquotes (3 μl) were removed after 30, 60 and 120 min. The reaction was quenched by pipetting the aliquots into 3 μl of stop-mix (10 mM EDTA in 90% formamide). Samples were heated to 90 °C for 1 min, then immediately cooled on ice and subsequently subjected onto a 15% denaturing gel (7 M urea) using an ALF DNA sequencer as described.[3]

Acknowledgements

We gratefully acknowledge financial support by the DFG and the Pinguinstiftung.

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Studies on montmorillonite K10-microwave assisted isomerisation of Baylis–Hillman adduct. Synthesis of *E*-trisubstituted alkenes and synthetic application to lignan core structures by vinyl radical cyclization

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Received 18 March 2004; revised 28 June 2004; accepted 22 July 2004

Available online 28 August 2004

Abstract—The isomerisation of acetates from the Baylis–Hillman adducts with Mont.K10 clay-microwave combination furnished *E*-trisubstituted alkenes in high yield. The simple Baylis–Hillman adducts with trimethyl orthoformate and unsaturated alcohols under clay catalytic condition gave densely functionalised-isomerized products under solvent free condition. Application of the propargyl derivatives thus obtained from the isomerisation of the Baylis–Hillman adducts with propargyl alcohol has been demonstrated in the synthesis of lignan core structures by tri-*n*-butyltin hydride mediated vinyl radical cyclization.

1. Introduction

Synthetic methodologies based on green chemistry processes are increasingly of interest in organic synthesis.[1] Amongst the several green chemistry processes known, methodologies based on eco-friendly clay catalysts play an important role in the manufacture of industrial products and in organic synthesis.[2] The use of clays in the later and its application as a catalyst for a number of organic reactions are well documented.[3–5] The Montmorillonite K10 and its structurally modified clays such as ion-exchanged and pillared clays, are known to act as both Bronsted and Lewis acid catalysts for a variety of industrially important organic reactions.[2] The clay catalysts are known as eco-friendly acid catalysts which have potential for replacing the conventional mineral acids and are non-pollutants. The advantages of the clay-catalyzed reactions are that they are generally mild, solvent free and easy work-up. The Baylis–Hillman reaction is one of the important carbon–carbon bond forming reactions and has been used in organic synthesis for the preparation of a variety of compounds having diverse functional groups. These adducts have been used as the starting point for a number of synthetic organic transformations.[6–14] Stereoselective construction of (*E*)-trisubstituted alkene is one of the more difficult tasks in organic synthesis and only a few methods are known in the literature.[9,10,15] The isomerisation of acetates of the Baylis–Hillman adducts catalyzed by TMSOTf,[9,10] trifluoroacetic acid,[11] benzyl trimethylammonium fluoride[12] have appeared in the literature. Montmorillonite K10-microwave combination has been utilized for carrying out many organic transformations as a catalyst.[16–18]

In continuation of our research on clay catalysis[19–23] in organic synthesis, herein we give an account on the mont-K10-microwave assisted stereoselective isomerisation of acetates of Baylis–Hillman adducts, a one-pot protection-isomerisation with trimethyl orthoformate and unsaturated alcohols. A synthetic application of propargyl derivatives of the Baylis–Hillman adduct thus obtained, in the synthesis of lignan core structures through a vinyl radical cyclization, have also been explored.

2. Results and discussion

2.1. Isomerisation of acetates of the Baylis–Hillman adducts

The general isomerisation studies of the acetates of Baylis–Hillman adduct is depicted in Scheme 1. The Baylis–Hillman adducts **1a–o** and its acetate adducts **2a–p** were prepared according to the literature.[9] The preliminary study was initiated by stirring acetate **2a** with 50% w/w montmorillonite K10 clay in CH_2Cl_2 at room temperature

Keywords: Baylis–Hillman adducts; Montmorillonite K10-microwave; Radical cyclization.
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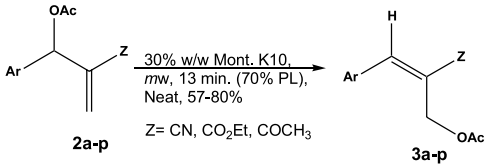
doi:10.1016/j.tet.2004.07.067



Scheme 1. Isomerization of acetates of Baylis–Hillman adducts catalysed by Mont. K10-microwave.

for 48 h afforded the starting material and the deacetylated product (20%). Heating the same reaction mixture at reflux temperature for 24 h furnished only the starting material. However, when a slurry of the acetate **2a** with 50% w/w mont-K10 clay without any solvent was irradiated in a microwave oven for 6 min, a clean isomerised product **3a** was obtained in 60% yield (~10% decomposition to aldehyde) as determined by ^{1}H NMR spectroscopy. Among the several variations tested to optimize the condition,[22] the condition involving acetate **2a** with 30% w/w of mont-K10 clay, 70% microwave power level (PL) and 13 min. irradiation time was found to be the best and yielded the clean isomerised product **3a** (in 9:1, *E*:*Z* isomer) in 74% after column purification. It should be noted that the microwave irradiation of acetate **2a** under similar conditions without any clay furnished the starting material quantitatively confirming the importance of clay catalyst for this reaction. The simple adduct **1** under similar conditions furnished only 20% of the isomerized product with remaining decomposed products. Hence, the acetate protection of the Baylis–Hillman adduct is essential for good yields.

In order to demonstrate the general nature of this reaction, we chose a variety of acetates of Baylis–Hillman adduct **2b–p**, which underwent a facile isomerisation with the mont-K10-microwave combination to give clean isomerised products **3b–p** in good yield. Yields of the adduct bearing nitrile and carbonyl groups were lower than that of the ester group and needed a longer irradiation time with higher power level (100% PL). The isomer ratios (*E*:*Z*) of the products were estimated by ^{1}H NMR spectroscopy and the results are summarized in Table 1.

The efficiency of commercial montmorillonite-K10 clay (2:1 layer type, available from Aldrich Co.)[2,3] in this reaction was compared with Fe^{3+}-mont-K10[24] (an ion exchanged clay) and an acid treated regional natural kaolinite clay.[25–26] The use of Fe^{3+}-mont-K10 was found to be as good as montmorillonite K10 clay, while with acid treated regional natural kaolinite (1:1 layer type) clay, the reaction was unsuccessful and starting material was recovered quantitatively. The reason for this observation with natural kaolinite clay[25,26] may be that the interlayer distance is <7 Å compared to Mont. K10 clay whose interlayer gap is 10 Å.[2,3] Hence, due to the small interlayer distance in the acid treated regional natural kaolinite clay,[26] the substrate molecules are presumably unable to enter the interlayer space where the reactions are believed to occur and hence the reaction found failed. It should be noted that we have tested the kaolinite clay catalyst only for the isomerisation of the acetates of the Baylis–Hillman adduct, which with Mont. K10 clay catalyst furnished desired products in good yield and we had not examined the smaller substrates for the comparative studies. The results are summarized in Table 2.

2.2. One-pot protection-isomerisation of Baylis–Hillman adducts with trimethyl orthoformate

Encouraged by the preliminary results, we were interested in the possibility of a one-pot protection-isomerisation of Baylis–Hillman adducts without acetate protection using a similar catalysts system with trimethyl orthoformate. The results are impressive and furnished a highly stereoselective

Table 1. Mont. K10 clay[a]-microwave assisted isomerisation of Baylis–Hillman acetate adducts **2a–p**

Entry	Substrate	Ar	Z	Condition[b]	Product (*E*/*Z*)[c]	Yield (%)[d]
1	**2a**	Ph	–CO_2Et	Clay, MW, 13 min	**3a**, 9:1	74
2	**2b**	Ph	–CN	Clay, MW, 15 min	**3b**, 9.5:0.5	68
3	**2c**	Naphth-1-yl	–CO_2Et	Clay, MW (80% PL), 13 min	**3c**, 9.4:0.6	70
4	**2d**	Naphth-1-yl	–CN	Clay, MW, 16 min	**3d**, 9.2:0.8	62
5	**2e**	4-Cl–Ph–	CO_2Et	Clay, MW, 13 min	**3e**, 9.3:0.7	60
6	**2f**	4-Cl–Ph–	CN	Clay, MW (80% PL), 16 min	**3f**, 9.5:0.5	57
7	**2g**	–Ph	$COCH_3$	Clay, MW, 13 min	**3g**, 9.6:0.4	59
8	**2h**	4-Me–Ph	CO_2Et	Clay, MW, 13 min	**3h**, 9:1	71
9	**2i**	4-Me–Ph	CN	Clay, MW (80% PL), 16 min	**3i**, 8:2	66
10	**2j**	2,4-Cl_2–Ph	CO_2Et	Clay, MW, 13 min	**3j**, 9.2:0.8	72
11	**2k**	2,4-Cl_2–Ph	CN	Clay, MW, 16 min	**3k**, 8.7:1.3	70
12	**2l**	4-MeO–Ph	CO_2Et	Clay, MW (80% PL), 13 min	**3l**, 9.6:0.4	80
13	**2m**	4-MeO–Ph	CN	Clay, MW, 16 min	**3m**, 9.2:0.8	76
14	**2n**	Naphth-2-yl	CO_2Et	Clay, MW, 13 min	**3n**, 9.1:0.9	68
15	**2o**	Naphth-2-yl	CN	Clay, MW (80% PL), 16 min	**3o**, 9.5:0.5	62
16	**2p**	4-Me–Ph	$COCH_3$	Clay, MW, 13 min	**3p**, 9.1:0.9	65

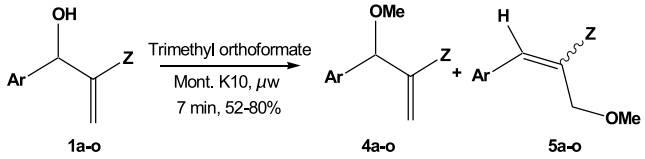
Microwave irradiation was carried out on a KenStar microwave oven with 70% PL.
[a] Montmorillonite K10 clay was dried at 85 °C for 2 h before each use.
[b] 30% w/w montmorillonite-K10 clay was used in each case.
[c] *E*/*Z*—ratio was assigned based on ^{1}H and ^{13}C NMR.
[d] After column purification.

Table 2. Comparison of mont-K10[a], Fe^{3+}-Mont.-K10[a] and acid treated regional natural kaolinite clay catalysts on isomerisation of acetate of the adduct **2a** into **3a**

Clay	Condition[b]	*E*/*Z*—ratio[c]	Yield (%)[d]
Montmorillonite-K10	30% w/w clay, MW, 13 min	9:1	74
Fe^{3+}-mont. K10	30% w/w clay, MW, 6 min	9:1	72
Natural kaolinite clay	30% w/w clay, MW, 8 min	—	No reaction

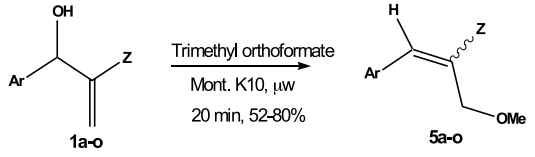
[a] All the clays were dried at 85 °C for 2 h before each use.
[b] Microwave irradiation was carried out on a KenStar microwave oven (70% PL).
[c] *E*/*Z*—ratio was estimated based on ^{1}H and ^{13}C NMR.
[d] After column purification.

E-alkene (99.9%) in good yield. The advantages of this methodology are **1**. Avoiding adducts bearing acetate protection (AcCl, Pyridine) **2**. The resulting isomer is highly *E*-selective (99.9%) and **3**. The procedure is one-pot and mild condition. The general one-pot protection-isomerisation studies are outlined in Scheme 2.



Scheme 2. Protection Isomerization of Baylis–Hillman adduct with trimethyl orthoformate under clay catalyst-microwave condition.

A slurry of the adduct **1a** with 30% w/w mont-K10 clay, trimethyl orthoformate without any solvent was irradiated in a microwave [100% PL] oven for 7 min, a mixture of products were obtained in 70% yield. The products were separated and identified as **4a** along with ~10% of the isomerised product **5a**. However, when the same was irradiated for 20 min with 100% PL yielded the only required isomerised product **5a** (in 99.8:0.2, *E*:*Z* isomer) in 74% yield after column purification (Scheme 3).



Scheme 3. Isomerization of Simple Baylis–Hillman adduct with trimethyl orthoformate.

As anticipated, the other Baylis–Hillman adducts **1b–o** underwent a facile isomerisation with mont-K10-microwave combination to give clean isomerised products **5b–o** in good yield. We observed that in all these cases, the yields of adduct with nitrile were lower than that of the ester functional group at the activated alkene and needed a longer irradiation time (22 min). The results are summarized in Table 3. Hence, the isomerisation reaction was very smooth without acetate protection with trimethyl orthoformate. Basavaiah et al.[10] have reported that the Baylis–Hillman adduct bearing CN substitution undergoes isomerisation in better in good yield (50–68%) under sulfuric acid conditions, while Kim et al.[11] have reported that the Baylis–Hillman adducts bearing CO_2Et substitution undergoes isomerisation better yield (51–72%) than that of substrates bearing CN substitution(27–40%) with trifluoroacetic acid conditions. It should be noted that the present clay catalyst condition holds good for both the cases furnished better yield and higher *E*-selectivity.

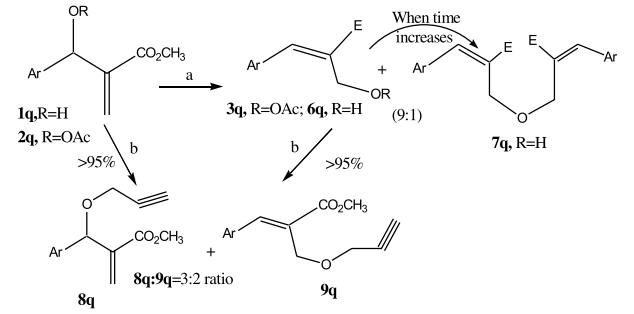
2.3. Isomerisation of the Baylis–Hillman adduct with unsaturated alcohols

We examined the behaviour of the Baylis–Hillman adduct with unsaturated alcohols under clay catalytic condition (Scheme 4). The results were good and yielded densely functionalised propargyl derivative of the Baylis–Hillman adduct.[23] Heating a slurry 75 °C, 1.5 h) made with the adduct **1q**, 2 equiv of propargyl alcohol and 60% w/w Mont. K10 without any solvent furnished ether **8q**[27] and its

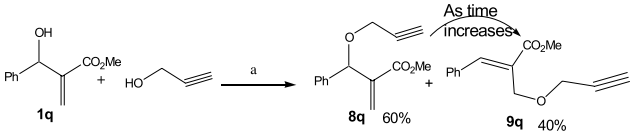
Table 3. Montmorillonite-K10[a]-Microwave assisted one-pot protection-isomerisation of the Baylis–Hillman adducts **1a–o** with trimethyl orthoformate

Entry	Reactant	R	Z	Condition[b,c]	Product[d]	Yield (%)[e]
1	**1a**	Ph	CO_2Et	Clay, MW, 20 min	**5a**	74
2	**1b**	Ph	CN	Clay, MW, 22 min	**5b**	70
3	**1c**	Naphth-1-yl	CO_2Et	Clay, MW, 21 min	**5c**	72
4	**1d**	Naphth-1-yl	CN	Clay, MW, 23 min	**5d**	60
5	**1e**	4-Cl–Ph–	CO_2Et	Clay, MW, 19 min	**5e**	62
6	**1f**	4-Cl–Ph–	CN	Clay, MW, 20 min	**5f**	52
7	**1h**	4-Me–Ph	CO_2Et	Clay, MW, 18 min	**5h**	70
8	**1i**	4-Me–Ph	CN	Clay, MW 21 min	**5i**	64
9	**1l**	4-MeO–Ph	CO_2Et	Clay, MW, 20 min	**5l**	80
10	**1m**	4-MeO–Ph	CN	Clay, MW 21 min	**5m**	77
11	**1n**	Naphth-2-yl	CO_2Et	Clay, MW, 21 min	**5n**	69
12	**1o**	Naphth-2-yl	CN	Clay, MW 22 min	**5o**	63

[a] Montmorillonite K10 clay was dried at 85 °C for 2 h before each use.
[b] Microwave irradiation was carried out on a KenStar microwave oven with 100% PL.
[c] 30% w/w montmorillonite-K10 clay was used in each case.
[d] *E*/*Z*—ratio was assigned based on ^{1}H and ^{13}C NMR.
[e] After column purification.



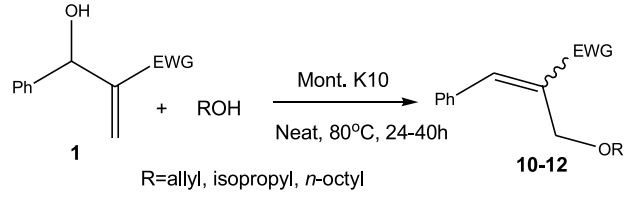
Scheme 4. Conditions: (a) 60% w/w Mont, K10, neat, 2 h 75 °C; (b) w/w% Mont.K10, propargyl alcohol, neat, 6 h, 75 °C.



Scheme 5. Conditions: (a) 60% w/w Mont, K10, neat, 2.5 equiv propargyl alcohol, neat, 75 °C, 2 h.

Table 4

Time (h)	8q (%)	9q (%)
6	42	58
15	25	75
22	<5	>95
24	<1	>99



Scheme 6.

isomerised product **9q** (99.9; *E*-selectivity)[28] in 90% combined yield and in 3:2 product ratio.[29] The reaction proceeded smoothly and furnished pure products as indicated. The compounds were separated by silica gel column chromatography and characterized by NMR spectroscopy.

The effect of the reactivity of the Baylis–Hillman adduct **1q**, its acetate protected adduct **2q** and their isomerised compounds **6q** and **3q** with propargyl alcohol under the reaction condition described above are compared and all the reactions furnished compounds **8q** and **9q**. All these reactions furnished the desired products almost in the same yield and product ratio (3:2).

Interestingly, the simple Baylis–Hillman adducts **1q** and **2q** underwent isomerisation and provided an excellent yield (95%) of compounds **8q** and **9q**. Compounds **6q** and **3q** with propargyl alcohol under similar conditions furnished **8q** and **9q** in excellent yield (>95%) and in a ratio of 3:2. The product ratio of compounds **8q** and **9q** was determined by proton NMR spectroscopy as integration of the protons at δ 5.51 and 7.92 respectively. Therefore, the nucleophilicity of the propargyl alcohol on the isomerised **6q** and **3q** and unisomerized Baylis–Hillman adducts (**1q** and **2q**) are identical since they afforded same products **8q** and **9q** in the same product ratio (3:2). Hence, the experiment reveals that the reaction of propargyl alcohol with simple unisomerized Baylis–Hillman adducts provide the required products in excellent yield. Hence, no protected/isomerised starting materials are necessary to effect this transformation. We also observed that the simple adduct **1q** with 60% w/w clay at 75 °C for 2 h under neat condition furnished the isomerised compound **6q** and ether **7q** in 60% combined yield and in a 9:1 ratio. As the reaction time increases, ether **7q** was found as sole product. The details are shown in Scheme 4. The formation of the only isomerised product **9q** with propargyl alcohol over **8q** under the conditions described above can be achieved by increasing the reaction time (Scheme 5). The complete conversion of **8q** into isomerised product **9q** was observed at a reaction time 24 h. The distribution of products with respect to reaction time is summarized in Table 4.

In order to demonstrate the general nature of this reaction, we have chosen three different alcohols and found that the reactions are clean and high yielding (**10**–**12**) under the optimized conditions described above (Scheme 6). However the reaction with higher boiling alcohols yielded only a complex reaction mixture and/or starting materials. The results are summarized in Table 5. The Mont. K10 clay recovered from the reaction mixture by filtration can be recycled three times without losing its activity by activating the clay at 100 °C for 3 h.

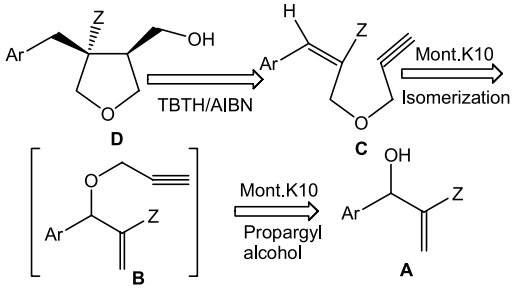
2.4. Synthetic application of the propargyl derivative of Baylis–Hillman adduct. Synthesis of lignan cores via vinyl radical cyclization

The lignans are common and structurally diverse group of

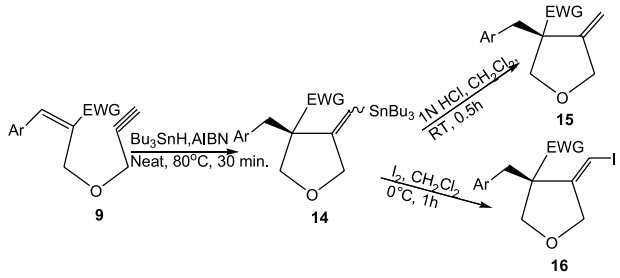
Table 5. Isomerisation of Baylis–Hillman adduct with alcohols[a,b,c]

Entry	Reactant	Alcohol	Z	Product	Yield (%)[d]
1	**1a**	Allyl	CO_2Et	**10a**	94
2	**1q**	Allyl	CO_2Me	**10q**	95
3	**1q**	Isopropyl	CO_2Me	**11q**	95
4	**1b**	*n*-Octyl	CN	**12b**	98
5	**1q**	*n*-Octyl	CO_2Me	**12q**	97

[a] Montmorillonite K10 clay was dried at 100 °C for 1 h before each use.
[b] 60% w/w Mont.-K10 clay was used in each case.
[c] Mont. K10, 75 °C, 24 h.
[d] After column purification.



Scheme 7. Retrosynthetic analysis.



Scheme 8.

plant natural products of phenyl propionoid origin, displaying physiological functions in planta, particularly in plant defence, in human nutrition and medicine, given their extensive health protective and curative properties.[30] A major sub-group of lignans such as lariciresinol, wikstromol, olivil and dihydrosesamine are comprised of di, tri and tetra substituted tetrahydrofurans.[30,31] Substituted tetrahydrofurans are the main constituents of many naturally occurring compounds including furanolignan and several methods are known for its synthesis.[32] A few reports are known using radical reactions for the construction of lignan cores[33,34] and other interesting routes[35] for the synthesis of lignan natural products as well.

The propargyl derivatives of the Baylis–Hillman adduct are suitable substrates for the construction of lignan core structures by a radical cyclization protocol. A key synthetic strategy is depicted in Scheme 7. The phenyl propionoid bearing furanolignan core **D** can be achieved by a 5-*exo*-trig vinyl radical cyclization of the alkenyl propargyl ether **C**. Compound **C** in turn can be synthesized from the compound **B** through a one-pot protection-isomerisation reaction of the Baylis–Hillman adduct **A** with propargyl alcohol catalyzed by Mont. K10 clay.[23]

The construction of spiroacetals from enyne ethers,[36a] α-methylene-γ-butyrolactone from allyl, crotyl propiolates,[36b] carbocycles and heterocyclics from dienes and enynes[36c] by a tin-mediated radical cyclization methods are known in the literature.

The synthetic study is represented in Scheme 8. The details of the preparation of enenyne ethers **9a–t** from adduct **1a–t** under clay catalytic condition is given in Table 6.

Radical cyclization of the alkenyl propargyl ether **9q** with 1.5 equiv of freshly distilled tri-*n*-butyltin hydride,[37] and a catalytic amount of azobisisobutyronitrile (AIBN) at 85 °C without any solvent under an inert atmosphere afforded crude vinylstannane **14a** through a 5-*exo*-trig cyclization process. The crude vinylstannane obtained was subjected to the protiodestannylation (without purification) with 1 N HCl in ether at room temperature for 4 h to give the cyclized product **15a** in 95% yield after column purification.

Table 6. Preparation of enyne ethers **9a–t** with propargyl alcohol

Entry	Reactant	Ar	Z	Product	Yield (%)
1	**1a**	C_6H_5	CO_2Et	**9a**	92
2	**1b**	C_6H_5	CN	**9b**	90
3	**1e**	4-Cl–C_6H_4	CO_2Et	**9e**	91
4	**1f**	4-Cl–C_6H_4	CN	**9f**	89
5	**1i**	4-Me–C_6H_4	CN	**9i**	86
6	**1m**	4-MeO–C_6H_4	CN	**9m**	72
7	**1q**	C_6H_5	CO_2Me	**9q**	95
8	**1r**	4-Cl–C_6H_4	CO_2Me	**9r**	90
9	**1s**	4-Me–C_6H_4	CO_2Me	**9s**	85
10	**1t**	4-MeO–C_6H_4	CO_2Me	**9t**	80

Table 7. Radical cyclization of enyne ethers **9a–t**

Entry	Reactant	Ar	Z	Product	Yield (%)
1	**9a**	C_6H_5	CO_2Et	**15a**	95
2	**9b**	C_6H_5	CN	**15b**	92
3	**9e**	4-Cl–C_6H_4	CO_2Et	**15e**	96
4	**9f**	4-Cl–C_6H_4	CN	**15f**	96
5	**9i**	4-Me–C_6H_4	CN	**15i**	94
6	**9m**	4-MeO–C_6H_4	CN	**15m**	94
7	**9q**	C_6H_5	CO_2Me	**15q**	95
8	**9r**	4-Cl–C_6H_4	CO_2Me	**15**r	97
9	**9s**	4-Me–C_6H_4	CO_2Me	**15s**	92
10	**9t**	4-MeO–C_6H_4	CO_2Me	**15t**	90

Table 8. Comparative NMR values of cyclized products

Cyclized products		Chemical shifts (δ) and coupling constants (J Hz)			
		C-2 protons(2H)	C-5 protons (2H)	Benzyl-H(2H)	Olefin-H
CO_2Me Substituted	Stannylated	d at δ 3.84 and 4.22 J=9.3 Hz	s δ 4.24	d at δ 2.78 & 3.33 J=13.7 Hz	s (1H), δ 6.1
	Destannylated **15a**	d at δ 4.0 and 4.24 J=9.3 Hz	d, δ 4.39 J=2.19 Hz	d at δ 2.89 & 3.34 J=13.7 Hz	s (1H), δ 5.13 t (1H), δ 5.35, J=2.4 Hz
	Iodo destannylated **16**	d at δ 4.05 and 4.25 J=9.3 Hz	dd at δ 4.31and 4.35 J=10.5, 2.6 Hz	d at δ 2.96 & 3.24 J=13.6 Hz	t (1H) δ 6.40 J=2.6 Hz
CN Substituted	Stannylated	d at δ 3.88 and 4.01, J=8.9 Hz	d ABq at δ 4.4 J=13.3, 2.4 Hz	s (2H), at δ 2.97	t (2H) δ 6.05, J=2.4 Hz
	Destannylated **15b**		d ABq at δ 4.4 J=13.3, 2.3 Hz		d at (2H) δ 5.2, J=2.3 Hz

Similarly, the corresponding nitrile substituted cyclized product **15b** was obtained in 92% yield from the enenyne ether **9b**. The ester group and or nitrile functional groups are available in the product for further manipulations on the tetrahydrofuran ring. To functionalize the vinylstannanes **14a**, treatment of the crude vinylstannane with iodine[38] in dichloromethane at 0 °C for 1 h afforded the iodo derivative **16** in quantitative yield as a solid. Similarly, following the same reaction sequence and experimental conditions other adducts **9e–t** bearing *p*-chlorophenyl, *p*-tolyl, *p*-anisyl aromatic moieties furnished the corresponding cyclized products **15e–t** in excellent yield (90–97%). The results are summarized in Table 7. All the new compounds were characterized by spectral and analytical data. The relative stereochemistry and structural determination of the cyclized products were assigned based on the detailed NMR analysis and in comparison with the literature report.[30,31] The benzyl proton of the compound **14a** showed two doublets at δ 2.78 and 3.33 due to geminal coupling while in the compound **14b** it appeared as a singlet at δ 2.97. The coupling constant of benzyl proton in the compound **14a** was found to be 13.7 Hz and is the same as that of literature known furanolignans.[30] The C-5 protons in **15a** and **15b** appeared as triplet and doublet of doublet at δ 4.39 and δ 4.3 and δ 4.4, respectively. Hence it is evident that in the compound **15b**, the allylic protons have considerable coupling with the vinylic protons in addition to geminal coupling. To confirm this observation, in the iodinated compound **16**, the allylic proton appeared as doublet of doublet while the same proton is appeared as triplet in the corresponding stannylated product (Table 8).

In conclusion, we have demonstrated the usefulness of montmorillonite K10 clay-microwave combination as an alternative, useful, speedy and efficient catalyst for the isomerisation of a variety of acetates of Baylis–Hillman adducts and with unsaturated alcohols which provides densely functionalised (*E*)-alkenes. We have also demonstrated the usefulness of same catalysts system for a one-pot protection isomerisation of a variety of Baylis–Hillman adducts with trimethyl orthoformate. Further, we showed the application of the propargyl derivative of the Baylis–Hillman adduct to the synthesis of furanolignan core structures by adopting tri-*n*-butyltin hydride mediated vinyl radical cyclization protocol as a key step. This methodology suggests that by incorporating suitably substituted propargyl alcohol at the isomerisation step, followed by radical cyclization would directly furnish the cores of furanolignan natural product. Studies on the total synthesis of lariciresinol and related natural products and use of clay catalytic conditions for other systems are being pursued in our laboratories.

3. Experimental

3.1. General consideration

All experiments were carried out in oven-dried glassware. Analytical thin layer chromatography was performed on silica gel TLC plates. Purification by gravity column chromatography was carried out using silica gel (100–200 mesh). Mixtures of ethyl acetate and hexane and pure ethyl acetate were used as eluent as required. Melting points were recorded on Aldrich Meltemp-II and are reported without corrections. IR spectra were run on a Nicolet (impact 400D FT-IR) spectrophotometer or Bomem MB-Series FT-IR spectrophotometer. NMR spectra were obtained using chloroform-d as solvent on Bruker DPX 300 MHz NMR spectrometer. Chemical shifts are given in δ scale with TMS as internal reference. HRMS were measured at the JMS 600 JEOL Mass Spectrometer. Micro analyses were performed at the Perkin–Elmer Series II 2400 analyser. Yields refer to quantities obtained after chromatography. Solvents used are reagent grade and were purified before use according to the literature procedure.

3.2. Typical experimental procedure for isomerisation of acetates of Baylis–Hillman adducts

A mixture of the acetates of Baylis–Hillman adducts (200 mg, 0.8 mmol) and montmorillonite K-10 (60 mg, 30% w/w of the adduct) was taken in a stoppered 25 mL conical flask and irradiated in the microwave oven (70% power mode) for 13 min. The mixture was cooled to room temperature and treated with CH_2Cl_2 (10 mL). Montmorillonite K-10 clay was recovered by filtration and washed with CH_2Cl_2 (2×5 mL). The solvent was removed in vacuo and the crude mixture was purified by silica gel column chromatography using petroleum ether–ethyl acetate (92:8) to give pure colourless isomerised products in 9:1 (*E*:*Z*) isomers as estimated by ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz).

3.2.1. Ethyl (2*E*)-2-acetoxymethyl-3-phenylprop-2-enoate (3a). Colourless oil; yield: 74%; IR(neat) ν_{max}: 1744, 1726, 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35 (t, 3H, J=7.1 Hz), 2.10 (s, 3H), 4.31 (q, 2H, J=

7.1 Hz), 4.95 (s, 2H), 7.39 (s, 5H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.25, 20.86, 59.22, 61.03, 126.77, 128.64, 129.37, 129.47, 134.23, 144.98, 166.57, 170.37. Mass spectra *m/z*: 248 (M^+). Elemental analysis: Calcd for $C_{14}H_{16}O_4$: C, 67.73%, H, 6.50%. Found: C, 67.60%, H, 6.42%.

3.2.2. (2*E*)-2-Acetoxymethyl-3-phenyl prop-2-enenitrile (3b). Colourless oil; yield: 68%; IR(neat) ν_{max}: 2213, 1748, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.16 (s, 3H), 4.82 (s, 2H), 7.23 (s, 1H), 7.45 (m, 3H), 7.79 (m, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 20.51, 65.02, 105.88, 117.04, 128.58, 128.86, 130.75, 132.16, 146.90, 169.76. Mass spectra *m/z*: 201 (M^+). Elemental analysis: Calcd for $C_{12}H_{11}NO_2$: C, 71.63%, H, 5.51%, N, 6.96%. Found: C, 71.60%, H, 5.44%, N, 6.90%.

3.2.3. Ethyl (2*E*)-2-acetoxymethyl-3-naphth-1-ylprop-2-enoate (3c). Colourless oil; yield: 70%; IR(neat) ν_{max}: 1744, 1728, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.36 (t, 3H, J=7.1 Hz), 2.09 (s, 3H), 4.31 (q, 2H, J=7.1cHz), 4.82 (s, 2H), 7.31–7.98 (m, 7H), 8.31 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 13.96, 20.55, 59.32, 60.92, 124.39, 125.25, 126.21, 126.61, 127.27, 128.54, 129.49, 131.60, 132.82, 133.36, 142.82, 166.13, 170.15. Mass spectra *m/z*: 298 (M^+). Elemental analysis: Calcd for $C_{18}H_{18}O_4$: C, 72.47%, H, 6.08%. Found: C, 72.40%, H, 6.01%.

3.2.4. (2*E*)-2-Acetoxymethyl-3-naphth-1-ylprop-2-enenitrile (3d). Colourless oil; yield: 62%; IR(neat) ν_{max}: 2214, 1745, 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.16 (s, 3H), 4.79 (s, 2H), 7.51–8.2 (m, 8H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 20.52, 65.02, 105.85, 117.04, 124.52, 125.01, 126.43, 126.93, 128.61, 129.10, 129.83, 131.33, 131.62, 133.24, 146.15, 170.15. Mass spectra *m/z*: 251 (M^+). Elemental analysis: Calcd for $C_{16}H_{13}NO_2$: C, 76.48%, H, 5.21%, N, 5.57%. Found: C, 76.43%, H, 5.15%, N, 5.51%.

3.2.5. Ethyl (2*E*)-2-acetoxymethyl-3-(4-chlorophenyl)-prop-2-enoate (3e). Colourless oil; yield: 60%; IR(neat) ν_{max}: 1742, 1720, 1638 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35 (t, 3H, J=7.1 Hz), 2.10 (s, 3H), 4.31 (q, 2H, J=7.1 Hz), 4.92 (s, 2H), 7.25–7.46 (m, 4H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.25, 20.82, 59.22, 61.00, 127.32, 129.01, 130.73, 132.62, 135.71, 143.89, 167.02, 170.51. Mass spectra *m/z*: 283 (M^+). HRMS: Calcd for $C_{14}H_{15}ClO_4$: 282.0659. Found: 282.0647.

3.2.6. (2*E*)-2-Acetoxymethyl-3-(4-chlorophenyl) prop-2-enenitrile (3f). Colourless oil; yield: 57%; IR(neat) ν_{max}: 2212, 1743, 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.15 (s, 3H), 4.80 (s, 2H), 7.17 (s, 1H), 7.42 (d, 2H, J=8.8 Hz), 7.72 (d, 2H, J=8.8 Hz); ^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 20.51, 65.04, 106.75, 116.93, 129.34, 130.45, 131.10, 137.23, 145.72, 170.20. Mass spectra *m/z*: 235 (M^+). HRMS: Calcd for $C_{12}H_{10}ClNO_2$: 235.0400. Found: 235.0380.

3.2.7. (3*E*)-3-Acetoxymethyl-4-phenyl but-3-en-2-one (3g). Colourless oil; yield: 59%; IR(neat) ν_{max}: 1744, 1670, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.50 (s, 3H), 4.90 (s, 2H), 7.43–7.65 (m, 5H), 7.70 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 20.86, 25.65, 60.72, 128.73, 129.61, 129.71, 134.28, 137.41, 142.68, 167.45, 197.07. Mass spectra *m/z*: 218 (M^+). Elemental analysis: Calcd for $C_{13}H_{14}O_3$: C, 71.54%, H, 6.47%. Found: C, 71.50%, H, 6.42%.

3.2.8. Ethyl (2*E*)-2-acetoxymethyl-3-(4-methylphenyl)-prop-2-enoate (3h). Colourless oil; yield: 71%; IR(neat) ν_{max}: 1742, 1722, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35 (t, 3H, J=7.1 Hz), 2.10 (s, 3H), 2.39 (s, 3H), 4.32 (q, 2H, J=7.1 Hz), 4.96 (s, 2H), 7.20 (d, 2H, J=8.0 Hz), 7.30 (d, 2H, J=8.0 Hz), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.25, 20.86, 21.22, 59.28, 60.95, 125.74, 129.37, 129.50, 131.33, 139.87, 145.37, 167.31, 170.49. Mass spectra *m/z*: 262 (M^+). Elemental analysis: Calcd for $C_{15}H_{18}O_4$: C, 68.68%, H, 6.92%. Found: C, 68.60%, H, 6.90%.

3.2.9. (2*E*)-2-Acetoxymethyl-3-(4-methyl phenyl)prop-2-enenitrile (3i). Colourless oil; yield: 66%; IR(neat) ν_{max}: 2214, 1745, 1626 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.14 (s, 3H), 2.39 (s, 3H), 4.78 (s, 2H), 7.18 (s, 1H), 7.24 (d, 2H, J=8.2 Hz), 7.69 (d, 2H, J=8.2 Hz); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 20.72, 21.56, 65.40, 104.50, 117.30, 129.24, 129.65, 129.84, 141.68, 147.32, 170.05. Mass spectra *m/z*: 215 (M^+). Elemental analysis: Calcd for $C_{13}H_{13}NO_2$: C, 72.54%, H, 6.09%, N, 6.51%. Found: C, 72.50%, H, 6.00%, N, 6.42%.

3.2.10. Ethyl (2*E*)-2-acetoxymethyl-3-(2,4-dichlorophenyl)prop-2-enoate (3j). Colourless oil; yield: 72%; IR(neat) ν_{max}: 1740, 1721, 1638 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35 (t, 3H, J=7.1 Hz), 2.11 (s, 3H), 4.32 (q, 2H, J=7.1 Hz), 4.94 (s, 2H), 7.27 (m, 2H), 7.57 (s, 1H), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.25, 20.85, 59.20, 61.10, 128.32, 129.21, 130.00, 131.41, 132.01, 134.95, 136.83, 144.71, 167.00, 170.55. Mass spectra *m/z*: 317 (M^+). HRMS: Calcd for $C_{14}H_{14}Cl_2O_4$:317.0260. Found: 317.0260.

3.2.11. (2*E*)-2-Acetoxymethyl-3-(2,4-dichlorophenyl)-prop-2-enenitrile (3k). Colourless oil; yield: 70%; IR(neat) ν_{max}: 2214, 1742, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.15 (s, 3H), 4.82 (s, 2H), 7.15 (s, 1H), 7.45 (d, 2H, J=8.9 Hz), 7.73 (d, 2H, J=8.9 Hz), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 20.71, 65.08, 106.80, 117.00, 129.40, 130.90, 131.10, 131.90, 135.23, 137.60, 145.90, 170.20. Mass spectra *m/z*: 270 (M^+). HRMS: Calcd for $C_{12}H_9Cl_2NO_2$: 269.0010. Found: 269.0008.

3.2.12. Ethyl (2*E*)-2-acetoxymethyl-3-(4-methoxyphenyl)prop-2-enoate (3l). Colourless oil; yield: 80%; IR(neat) ν_{max}: 1740, 1718, 1628 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35 (t, 3H, J=7.1 Hz), 2.10 (s, 3H), 3.80 (s, 3H), 4.31 (q, 2H, J=7.1 Hz), 4.95 (s, 2H), 7.20 (d, 2H, J=8.8 Hz), 7.70 (d, 2H, J=8.8 Hz), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.25, 20.84, 55.34, 59.26, 60.95, 116.34, 125.82, 131.93, 144.45, 161.51, 167.31, 170.40. Mass spectra *m/z*: 278 (M^+). Elemental analysis: $C_{15}H_{18}O_5$: Cacld C, 64.74%, H, 6.52%. Found: C, 64.70%, H, 6.50%.

3.2.13. (2*E*)-2-Acetoxymethyl-3-(4-methoxyphenyl)prop-2-enenitrile (3m). Colourless oil; yield: 76%; IR(neat) ν_{max}:

2210, 1742, 1622 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.10 (s, 3H), 3.80 (s, 3H), 4.85 (s, 2H), 7.00 (d, 2H, J=8.8 Hz), 7.15 (s, 1H), 7.78 (d, 2H, J=8.8 Hz); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 20.84, 55.34, 60.30, 104.95, 115.34, 118.14, 125.82, 130.01, 144.39, 160.51, 170.70. Mass spectra *m/z*: 231 (M^+). Elemental analysis: Calcd for $C_{13}H_{13}NO_3$: C, 67.52%, H, 5.67%, N, 6.06%. Found: C, 67.48%, H, 5.62%, N, 6.02%.

3.2.14. Ethyl (2*E*)-2-acetoxymethyl-3-naphth-2-yl prop-2-enoate (3n). Colourless oil; yield: 68%; IR(neat) ν_{max}: 1743, 1726, 1630 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35 (t, 3H, J=7.1 Hz), 2.07 (s, 3H), 4.31 (q, 2H, J=7.1 Hz), 4.82 (s, 2H), 7.40–7.50 (m, 4H), 7.81–7.86 (m, 3H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 13.96, 20.54, 59.32, 60.92, 124.14, 124.92, 126.06, 126.38, 126.46, 128.28, 128.96, 129.37, 131.07, 131.23, 133.05, 143.12, 166.16, 170.05. Mass spectra *m/z*: 298 (M^+). Elemental analysis: Calcd for $C_{18}H_{18}O_4$: C, 72.47%, H, 6.08%. Found: C, 72.43%, H, 6.02%.

3.2.15. (2*E*)-2-Acetoxymethyl-3-naphth-1-yl prop-2-enenitrile (3o). Colourless oil; yield: 62%; IR(neat) ν_{max}: 2212, 1745, 1620 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.16 (s, 3H), 4.79 (s, 2H), 7.52–7.60 (m, 4H), 7.81–7.89 (m, 3H), 78.25 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 20.52, 65.02, 105.85, 117.04, 124.52, 125.00, 126.43, 126.93, 128.50, 129.05, 129.85, 131.31, 131.62, 133.21, 148.15, 170.15. Mass spectra *m/z*: 251 (M^+). Elemental analysis: Calcd for $C_{16}H_{13}$ N O_2: C, 76.48%, H, 5.21%, N, 5.57. Found: C, 76.42%, H, 5.18%, N, 5.50%.

3.2.16. (2*E*)-2-Acetoxymethyl-4-(4-methylphenyl)but-3-en-2-one (3p). Colourless oil; yield: 65%; IR(neat) ν_{max}: 1742, 1665, 1620 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.10 (s, 3H), 2.39 (s, 3H), 4.90 (s, 2H), 7.20 (d, 2H, J=8.0 Hz), 7.30 (d, 2H, J=8.0 Hz), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 20.86, 21.22, 25.65, 60.72, 125.74, 129.37, 129.50, 131.33, 137.87, 144.63, 170.49, 197.07. Mass spectra *m/z*: 232 (M^+). Elemental analysis: Calcd for $C_{14}H_{16}O_3$: C, 72.39%, H, 6.94%. Found: C, 72.32%, H, 6.90%.

3.3. Typical experimental procedure for one-pot protection-isomerisation reaction

A mixture of the Baylis–Hillman adducts (200 mg, 0.8 mmol) and montmorillonite K-10 (60 mg, 30% w/w of the adduct) and trimethyl orthoformate (125 mg, 1.15 mol) was taken in a stoppered 25 mL conical flask and irradiated in the microwave oven (100% power mode) for 20 min. The mixture was cooled to room temperature and treated with CH_2Cl_2 (10 mL). Montmorillonite K-10 clay was recovered by filtration and washed with CH_2Cl_2 (2×5 mL). The solvent was removed in vacuum and the crude mixture was purified by silica gel column chromatography using petroleum ether–ethyl acetate (99.8:0.2) to give pure colourless isomerised products in 99.1:0.9 (*E*:*Z*) isomers as estimated by ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz). By reducing irradiation time (7 min 100% PL) the –OMe protected compounds are obtained.

3.3.1. Ethyl (2*E*)-2-methoxymethyl-3-phenyl prop-2-enoate (5a). Colourless oil; yield: 74%; IR(neat) ν_{max}: 1718, 1635 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.36 (t, 3H J=7.1 Hz), 3.43 (s, 3H), 4.22 (s, 2H), 4.28 (q, 2H J=7.1 Hz), 7.35–7.52 (m, 5H), 7.9 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.36, 58.27, 60.94, 66.50, 128.51, 129.07, 129.29, 129.85, 134.87, 144.33, 167.45. Mass spectra *m/z*: 220 (M^+). Elemental analysis: Calcd for $C_{13}H_{16}O_3$: C, 70.89%, H, 7.32%. Found: C, 70.85%, H, 7.32%.

3.3.2. (2*E*)-2-Methoxymethyl-3-phenyl prop-2-enenitrile (5b). Colourless oil; yield: 70%; IR(neat) ν_{max}: 2208, 1626 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.43 (s, 3H), 4.16 (s, 2H), 7.14 (s, 1H), 7.14–7.42 (m, 3H), 7.75–7.78 (m, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 58.25, 73.46, 108.04, 117.41, 128.83, 128.93, 130.53, 132.95, 144.45. Mass spectra *m/z*: 173 (M^+). Elemental analysis: Calcd for $C_{11}H_{11}NO$: C, 76.28%, H, 6.40%, N, 8.09%. Found: C, 76.23%, H, 6.33%, N, 8.05%.

3.3.3. Ethyl (2*E*)-2-methoxymethyl-3-naphth-1-yl prop-2-enoate (5c). Colourless oil; yield: 72%; IR(neat) ν_{max}: 1720, 1630 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.36 (t, 3H J=7.1 Hz), 3.43 (s, 3H), 4.22 (s, 2H), 4.30 (q, 2H J=7.1 Hz), 7.44–7.60 (m, 4H), 7.81–7.98 (m, 3H), 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.36, 58.27, 60.94, 66.55, 124.39, 125.24, 126.20, 126.62, 127.27, 128.54, 129.48, 131.40, 131.60, 132.82, 133.86, 142.83, 167.45. Mass spectra *m/z*: 270 (M^+). Elemental analysis: Calcd for $C_{17}H_{18}O_3$: C, 75.53%, H, 6.71%. Found: C, 75.50%, H, 6.22%.

3.3.4. (2*E*)-2-Methoxymethyl-3-naphth-1-yl prop-2-enenitrile (5d). Colourless oil; yield: 60%; IR(neat) ν_{max}: 2214, 1618 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): 3.43 (s, 3H), 4.16 (s, 2H), 7.51–7.59 (m, 4H), 7.80–7.89 (m, 3H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 58.25, 73.46, 108.04, 117.41, 124.52, 125.01, 126.43, 126.93, 128.61, 129.00, 129.83, 131.33, 131.63, 133.22, 146.15. Mass spectra *m/z*: 223 (M^+). Elemental analysis: Calcd for $C_{15}H_{13}NO$: C, 80.69%, H, 5.87%. Found: C, 80.66%, H, 5.86%, N, 6.22%.

3.3.5. Ethyl (2*E*)-2-methoxymethyl-3-(4-chlorophenyl)-prop-2-enoate (5e). Colourless oil; yield: 62%; IR(neat) ν_{max}: 1715, 1638 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35 (t, 3H J=7.1 Hz), 3.42 (s, 3H), 4.18 (s, 2H), 4.29 (q, 2H J=7.1 Hz), 7.37 (d, 5H J=8.5 Hz), 7.47 (d, 2H J=8.5 Hz), 7.9 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.21, 58.29, 61.17, 66.30, 128.50, 129.42, 131.12, 133.17, 135.41, 143.05, 167.32. Mass spectra *m/z*: 254 (M^+). HRMS: Calcd for $C_{13}H_{15}ClO_3$: 254.0710. Found: 254.0701.

3.3.6. (2*E*)-2-Methoxymethyl-3-(4-chlorophenyl)prop-2-enenitrile (5f). Colourless oil; yield: 52%; IR(neat) ν_{max}: 2210, 1634 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.44 (s, 3H), 4.15 (s, 2H), 7.10 (s, 1H), 7.50 (d, 2H J=8.4 Hz), 7.80 (d, 2H J=8.4 Hz); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 58.31, 73.16, 108.52, 117.15, 128.98, 130.00, 131.22, 136.36, 142.96. Mass spectra *m/z*: 208 (M^+).

HRMS: Calcd for $C_{11}H_{10}ClNO$: 207.0451. Found: 207.0444.

3.3.7. Ethyl (2*E*)-2-methoxymethyl-3-(4-methylphenyl)-prop-2-enoate (5h). Colourless oil; yield: 70%; IR(neat) ν_{max}: 1720, 1638 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35 (t, 3H J=7.1 Hz), 2.39 (s, 3H), 3.43 (s, 3H), 4.21 (s, 2H), 4.32 (q, 2H J=7.1 Hz), 7.20 (d, 5H J=8.0 Hz), 7.30 (d, 2H J=8.0 Hz), 7.9 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.36, 21.22, 58.27, 60.95, 66.56, 125.74, 129.37, 129.52, 131.34, 139.87, 144.37, 167.45. Mass spectra *m*/*z*: 234 (M^+). Elemental analysis: Calcd for $C_{14}H_{18}O_3$: C, 71.77%, H, 7.74%. Found: C, 71.72%, H, 7.70%.

3.3.8. (2*E*)-2-Methoxymethyl-3-(4-methylphenyl)prop-2-enenitrile (5i). Colourless oil; yield: 64%; IR(neat) ν_{max}: 2212, 1624 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.43 (s, 3H), 4.16 (s, 2H), 7.10 (s, 1H), 7.24 (d, 2H J=8.2 Hz), 7.69 (d, 2H J=8.2 Hz); ^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 58.24, 73.45, 104.04, 117.41, 129.22, 129.64, 129.92, 141.76, 146.35, 170.20. Mass spectra *m*/*z*: 187 (M^+). Elemental analysis: Calcd for $C_{12}H_{13}NO$: C, 76.98%, H, 7.00%, N, 7.48%. Found: C, 76.90%, H, 6.92%, N, 7.41%.

3.3.9. Ethyl (2*E*)-2-methoxymethyl-3-(4-methoxyphenyl)prop-2-enoate (5l). Colourless oil; yield: 80%; IR(neat) ν_{max}: 1728, 1635 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35 (t, 3H, J=7.1 Hz), 3.43 (s, 3H), 3.85 (s, 3H), 4.22 (s, 2H), 4.32 (q, 2H, J=7.1 Hz), 7.00 (d, 2H, J=8.8 Hz), 7.60 (d, 2H J=8.8 Hz), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.36, 55.34, 58.28, 60.95, 66.55, 114.34, 118.34, 125.82, 131.93, 144.45, 160.50, 167.31. Mass spectra *m*/*z*: 250 (M^+). Elemental analysis: Calcd for $C_{14}H_{18}O_4$: C, 67.18%, H, 7.25%. Found: C, 67.10%, H, 7.20%.

3.3.10. (2*E*)-2-Methoxymethyl-3-(4-methoxyphenyl)-prop-2-enenitrile (5m). Colourless oil; yield: 77%; IR(neat) ν_{max}: 2214, 1622 cm^{-1}. ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.43 (s, 3H), 3.85, 4.15 (s, 2H), 6.95 (d, 2H J=8.8 Hz), 7.06 (s, 1H), 7.75 (d, 2H, J=8.8 Hz); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 55.34, 58.23, 73.86, 104.95, 114.34, 118.14, 125.82, 130.93, 144.48, 161.51. Mass spectra *m*/*z*: 203 (M^+). Elemental analysis: Calcd for $C_{12}H_{13}NO_2$: C, 70.92%, H, 6.45%, N, 6.89. Found: C, 70.90%, H, 6.40%, N, 6.80%.

3.3.11. Ethyl (2*E*)-2-Methoxymethyl-3-naphth-2-yl prop-2-enoate (5n). Colourless oil; yield: 69%; IR(neat) ν_{max}: 1726, 1630 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35 (t, 3H J=7.1 Hz), 3.43 (s, 3H), 3.85 (s, 3H), 4.32 (q, 2H J=7.1 Hz), 7.41–7.56 (m, 4H), 7.81–7.84 (m, 3H), 8.2 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.36, 58.20, 60.72, 73.45, 124.14, 124.92, 126.06, 126.38, 126.96, 128.29, 128.96, 129.31, 131.01, 131.23, 133.05, 143.12, 166.16. Mass spectra *m*/*z*: 270 (M^+). Elemental analysis: Calcd for $C_{17}H_{18}O_3$: C, 75.53%, H, 6.71%. Found: C, 75.50%, H, 6.68%.

3.3.12. (2*E*)-2-Methoxymethyl-3-naphth-2-yl prop-2-enenitrile (5o). Colourless oil; yield: 63%; IR(neat) ν_{max}: 2212, 1620 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.43 (s, 3H), 4.16 (s, 2H), 7.52–7.6 (m, 4H), 7. 81–7.92 (m, 4H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 58.24, 73.43, 105.85, 117.80, 124.52, 125.01, 126.43, 126.93, 128.50, 129.05, 129.85, 131.31, 131.62, 133.21, 146.15. Mass spectra *m*/*z*: 223 (M^+). Elemental analysis: Calcd for $C_{15}H_{13}NO$: C, 80.69%, H, 5.87%, N, 6.27%. Found: C, 80.65%, H, 6.21%, N, 5.82%

3.4. Typical experimental procedure for the reaction of Baylis–Hillman adducts with various alcohol

A slurry made of the adduct **1q** (150 mg, 0.78 mmol), propargyl alcohol (109 mg, 2.5 equiv, 1.95 mmol) and montmorillonite K10 clay (60% w/w) was taken in a 50 mL RB flask and was tightly closed and kept in an oil bath (85 °C) for 24 h. Then the flask was cooled to room temperature and 20 mL of CH_2Cl_2 was added and filtered through a celite pad. The clay was repeatedly washed with (3×10 mL) CH_2Cl_2 and the combined solvent was removed under vacuum. The crude mixture was purified through a column of silica gel using 98:2 mixture of hexane/ethyl acetate afforded 95% isomerised compound **9q** with 99.9% *E*-selectivity.

3.4.1. Methyl (2*E*)-2-[(allyloxy)methyl]-3-phenylacrylate (10q). Colourless oil; yield: 95%; IR(neat) ν_{max}: 1605, 1615, 1710 cm^{-1}; ^1H NMR: δ 3.83 (s, 3H), 4.09 (d, 2H, J=5.67 Hz), 4.27 (s, 2H), 5.16 (d, 1H, J=10.41 Hz), 5.28 (ABq, 1H, H=1.55 and 17.19 Hz), 5.97 (m, 1H), 7.38 (m, 3H), 7.53 (m, 2H), 7.89 (s, 1H); ^{13}CNMR: δ 51.94, 64.07, 71.60, 117.11, 128.36, 128.77, 129.18, 129.76, 134.67, 134.71, 144.44, 167.72. Mass spectra *m*/*z*: 232 (M^+). Elemental analysis: Calcd for $C_{14}H_{16}O_3$: C, 72.39%, H, 6.94%. Found: C, 72.35%, H, 6.98%.

3.4.2. Ethyl (2*E*)-2-[(allyloxy)methyl]-3-phenylacrylate (10a). Colourless oil; yield: 94%; IR(neat) ν_{max}: 1604, 1617, 1712 cm^{-1}; ^1H NMR: δ 1.36 (t, 3H, J=7.11 Hz), 4.15 (d, 2H, J=5.67), 4.27 (s, 2H), 4.30 (q, 2H, J=7.11 Hz), 5.2 (dd, 2H, J=17.19 and 10.23 Hz), 5.98 (m, 1H), 7.33 (m, 3H), 7.52 (m, 2H), 7.89 (s, 1H); ^{13}C NMR: δ 14.29, 61.09, 64.07, 71.60, 117.11, 128.36, 128.77, 129.18, 129.76, 134.67, 134.71, 144.4, 167.72. Mass spectra *m*/*z*: 246 (M^+). Elemental analysis: Calcd for $C_{15}H_{18}O_3$: C, 73.15%, H, 7.37%. Found: C, 73.10%, H, 7.32%.

3.4.3. Methyl (2*E*)-2-(isopropoxymethyl)-3-phenylacrylate (11q). Colourless oil; yield: 95%; IR(neat) ν_{max}: 1600, 1620, 1716 cm^{-1}; ^1H NMR: δ 1.24 (d, 6H, J=6.12 Hz), 3.72 (sextet, 1H, J=6.12 Hz), 3.83 (s, 3H), 4.27 (s, 2H), 7.38 (m, 3H), 7.58 (m, 2H), 7.9 (s, 1H); ^{13}C NMR: δ 21.04, 21.51, 51.08, 61.42, 70.81, 127.41, 128.13, 128.25, 128.86, 133.87, 143.28, 167.23. Mass spectra *m*/*z*: 234 (M^+). Elemental analysis: Calcd for $C_{14}H_{18}O_3$: C, 71.77%, H, 7.74%. Found: C, 71.85%, H, 7.70%.

3.4.4. (2*E*)-2-[(Octyloxy)methyl]-3-phenylacrylonitrile (12b). Colourless oil; yield: 98%; IR(neat) ν_{max}: 1600, 1622, 2214 cm^{-1}; ^1H NMR: δ 0.98 (t, 3H, J=6.9 Hz), 1.3 (m, 10H), 1.7 (m, 2H), 3.62 (t, 2H, J=6.52 Hz), 4.3 (s, 2H), 7.24 (s, 1H), 7.47 (m, 3H), 7.85 (m, 2H); ^{13}C NMR: δ 14.09, 22.62, 26.10, 29.21, 29.36, 29.58, 31.78, 71.03, 71.73,

106.03, 126.89, 128.65, 128.78, 128.91, 130.38, 143.83. Mass spectra *m/z*: 271 (M^+). Elemental analysis: Calcd for $C_{18}H_{25}NO$: C, 79.60%, H, 9.28%, N, 5.16%. Found: C, 79.63%, H, 9.23% N, 5.13%.

3.4.5. Methyl (2*E*)-2-[(octyloxy)methyl]-3-phenylacrylate (12q). Colourless oil; yield: 97%; IR(neat) ν_{max}: 1601, 1622, 2214 cm^{-1}; ^1H NMR: δ 0.88 (t, 3H, $J=6.93$ Hz), 1.25 (m, 10H), 1.63 (m, 2H), 3.54 (t, 2H, $J=6.54$ Hz), 3.83 (s, 3H), 4.26 (s, 2H), 7.39 (m, 3H), 7.53 (m, 2H), 7.9 (s, 1H); ^{13}C NMR: δ 14.14, 26.33, 27.71, 29.17, 29.35, 29.47, 29.77, 51.90, 64.81, 70.91, 128.29, 128.52, 129.36, 129.96, 134.88, 144.58, 167.42. Mass spectra *m/z*: 304 (M^+). Elemental analysis: Calcd for $C_{19}H_{28}O_3$: C, 74.96%, H, 9.27%. Found: C, 74.89%, H, 9.32%.

3.4.6. Ethyl (2*E*)-3-phenyl-2-[(prop-2-ynyloxy)methyl] acrylate (9a). Colourless oil; yield: 92%; IR(neat) ν_{max}: 1600, 1622, 1720, 2150, 3300 cm^{-1}; ^1H NMR: δ 1.36 (t, 3H, $J=7.11$ Hz), 2.4 (t, 1H, $J=2.34$ Hz), 4.26 (d, 2H, $J=2.34$ Hz), 4.30 (q, 2H, $J=7.11$ Hz), 4.37 (s, 2H), 7.38 (m, 3H), 7.55 (m., 2H), 7.89 (s, 1H); ^{13}C NMR: δ 14.29, 58.05, 61.09, 64.21, 74.64, 79.69, 128.30, 128.50, 129.44, 129.95, 134.58, 144.90, 167.45. Mass spectra *m/z*: 244 (M^+). Elemental analysis: Calcd for $C_{15}H_{16}O_3$: C, 73.75%, H, 6.60%. Found: C, 73.80%, H, 6.63%.

3.4.7. (2*E*)-3-Phenyl-2-[(prop-2-ynyloxy)methyl]acrylonitrile (9b). Colourless oil; yield: 90%; IR(neat) ν_{max}: 1600, 1620, 2200, 3300 cm^{-1}; ^1H NMR: δ 2.48 (s, 1H), 4.25 (s, 2H), 4.32 (s, 2H), 7.18 (s, 1H), 7.41 (m, 3H), 4.77 (m, 2H); ^{13}C NMR: δ 57.47, 70.35, 75.67, 79.10, 108.17, 117.01, 128.93, 129.10, 130.53, 132.95, 144.45. Mass spectra *m/z*: 197 (M^+). Elemental analysis: Calcd for $C_{13}H_{11}NO$: C, 79.16%, H, 5.62, N, 7.10%. Found: C, 79.15%, H, 5.60% N, 7.13%.

3.4.8. Ethyl (2*E*)-3-(4-chlorophenyl)-2-[(prop-2-ynyloxy)methyl]acrylate (9e). Colourless oil; yield: 91%; IR(neat) ν_{max}: 1600, 1622, 1712, 2150, 3305 cm^{-1}; ^1H NMR: δ 1.36 (t, 3H, $J=7.11$ Hz), 2.4 (t, 1H, $J=2.34$ Hz), 4.25–4.32 (m, 4H), 4.35 (s, 2H), 7.35 (d, 2H, $J=8.4$ Hz), 7.5 (d, 2H, $J=8.4$ Hz), 7.83 (s, 1H); ^{13}C NMR: δ 14.29, 58.10, 61.12, 64.25, 74.61, 79.64, 128.77, 128.40, 130.98, 13.20, 135.45, 143.12, 167.42. Mass spectra *m/z*: 278 (M^+). HRMS: Calcd for $C_{15}H_{15}ClO_3$: 278.0710. Found: 278.0701.

3.4.9. (2*E*)-3-(4-Chlorophenyl)-2-[(prop-2-ynyloxy)-methyl]acrylonitrile (9f). Colourless oil; yield: 89%; IR(neat) ν_{max}: 1605, 2140, 3302 cm^{-1}; ^1H NMR: δ 2.47 (t, 1H, $J=2.34$ Hz), 4.28 (s, 2H), 4.30 (s, 2H), 7.19 (s, 1H), 7.38 (d, 2H, $J=8.4$ Hz), 7.5 (d, 2H, $J=8.4$ Hz); ^{13}C NMR: δ 57.45, 70.32, 75.66, 79.10, 108.52, 117.12, 128.98, 130.02, 131.23, 136.36, 143.06. Mass spectra *m/z*: 231 (M^+). HRMS: Calcd for $C_{13}H_{10}ClO_3$: 231.0451. Found: 231.0450.

3.4.10. (2*E*)-3-(4-Methylphenyl)-2-[(prop-2-ynyloxy)-methyl]acrylonitrile (9i). Colourless oil; yield: 86%; IR(neat) ν_{max}: 1600, 2145, 3300 cm^{-1}; ^1H NMR: δ 2.34 (s, 3H), 2.42 (t, 1H, $J=2.3$ Hz), 4.25 (s, 2H), 4.32 (s, 2H), 7.18 (s, 1H), 7.12 (d, 2H, $J=7.8$ Hz), 7.22 (d, 2H, $J=7.8$ Hz); ^{13}C NMR: δ 42.10, 57.45, 70.40, 75.62, 79.13, 108.18, 117.04, 127.58, 129.00, 135.12, 138.00, 144.39. Mass spectra *m/z*: 211 (M^+). Elemental analysis: $C_{14}H_{13}NO$, Calcd C, 79.59%, H, 6.20%, N, 6.63%. Found: C, 79.55%, H, 6.21%, N, 6.60%.

3.4.11. (2*E*)-3-(4-Methoxyphenyl)-2-[(prop-2-ynyloxy)-methyl]acrylonitrile (9m). Colourless oil; yield: 72%; IR(neat) ν_{max}: 1600, 2100, 3300 cm^{-1}; ^1H NMR: δ 2.48 (s, 1H), 3.83 (s, 3H), 4.25 (s, 2H), 4.32 (s, 2H), 7.00 (d, 2H, $J=8.8$ Hz), 7.09 (s, 1H), 7.74 (d, 2H, $J=8.8$ Hz); ^{13}C NMR: δ 55.34, 57.45, 70.35, 75.66, 79.15, 105.01, 114.34, 118.12, 125.82, 130.94, 144.50, 161.52. Mass spectra *m/z*: 227 (M^+). Elemental analysis: $C_{14}H_{13}NO_2$: Calcd C, 73.99%, H, 5.77%, N, 6.16%. Found: C, 73.95%, H, 5.79%, N, 6.10%;.

3.4.12. Methyl (2*E*)-3-phenyl-2-[(prop-2-ynyloxy)-methyl]acrylate (9q). Colourless oil; yield: 95%; IR(neat) ν_{max}: 1600, 1715, 2100, 3300 cm^{-1}; ^1H NMR: δ 2.42 (t, 1H, $J=2.34$ Hz), 3.84 (s, 3H), 4.26 (d, 2H, $J=2.34$ Hz), 4.39 (s, 2H), 7.32 (m, 3H), 7.53 (m, 2H), 7.92 (s, 1H); ^{13}C NMR: δ 52.26, 58.08, 64.25, 74.70, 79.63, 128.51, 18.54, 129.55, 129.99, 134.51, 145.27, 167.98. Mass spectra *m/z*: 230 (M^+). Elemental analysis: $C_{14}H_{14}O_3$: Calcd C, 73.03%, H, 6.13%. Found: C, 73.00%, H, 6.12%.

3.4.13. Methyl (2*E*)-3-(4-chlorophenyl)-2-[(prop-2-ynyloxy)methyl]acrylate (9r). Colourless oil; yield: 90%; IR(neat) ν_{max}: 1600, 1710, 2100, 3300 cm^{-1}; ^1H NMR: δ 2.42 (t, 1H, $J=2.3$ Hz), 3.85 (s, 3H), 4.28 (d, 2H, $J=2.34$ Hz), 4.4 (s, 2H), 7.35 (d, 2H, $J=8.4$ Hz), 7.5 (d, 2H, $J=8.4$ Hz), 7.84 (s, 1H); ^{13}C NMR: δ 52.08, 58.10, 64.20, 74.68, 79.64, 128.75, 129.42, 131.12, 133.17, 135.41, 143.03, 167.96. Mass spectra *m/z*: 264 (M^+). HRMS: Calcd for $C_{14}H_{13}ClO_3$: 264.0553. Found: 264.0550.

3.4.14. Methyl (2*E*)-3-(4-methylphenyl)-2-[(prop-2-ynyloxy)methyl]acrylate (9s). Colourless oil; yield: 85%; IR(neat) ν_{max}: 1600, 1710, 2100, 3300 cm^{-1}; ^1H NMR: δ 2.32 (s, 3H), 2.42 (t, 1H, $J=2.3$ Hz), 3.83 (s, 3H), 4.25 (d, 2H, $J=2.3$ Hz), 4.39 (s, 2H), 7.14 (d, 2H, $J=7.8$ Hz), 7.26 (d, 2H, $J=7.8$ Hz), 7.9 (s, 1H); ^{13}C NMR: δ 42.08, 52.24, 58.10, 64.26, 74.68, 79.60, 127.80, 129.04, 134.54, 135.20, 138.10, 145.22, 167.89. Mass spectra *m/z*: 244 (M^+). Elemental analysis: $C_{15}H_{16}O_3$: Calcd C, 73.75%, H, 6.60%. Found: C, 73.70%, H, 6.57%.

3.4.15. Methyl (2*E*)-3-(4-methoxyphenyl)-2-[(prop-2-ynyloxy)methyl]acrylate (9t). Colourless oil; yield: 80%; IR(neat) ν_{max}: 1600, 1705, 2100, 3300 cm^{-1}; ^1H NMR: δ 2.41 (t, 1H, $J=2.3$ Hz), 3.78 (s, 3H), 3.83 (s, 3H), 4.24 (d, 2H, $J=2.3$ Hz), 4.38 (s, 2H), 6.94 (d, 2H, $J=8.78$ Hz), 7.75 (d, 2H, $J=8.78$ Hz), 7.86 (s, 1H); ^{13}C NMR: δ 52.30, 55.43, 58.06, 64.20, 74.68, 79.62, 114.34, 125.82, 130.93, 134.40, 145.20, 161.51, 166.24. Mass spectra *m/z*: 260 (M^+). Elemental analysis: $C_{15}H_{16}O_4$: Calcd C, 69.22%, H, 6.20%. Found: C, 69.20%, H, 6.15%.

3.5. Typical experimental procedure for radical cyclization and protiodestannylation

A mixture of alkenyl propargyl ether **6a** (200 mg, 0.86 mmol), 1.5 equiv of freshly prepared tri-*n*-butyltin

hydride(1.3 mmol, 379 mg) and 5 mg of AIBN were taken in a 25 mL RB-Flask under inert atmosphere. The above mixture was stirred well and immersed into a preheated oil bath at 85 °C. The reaction was continued to stir until complete disappearance of starting material (TLC) and formation of the cyclized product. The crude cyclized stannylated product thus obtained was dissolved in diethyl ether (10 mL) and Con. HCl was added (5 drops) and the mixture was stirred for 2 h at RT. After the disappearance of stannylated compound (TLC), it was diluted with ether (50 mL) and washed with brine (15 mL×2). The organic layer was separated and dried (Na_2SO_4) and concentrated. The crude was purified by a silica gel column chromatography using gradient elution with hexane and hexane and EtOAc solvent system afforded pure cyclized product **15a** in 97% yield.

Iododestannylation. The stannylated product was taken in CH_2Cl_2 (15 mL) and iodine in CH_2Cl_2 was added until purple colour persists at 0 °C. The reaction was allowed to stir for 1 h. Saturated sodium disulphide ($Na_2S_2O_5$) was added drop wise till the purple colour disappears. The mixture was diluted with CH_2Cl_2 (15 mL) and washed with brine solution, separated and dried over anhyd.Na_2SO_4. The solvent was removed under vacuum. The crude compound was purified through a column of silica gel using hexane–ethyl acetate as eluent affording the iodinated compound **16** as a solid in 99% yield.

3.5.1. Ethyl 3-benzyl-4-methylenetetrahydrofuran-3-carboxylate (15a). Yield: 95%; IR(neat) ν_{max}: 1600, 1650, 1720 cm^{-1}; ^1H NMR: δ 1.21 (t, 3H, J=7.13 Hz), 2.88 (d, 1H, J=13.7 Hz), 3.32 (d, 1H, J=3.71 Hz), 3.86 (d, 1H, J=9.27 Hz), 4.13 (m, 3H), 4.36 (d, 2H, J=2 Hz), 5.1 (s, 1H), 5.32 (t, 1H, J=2.3 Hz), 7.12–7.27 (m, 5H); ^{13}C NMR: δ 14.32, 42.30, 57.75, 58.00, 71.89, 73.55, 106.68, 126,.69, 128.22, 128.35, 129.53, 129.69, 136.85, 149.90, 172.34. Mass spectra *m/z*: 246 (M^+). HRMS: Calcd for $C_{15}H_{18}O_3$: 246.1256. Found: 246.1252.

3.5.2. 3-Benzyl-4-methylenetetrahydrofuran-3-carbonitrile (15b). Yield: 92%; IR(neat) ν_{max}: 1595, 1647, 2200 cm^{-1}; ^1H NMR: δ 2.97 (s, 2H), 3.86 (d, 1H, J=8.9 Hz), 4.02 (d, 1H, J=8.9 Hz), 4.42 and 4.50 (dABq, 2H, J=13.5, 2.2 Hz), 5.2 (s, 2H), 7.28–7.36 (m, 5H); ^{13}C NMR: δ 42.34, 47.51, 70.85, 75.0, 108.91, 120.00, 127.74, 128.57, 128.64, 130.20, 134.87, 147.47. Mass spectra *m/z*: 199 (M^+). HRMS: Calcd for $C_{13}H_{13}NO$: 199.0997. Found: 199.0993.

3.5.3. Ethyl 3-(4-chlorobenzyl)-4-methylenetetrahydrofuran-3-carboxylate (15e). Yield: 96%; IR(neat) ν_{max}: 1600, 1650, 1719 cm^{-1}; ^1H NMR: δ 1.23 (t, 3H, J=7.13 Hz), 2.85 (d, 1H, J=13.75 Hz), 3.25 (d, 1H, 13.75 Hz), 3.84 (d, 1H, J=9.3 Hz), 4.13 (m, 3H), 4.36 (s, 2H), 5.09 (s, 1H), 5.27 (t, 1H, J=2.2 Hz), 7.08 (d, 2H, J=8.32 Hz), 7.20 (d, 2H, J=8.34 Hz); ^{13}C NMR: δ 14.30, 42.25, 58.05, 57.80, 72.01, 73.65, 107.53, 127.32, 129.61, 132.41, 135.90, 142.83, 170.82. Mass spectra *m/z*: 280 (M^+). HRMS: Calcd for $C_{15}H_{17}ClO_3$: 280.0866. Found: 280.0864.

3.5.4. 3-(4-Chlorobenzyl)-4-methylenetetrahydrofuran-3-carbonitrile (15f). Yield: 96%; IR(neat) ν_{max}: 1600, 1650, 2200 cm^{-1}; ^1H NMR: δ 2.95 (s, 2H), 3.84 (d, 1H, J=8.9 Hz), 4.02 (d, 1H, J=8.9 Hz), 4.40 and 4.48 (d ABq, 2H, J=13.5 and 2.2 Hz), 5.32 (s, 2H), 7.08 (d, 2H, J=8.32 Hz), 7.18 (d, 2H, J=8.32 Hz); ^{13}C NMR: δ 43.01, 48.00, 71.00, 75.61, 69.00, 121.01, 127.50, 129.00, 131.32, 134.74, 142.21. Mass spectra *m/z*: 233 (M^+). HRMS: Calcd for $C_{13}H_{12}NO$: 233.0607. Found: 233.0600.

3.5.5. 3-(4-Methylbenzyl)-4-methylenetetrahydrofuran-3-carbonitrile (15i). Yield: 94%; IR(neat) ν_{max}: 1600, 1652, 2205 cm^{-1}; ^1H NMR: δ 2.34 (s, 3H), 2.95 (s, 2H), 3.89 (d, 1H, J=8.9 Hz), 4.05 (d, 1H, J=8.9 Hz), 4.40 and 4.50 (dABq, 2H, J=13.5 and 2.2 Hz), 5.4 (s, 2H), 7.12 (d, 2H, J=7.8 Hz), 7.26 (d, 2H, J=7.8 Hz); ^{13}C NMR: δ 20.89, 42.06, 47.49, 70.86, 75.21, 108.88, 120.12, 127.75, 128.55, 134.18, 137.83, 147.56. Mass spectra *m/z*: 213 (M^+). HRMS: Calcd for $C_{14}H_{15}NO$: 213.1154. Found: 213.1150.

3.5.6. 3-(4-Methoxybenzyl)-4-methylenetetrahydrofuran-3-carbonitrile (15m). Yield: 94%; IR(neat) ν_{max}: 1600, 1650, 2200 cm^{-1}; ^1H NMR: δ 3.12, 3.78 (s, 3H), 3.9 (d, 1H, J=8.9 Hz), 4.08 (d, 1H, J=8.9 Hz), 4.4 and 4.5 (dABq, 2H, J=13.5, 2.2 Hz), 5.2 (s, 2H), 7.04 (d, 2H, J=8.6 Hz), 7.25 (d, 2H, J=8.6 Hz); ^{13}C NMR: δ 42.81, 55.42, 47.22, 70.90, 75.00, 108.88, 120.04, 114.51, 126.10, 130.85, 148.85, 158.72. Mass spectra *m/z*:229 (M^+). HRMS: Calcd for $C_{14}H_{15}NO_2$: 229.1103. Found: 229.1100.

3.5.7. Methyl 3-benzyl-4-methylenetetrahydrofuran-3-carboxylate (15q). Yield: 95%; IR(neat) ν_{max}: 1600, 1650, 1718 cm^{-1}; ^1H NMR: δ 2.88 (d, 1H, J=13.71 Hz), 3.35 (d, 1H, J=13.7 Hz), 3.7 (s, 3H), 3.88 (d, 1H, J=9.3 Hz), 4.20 (d, 1H, J=9.3 Hz), 4.39 (t, 2H, J=2.2 Hz), 5.13 (s, 1H), 5.34 (t, 1H, J=2.4 Hz, 7.13–7.21 (m, 2H), 7.24–7.39 (m, 3H); ^{13}C NMR: δ 42.38, 52.16, 57.77, 71.55, 73.73, 106.68, 126.76, 128.24, 128.33, 129.53, 129.75, 137.01, 149.84, 172.64. Mass spectra *m/z*: 232 (M^+). HRMS: Calcd for $C_{14}H_{16}O_2$: 232.1099. Found: 232.1097.

3.5.8. Methyl 3-(4-chlorobenzyl)-4-methylenetetrahydrofuran-3-carboxylate (15r). Yield: 97%; IR(neat) ν_{max}: 1600, 1650, 1720 cm^{-1}; ^1H NMR: δ 2.82 (d, 1H, J=13.75 Hz), 3.23 (d, 1H, 13.75 Hz), 3.68 (s, 3H), 3.80 (d, 1H, J=9.3 Hz), 4.1 (d, 1H, J=9.3 Hz), 4.39 (s, 2H), 5.11 (s, 1H), 5.24 (t, 1H, J=2.2 Hz), 7.10 (d, 2H, J=8.3 Hz), 7.2 (d, 2H, J=8.3 Hz); ^{13}C NMR: δ 42.35, 52.25, 57.80, 71.50, 73.70, 107.00, 127.60, 129.40, 132.40, 135.05, 142.10, 170.51. Mass spectra *m/z*: 266 (M^+). HRMS: Calcd for $C_{14}H_{15}ClO_3$: 266.0710. Found: 266.0708.

3.5.9. Methyl 3-(4-methylbenzyl)-4-methylenetetrahydrofuran-3-carboxylate (15s). Yield: 92%; IR(neat) ν_{max}: 1600, 1650, 1720 cm^{-1}; ^1H NMR: δ 2.32 (s, 3H), 2.85 (d, 1H, J=13.71 Hz), 3.32 (d, 1H, J=13.71 Hz), 3.7 (s, 3H), 3.85 (d, 1H, J=9.3 Hz), 4.22 (d, 1H, J=9.3 Hz), 4.36 (t, 2H, J=2.2 Hz), 5.1 (s, 1H), 5.34 (t, 1H, J=2.4 Hz), 7.15 (d, 2H, J=7.8 Hz), 7.28 (d, 2H, J=7.8 Hz); ^{13}C NMR: δ 20.98, 42.35, 52.15, 57.80, 71.50, 74.00, 107.01, 127.78, 129.00, 135.21, 138.02, 148.96, 172.32. Mass spectra *m/z*: 246 (M^+). HRMS: Calcd for $C_{15}H_{18}O_3$: 246.1256. Found: 246.1253.

3.5.10. Methyl 3-(4-methoxybenzyl)-4-methylene

tetrahydrofuran-3-carboxylate (15t). Yield: 90%; IR(neat) ν_{max}: 1600, 1650, 1720 cm^{-1}; ^1H NMR: δ 2.85 (d, 1H, $J=13.71$ Hz), 3.4 (d, 1H, $J=13.71$ Hz), 3.69 (s, 3H), 3.80 (s, 3H), 3.9 (d, 1H, $J=9.3$ Hz), 4.22 (d, 1H, $J=9.3$ Hz), 4.35 (t, 2H, $J=2.2$ Hz), 5.18 (s, 1H), 5.39 (t, 1H, $J=2.2$ Hz), 7.0 (d, 2H, $J=8.6$ Hz), 7.28 (d, 2H, $J=8.6$ Hz); ^{13}C NMR: δ 44.25, 52.18, 55.41, 58.20, 71.43, 73.65, 106.77, 114.32, 125.82, 130.95, 150.00, 160.59, 172.52. Mass spectra *m/z*: 262 (M^+). HRMS: Calcd for $C_{15}H_{18}O_4$: 254.0710. Found: 254.0701.

3.5.11. Iodo compound 16. Yield: 99%; IR(neat) ν_{max}: 1600, 1620, 1720 cm^{-1}; ^1H NMR (300.1 MHz): δ 2.96 (d, 1H, $J=13.6$ Hz, benzylic), 3.25 (d, 1H, $J=13.6$ Hz, benzylic), 3.69 (s, 3H, CO_2Me), 4.05 (d, 1H, $J=9.3$ Hz, C2), 4.25 (d, 1H, $J=9.3$ Hz, C2), 4.31 & 4.35 (dd, 2H, $J=10.5$, 2.6 Hz), 6.40 (t, H, $J=2.6$ Hz), 7.(m, 2H, Ar), 7.27 (m, 3H, Ar); ^{13}C NMR: δ 42.91, 52.10, 60.70, 71.76, 4.87, 78.61, 127.22, 127.88, 128.12, 128.64, 129.81, 136.34, 151.69, 171.15. HRMS: Calcd for $C_{14}H_{15}IO_3$: 358.0086. Found 358.0084.

Acknowledgements

The authors thank the Professor T. K. Chandrasekhar, Director and Dr. Mangalam S. Nair, Head, Organic Division for infrastructure facilities provided. One of the authors (PR) thanks CSIR (New Delhi) for the award of Senior Research Fellowship. Thanks are due to the reviewers of this article for constructive suggestions.

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PS-PEG resin-supported palladium–MOP complexes. Application in asymmetric π-allylic reduction

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Received 25 May 2004; accepted 17 July 2004

Available online 28 August 2004

Abstract—Homochiral palladium complexes of polymeric 2′-, 6-, and 6′-anchored 2-diphenylphosphino-1,1′-binaphthyl (MOP) ligands were prepared on polystyrene-poly(ethylene glycol) (PS-PEG) resin. The PS-PEG resin-supported palladium–MOP complexes exhibited high catalytic activity, stereoselectivity (up to 80% ee), and recyclability (six times) in the asymmetric allylic reduction of 1-vinyl-1,2,3,4-tetrahydronaphth-1-yl benzoate to give 1-vinyl-1,2,3,4-tetrahydronaphthalene.

1. Introduction

Homogeneous transition metal complexes with chiral ligands are among the most versatile and powerful enantioselective catalysts to date. Consequently, a number of chiral ligands have been developed to achieve various homogeneous asymmetric processes with high stereoselectivity.[1,2] 2-Diphenyl-phosphino-2′-substituted-1,1′-binaphthyls (the so-called MOPs),[3] which were originally developed by this author (YU) and Hayashi,[3a] have found widespread utility as chiral ligands for various transition metal-catalyzed reactions.[4–6] In addition, the immobilization of homogeneous catalysts has been recognized as a useful means for carrying out high-throughput synthesis as well as for the industrial production of fine chemicals, where the catalyst residue is readily removed by simple manipulation and subjected to the next reaction (recycling).[7,8] Efficient removal of the chiral metal complexes from the reaction mixture of the catalytic asymmetric process would allow not only the recovery of costly noble metal species and the chiral auxiliary but also the production of chiral compounds un-contaminated by metal species to provide compounds with improved biological utility. If MOP ligands and/or their metal complexes were immobilized on polymer supports to exhibit the same high stereoselectivity in a given catalytic process as their homogeneous counterparts, the catalytic systems would be excellent green chiral catalysts. One of the major problems associated with immobilization of a chiral catalyst lies in the introduction of an anchoring group on the catalysts without any loss of the activity and/or selectivity of their homogeneous counterparts.[9–11]

Here, we report the preparation of polymeric palladium complexes of 2′-, 6-, and 6′-anchored MOP ligands where the ligand moieties were immobilized on polystyrene-poly(ethylene glycol) (PS-PEG) resin[12,13] by appropriate linkers at the 2′-, 6-, and 6′-positions of the binaphthyl backbone, respectively (Fig. 1). Since the MOP-ligand does not have C_{2v} symmetry, the outcome of a given reaction

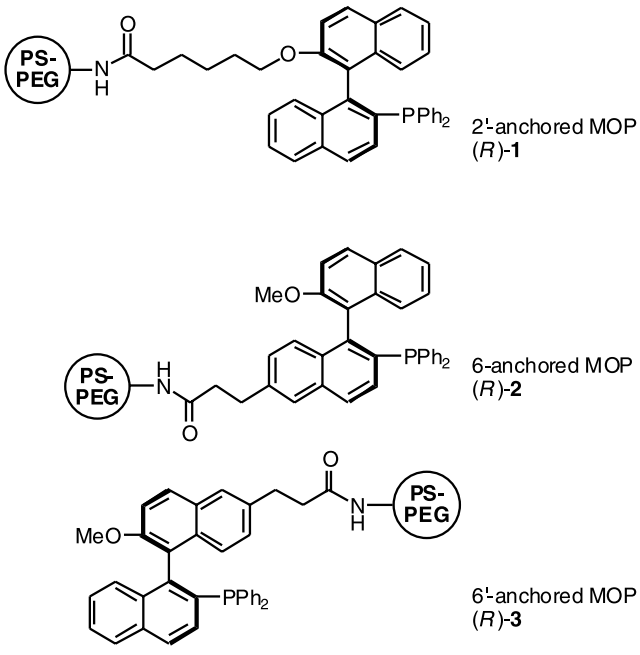

Figure 1. 2′-, 6-, and 6′-Anchored MOP ligands.

Keywords: MOP; Immobilized recyclable catalysts; Asymmetric catalysis; π-Allylic reduction.

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doi:10.1016/j.tet.2004.07.093

therefore may be different depending on the substituents at the 6- and 6′ positions. The stereocontrolling potential of the polymeric palladium–MOP complexes was examined for asymmetric π-allylic reduction of 1-vinyl-1,2,3,4-tetrahydronaphth-1-yl benzoate to reveal that the polymeric 6-, and 6′-anchored MOP ligands exhibited stereoselectivity as high as the homogeneous MeO–MOP ligand.

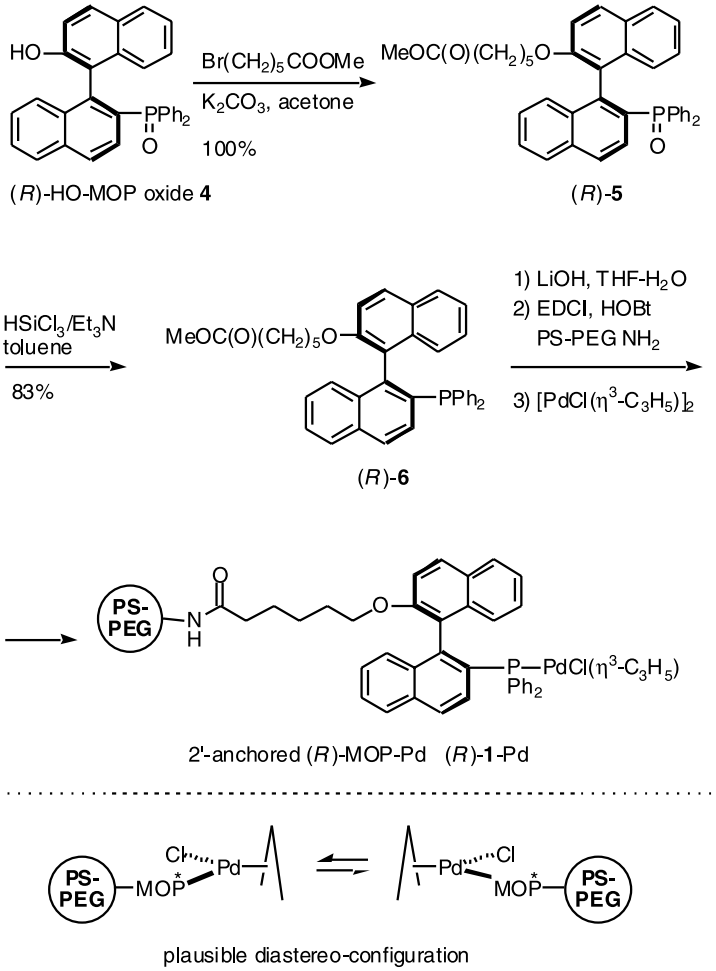
2. Results and discussion

2.1. 2′-Anchored polymeric MOP[14]

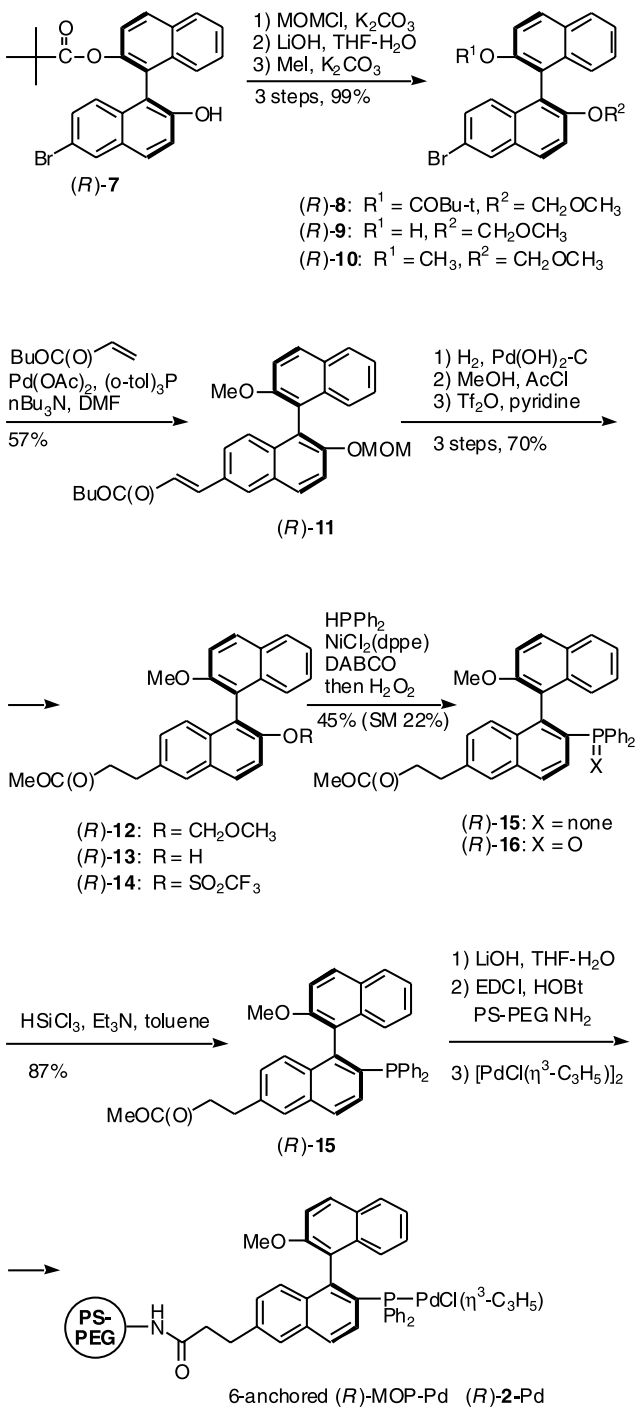
The precursor for the immobilization using the 2′-position was readily obtained by etherification of (*R*)-2-diphenylphosphinyl-2′-hydroxy-1,1′-binaphthyl ((*R*)-**4**) (Scheme 1).[3b] Thus, (*R*)-**4** was treated with 6-bromohexanoic acid methyl ester and K_2CO_3 in refluxing acetone to give the methoxycarbonylpentyl ester (*R*)-**5** in a quantitative yield. The diphenylphosphinyl group was reduced by $HSiCl_3/Et_3N$ in toluene to give (*R*)-2′-(1-(methoxycarbonyl)pentan-5-oxy)-MOP ((*R*)-**6**) (Scheme 1). The immobilization of **6** having a tether group at the 2′-position thus prepared was examined on the polystyrene-poly(ethylene glycol) (PS-PEG) bearing a terminal amino group. After alkaline hydrolysis of the methyl ester **6** with lithium hydroxide in aqueous THF, the resulting crude carboxylic acid was treated with PS-PEG amino resin under standard conditions of solid-phase amide bond formation using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole hydrate (HOBt). A negative Kaiser test[15] indicated that the condensation was completed to give the PS-PEG supported 2′-anchored MOP (*R*)-**1**. The 2′-anchored polymeric ligand (*R*)-**1** was then subjected to complexation with $[PdCl(\pi\text{-}C_3H_5)]_2$ in DMF (P/Pd = 1:1.1) to give the PS-PEG-supported 2′-anchored-MOP-$PdCl(\eta^3\text{-}C_3H_5)$ (*R*)-**1**-Pd. Two singlet peaks were observed at +13 and +16 ppm, respectively, on gel phase $^{31}P\{^1H\}$ MAS NMR spectroscopy of the resulting polymeric complex demonstrating that the polymeric (*R*)-**1**-Pd was obtained as a mixture of a set of two diastereomeric isomers in a ratio of 1.4:1.0 (25 °C). These spectroscopic data agreed closely with those observed in the PdCl(π-cyclohexenyl)-MeO–MOP complex which consists of a pair of diastereomers as shown in Scheme 1.[5f,h]

2.2. 6-Anchored polymeric MOP

The 6-anchored MOP ligand was prepared from (*R*)-6-bromo-2-hydroxy-2′-pivaloyloxy-1,1′-binaphthyl ((*R*)-**7**) (Scheme 2).[16] Recently, we have developed a method for the immobilization of 2,2′-bis(oxazolyl)-1,1′-binaphthyl (boxax) ligands on various polymer support[17] where the 6-bromo-2-hydroxy-2′-pivaloyloxy-1,1′-binaphthyl (**7**) was



Scheme 1. Preparation of the polymeric 2′-anchored Pd–MOP complex.



Scheme 2. Preparation of the 6-anchored polymeric Pd–MOP complex.

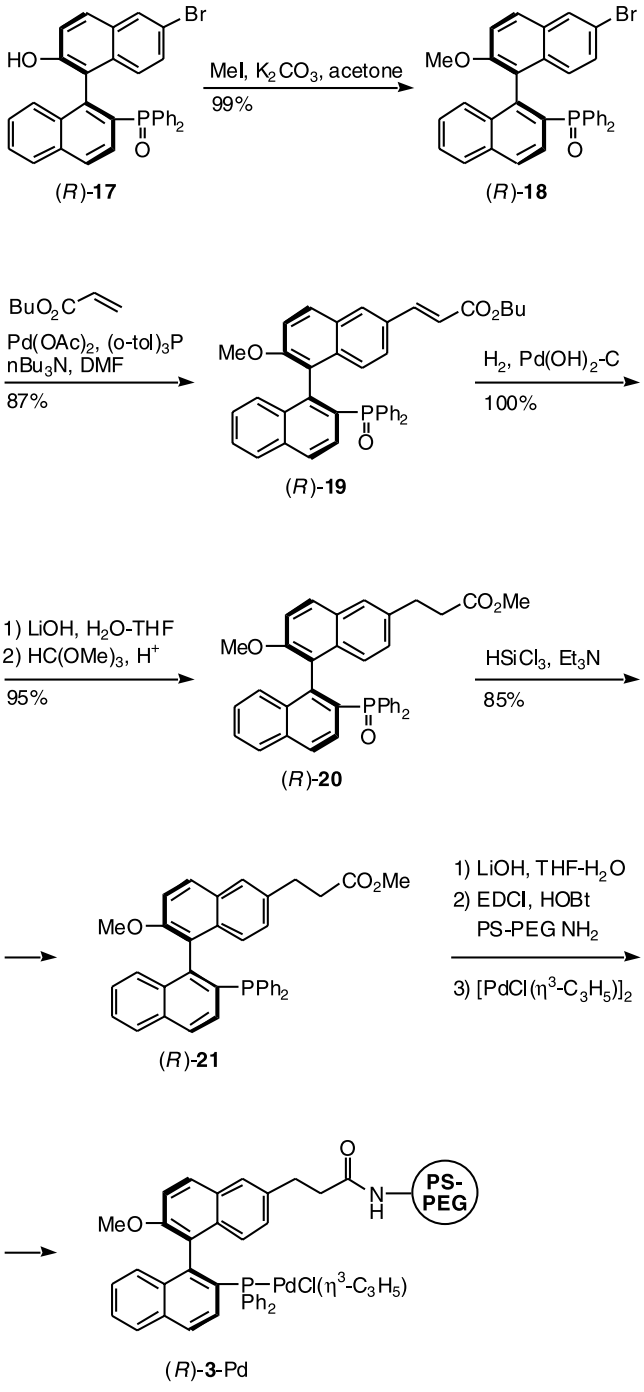
prepared and used as the key intermediate for introduction of an anchoring tether at the 6-position of the binaphthyl skeleton. The phenolic hydroxyl group of the pivalate (*R*)-**7** was protected as the methoxymethyl ether using chloromethyl methyl ether and potassium carbonate in acetone to give (*R*)-**8** in a quantitative yield. Cleavage of the pivaloyl group under aqueous alkaline conditions gave the monohydroxy binaphthyl (*R*)-**9**, and treatment of (*R*)-**9** with methyl iodide and potassium carbonate in acetone furnished 6-bromo-2-methoxymethoxy-2′-methoxy-1,1′-binaphthyl ((*R*)-**10**) (two steps, 99% yield). Introduction of the tether group was achieved via the Heck reaction. Thus, the palladium-catalyzed Heck reaction of (*R*)-**10** with *n*-butyl acrylate proceeded smoothly at 130 °C in DMF in the presence of $Pd(OAc)_2$/(*o*-tol)$_3$P as a catalyst and tri-*n*-butylamine as the base to give (*R*)-**11** in 57% yield. The Heck product (*R*)-**11** underwent hydrogenation and subsequent acidic hydrolysis of the methoxymethyl ether to give compound (*R*)-**13** (two steps, 87% yield). Treatment of the phenol (*R*)-**13** with triflic anhydride and pyridine afforded the triflate (*R*)-**14** in 81% yield. Coupling of the triflate (*R*)-**14** and diphenylphosphine with $NiCl_2$(dppe)/DABCO[18] gave the MOP derivative (*R*)-**15** as a mixture with small amounts of its oxide (*R*)-**16** and unreacted triflate (*R*)-**14**. The crude reaction mixture was treated with H_2O_2 and the desired phosphine (*R*)-**15** was readily purified in its oxidized form (*R*)-**16** in 45% yield along with the triflate (*R*)-**14** (22%). The reduction of (*R*)-**16** was performed with $HSiCl_3/Et_3N$ in toluene to give (*R*)-**15** in 87% yield. The phosphine (*R*)-**15** was then subjected to the immobilization procedure under similar conditions as employed for the 2′-anchored **1** to give the π-allylpalladium chloride complex of the PS-PEG-supported 6-anchored-MeO–MOP (*R*)-**2**-Pd which was also a pair of diastereoisomers.

2.3. 6′-Anchored polymeric MOP

The anchoring group was introduced at the 6′-position of the MOP-ligand via the Heck alkenylation starting from (*R*)-6′-bromo-2-diphenylphosphinyl-2′-hydroxy-1,1′-binaphthyl ((*R*)-**17**)[19] which was readily prepared from the HO–MOP oxide (Scheme 3). Thus, after methylation of **17**, a tether group was introduced into the resulting 6′-bromo-MeO–MOP oxide **18** by the Heck reaction with *n*-butyl acrylate to give (*R*)-**19** in 87% yield. The Heck product **19** was converted to the MOP-derivative (*R*)-**20** via hydrogenation of the olefin, transesterification and reduction of the phosphinyl group with $HSiCl_3/Et_3N$ in toluene (five steps, 81%). The phosphine (*R*)-**20** was attached to the PS-PEG amino resin and then reacted with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ to give a mixture of the diastereomers of the PS-PEG-supported 6′-anchored-MeO–MOP-$PdCl(\eta^3\text{-}C_3H_5)$ ((*R*)-**3**-Pd).

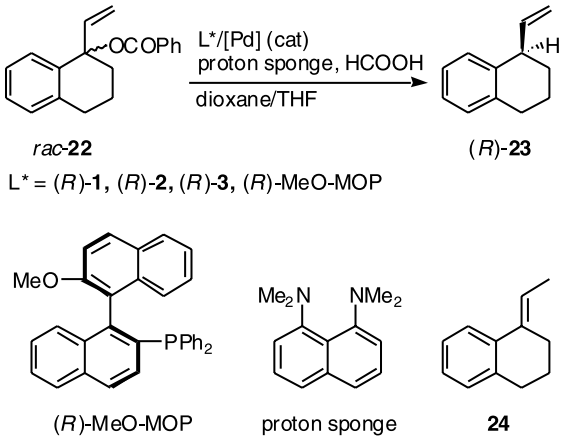
2.4. Asymmetric π-allylic reduction with polymeric Pd–MOP complexes

The enantiocontrolling ability of the PS-PEG resin-supported palladium–MOP catalysts prepared above was examined for palladium-catalyzed asymmetric π-allylic reduction of *rac*-1-vinyl-1,2,3,4-tetrahydronaphth-1-yl benzoate (*rac*-**22**) to produce 1-vinyl-1,2,3,4-tetrahydronaphthalene (**23**) (Scheme 4). Allylic reduction has attracted our attention because a series of MOP ligands have so far demonstrated higher catalytic activity and stereoselectivity in the π-allylic reductions than other types of chiral bis(phosphine) ligands under homogeneous conditions. Reaction of the cyclic benzoate *rac*-**22** with formic acid was catalyzed by the polymeric palladium–MOP complexes to give the vinyl tetralin **23**. The enantiomeric purity of the reduced product **23** was determined by GC analysis using a chiral stationary phase capillary column (Cyclodex CB). The results obtained are summarized in Table 1, which also includes the results obtained with the homogeneous 2-, 6-, 6′-substituted MOP ligands ((*R*)-MeO–MOP, (*R*)-**6**, (*R*)-**15**, (*R*)-**21**) for better comparison. Of the 2-, 6-, 6′-substituted



Scheme 3. Preparation of the 6′-anchored polymeric Pd–MOP complex.

MOP ligands, 6-substituted MOP ligand **15** was found to give good stereoselectivity and catalytic activity (94% yield, 73% ee), comparable to that obtained with the MeO–MOP ligand (Table 1, entries 1–4). Thus, the MOP ligand **6** bearing a long alkoxy chain at the 2-position gave lower stereoselectivity (60% ee, entry 2) while MeO–MOP gave 78% stereoselectivity under otherwise the same reaction conditions (entry 1). It has been well-discussed that stereocontrolling potential of MOP derivatives are strongly affected by the steric and/or electronic properties of substituents at the 2-position.[20] It is also noteworthy that 6′-substituted **21** exhibited lower catalytic activity in the asymmetric reduction (71% yield, entry 4). As a model for



Scheme 4. Asymmetric reduction of allylic ester **22** with HCOOH.

the key intermediate of the asymmetric π-allylic reduction, the structure of a PdCl(π-allyl)MOP complex has been thoroughly studied to reveal that 6′-position is in relatively close proximity to the π-allylic moiety.[5a] The sterically bulky 6′-substituent of **21** might decrease the catalytic activity of its palladium complex. Similar trend was observed in the asymmetric catalysis with polymeric MOP ligands (Table 1, entries 5–7). The 2-anchored complex **1**-Pd gave lower stereoselectivity compared to the palladium complex of MeO–MOP (MeO–MOP–Pd: 78% ee, **1**-Pd: 59% ee,) (entries 1 and 5). The 6-anchored polymeric MOP ligand **2**-Pd was found to provide good stereoselectivity under heterogeneous conditions. Thus, allylic reduction of a *rac*-**22** with formic acid was carried out in dioxane–THF in the presence of 5 mol% palladium of the 6-anchored MOP–Pd complex (**2**-Pd) and 1,8-bis(dimethylamino)naphthalene (1.2 equiv) at 20 °C. The reduced product **23** was isolated in 91% yield (Table 1, entry 6) along with a trace amount of its regioisomeric **24** by silica

Table 1. Asymmetric reduction of *rac*-**22** with HCOOH using polymeric MOP–Pd complexes[a]

Entry	Catalyst	Yield (%)[b]	% ee[c] (config.)[d]
1[e]	MeO–MOP/[Pd]	88	78 (*R*)
2[e]	(*R*)-**6**/[Pd]	90	60 (*R*)
3[e]	(*R*)-**15**/[Pd]	94	73 (*R*)
4[e]	(*R*)-**21**/[Pd]	71	73 (*R*)
5	(*R*)-**1**-Pd	94	59 (*R*)
6	(*R*)-**2**-Pd	91	74 (*R*)
7	(*R*)-**3**-Pd	80	72 (*R*)
8	(*R*)-**2**-Pd	75	79 (*R*)
9	(*R*)-**2**-Pd (first reuse)	82	80 (*R*)
10	(*R*)-**2**-Pd (second reuse)	75	79 (*R*)
11	(*R*)-**2**-Pd (third reuse)	76	79 (*R*)
12	(*R*)-**2**-Pd (fourth reuse)	71	79 (*R*)
13	(*R*)-**2**-Pd (fifth reuse)	82	80 (*R*)
14	(*R*)-**2**-Pd (sixth reuse)	72	79 (*R*)

[a] A ratio of **22** (mol)/HCOOH (mol)/proton sponge (mol)/[Pd] (mol)/solv (L)=1:2.2:1.2:0.05:8. Entries 1–7 were carried out at 20 °C for 48 h. Entries 8–14 were carried out at 0 °C for 7 days.
[b] Isolated yield by silica gel column chromatography.
[c] Determined by GC analysis with chiral stationary phase column (CP Cyclodex β236M).
[d] Determined by comparing with authentic sample.
[e] MOP–Pd complex was generated in situ by mixing (*R*)-MOP and [PdCl(η^3-C_3H_5)]$_2$ (P/Pd=2:1).

gel column chromatography (<2%). Both the enantioselectivity and the regioselectivity of **23** were determined by GC analysis to be 74% ee and 98% selectivity. The absolute configuration of **23** was determined to be *R* by comparison of its chiral GC chromatogram with that of the authentic sample. A similar stereoselectivity was observed with the 6′-anchored palladium–MOP catalyst **3**-Pd whereas the chemical yield was lower than the reaction with **2**-Pd under otherwise similar conditions (entry 7). Thus, the allylic reduction with (*R*)-**3**-Pd afforded 72% ee of (*R*)-**23** in 80% isolated yield. Recycling experiments of the immobilized chiral catalyst were performed with (*R*)-**2**-Pd using an excess amount of the allylic substrate *rac*-**22**, a relatively stable π-allylpalladium complex formed after consumption of the reducing agent, formic acid, under these conditions (entries 8–14). After the first run of the asymmetric reduction of *rac*-**22** using the 6-anchored **2**-Pd at 0 °C giving 79% ee of (*R*)-**23** in 75% yield (entry 8), the recovered polymeric catalyst was subjected to the second use without an additional charge of a palladium species, under otherwise similar conditions, to give 80% ee of the same product in 82% yield (entry 9).[21] The enantiomeric selectivity observed in the third to sixth reuses were 79, 79, 79, 80, and 79% ee, respectively (entries 10–14), demonstrating high recyclability of the PS-PEG resin-supported 6-anchored palladium–MOP complex **2**-Pd.

3. Conclusion

Homochiral palladium complexes of the polymeric 2′-, 6-, and 6′-anchored 2-diphenylphosphino-1,1′-binaphthyl (MOP) ligands **1**-Pd, **2**-Pd, and **3**-Pd were prepared on polystyrene-poly(ethylene glycol) (PS-PEG) resin. Asymmetric π-allylic reduction was examined with the polymeric complexes as a test reaction to reveal that the **2**-Pd anchoring on PS-PEG at the 6-position provided as good stereoselectivity as its homogeneous counterpart without significant loss of catalytic activity. Thus, the 6-anchored PS-PEG resin-supported palladium–MOP complex (*R*)-**2**-Pd exhibited good catalytic activity and stereoselectivity in the asymmetric reduction of 1-vinyl-1,2,3,4-tetrahydronaphth-1-yl benzoate (*rac*-**22**) forming (*R*)-1-vinyl-1,2,3,4-tetrahydronaphthalene ((*R*)-**23**) (up to 82% yield and 80% ee) with good recyclability (six times).

4. Experimental

4.1. General

All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. NMR spectra were recorded on a JEOL JNM-AL400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 162 MHz for ^{31}P), JEOL JNM-AL500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C), or JEOL JNM-LA500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^{1}H NMR. Chemical shifts of ^{13}C NMR are given relative to $CDCl_3$ as an internal standard (δ 77.0). The ^{31}P NMR data are reported relative to external 85% H_3PO_4. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted. Gel-phase MAS NMR was recorded on JEOL AL400. FAB mass spectra were recorded on a JEOL JMS-777V spectrometer; 3-nitrobenzyl alcohol was used as the matrix. Optical rotations were measured on a JASCO P-1020 polarimeter. GC analysis was carried out on a Hewlett Packard 4890 system. Commercially available reagents were used without any purification. Compounds **4**, **7**, and **17** were prepared according to the procedures in the literature.[3,17,19]

4.1.1. (*R*)-2-Diphenylphosphinyl-2′-(1-(methoxycarbonyl)pentan-5-oxy)-1,1′-binaphthyl ((*R*)-5). A mixture of (*R*)-2-hydroxy-2′-phosphinylbinaphthyl ((*R*)-**4**) (1.39 g, 3.16 mmol), methyl 6-bromohexanoate (1.12 g, 4.75 mmol), K_2CO_3 (1.38 g, 10.0 mmol) and acetone (30 mL) was refluxed for 15 h. The reaction mixture was concentrated in vacuo, and the crude residue was diluted with EtOAc (50 mL). The organic phase was washed with water, brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was purified by a short column chromatography over silica gel with EtOAc/*n*-hexane (2:1). Yield: 1.88 g (100%) colorless oil; $[\alpha]_D^{22} = +64.4$ (THF, *c* 1.07); ^{1}H NMR δ 0.83 (m, 2H), 1.26 (m, 2H), 1.43 (m, 2H), 1.93 (m, 2H), 3.61 (s, 3H), 3.73 (m, 1H), 3.90 (m, 1H), 6.89 (d, *J*=8.4 Hz, 1H), 6.94–6.98 (m, 3H), 7.05–7.24 (m, 9H), 7.35 (t, *J*=7.6 Hz, 1H), 7.49 (d, *J*=7.6 Hz, 1H), 7.52 (d, *J*=7.6 Hz, 2H), 7.58 (d, *J*=8.0 Hz, 1H), 7.61 (d, *J*=9.2 Hz, 1H), 7.92 (d, *J*=7.6 Hz, 1H), 7.96–7.99 (m, 2H); ^{13}C NMR δ 24.35, 25.22, 28.93, 33.81, 51.46, 67.88, 113.12, 119.87, 123.08, 125.42, 126.03, 126.46, 126.81, 126.92, 127.24, 127.48, 127.60, 127.71, 128.19, 128.83, 128.94, 129.61, 130.12, 130.17, 130.37, 130.64, 130.84, 131.00, 131.09, 131.71, 132.04, 132.94, 133.06, 133.97, 134.58, 140.41, 140.50, 153.92, 173.68; ^{31}P NMR δ +27.67; HRMS (FAB$^+$): calcd for $C_{39}H_{35}O_4P$ (M^+) 598.2273. Found 589.2270.

4.1.2. (*R*)-2-Diphenylphosphino-2′-(1-(methoxycarbonyl)pentan-5-oxy)-1,1′-binaphthyl ((*R*)-6). A mixture of (*R*)-**5** (1.88 g, 3.16 mmol), trichlorosilane (1.2 mL, 12.0 mmol) and triethylamine (4.80 mL, 36.0 mmol) was heated in toluene under reflux for 15 h. The reaction was cooled to ambient temperature, a solution of saturated aqueous $NaHCO_3$ (2 mL) was added slowly (Caution! Sometimes a violent reaction occurs!), and the mixture was stirred for 15 min. The white precipitate formed was removed by filtration and washed several times with toluene. The filtrates were combined and dried with $MgSO_4$. After the solvent was removed in vacuo, the residue was purified by column chromatography over silica gel with CH_2Cl_2. Yield: 1.52 g (83%) white foam; $[\alpha]_D^{22} = +60.7$ (THF, *c* 1.41); ^{1}H NMR δ 0.81 (m, 2H), 1.26 (m, 4H), 1.90 (m, 2H), 3.62 (s, 3H), 3.74 (m, 2H), 6.92 (d, *J*=8.8 Hz, 1H), 7.07–7.29 (m, 12H), 7.31 (d, *J*=9.2 Hz, 1H), 7.42–7.47 (m, 4H), 7.84 (d, *J*=8.4 Hz, 2H), 7.87 (d, *J*=9.2 Hz, 1H), 7.96 (d, *J*=9.2 Hz, 1H); ^{13}C NMR δ 24.35, 25.17, 28.81, 33.79, 51.44, 68.12, 113.86, 113.94, 122.32, 122.41, 123.18, 125.21, 125.95, 126.08, 126.44, 126.59, 127.47, 127.64, 127.90, 128.49, 129.49, 129.58, 130.12, 130.20, 132.88, 133.16, 133.36, 133.47, 134.03, 135.44, 135.53, 137.91, 138.01, 138.15, 142.19, 142.53, 154.06, 173.75; ^{31}P NMR δ −14.53; HRMS (FAB$^+$): calcd for $C_{39}H_{35}O_3P$ (M^+) 582.2324. Found 582.2310.

4.1.3. PS-PEG-2′-Anchored MOP–palladium complex ((*R*)-1-Pd). *General procedure for the immobilization of the MOP ligands*. The MOP methyl ester (1.00 equiv) and $LiOH \cdot H_2O$ (1.05 equiv) were stirred in a mixture of THF/H_2O (degassed by three pump-thaw cycles) for 24 h at 25 °C under a nitrogen-atmosphere. The solvent was removed in vacuo and a white precipitate was obtained. The PS-PEG amino resin (Argo gel NH_2) (0.35 mmol amino residue/g, 0.90 equiv) was washed with CH_2Cl_2, MeOH, MeCN and again with CH_2Cl_2. The gel was then dried in vacuo and was swollen in DMF. The white precipitate (1.1 equiv), HOBt (1.0 equiv) and EDCI (2.5 equiv) were dissolved in DMF and added to the gel. Air was removed by several vacuo/nitrogen-gas cycles. The mixture was stirred for 2 h at 25 °C, EDCI (5 equiv) was added again and stirring was resumed for 12 h. Quantification of the coupling reaction was determined by the Kaiser test. The solvent was removed using a syringe and the beads were washed several times with DMF. $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.1 equiv) was dissolved in DMF and added via syringe to the beads. The reaction mixture was stirred for 2 h, the solvent was removed, the beads were washed several times with DMF and EtOH, and dried in vacuo to give yellow colored beads (loading about 0.28 mmol/g). The catalysts were obtained as diastereomeric mixtures. (*R*)-**1**-Pd: (dr 1.4:1) Gel-phase ^{13}C MAS NMR δ 24.68, 28.05, 35.92, 38.77, 67.14, 102.34, 114.28, 114.86, 116.90, 119.43, 122.81, 129.24, 130.93, 132.20, 132.66, 133.00, 133.74, 154.94, 172.56; Gel-phase ^{31}P MAS NMR δ +13.05, +15.90.

4.1.4. (*R*)-6-Bromo-2′-pivaloyloxy-2-methoxymethoxy-1,1′-binaphthyl ((*R*)-8). A mixture of (*R*)-6-bromo-2′-pivaloyloxybinaphthyl ((*R*)-**7**) (1.796 g, 4.0 mmol), chloromethyl methyl ether (0.966 g, 12.0 mmol), K_2CO_3 (1.65 g, 12.0 mmol) and acetone (30 mL) was refluxed for 15 h. The reaction mixture was concentrated in vacuo and the resulting crude residue was dissolved in EtOAc (50 mL). The solution was washed with water and brine, and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was purified by a short column chromatography over silica gel with EtOAc/*n*-hexane (4:1). Yield: 1.97 g (100%) light-green viscous oil; $[\alpha]_D^{22} = +21.9$ (THF, *c* 1.26); ^1H NMR δ 0.74 (s, 9H), 3.20 (s, 3H), 5.03 (s, 2H), 7.02 (d, J=9.2 Hz, 1H), 7.24–7.33 (m, 3H), 7.39, (d, J=9.2 Hz, 1H), 7.46 (td, J_1=7.4 Hz, J_2=0.8 Hz, 1H), 7.57 (d, J=9.6 Hz, 1H), 7.83 (d, J=9.2 Hz, 1H), 7.94 (d, J=8.4 Hz, 1H), 7.99 (m, 2H); ^{13}C NMR δ 26.52, 38.65, 55.96, 94.76, 117.38, 117.89, 119.49, 121.89, 124.46, 125.45, 125.73, 126.48, 127.35, 128.07, 128.75, 129.16, 129.47, 129.66, 130.51, 131.56, 132.21, 133.43, 146.84, 152.86, 176.26; HRMS (FAB^+): calcd for $C_{27}H_{25}O_4Br$ (M^+) 494.0937. Found 494.0922.

4.1.5. (*R*)-6-Bromo-2′-hydroxy-2-methoxymethoxy-1,1′-binaphthyl ((*R*)-9). A mixture of (*R*)-**8** (1.97 g, 4.0 mmol), $LiOH \cdot H_2O$ (0.504 g, 12.0 mmol), water (20 mL) and THF (20 mL) was stirred at 50 °C for 16 h. After THF was removed in vacuo, AcOH (0.5 g) and water were added to the resulting aqueous residue. The aqueous solution was extracted with CH_2Cl_2 (three times, 20 mL). The organic phase was washed with aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The organic phase was concentrated in vacuo to give (*R*)-**9**, which was taken to the next step without further purification. Yield: 1.62 g (99%) white-greenish foam; $[\alpha]_D^{22} = +18.4$ (THF, *c* 1.1); ^1H NMR δ 3.18 (s, 3H), 4.90 (s, 1H), 5.10 (m, 2H), 7.01 (d, J=8.4 Hz, 1H), 7.05 (d, J=9.2 Hz, 1H), 7.21–7.36 (m, 4H), 7.62, (d, J=9.2 Hz, 1H), 7.90 (m, 3H), 8.06 (d, J=2.0 Hz, 1H); ^{13}C NMR δ 56.25, 94.88, 114.44, 117.50, 117.83, 118.03, 118.59, 123.35, 124.50, 126.55, 126.94, 128.07, 128.99, 129.88, 129.99, 130.43, 131.12, 132.42, 133.55, 151.12, 153.72; HRMS (FAB^+): calcd for $C_{22}H_{17}O_3Br$ (M^+) 408.0362. Found 408.0333.

4.1.6. (*R*)-6-Bromo-2′-methoxy-2-methoxymethoxy-1,1′-binaphthyl ((*R*)-10). A mixture of (*R*)-**9** (1.62 g, 3.96 mmol), methyl iodide (1.704 g, 12.0 mmol), K_2CO_3 (1.65 g, 12.0 mmol) and acetone (40 mL) was refluxed for 15 h. The reaction mixture was concentrated in vacuo, and the resulting residue was dissolved with CH_2Cl_2 (50 mL). The solution was washed water and brine, and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was purified by a short column chromatography over silica gel with EtOAc/*n*-hexane (4:1) to give (*R*)-**10**. Yield: 1.68 g (100%) light-green foam; $[\alpha]_D^{22} = +35.8$ (THF, *c* 1.00); ^1H NMR δ 3.16 (s, 3H), 3.76 (s, 3H), 5.03 (br, 2H), 6.99 (d, J=8.8 Hz, 1H), 7.07 (dd, J_1=8.8 Hz, J_2=0.8 Hz, 1H), 7.20–7.34 (m, 2H), 7.44, (d, J=9.2 Hz, 1H), 7.46 (d, J=9.2 Hz, 1H), 7.58 (d, J=8.8 Hz, 1H), 7.85 (m, 2H), 7.98 (d, J=9.2 Hz, 1H), 8.02 (d, J=2.0 Hz, 1H); ^{13}C NMR δ 55.85, 56.64, 94.99, 113.66, 117.82, 118.26, 118.58, 121.51, 123.55, 124.95, 126.44, 127.29, 127.87, 128.29, 128.99, 129.45, 129.63, 129.74, 130.90, 132.46, 133.77, 152.75, 154.74; HRMS (FAB^+): calcd for $C_{23}H_{19}O_3Br$ (M^+) 422.0518. Found 422.0521.

4.1.7. (*R*)-6-((*E*)-1-(*n*-Butyloxycarbonyl)-ethen-2-yl)-2′-methoxy-2-methoxymethoxy-1,1′-binaphthyl ((*R*)-11). A mixture of (*R*)-**10** (1.67 g, 3.96 mmol), *n*-butyl acrylate (564 mg, 4.40 mmol), tri-*n*-butylamine (3.70 g, 20.00 mmol), tri-*o*-tolylphosphine (61.0 mg, 0.20 mmol), palladium diacetate (22.0 mg, 0.10 mmol) and DMF (10 mL) was stirred at 130 °C for 48 h under nitrogen. After the reaction was cooled to ambient temperature, CH_2Cl_2 (200 mL) was added and the mixture was extracted with aqueous 1 N HCl (50 mL, two times), aqueous $NaHCO_3$ (50 mL) and brine. The organic phase was dried over $MgSO_4$, concentrated in vacuo, and the residue was purified by column chromatography over silica gel using *n*-hexane/EtOAc (4:1) to give (*R*)-**11**. Yield: 1.06 g (57%) brown viscous oil; $[\alpha]_D^{22} = -10.3$ (THF, *c* 1.50); ^1H NMR δ 0.96 (t, J=7.25 Hz, 3H), 1.44 (sext., J=7.0 Hz, 2H), 1.69 (quint., J=7.0 Hz, 2H), 3.17 (s, 3H), 3.76 (s, 3H), 4.21 (t, J=6.75 Hz, 2H), 5.05 (m, 2H), 6.43 (d, J=16 Hz, 1H), 7.11 (m, 2H), 7.21, (m, 1H), 7.32 (td, J_1=8.0 Hz, J_2=1.0 Hz, 1H), 7.39 (dd, J_1=8.5 Hz, J_2=1.5 Hz, 1H), 7.45 (d, J=9.0 Hz, 1H), 7.60 (d, J=9.0 Hz, 1H), 7.81 (d, J=16.0 Hz, 1H), 7.87 (d, J=8.5 Hz, 1H), 7.96 (m, 2H), 7.99 (d, J=8.5 Hz, 1H); ^{13}C NMR δ 13.97, 19.42, 30.96, 55.92, 56.71, 64.41, 94.79, 113.63, 117.31, 117.55, 118.66, 121.29, 123.42, 123.73, 124.86, 126.02, 126.30, 127.75, 128.89, 129.40, 129.47, 129.82, 129.95, 133.66, 134.77, 144.46, 153.51, 154.57, 166.98; HRMS (FAB^+): calcd for $C_{30}H_{30}O_5$ (M^+) 470.2093. Found 470.2123.

4.1.8. (*R*)-6′-(2-(Methoxycarbonyl)ethyl)-2′-methoxy-2-

hydroxy-1,1′-binaphthyl ((*R*)-13). A solution of (*R*)-**11** (1.06 g, 2.25 mmol), *tert*-butanol (1 mL), EtOAc (30 mL) and Pearlman's catalyst (50 mg) was stirred at 60 °C for 6 h under a hydrogen atmosphere (balloon). The temperature was reduced to 40 °C and the mixture was stirred for an additional 15 h. The solvent was removed in vacuo and the catalyst was separated by a short column chromatography over silica gel with *n*-hexane/EtOAc (3:1). The filtrate contained a mixture of the product and the MOM-deprotected products **12** and **13** (on TLC and GC–MS). The solvent was removed, and to the residue was added a mixture of AcCl (0.5 mL) in methanol (20 mL) at 0 °C. After the mixture was stirred for 15 h, the solvent was removed in vacuo to give (*R*)-**13**. Yield: 760 mg (87%) light brown foam; $[\alpha]_D^{22}=+10.6$ (THF, *c* 1.30); ^{1}H NMR δ 2.67 (t, $J=8.0$ Hz, 2H), 3.04 (t, $J=8.0$ Hz, 2H), 3.66 (s, 3H), 3.79 (s, 3H), 4.90 (s, 1H), 6.97 (d, $J=8.5$ Hz, 1H), 7.06 (dd, $J_1=8.5$ Hz, $J_2=2.0$ Hz, 1H), 7.16, (d, $J=8.5$ Hz, 1H), 7.26 (t, $J=8.5$ Hz, 1H), 7.32 (d, $J=8.5$ Hz, 1H), 7.36 (td, $J_1=9.0$ Hz, $J_2=1.0$ Hz, 1H), 7.46 (d, $J=9.5$ Hz, 1H), 7.65 (s, 1H), 7.83 (d, $J=9.0$ Hz, 1H), 7.89 (d, $J=8.0$ Hz, 1H), 8.04 (d, $J=9.0$ Hz, 1H); ^{13}C NMR δ 30.91, 35.75, 51.70, 56.72, 113.60, 114.76, 115.17, 117.43, 123.95, 124.68, 124.88, 126.54, 127.10, 127.27, 127.93, 128.99, 129.13, 129.17, 130.80, 132.18, 133.77, 134.95, 150.64, 155.62, 173.07; HRMS (FAB$^+$): calcd for $C_{25}H_{22}O_4$ (M^+) 386.1518. Found 386.1505.

4.1.9. (*R*)-6-(2-(Methoxycarbonyl)ethyl)-2′-methoxy-2-(trifluoromethane)sulfonyloxy-1,1′-binaphthyl ((*R*)-14). To a solution of (*R*)-**13** (760 mg, 1.47 mmol) and pyridine (242 μL, 3.0 mmol) in CH_2Cl_2 (20 mL) triflic anhydride (500 μL, 2.95 mmol) was added dropwise at 0 °C with stirring. The mixture was allowed to warm to 25 °C and stirred for an additional 2 h. To the reaction mixture was added water, and the organic phase was washed with aqueous 1 N HCl, aqueous $NaHCO_3$ and brine. After the solvent was removed, the residue was purified by column chromatography over silica gel with *n*-hexane/EtOAc (4:1) to give (*R*)-**14**. Yield: 821 mg (81%) light yellow oil; $[\alpha]_D^{22}=-68.3$ (THF, *c* 0.50); ^{1}H NMR δ 2.70 (t, $J=8.0$ Hz, 2H), 3.10 (t, $J=7.6$ Hz, 2H), 3.67 (s, 3H), 3.82 (s, 3H), 6.99 (d, $J=8.4$ Hz, 1H), 7.18–7.26 (m, 3H), 7.33 (td, $J_1=6.8$ Hz, $J_2=0.8$ Hz, 1H), 7.44 (d, $J=9.2$ Hz, 1H), 7.53 (d, $J=9.2$ Hz, 1H), 7.73 (s, 1H), 7.88 (d, $J=8.0$ Hz, 1H), 7.96 (d, $J=9.2$ Hz, 1H), 8.04 (d, $J=9.2$ Hz, 1H); ^{13}C NMR δ 30.81, 35.36, 51.78, 56.22, 112.74, 114.94, 119.56, 123.53, 124.62, 126.63, 126.69, 126.95, 127.88, 127.96, 128.38, 128.60, 129.55, 129.62, 130.86, 132.11, 132.55, 133.34, 139.00, 145.11, 154.87, 172.85; HRMS (FAB$^+$): calcd for $C_{26}H_{21}O_6F_3S$ (M^+) 518.1011. Found 518.1028.

4.1.10. (*R*)-6-(2-(Methoxycarbonyl)ethyl)-2′-methoxy-2-diphenylphosphinyl-1,1′-binaphthyl ((*R*)-16). In a flame-dried Schlenck vessel equipped with a magnetic stirring bar were placed $NiCl_2$(dppe) (41.7 mg, 0.075 mmol), DMF (6 mL) and diphenylphosphine (0.12 mL, 0.72 mmol) at 25 °C under a nitrogen atmosphere. The mixture was heated with stirring to 100 °C and maintained at this temperature for 30 min. A solution of (*R*)-**14** (821 mg, 1.58 mmol) and DABCO (335 mg, 3.16 mmol) in DMF (4 mL) was added via syringe and stirring was continued at 100 °C for 46 h. After 1, 3 and 7 h intervals, three more portions of diphenylphosphine (0.12 mL, 0.72 mmol) were added. The reaction mixture was cooled to ambient temperature, diluted with water and extracted with CH_2Cl_2. The organic phase was washed with aqueous 1 N HCl, aqueous $NaHCO_3$ and water, and dried over $MgSO_4$. The solution was concentrated in vacuo, then THF (10 mL) and H_2O_2 (0.5 mL, 33%) were added. The mixture was stirred for 2 h, the volatile solvent was removed and the aqueous mixture was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was purified by column chromatography over silica gel with CH_2Cl_2/EtOAc (1:0 to 1:1) to give unreacted starting material (180 mg, 22%) and (*R*)-**16** as white powder. Yield: 404 mg (45%); $[\alpha]_D^{22}=+60.0$ (THF, *c* 0.92); ^{1}H NMR δ 2.69 (t, $J=8.0$ Hz, 2H), 3.10 (t, $J=7.6$ Hz, 2H), 3.57 (s, 3H), 3.67 (s, 3H), 6.79 (d, $J=8.4$ Hz, 1H), 7.00–7.10 (m, 6H), 7.17 (m, 4H), 7.27 (m, 2H), 7.43 (dd, $J_1=12$ Hz, $J_2=1.6$ Hz, 1H), 7.45 (d, $J=12.0$ Hz, 1H), 7.59 (d, $J=8.4$ Hz, 1H), 7.66 (d, $J=8.8$ Hz, 1H), 7.72 (s, 1H), 7.90 (m, 2H), 8.29 (s, 1H); ^{13}C NMR δ 30.89, 35.19, 51.74, 55.35, 111.95, 119.34, 123.10, 125.37, 126.16, 126.52, 127.12, 127.23, 127.37, 127.56, 127.67, 127.91, 128.20, 128.69, 129.23, 129.34, 129.73, 130.35, 130.59, 130.89, 131.24, 131.34, 131.63, 131.73, 131.81, 131.92, 132.08, 132.53, 133.12, 133.56, 134.03, 135.00, 140.25, 140.51, 154.53, 173.05; ^{31}P NMR δ +28.31; HRMS (FAB$^+$): calcd for $C_{37}H_{31}O_4P$ (M^+) 570.1960. Found 570.1942.

4.1.11. (*R*)-6-(2-(Methoxycarbonyl)ethyl)-2′-methoxy-2-diphenylphosphino-1,1′-binaphthyl ((*R*)-15). The reduction was performed under the same conditions as described for the preparation of (*R*)-**6** (Section 4.1.2) using (*R*)-**16** (404 mg, 0.71 mmol). Yield: 340 mg (87%) white solid; $[\alpha]_D^{22}=+79.4$ (THF, *c* 1.00); ee >99% (Daicel AD, *n*-hexane/iso-propanol 97:3, flow 1.0 mL (*R*) 8.8 min, (*S*) 13.4 min); ^{1}H NMR δ 2.68 (t, $J=7.6$ Hz, 2H), 3.07 (t, $J=7.6$ Hz, 2H), 3.34 (s, 3H), 3.67 (s, 3H), 6.92 (d, $J=7.6$ Hz, 1H), 7.07–7.30 (m, 15H), 7.36 (dd, $J_1=8.8$ Hz, $J_2=2.8$ Hz, 1H), 7.68 (s, 1H), 7.79 (d, $J=8.4$ Hz, 1H), 7.85 (d, $J=8.0$ Hz, 1H), 7.98 (d, $J=8.8$ Hz, 1H); ^{13}C NMR δ 30.97, 35.43, 51.70, 55.51, 112.55, 121.71, 121.80, 123.28, 125.18, 126.33, 126.52, 126.96, 127.37, 127.82, 127.92, 127.99, 128.53, 129.76, 130.66, 131.75, 133.08, 133.28, 133.35, 133.55, 133.80, 133.97, 134.77, 134.86, 137.59, 137.72, 138.37, 138.50, 138.83, 141.87, 142.22, 154.93, 173.14; ^{31}P NMR δ −14.80; HRMS (FAB$^+$): calcd for $C_{37}H_{31}O_3P$ (M^+) 554.2011. Found 554.1998.

4.1.12. PS-PEG-6-Anchored MOP–palladium complex ((*R*)-2-Pd). According to the general procedure as described for preparation of **1**-Pd (Section 4.1.3), (*R*)-**15** was converted to PS-PEG amino resin-supported 6-anchored MOP–Pd complex (*R*)-**2**-Pd (loading about 0.28 mmol/g): (dr 1.2:1) Gel-phase ^{13}C MAS NMR δ 31.1, 37.7, 38.9, 54.8, 55.2, 101.8, 113.5, 114.0, 116.8, 118.9, 128.8, 129.2, 130.6, 130.9, 132.4, 133.0, 133.8, 135.6, 154.9, 171.6; Gel-phase ^{31}P MAS NMR δ +14.0, +16.0.

4.1.13. (*R*)-6′-Bromo-2′-methoxy-2-diphenylphosphinyl-1,1′-binaphthyl ((*R*)-18). A mixture of (*R*)-6′-bromo-2′-hydroxy-2-phosphinylbinaphthyl ((*R*)-**17**) (2.96 g, 5.40 mmol), methyl iodide (1.927 g, 13.20 mmol), K_2CO_3

(2.30 g, 16.50 mmol) and acetone (40 mL) was refluxed for 15 h. The mixture was concentrated in vacuo. To the resulting crude residue was added CH_2Cl_2 (50 mL) and water. After separation, the organic phase was washed with water and brine, and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was purified by a short column chromatography over silica gel with CH_2Cl_2/EtOAc (3:1 to 1:1) to give (*R*)-**18**. Yield: 3.00 g (99%) white foam; $[\alpha]_D^{22}=+63.3$ (THF, *c* 0.57); ^{1}H NMR δ 3.57 (s, 3H), 6.65 (d, $J=8.8$ Hz, 1H), 7.05–7.13 (m, 5H), 7.19–7.35 (m, 6H), 7.43 (dd, $J_1=11.6$ Hz, $J_2=1.6$ Hz, 1H), 7.45 (d, $J=12.0$ Hz, 1H), 7.54 (t, $J=7.4$ Hz, 1H), 7.61 (d, $J=9.2$ Hz, 1H), 7.77 (d, $J=2.0$ Hz, 1H), 7.84 (d, $J=8.4$ Hz, 1H), 7.87 (d, $J=8.8$ Hz, 1H), 7.93 (d, $J=8.4$ Hz, 1H), 7.98 (dd, $J_1=8.8$ Hz, $J_2=2.4$ Hz, 1H); ^{13}C NMR δ 55.53, 112.99, 116.80, 119.69, 126.56, 126.83, 127.17, 127.23, 127.36, 127.59, 127.71, 127.83, 127.94, 128.82, 128.93, 129.14, 129.22, 129.30, 130.62, 130.23, 131.22, 131.31, 131.50, 131.60, 132.19, 132.48, 132.88, 133.00, 133.23, 133.48, 134.66, 140.04, 154.86; ^{31}P NMR δ +27.10; HRMS (FAB$^+$): calcd for $C_{33}H_{24}BrO_2P$ (M^+) 562.0697. Found 562.0701.

4.1.14. (*R*)-6′-((*E*)-1-(*n*-Butyloxycarbonyl)ethen-2-yl)-2′-methoxy-2-diphenylphosphinyl-1,1′-binaphthyl ((*R*)-19). A mixture of (*R*)-**18** (3.00 g, 5.33 mmol), *n*-butyl acrylate (1.36 g, 10.66 mmol), tri-*n*-butylamine (4.93 g, 26.65 mmol), tri-*o*-tolylphosphine (81.3 mg, 0.266 mmol), palladium diacetate (29.3 mg, 0.133 mmol) and DMF (20 mL) was stirred at 130 °C for 40 h under nitrogen. After being cooled to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (200 mL), and was washed with aqueous 1 N HCl (50 mL, two times), saturated aqueous $NaHCO_3$ (50 mL) and brine. The organic phase was dried over $MgSO_4$, concentrated in vacuo and the residue was purified by column chromatography over silica gel using CH_2Cl_2/EtOAc (3:1) to give (*R*)-**19**. Yield: 2.83 g (87%) light yellow foam; $[\alpha]_D^{22}=+51.8$ (THF, *c* 1.14); ^{1}H NMR δ 0.95 (t, $J=7.6$ Hz, 3H), 1.45 (sext., $J=7.6$ Hz, 2H), 1.70 (quint., $J=7.6$ Hz, 2H), 3.58 (s, 3H), 4.21 (t, $J=6.6$ Hz, 2H), 6.38 (d, $J=16.0$ Hz, 1H), 6.77 (d, $J=9.2$ Hz, 1H), 7.06–7.47 (m, 13H), 7.54 (t, $J=7.2$ Hz, 1H), 7.71–7.77 (m, 3H), 7.84 (d, $J=8.8$ Hz, 1H), 7.87 (d, $J=8.8$ Hz, 1H), 7.94 (d, $J=8.8$ Hz, 1H), 7.99 (dd, $J_1=8.8$ Hz, $J_2=2.0$ Hz, 1H); ^{13}C NMR δ 13.74, 19.18, 30.72, 55.45, 64.21, 112.42, 116.71, 119.60, 123.38, 125.84, 126.40, 126.64, 127.04, 127.16, 127.37, 127.62, 128.63, 128.75, 129.01, 129.24, 129.53, 130.44, 130.59, 130.86, 131.05, 131.45, 131.31, 131.41, 132.05, 132.27, 132.70, 133.08, 133.31, 134.45, 134.68, 139.98, 144.41, 155.62, 166.97; ^{31}P NMR δ +27.14; HRMS (FAB$^+$): calcd for $C_{40}H_{35}O_4P$ (M^+) 610.2273. Found 610.2275.

4.1.15. (*R*)-6′-(2-(*n*-Butyloxycarbonyl)ethyl)-2′-methoxy-2-diphenylphosphinyl-1,1′-binaphthyl. A mixture of (*R*)-**19** (2.80 g, 4.60 mmol), Pearlman's catalyst (145 mg), *tert*-butanol (5 mL) and EtOAc (40 mL) was stirred at 100 °C for 41 h under a hydrogen atmosphere (7 atm). The catalyst was filtered off (Caution! Pyrophoric!), and the solvent was removed in vacuo. The residue was purified by a short column chromatography over silica gel using CH_2Cl_2/EtOAc (3:1) to give (*R*)-6′-(2-(*n*-butyloxycarbonyl)ethyl)-2′-methoxy-2-diphenyl-phosphinyl-1,1′-binaphthyl. Yield: 2.81 g (100%) yellow viscous oil; $[\alpha]_D^{22}=+68.5$ (THF, *c* 1.31); ^{1}H NMR δ 0.92 (t, $J=7.6$ Hz, 3H), 1.36 (sext., $J=7.6$ Hz, 2H), 1.60 (quint., $J=8.0$ Hz, 2H), 2.65 (t, $J=8.4$ Hz, 2H), 2.98 (t, $J=7.6$ Hz, 2H), 3.56 (s, 3H), 4.10 (t, $J=7.2$ Hz, 2H), 6.71 (d, $J=8.4$ Hz, 1H), 6.99–7.60 (m, 17H), 7.91–7.98 (m, 3H); ^{13}C NMR δ 13.87, 19.27, 20.94, 30.80, 36.00, 55.55, 64.42, 112.07, 125.55, 125.83, 126.69, 126.84, 127.02, 127.14, 127.21, 127.49, 127.60, 127.77, 127.87, 128.22, 128.85, 128.96, 129.86, 130.51, 130.81, 131.17, 131.27, 131.58, 131.68, 132.65, 134.70, 135.08, 154.22, 172.83; ^{31}P NMR δ +28.44. (*R*)-6′-(2-(*n*-Butyloxycarbonyl)ethyl)-2′-methoxy-2-diphenyl-phosphinyl-1,1′-binaphthyl was then converted to its methyl ester **20**.

4.1.16. (*R*)-6′-(2-(Methoxycarbonyl)ethyl)-2′-methoxy-2-diphenylphosphinyl-1,1′-binaphthyl ((*R*)-20). To a mixture of THF/H_2O (1:1, 50 mL) were added (*R*)-6′-(2-(*n*-butyloxycarbonyl)ethyl)-2′-methoxy-2-diphenyl-phosphinyl-1,1′-binaphthyl (2.80 g, 4.58 mmol) and $LiOH\cdot H_2O$ (0.577 g, 13.74 mmol). The reaction mixture was stirred at 40 °C for 15 h then acidified with aqueous HCl (10 N, 15 mL. The solvent was removed and to the resulting white solid was added a mixture of AcCl (0.5 mL) in methanol (30 mL) and trimethoxymethane (3 mL). The reaction mixture was stirred for 24 h. The solvent was removed in vacuo and the crude residue was purified by a short column chromatography over silica gel with CH_2Cl_2/EtOAc (1:1) to give (*R*)-**20**. Yield: 2.47 g (95%) light yellow foam; $[\alpha]_D^{22}=+77.4$ (THF, *c* 1.02); ^{1}H NMR δ 2.67 (t, $J=7.2$ Hz, 2H), 2.99 (t, $J=7.6$ Hz, 2H), 3.57 (s, 3H), 3.70 (s, 3H), 6.72 (d, $J=8.4$ Hz, 1H), 6.89 (dd, $J_1=8.4$ Hz, $J_2=1.2$ Hz, 1H), 6.98–7.03 (m, 3H), 7.10–7.31 (m, 7H), 7.39 (s, 1H), 7.47 (m, 3H), 7.52 (t, $J=7.6$ Hz, 1H), 7.60 (d, $J=9.6$ Hz, 1H), 7.92–7.98 (m, 3H); ^{13}C NMR δ 30.63, 35.57, 51.53, 55.39, 111.92, 119.08, 125.43, 125.65, 126.48, 126.65, 126.78, 126.91, 127.26, 127.39, 127.53, 127.68, 128.04, 128.71, 128.81, 129.19, 129.66, 130.22, 130.52, 130.95, 131.05, 131.38, 131.48, 131.96, 132.50, 132.78, 133.50, 134.47, 134.78, 140.29, 140.38, 154.06, 172.96; ^{31}P NMR δ +27.67; HRMS (FAB$^+$): calcd for $C_{37}H_{31}O_4P$ (M^+) 570.1960. Found 570.1956.

4.1.17. (*R*)-6′-(2-(Methoxycarbonyl)ethyl)-2′-methoxy-2-diphenylphosphino-1,1′-binaphthyl ((*R*)-21). The reduction was performed under the same conditions as described for (*R*)-**15** using (*R*)-**20** (2.30 g, 4.04 mmol) to give (*R*)-**21**. Yield: 1.90 g (85%) white foam; $[\alpha]_D^{22}=+91.4$ (THF, *c* 1.03); ee > 99% (Daicel AD, *n*-hexane/iso-propanol 97:3, flow 1.0 mL, (*R*) 8.1 min, (*S*) 10.1 min); ^{1}H NMR δ 2.68 (t, $J=7.6$ Hz, 2H), 3.04 (t, $J=8.0$ Hz, 2H), 3.34 (s, 3H), 3.68 (s, 3H), 6.84 (d, $J=8.8$ Hz, 1H), 6.96 (dd, $J_1=8.8$ Hz, $J_2=2.0$ Hz, 1H), 7.06 (m, 2H), 7.15–7.29 (m, 11H), 7.38 (dd, $J_1=8.4$ Hz, $J_2=2.4$ Hz, 1H), 7.45 (td, $J_1=6.2$ Hz, $J_2=2.0$ Hz, 1H), 7.64 (s, 1H), 7.84 (d, $J=8.4$ Hz, 1H), 7.87 (d, $J=8.0$ Hz, 1H), 7.92 (d, $J=8.8$ Hz, 1H); ^{13}C NMR δ 30.93, 35.65, 51.70, 55.53, 112.70, 125.37, 126.19, 126.28, 126.51, 127.36, 127.63, 127.74, 127.81, 127.86, 127.92, 127.98, 128.53, 129.25, 130.24, 132.59, 132.83, 132.90, 133.06, 133.26, 133.29, 133.49, 135.03, 135.22, 138.16, 138.30, 142.27, 154.57, 173.22; ^{31}P NMR δ −14.67; HRMS (FAB$^+$): calcd for $C_{37}H_{31}O_3P$ (M^+) 554.2011. Found 554.2013.

4.1.18. PS-PEG-6′-Anchored MOP–palladium complex ((*R*)-3-Pd). According to the general procedure as described for preparation of **1**-Pd (Section 4.1.3), (*R*)-**15** was converted to the PS-PEG amino resin-supported 6′-anchored MOP–Pd complex (*R*)-**3**-Pd (loading about 0.28 mmol/g): (dr 1:1) Gel-phase ^{13}C MAS NMR δ 31.08, 37.72, 38.94, 54.79, 55.18, 101.76, 113.50, 113.95, 116.82, 118.93, 128.85, 129.22, 130.60, 130.85, 132.44, 132.97, 133.84, 135.60, 154.91, 171.60; Gel-phase ^{31}P MAS NMR δ +13.98, +15.98.

4.1.19. Asymmetric reduction of *rac*-22 with HCOOH. A typical procedure is given for the catalytic asymmetric reduction of *rac*-**22** with (*R*)-**2**-Pd (Table 1, entry 8): in a flame-dried flask equipped with magnetic stirring bar, were placed catalyst (*R*)-**2**-Pd (44.6 mg, 0.0125 mmol) and *rac*-**22** (69.5 mg, 0.25 mmol). The flask was evacuated and flashed with argon (three times). A solution of proton sponge (64.3 mg, 0.30 mmol) and formic acid (25.3 mg, 0.55 mmol) in dioxane/THF (1:1, 2 mL, degassed) was added via syringe. The mixture was stirred for 7 days at 0 °C. The beads were filtered off and washed with THF. The collected filtrate was diluted with *n*-hexane and washed with aqueous 1 N HCl, aqueous $NaHCO_3$ and water. The filtrate was dried over $MgSO_4$, the solvent was removed and the resulting residue was purified by column chromatography using silica gel and *n*-hexane/EtOAc (100:1 to 95:5) to give 29.7 mg (75%) (*R*)-**23** with 79% ee.

Acknowledgements

This work was supported by the CREST program sponsored by JST. We also thank the JSPS (Creative Scientific Research, No. 13GS0024; GRANT-in-AID for Scientific Research, No.15205015) and the MEXT (Scientific Research on Priority Areas, Nos. 412 and 420) for partial financial support of this work.

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21. After the reaction, the catalyst beads were removed by filtration and the resulting filtrate did not catalyze the allylic reduction to demonstrate no leaching of palladium species from the beads during the catalytic reaction.

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Tetrahedron 60 (2004) 9307–9317
Tetrahedron

Total synthesis of pyridovericin

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Received 21 May 2004; revised 23 June 2004; accepted 15 July 2004

Abstract—The total synthesis of the naturally occurring kinase inhibitor pyridovericin **1** is reported. A flexible and efficient synthesis has been accomplished in good yield from readily available 2,4-dihydroxypyridine. Pyridovericin is a key intermediate in our proposed biomimetic synthesis of pyridomacrolidin **2**.

As part of our studies towards the synthesis of novel tyrosine kinase inhibitors, we have become particularly interested in the biomimetic synthesis of pyridovericin **1** and pyridomacrolidin **2**. Pyridovericin and pyridomacrolidin are novel metabolites isolated from the entomopathogenic fungus *Beauveria bassiana* in 1998 by Nakagawa and co-workers.[1] Structurally, pyridovericin **1** and pyridomacrolidin **2** contain the same *p*-hydroxyphenyl pyridone unit present in the related fungal metabolites tenellin **3**,[2] bassianin **4**,[3] and ilicicolin H **5**.[4] Biologically, pyridovericin **1** and pyridomacrolidin **2** have been shown to inhibit the protein tyrosine kinase (PTK) activity at concentrations of 100 μg/ml[1] making them potential therapeutic leads against a variety of proliferative and inflammatory diseases (Fig. 1).[5]

Interest in this type of compounds has largely focussed on the determination of the biosynthetic pathway for the generation of tenellin **3**, bassianin **4**, and ilicicolin H **5**.[6–8] Biosynthetically, it has been shown through a series of feeding experiments that tenellin **3** originates from a polyketide chain **6** and the aromatic amino-acid L-phenylalanine **7**. Mechanistically, it has been proposed that L-phenylalanine **7** combines with the polyketide **6** unit to generate the acyltetramic acid intermediate **8**. Oxidation of acid **8** then generates the transient *p*-quinonemethide intermediate **9**, which undergoes a ring expansion to generate the 2-pyridone ring **10**. Finally, oxidation of the newly formed pyridone unit **10** generates tenellin **3** (Scheme 1).[6,8]

Although it is believed that the biosynthesis of pyridovericin **1** presumably follows a similar pathway as that of tenellin **3**, the biosynthesis of pyridomacrolidin **2** has not yet been elucidated. However, it is possible to propose a biomimetic formation of pyridomacrolidin **2** from pyridovericin **1** via a number of simple steps (Scheme 2); (i) oxidation of pyridovericin **1** to hydroxamic acid **11**, (ii) further oxidation to the acyl nitrone intermediate **12**, (iii) 1,3-dipolar cycloaddition[9] with cephalosporolide B **13**, and (iv) re-aromatisation to form pyridomacrolidin **2**. Cephalosporolide B **13** is itself a natural product, and has been independently isolated from the fungus *Cephalosporium aphidicola*,[10] although it has not yet been isolated from *B. bassiana*.

Chemically, this novel class of compounds has elucidated a significant amount of interest as demonstrated by the synthetic work already published.[11–15] Herein, we would like to describe full details of our progress towards the biomimetic synthesis of pyridomacrolidin **2** by reporting a convergent and efficient total synthesis of pyridovericin **1** from readily available starting materials.[16]

Retrosynthetically, we envisaged that the core structure of pyridovericin **1** could be constructed via addition of lithiated pyridine **15** to aldehyde **16**, giving after oxidation the pyridomacrolidin precursor **14**. The organolithium reagent **15** would in turn be generated via metal–halogen exchange from the corresponding bromide **17**, which itself could be synthesised via selective palladium-catalysed

Keywords: Pyridovericin; Pyridomacrolidin; Suzuki coupling; Metal–halogen exchange.
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doi:10.1016/j.tet.2004.07.035

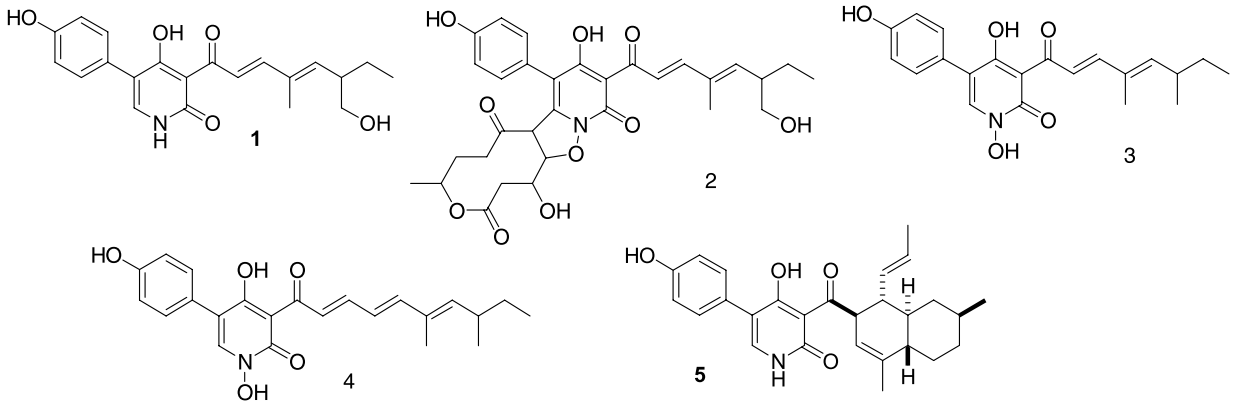
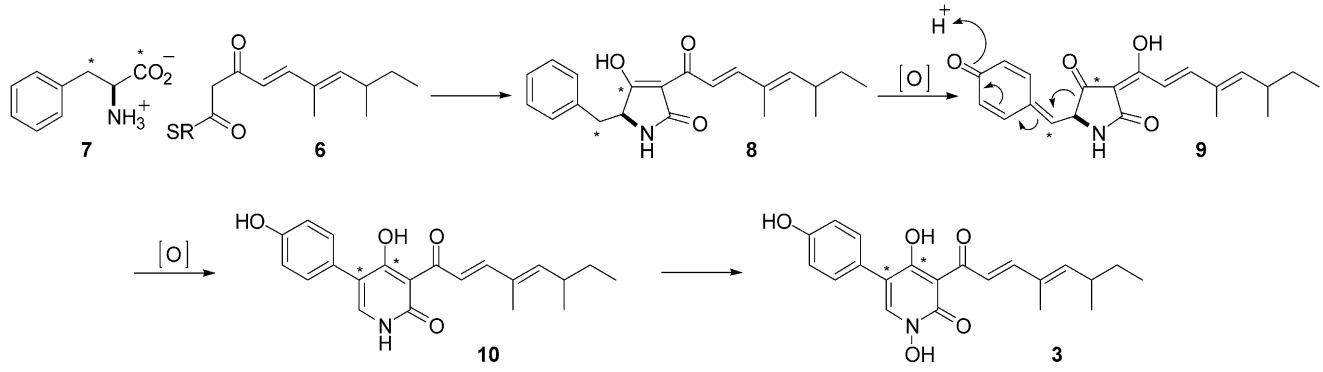
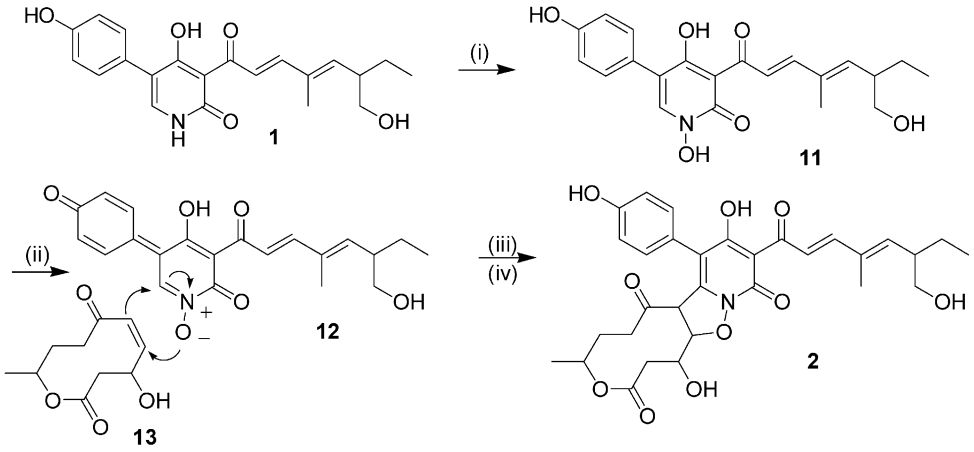


Figure 1. Pyridovericin **1**, pyridomacrolidin **2**, and related analogues.



Scheme 1. Proposed biosynthesis of tenellin **3**.

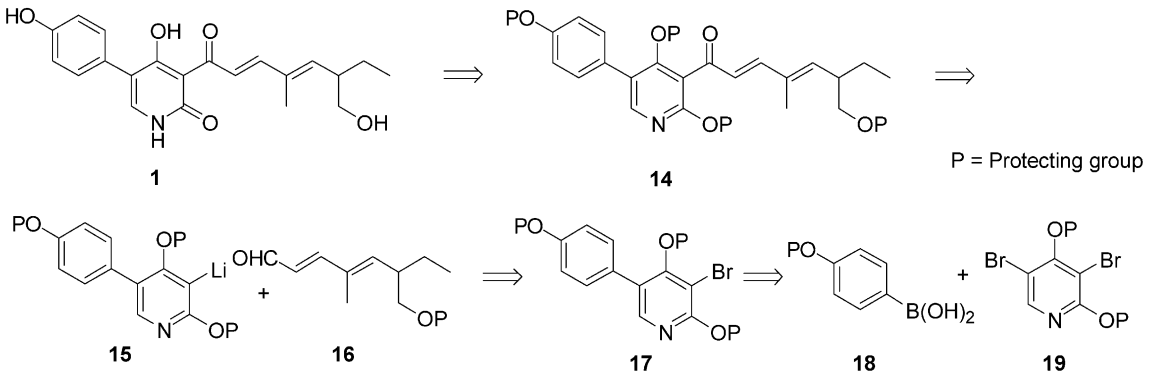


Scheme 2. Proposed biosynthesis of pyridomacrolidin **2**.

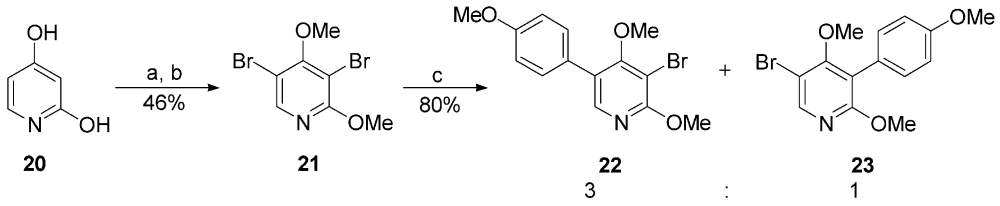
mono-coupling between boronic acid **18** and dibromide **19** (Scheme 3).

Our convergent synthesis began with commercially available 2,4-dihydroxypyridine **20**, which was dibrominated at the C_3 and C_5 positions[17] and then *bis*-O-methylated[18] to give pyridine **21** in good yield. At this stage we decided to perform a model reaction for Suzuki coupling with commercially available 4-methoxyphenylboronic acid. Coupling of bromo pyridine **21** and 4-methoxyphenyl boronic acid under Suzuki-type conditions afforded a separable mixture of coupled adducts **22** and **23**, in which the major product was the desired biaryl **22** (Scheme 4). The regio-selectivity observed in this reaction is consistent with the major coupling being at the less hindered C_5 position (Fig. 2).[19]

At this point, the feasibility of the metal–halogen exchange procedure was tested. Thus, treatment of bromo pyridine **22** with *t*-butyl lithium generated the desired lithiated intermediate **24** which was subsequently trapped with a variety of electrophiles (Table 1).



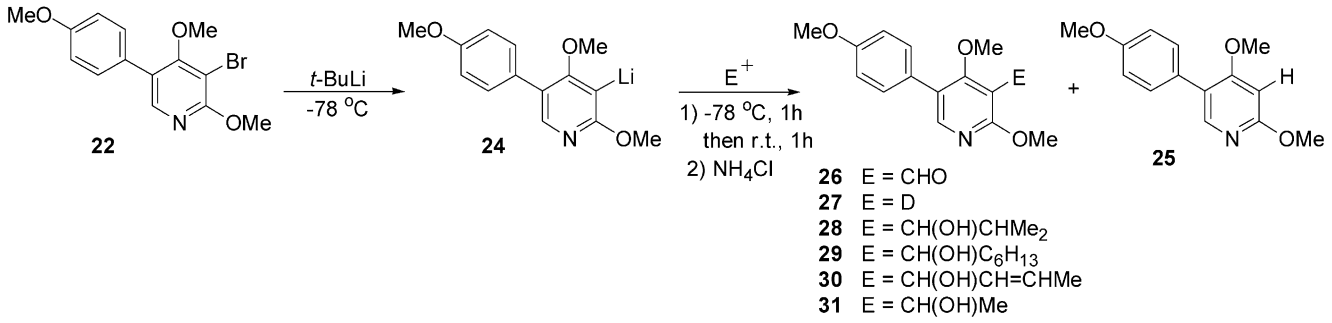
Scheme 3. Retrosynthetic scheme for pyridovericin **1**.

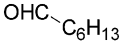
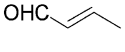


Scheme 4. Reagents and conditions: (a) Br_2(2 eq.), 47% aq. HBr, r.t., 1h; (b) excess MeI, Ag_2CO_3, DCM, r.t., 5 days; (c) 4-methoxyphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene:ethanol (4:1), reflux, 12h. Synthesis of pyridovericin core synthon **22**.

Figure 2. Observed 2D NOESY's of **22** and **23**.

Table 1. Model additions to lithio-pyridine derivative **24**



Entry	Electrophile	Products (addition/protonation ratio)	Overall yield (%)
1	HCO_2Et	**26**:**25** 32:68	Quantitative
2	D_2O	**27**	96
3		**28**:**25** 95:5	93
4		**29**:**25** 90:10	90
5		**30**:**25** 90:10	92
6		**31**:**25** 40:60	Quantiative

Not surprisingly, suitable electrophiles were aldehydes either lacking or with hindered α-hydrogens (entries 3, 4 and 5). We were particularly encouraged by the addition of crotonaldehyde (entry 5), which resembles aldehyde **16** as the proposed electrophile in our retrosynthetic analysis of pyridovericin **1** (Scheme 3).

After having succeeded in the regio-selective Suzuki coupling and in the introduction of various electrophiles to lithiated pyridine **24**, we focussed our attention towards the synthesis of tetrasubstituted pyridine core of pyridovericin **1**. Synthesis of the required boronic acid coupling partner began with 4-bromophenol **32**, which was readily protected under standard conditions[20] to generate the corresponding benzyl ether in good yield. Metal–halogen exchange followed by treatment with boron triisopropoxide[21] proceeded cleanly to afford, after hydrolysis, the desired boronic acid **33**.

Synthesis of the tetrasubstituted pyridine coupling partner was achieved by the reaction of pyridine **21** and boronic acid **33** under slightly modified Suzuki-type conditions[22] which generated a separable mixture of mono- and bis-coupled adducts **34**-**36** (Scheme 5), in which the major product was confirmed once again by nOe analysis as the desired biaryl **34** (Fig. 3).[19]

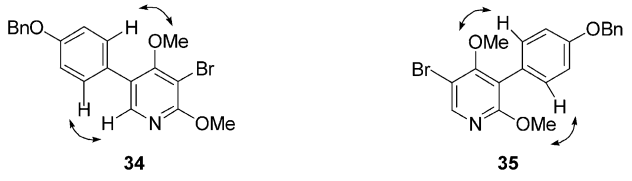


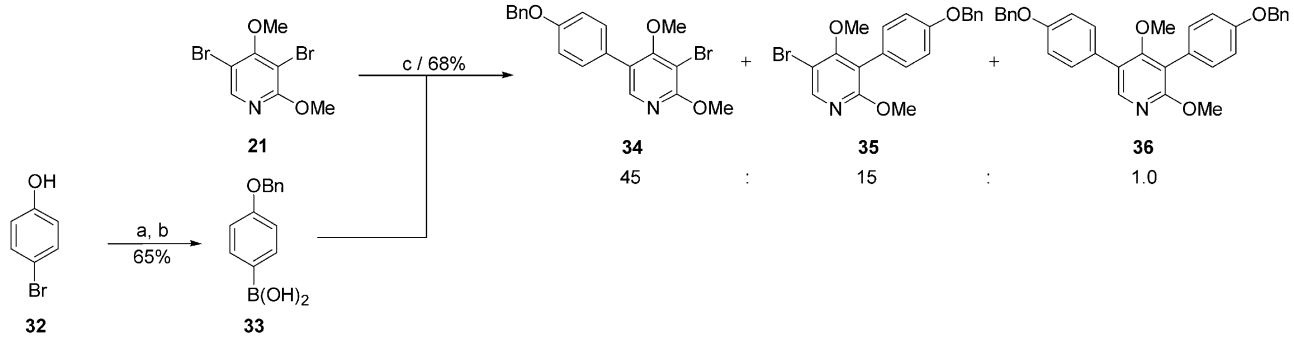
Figure 3. Observed 2D NOESY's of **34** and **35**.

Our synthesis of the C_7–C_{15} side-chain aldehyde began with dimethyl-2-ethylmalonate **37**, which was reduced to the corresponding diol[23] and then monoprotected[24] to afford the desired TBS-silyl ether **38** in good yield. Swern oxidation[25] then Wittig olefination gave ester **39**, which after reduction followed by another Swern oxidation/Wittig olefination sequence gave diene **40** in excellent overall yield. Finally, reduction of the ester to the corresponding alcohol followed by oxidation gave the desired TBS-protected aldehyde intermediate **41**, suitable for coupling to the pyridine unit (Scheme 6).

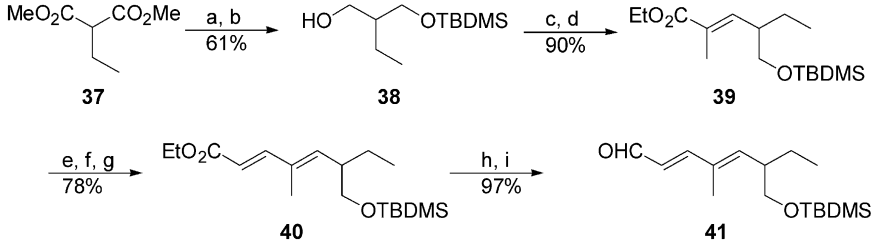
With the benzyl protected pyridine unit **34** and dienal **41** readily available, we focused our attention on the last steps of the synthesis. Thus, metal–halogen exchange of bromopyridine **34** followed by treatment with aldehyde **41** gave the desired alcohol **42**, together with the dehalogenated product **43** (2.6:1) (Scheme 7). The formation of compound **43** is easily explained as the product of the deprotonation of the aldehyde's ε-position or from *t*-butyl bromide by-product by the lithiated pyridine. Subsequent oxidation of alcohol **42** afforded the fully protected pyridovericin **44** in high yield and with no observable side products.

The deprotection of compound **44** at this point proved to be challenging, as most of the methods attempted for removal of the protecting groups either resulted in no reaction or caused complete decomposition of the starting material. It was only after considerable experimentation that it was found that in situ generated trimethylsilyl iodide[26] successfully removed both methyl ethers and TBDMS to afford diol **45**, however the benzyl group was left intact (Scheme 8).

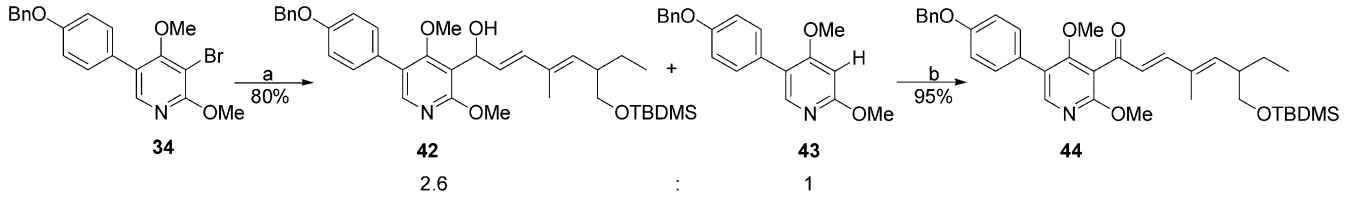
Finally, removal of the adamant benzyl protecting group was carefully effected using boron tribromide,[27] to generate



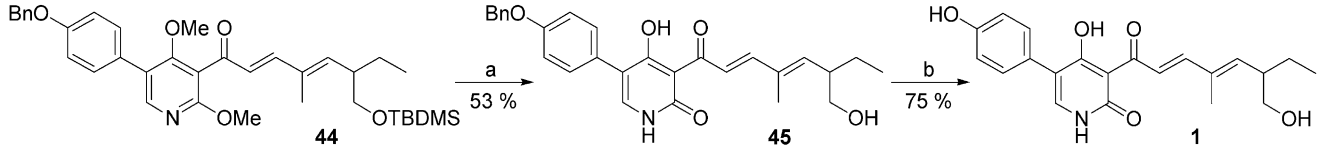
Scheme 5. Reagents and conditions: (a) BnBr, TBAI, NaH, THF, r.t., 4h; (b) (i) $_n$-BuLi, $B(O^iPr)_3$, THF, −78 °C then r.t., overnight; (ii) sat. NH_4Cl; (c) $Pd(PPh_3)_4$, Na_2CO_3, 4:1 toluene:ethanol, reflux, overnight. Modified synthesis of pyridovericin core **34**.



Scheme 6. Reagents and conditions: (a) LAH, THF, r.t., overnight; (b) TBDMSCl, NaH, THF, r.t., overnight; (c) Swern, −78 °C; (d) $PPh_3C(CH_3)CO_2Et$, Benzene, reflux, 20h; (e) Dibal-H, THF; (f) Swern, −78 °C; (g) PPh_3CHCO_2Et, Tol., reflux, 20h; (h) Dibal-H, THF; (i) Swern, −78 °C. Synthesis of TBS-protected aldehyde **41**.



Scheme 7. Reagents and conditions: (a) *t*-BuLi, **41**, THF, −78 °C, 1h then r.t., 1h; (b) MnO_2, DCM, r.t., 48h. Synthesis of protected pyridovericin **44**.



Scheme 8. Reagents and conditions: (a) TMSCl, NaI, MeCN, r.t., 3 days; (b) BBr_3, DCM, −78 °C, 1h. Completion of the synthesis of pyridovericin **1**.

racemic pyridovericin **1** in thirteen steps for the longest linear sequence. The spectral data (^1H, ^{13}C, HRMS, TLC) for synthetic **1** exactly matched that reported for natural pyridovericin **1**.[1] Furthermore, doping experiments of synthetic and natural pyridovericin samples generated a single set of NMR signals.

In conclusion, we have completed the total synthesis of pyridovericin **1** starting from cheap and readily available starting materials. Our synthesis is convergent, fast, efficient and flexible enough to allow for the ready synthesis of a variety of analogues if desired.

1. Experimental

1.1. General

Melting points were recorded using a Cambridge Instruments Gallen™ III Kofler Block melting apparatus or a Buchi 510 capillary apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX-500, Bruker DQX-400, Bruker DPX-400, Varian Gemini DPX-200 spectrometers. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Proton assignments are supported by ^1H–^1H COSY where necessary. Data are reported in the following manner: chemical shift (multiplicity, coupling constant, integration if appropriate). Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are given in hertz to the nearest 0.5 Hz.

^{13}C NMR spectra were recorded at 50.3, 100.6 and 125.8 MHz using Varian Gemini 200, Bruker DQX400, Bruker DPX400 and Bruker AMX500 instruments. Carbon spectra assignments are supported by DEPT-135 spectra, ^{13}C–^1H (HMQC and HMBC) correlations where necessary. Chemical shifts are quoted in ppm and are referenced to the appropriate residual solvent peak.

IR-spectra were recorded as a KBr disc or Neat (as indicated) on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Strong (s) and medium (m) absorption bands are reported in wavenumbers (cm^{-1}).

Low resolution mass spectra were recorded on V. G. Micromass ZAB 1F and V. G. Masslab instruments as appropriate with modes of ionisation being indicated as CI, EI, ES or APCI with only molecular ions, molecular ion fragments and major peaks being reported. High-resolution mass spectrometry was measured on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer and on a VG autospec chemical ionisation mass spectrometer. Thin layer chromatography (TLC) was performed using Merck aluminium foil backed sheets precoated with Kieselgel $60F_{254}$. Column chromatography was carried out on Sorbsil™ C60 (40–63 μm, 230–400 mesh) silica gel.

Elemental analyses were performed by David Lawrence at Elemental Microanalysis Limited, Okehampton, Devon.

All solvents and reagents were purified by standard techniques reported in Perrin, D. D.; Amarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988 or used as supplied from commercial sources as appropriate. Solvents were removed under reduced pressure using a Buchi R110 or R114 Rotavapor fitted with a water or dry ice condenser as necessary. Final traces of solvent were removed from samples using an Edwards E2M5 high vacuum pump with pressures below 1 mm Hg.

All experiments were carried out under inert atmosphere unless otherwise stated.

1.1.1. 3,5-Dibromo-2,4-dimethoxy pyridine, 21. To a 0 °C cooled and stirred solution of 2,4-dihydroxy pyridine **20** (4.0 g, 36.0 mmol) in 47% aqueous hydrobromic acid (40 mL) was added bromine (4.1 mL, 79.3 mmol) and the resulting mixture stirred at room temperature for 1 h. The reaction mixture was diluted with water (100 mL), and stirred for further 30 min at room temperature. The solid product was then filtered, washed with water (75 mL), and dried under vacuum. The crude residue was recrystallised from 95% ethanol to afford 7.0 g (72%) of the known[17] 3,5-dibromo-2,4-dihydroxy pyridine as a white solid, mp 245 °C (dec.) (lit.[17] 225–240 °C dec.). ν_{max} (KBr)/cm^{-1} 3101, 2951, 1648, 1618, 1455, 1443, 1429, 1170; δ_H (200 MHz, DMSO) 7.63 (s, 1H); δ_C (50 MHz, DMSO) 161.2, 160.1, 135.8, 98.1, 93.2; *m/z* (CI+) 272 (35%), 270 (MH^+ ^{79}Br ^{81}Br, 65%), 268 (30%), 112 (100%).

A heterogenous mixture of the above described 3,5-dibromo-2,4-dihydroxy pyridine (6.60 g, 24.5 mmol), methyl iodide (15 mL, 245.0 mmol) and silver carbonate (13.54 g, 49.0 mmol) in dichloromethane (500 mL) was stirred at 20 °C for 5 days. The reaction mixture was filtered through celite, and the filtrate evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 2% ethyl acetate in 30–40 petroleum ether) to afford 4.65 g (64%) desired titled product **21** as a white solid, mp 115–116 °C. ν_{max} (KBr)/cm^{-1} 2971, 2939, 1563, 1537, 1463, 1411, 1374, 1296, 1091, 1068; δ_H (200 MHz, $CDCl_3$) 8.17 (s, 1H), 3.99 (s, 3H), 3.96 (s, 3H); δ_C (50 MHz, $CDCl_3$) 162.4, 161.4, 147.2, 107.8, 102.4, 60.8, 55.1; *m/z* (CI+) 300 (20%), 298 (MH^+ ^{79}Br ^{81}Br, 60%), 296 (30%), 121 (100%).

1.1.2. 3-Bromo-2,4-dimethoxy-5-(*p*-methoxyphenyl)pyridine, 22; 5-bromo-2,4-dimethoxy-3-(*p*-methoxyphenyl)-pyridine, 23.[19] To a solution of 3,5-dibromopyridine **21** (2.87 g, 9.7 mmol) in a 4:1 mixture of toluene/ethanol (25 mL) was added a 2 M sodium carbonate solution (20 mL), followed by 4-methoxyphenylboronic acid (1.47 g, 9.7 mmol), and tetrakis(triphenylphosphine)palladium(0) (558 mg, 0.5 mmol). The reaction mixture was then refluxed for 12 h, before being cooled back down to room temperature and partitioned in a 1:1 mixture of ethyl acetate/water (100 mL). The phases were separated, and the organic layer dried ($MgSO_4$). The solvent was removed under reduced pressure, and the crude residue purified by flash column chromatography (9:1, hexane/ethyl acetate) to afford 1.88 g (60%) of 3-bromo-2,4-dimethoxy-5-(*p*-methoxyphenyl)pyridine **22**, mp 114–115 °C and 626 mg (20%) of 5-bromo-2,4-dimethoxy-3-(*p*-methoxyphenyl)pyridine **23**, mp 119–120 °C as white solids (Fig. 2).

Spectral data for **22**.[19] ν_{max} (KBr)/cm^{-1} 2972, 2935, 2938, 1562, 1514, 1463, 1394, 1117, 1089, 1006; δ_H (400 MHz, $CDCl_3$) 8.01 (s, 1H), 7.44 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 4.05 (s, 3H), 3.86 (s, 3H), 3.54 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 163.1, 160.7, 159.3, 146.1, 130.0, 126.7, 125.8, 114.1, 101.3, 60.3, 55.3, 54.7; *m/z* (APCI+) 326 (MH^+ ^{81}Br, 100%), 324 (80%); HRMS found 324.0242 (MH^+ ^{79}Br). $C_{14}H_{15}BrNO_3$ requires 324.0235. Anal. calcd for $C_{14}H_{14}BrNO_3$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.48; H, 4.38; N, 4.22.

Spectral data for **23**.[19] ν_{max} (neat)/cm^{-1} 2971, 2943, 2939, 1607, 1560, 1510, 1455, 1385, 1379, 1242, 1176, 1089, 1006; δ_H (400 MHz, $CDCl_3$) 8.20 (s, 1H), 7.35 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.47 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 162.2, 162.1, 159.2, 147.1, 131.5, 123.8, 118.3, 113.6, 108.1, 60.5, 55.2, 54.2; *m/z* (APCI+) 326 (MH^+ ^{81}Br, 100%), 324 (96%); HRMS found 324.0224 (MH^+ ^{79}Br). $C_{14}H_{15}BrNO_3$ requires 324.0235. Anal. calcd for $C_{14}H_{14}BrNO_3$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.86; H, 4.46; N, 4.07.

1.2. General procedure for the synthesis of 3-substituted-2,4-dimethoxy-5-(4-methoxyphenyl)pyridine

A −78 °C solution of 3-bromo-2,4-dimethoxy-5-(4-methoxyphenyl)pyridine **22** (80 mg, 0.25 mmol) in dry THF (2 mL) was slowly treated with 1.7 M *t*-BuLi soln. in pentanes (294 μL, 0.5 mmol). The reaction was then stirred at −78 °C for 10 min before being treated with the freshly distilled electrophile (0.27 mmol), and the resulting mixture stirred at −78 °C for 1 h, then at room temperature for an additional 1 h. The reaction was then quenched with saturated ammonium chloride solution (5 mL) and the mixture extracted with ethyl acetate (2×15 mL) after the addition of water (5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude residue, which was purified by flash column chromatography.

1.2.1. 2,4-Dimethoxy-5-(4-methoxyphenyl)pyridine, 25 (by-product). ν_{max} (neat)/cm^{-1} 2974, 2946, 1602, 1564, 1488, 1455, 1430, 1372, 1248, 1053, 832; δ_H (400 MHz, $CDCl_3$) 7.95 (s, 1H), 7.38 (d, J=8.5 Hz, 2H), 6.95 (d, J=8.5 Hz, 2H), 6.27 (s, 1H), 3.95 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 165.0, 164.8, 158.8, 146.7, 130.5, 127.3, 121.3, 113.7, 92.2, 55.4, 55.3, 53.5; *m/z* (APCI+) 246 (MH^+, 100%); HRMS (CI+) found 246.1125 (MH^+) $C_{14}H_{16}NO_3$ requires 246.1130.

1.2.2. 2,4-Dimethoxy-5-(4-methoxyphenyl)pyridine-3-carbaldehyde, 26. The lithiopyridine **24**, was quenched with freshly distilled ethyl formate to afford aldehyde **26** in 32% as a colourless oil. ν_{max} (neat)/cm^{-1} 2952, 2927, 2841, 1692, 1580, 1556, 1470, 1396, 1248, 1090; δ_H (500 MHz, $CDCl_3$) 10.48 (s, 1H), 8.24 (s, 1H), 7.41 (d, J=9.0 Hz, 2H), 7.00 (d, J=9.0 Hz, 2H), 4.08 (s, 3H), 3.87 (s, 3H), 3.61 (s, 3H); δ_C (125.8 MHz, $CDCl_3$) 188.8, 167.8, 164.2, 159.4, 153.1, 130.1, 126.3, 124.9, 114.2, 111.7, 61.9, 55.2, 54.4; *m/z* (APCI+) 274 (MH^+, 100%), 246 (10%); HRMS (EI+) found 274.1071 (MH^+) $C_{15}H_{16}NO_4$ requires 274.1079.

1.2.3. 3-Deuterio-2,4-dimethoxy-5-(4-methoxyphenyl)-pyridine, 27. The lithiopyridine **24**, was quenched with D_2O to give pyridine **27** in 96% as a colourless oil. ν_{max} (neat)/cm^{-1} 2974, 2948, 2835, 1596, 1558, 1472, 1419, 1370, 1247, 1221, 1198, 1179, 1095, 1030, 832; δ_H (400 MHz, $CDCl_3$) 7.98 (s, 1H), 7.41 (d, J=8.5 Hz, 2H), 6.97 (d, J=8.5 Hz, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 165.0, 164.8, 158.8, 146.7, 130.4, 127.3, 121.2, 113.7, 92.1, 55.4, 55.3, 53.5; *m/z* (APCI+) 247 (MH^+, 100%); HRMS (CI+) found 247.1188 (MH^+) $C_{14}H_{15}DNO_3$ requires 247.1193.

1.2.4. 1-[2,4-Dimethoxy-5-(4-methoxyphenyl)pyridin-3-yl]-2-methylpropan-1-ol, 28. Pyridine **24**, was quenched with freshly distilled *iso*-butyraldehyde to afford alcohol **28** in 88% as a colourless oil. ν_{max} (neat)/cm^{-1} 3357, 2957, 2868, 2836, 1610, 1588, 1559, 1516, 1468, 1413, 1297, 1247, 1107; δ_H (400 MHz, $CDCl_3$) 7.97 (s, 1H), 7.41 (d, J=9.0 Hz, 2H), 6.97 (d, J=9.0 Hz, 2H), 4.66 (dd, J=11.5, 9.0 Hz, 1H), 4.01 (s, 3H), 3.86 (s, 3H), 3.40 (s, 3H), 3.39 (d, J=11.5 Hz, 1H), 2.11 (m, 1H), 1.15 (d, J=7.0 Hz, 3H), 0.80 (d, J=7.0 Hz, 3H); δ_C (100.6 MHz, $CDCl_3$) 163.5, 161.6, 159.1, 146.8, 129.9, 127.8, 124.5, 117.5, 114.0, 73.3, 60.6, 55.3, 53.6, 34.3, 19.5; *m/z* (APCI+) 318 (MH^+, 100%), 300 (25%).

1.2.5. 1-[2,4-Dimethoxy-5-(4-methoxyphenyl)pyridin-3-yl]heptan-1-ol, 29. The lithiopyridine **24**, was quenched with freshly distilled heptanal to produce pyridine **29** in

81% as a colourless oil. ν_{max} (neat)/cm^{-1} 3560, 2956, 2928, 2856, 1610, 1589, 1560, 1515, 1468, 1415, 1377, 1107, 1012, 833; δ_H (500 MHz, $CDCl_3$) 7.98 (s, 1H), 7.42 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 5.05 (m, 1H), 4.02 (s, 3H), 3.87 (s, 3H), 3.42 (s, 3H), 3.41 (d, J=11.5 Hz, 1H), 1.92 (m, 1H), 1.73 (m, 1H), 1.54 (m, 1H), 1.32 (m, 7H), 0.89 (t, J=6.5 Hz, 3H); δ_C (125.8 MHz, $CDCl_3$) 162.9, 161.5, 159.1, 146.5, 129.9, 127.7, 124.6, 118.5, 114.0, 67.6, 60.6, 55.3, 53.6, 37.7, 31.7, 29.0, 26.2, 22.5, 14.1; *m/z* (APCI+) 360 (MH^+, 100%), 342 (35%); HRMS (CI+) found 360.2178 (MH^+) $C_{21}H_{30}NO_4$ requires 360.2175.

1.2.6. (2*E*)-1-[2,4-Dimethoxy-5-(4-methoxyphenyl)pyridin-3-yl]but-2-en-1-ol, 30. The pyridine **24**, was quenched with freshly distilled crotonaldehyde to produce allylic alcohol **30** in 83% as a colourless oil. ν_{max} (neat)/cm^{-1} 3548, 2944, 2918, 2841, 1585, 1463, 1416, 1246, 1034, 1071; δ_H (400 MHz, $CDCl_3$) 7.99 (s, 1H), 7.42 (d, J=8.5 Hz, 2H), 6.97 (d, J=8.5 Hz, 2H), 5.87 (m, 1H), 5.71 (m, 1H), 5.54 (m, 1H), 4.02 (s, 3H), 3.86 (s, 3H), 3.72 (d, J=11.0 Hz, 1H), 3.41 (s, 3H), 1.71 (d, J=6.5 Hz, 3H); δ_C (100.6 MHz, $CDCl_3$) 162.9, 161.4, 159.1, 146.9, 132.4, 129.9, 127.5, 126.8, 124.8, 117.5, 114.1, 67.9, 60.7, 55.3, 53.8, 17.7; *m/z* (APCI+) 316 (MH^+, 100%); HRMS (ES+) found 316.1563 (MH^+) $C_{18}H_{22}NO_4$ requires 316.1549.

1.2.7. 1-[2,4-Dimethoxy-5-(4-methoxyphenyl)pyridin-3-yl]ethanol, 31. The lithiopyridine **24**, was quenched with freshly distilled acetaldehyde to yield alcohol **31** in 40% as a colourless oil. ν_{max} (neat)/cm^{-1} 3436, 2957, 2950, 2836, 1610, 1590, 1561, 1470, 1297, 1178, 1055, 1032; δ_H (400 MHz, $CDCl_3$) 7.98 (s, 1H), 7.42 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 5.26 (dq, J=11.5, 6.5 Hz, 1H), 4.03 (s, 3H), 3.86 (s, 3H), 3.63 (d, J=11.5 Hz, 1H), 3.43 (s, 3H), 1.56 (d, J=6.5 Hz, 3H); δ_C (100.6 MHz, $CDCl_3$) 162.7, 161.5, 159.1, 146.6, 129.9, 127.6, 124.8, 119.2, 114.1, 63.6, 60.8, 55.3, 53.7, 23.8; *m/z* (APCI+) 290 (MH^+, 100%), 272 (40%); HRMS (ES+) found 290.1394 (MH^+) $C_{16}H_{20}NO_4$ requires 290.1392.

1.2.8. *p*-Benzyloxyphenylboronic acid, 33. 4-Benzyloxybromobenzene was prepared by following the literature procedure[20] as a white solid, mp 55–56 °C (lit.[20] 60–61 °C); δ_H (200 MHz, $CDCl_3$) 7.40, (m, 7H), 6.90 (d, J=8.0 Hz, 2H), 5.05 (s, 2H); *m/z* (CI) 183 (10%), 121 (100%).

p-Benzyloxyphenylboronic acid, **33** was prepared from 4-benzyloxybromobenzene by following the literature procedure[21] as a white solid, mp 187–192 °C (lit.[21] 189–194 °C); δ_H (250 MHz, $CDCl_3$) 8.20 (d, J=7.0 Hz, 2H), 7.40 (m, 5H), 7.12 (d, J=7.0 Hz, 2H), 5.18 (s, 2H); δ_C (50 MHz, $CDCl_3$) 162.4, 137.6, 136.7, 128.7, 128.1, 127.6, 114.4, 69.9; *m/z* (CI+) 121 (100%).

1.2.9. 3-Bromo-2,4-dimethoxy-5-(*p*-benzyloxyphenyl)-pyridine, 34; 5-bromo-2,4-dimethoxy-3-(*p*-benzyloxyphenyl)pyridine, 35; 3,5-di (*p*-benzyloxyphenyl)-2,4-dimethoxypyridine, 36. A solution of 3,5-dibromo-2,4-dimethoxy pyridine, **21** (2.30 g, 7.74 mmol) and *p*-benzyloxyphenylboronic acid, **33** (1.75 g, 7.68 mmol) in a 4:1 mixture of a toluene/ethanol (22.5 mL) was sequentially treated with tetrakis(triphenylphosphine)palladium(0) (447 mg, 0.39 mmol), 2 M sodium carbonate solution (18 mL), and the resulting mixture refluxed for 12 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate (100 mL). The organic layer was washed with water (2×50 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was evaporated under vacuum and the crude product purified by flash column chromatography (silica gel, 4% ethyl acetate in 30–40 petroleum ether), to afford the desired titled products as white solids, **34**, 1.40 g (45%), mp 115–116 °C. **35**, 450 mg (15%), mp 97–99 °C. **36**, 32 mg (1%).

Spectral data for **34**.[19] ν_{max} (neat)/cm^{-1} 2971, 2947, 2939, 1561, 1584, 1514, 1470, 1410, 1379, 1243, 1087, 1006; δ_H (200 MHz, $CDCl_3$) 8.01 (s, 1H), 7.42 (m, 7H), 7.05 (d, J=7.0 Hz, 2H), 5.12 (s, 2H), 4.05 (s, 3H), 3.55 (s, 3H); δ_C (100 MHz, $CDCl_3$) 163.1, 160.8, 158.5, 146.1, 136.8, 130.1, 128.4, 128.1, 127.5, 127.0, 125.8, 114.9, 101.3, 70.0, 60.3, 54.7; *m/z* (CI+) 402 (MH^+ ^{81}Br, 100%), 400 (90%); HRMS (ES+) found 400.0540 (MH^+^{79}Br) $C_{20}H_{19}BrNO_3$ requires 400.0548.

Spectral data for **35**.[19] ν_{max} (neat)/cm^{-1} 2971, 2943, 2939, 1607, 1560, 1510, 1455, 1385, 1379, 1242, 1176, 1089, 1006; δ_H (200 MHz, $CDCl_3$) 8.20 (s, 1H), 7.45 (m, 5H), 7.33 (d, J=7.0 Hz, 2H), 7.05 (d, J=7.0 Hz, 2H), 5.11 (s, 2H), 3.87 (s, 3H), 3.47 (s, 3H); δ_C (100 MHz, $CDCl_3$) 162.7, 158.9, 147.6 (2C), 137.3, 132.0, 129.1, 128.5, 128.1, 124.6, 118.8, 114.9, 108.6, 70.5, 61.0, 54.7; *m/z* (CI+) 402 (MH^+ ^{81}Br, 100%), 400 (90%); HRMS (ES+) found 400.0554 (MH^+^{79}Br) $C_{20}H_{19}BrNO_3$ requires 400.0548.

Spectral data for **36**. δ_H (200 MHz, $CDCl_3$) 8.08 (s, 1H), 7.42 (m, 14H), 7.06 (d, J=7.0 Hz, 4H), 5.11 (s, 4H), 3.92 (s, 3H), 3.23 (s, 3H); *m/z* (CI+) 504 (MH^+, 100%).

1.2.10. 2-(*tert*-Butyldimethylsilanyloxymethyl)-1-butanol, 38. To a 0 °C suspension of 60% sodium hydride (1.88 g, 47.1 mmol) in THF (100 mL), was added dropwise a solution of 2-ethylpropan-1,3-diol[23] (4.90 g, 47.1 mmol) in THF (30 mL) and the reaction mixture stirred at room temperature for 1 h, during which time a large amount of an opaque white precipitate formed. The reaction mixture was cooled to 0 °C and a solution of *tert*-butyldimethylsilyl chloride (7.11 g, 47.1 mmol) in THF (30 mL) was added slowly. The reaction was warmed up and stirred at room temperature overnight, and was then quenched with water (100 mL) and extracted with ethyl acetate (3×100 mL). The combined organic extracts were washed with water (2×100 mL), brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% ethyl acetate in 30–40 petroleum ether) to afford 8.1 g, (79%) of known[24] desired titled product **38** as a clear oil. ν_{max} (neat)/cm^{-1} 3368, 2957, 1472, 1255, 1091, 836; δ_H (200 MHz, $CDCl_3$) 3.80 (m, 4H), 2.92 (dd, J=7.0, 5.0 Hz, 1H), 1.63 (m, 1H), 1.25 (m, 1H), 0.91 (t, J=7.0 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); δ_C (50 MHz, $CDCl_3$) 67.2, 66.4, 43.6, 25.7, 20.6, 18.1, 11.7, −5.57, −5.63; *m/z* (CI+) 219 (MH^+, 100%).

1.2.11. Ethyl-(2*E*)-4-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2-hexenoate, 39. To a −78 °C solution of oxalyl chloride (6.62 mL, 75.6 mmol) in

dichloromethane (500 mL) was added dropwise a 1:1 (v/v) solution of DMSO (10.72 mL, 151.2 mmol) in dichloromethane. After stirring at −78 °C for 10 min, a solution of 2-(*tert*-butyldimethylsilanyloxymethyl)-1-butanol, **38** (10.30 g, 47.2 mmol) in dichloromethane (45 mL) was added dropwise and the resulting mixture stirred for 30 min at −78 °C. Triethylamine (42 mL, 302 mmol) was then added slowly, and the reaction raised to room temperature. After stirring for 1 h at room temperature, water (200 mL) was added to the reaction mixture, and the layers separated. The aqueous layer was extracted with dichloromethane (3×150 mL) and the combined organic phases washed with 1 M hydrochloric acid (2×150 mL), 5% aq. sodium bicarbonate (2×150 mL), brine (150 mL), and dried ($MgSO_4$). The solvent was then evaporated under vacuum, to afford 10.20 g (100%) of the known[25] 2-(*tert*-butyldimethylsilanyloxymethyl) butyraldehyde, as a clear oil, which was used for next step without further purification; δ_H (250 MHz, $CDCl_3$) 9.69 (d, J=2.5 Hz, 1H), 3.89 (d, J=6.0 Hz, 2H), 2.32 (m, 1H), 1.72 (m, 1H), 1.52 (m, 1H), 0.97 (t, J=7.0 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H); δ_C (50 MHz, $CDCl_3$) 204.8, 61.6, 55.8, 25.8, 18.5, 18.2, 11.4, −5.6.

A mixture of 2-(*tert*-butyldimethylsilanyloxymethyl)butyraldehyde (10.20 g, 47.2 mmol) and (carbethoxyethylidene)-triphenylphosphorane (34.2 g, 94.4 mmol) in benzene (250 mL) was refluxed for 20 h. After cooling to room temperature, the solvent was evaporated under vacuum and the residue was purified by flash column chromatography (silica gel, 3% ethyl acetate in 30–40 petroleum ether) to afford 12.75 g, (90%) of the desired titled product **39** as a clear oil. ν_{max} (neat)/cm^{-1} 2959, 1713, 1252, 1230, 1096, 837; δ_H (250 MHz, $CDCl_3$) 6.57 (dq, J=10.5, 1.5 Hz, 1H), 4.22 (q, J=7.0 Hz, 2H), 3.55 (m, 2H), 2.56 (m, 1H), 1.88 (d, J=1.5 Hz, 3H), 1.62 (m, 1H), 1.35 (t, J=7.0 Hz, 3H), 1.32 (m, 1H), 0.90 (s, 9H), 0.88 (t, J=5.5 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H); δ_C (50 MHz, $CDCl_3$) 168.2, 143.8, 128.9, 65.6, 60.3, 43.5, 25.8, 24.0, 18.3, 14.3, 12.9, 11.7, −5.4, −5.5; HRMS (CI+) found 301.2190 (MH^+) $C_{16}H_{33}O_3Si$ requires 301.2199.

1.2.12. (2*E*,4*E*)-6-(*tert*-Butyldimethylsilanyloxymethyl)-4-methylocta-2,4-dienoicacid ethyl ester, 40. A −78 °C solution of ethyl-(2*E*)-4-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2-hexenoate, **39** (9.50 g, 31.7 mmol) in THF (150 mL) was treated dropwise with a 1 M solution of DiBAL-H in hexanes (66.5 mL, 66.5 mmol) and reaction mixture stirred at −78 °C for 2 h. The reaction was then sequentially warmed up to room temperature and then cooled to 0 °C before being quenched with saturated sodium potassium tartrate solution (200 mL) and the resulting mixture stirred for 2 h. Ethyl acetate (150 mL) was then added to the above reaction mixture and the layers separated. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic layers washed with brine (150 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in 30–40 petroleum ether) to afford 6.70 g (82%) of 4-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2-hexene-1-ol, as a clear oil. ν_{max} (neat)/cm^{-1} 3338, 2957, 1255, 1102, 836; δ_H (250 MHz, $CDCl_3$) 5.18 (dq, J=10.0, 1.5 Hz, 1H), 4.05 (m, 2H), 3.48 (m, 2H), 2.37 (m, 1H), 1.72 (brs, 3H), 1.62 (m, 1H), 1.31 (t, J=6.0 Hz, D_2O exchangeable, 1H), 1.12 (m, 1H), 0.91 (s, 9H), 0.87 (t, J=7.5 Hz, 3H), 0.05 (s, 6H); δ_C (50 MHz, $CDCl_3$) 136.3, 127.8, 69.1, 66.5, 42.3, 25.9, 24.5, 18.4, 14.3, 11.7, −5.3.

To a −78 °C solution of oxalyl chloride (3.53 mL, 40.3 mmol) in dichloromethane (275 mL) was dropwise added a 1:1 (v/v) solution of DMSO (5.71 mL, 80.6 mmol) in dichloromethane (5.71 mL). After stirring for 10 min, a solution of 4-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2-hexene-1-ol (6.50 g, 25.2 mmol) in dichloromethane (25 mL) was added dropwise and the resulting mixture stirred for 30 min at −78 °C. Triethylamine (22.4 mL, 161.2 mmol) was then added dropwise and the reaction raised to room temperature. After stirring for 1 h at room temperature, water (150 mL) was added to the reaction mixture, and the layers separated. The aqueous layer was extracted with dichloromethane (3×100 mL) and the combined organic phases washed with 1 M hydrochloric acid (2×100 mL), 5% aq. sodium bicarbonate (2×100 mL), brine (100 mL), and dried ($MgSO_4$). The solvent was evaporated under vacuum, to afford 6.45 g (100%) of (2*E*)-4-(*tert*-butyldimethylsilanyloxymethyl)-2-methylhex-2-enal as a clear oil, which was used for next step without further purification. ν_{max} (neat)/cm^{-1} 2959, 2930, 2858, 1693, 1644, 1472, 1255, 1102, 837; δ_H (250 MHz, $CDCl_3$) 9.45 (s, 1H), 6.33 (dq, J=10.0, 1.5 Hz, 1H), 3.63 (m, 2H), 2.73 (m, 1H), 1.81 (brs, 3H), 1.72 (m, 1H), 1.35 (m, 1H), 0.91 (s, 9H), 0.89 (t, J=7.5 Hz, 3H), 0.03 (s, 6H); HRMS (CI+) found 257.1933 (MH^+) $C_{14}H_{29}O_2Si$ requires 257.1937.

A mixture of (2*E*)-4-(*tert*-butyldimethylsilanyloxymethyl)-2-methylhex-2-enal (6.45 g, 25.1 mmol) and (ethoxycarbonylmethylidene)triphenylphosphorane (17.53 g, 50.2 mmol) in toluene (150 mL) was refluxed for 20 h. After cooling to room temperature, the solvent was evaporated under reduced pressure, and the residue purified by flash column chromatography (silica gel, 5% ethyl acetate in 30–40 petroleum ether) to afford 7.80 g (95%) of the desired titled product, **40** as a clear oil. ν_{max} (neat)/cm^{-1} 2959, 1716, 1625, 1471, 1366, 1298, 1258, 1173, 1100, 1034, 836; δ_H (250 MHz, $CDCl_3$) 7.35 (d, J=15.5 Hz, 1H), 5.82 (d, J=15.5 Hz, 1H), 5.70 (dq, J=10.0 Hz, 1.5 Hz, 1H), 4.24 (q, J=7.0 Hz, 2H), 3.52 (m, 2H), 2.57 (m, 1H), 1.85 (brd, 3H), 1.62 (m, 1H), 1.33 (t, J=7.0 Hz, 3H), 1.23 (m, 1H), 0.91 (s, 9H), 0.89 (t, J=7.5 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); δ_C (50 MHz, $CDCl_3$) 167.6, 149.7, 144.0, 134.0, 115.8, 66.0, 60.2, 43.5, 25.9, 24.4, 18.3, 14.4, 12.8, 11.8, −5.4; HRMS (CI+) found 327.2363 (MH^+) $C_{18}H_{35}O_3Si$ requires 327.2355.

1.2.13. (2*E*,4*E*)-6-(*tert*-Butyldimethylsilanyloxymethyl)-4-methylocta-2,4-diene-1-al, 41. A −78 °C solution of (2*E*,4*E*)-6-(*tert*-butyldimethylsilanyloxymethyl)-4-methylocta-2,4-dienoicacid ethyl ester, **40** (7.30 g, 22.4 mmol) in THF (75 mL) was treated dropwise with a 1.5 M solution of DiBAL-H in toluene (31 mL, 46.5 mmol) and reaction mixture stirred at −78 °C for 2 h. The reaction was then warmed up to room temperature, and then cooled back down to 0 °C before being quenched with saturated sodium potassium tartrate solution (100 mL) and the resulting

mixture stirred for 2 h. Ethyl acetate (100 mL) was added to the above reaction mixture and the layers separated. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic layers washed with brine (100 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in 30–40 petroleum ether) to afford 6.15 g (97%) of (2*E*,4*E*)-6-(*tert*-butyldimethylsilanyloxymethyl)-4-methylocta-2,4-dien-1-ol, as a clear oil. ν_{max} (neat)/cm^{-1} 3399, 2957, 1719, 1695, 1471, 1387, 1255, 1100, 1006, 776; δ_H (200 MHz, $CDCl_3$) 6.27 (d, J=15.5 Hz, 1H), 5.85 (dt, J=15.5, 7.0 Hz, 1H), 5.24 (brd, J=10.0 Hz, 1H), 4.21 (t, J=6.0 Hz, 2H), 3.47 (m, 2H), 2.51 (m, 1H), 1.79 (d, J=1.0 Hz, 3H), 1.61 (m, 1H), 1.29 (t, J=6.0 Hz, D_2O exchangeable, 1H), 1.21 (m, 1H), 0.91 (s, 9H), 0.87 (t, J=7.0 Hz, 3H), 0.05 (s, 6H); δ_C (50 MHz, $CDCl_3$) 137.0, 135.3, 134.2, 125.4, 66.4, 64.0, 42.9, 25.9, 24.6, 18.4, 13.1, 11.7, −5.3, −5.4; HRMS (CI+) found 285.2253 (MH^+) $C_{16}H_{33}O_2Si$ requires 285.2250.

To a −78 °C solution of oxalyl chloride (0.23 mL, 2.6 mmol) in dichloromethane (25 mL), was dropwise added a 1:1 (v/v) solution of DMSO (0.37 mL, 5.2 mmol) in dichloromethane. After stirring for 10 min, a solution of (2*E*,4*E*)-6-(*tert*-butyldimethylsilanyloxymethyl)-4-methylocta-2,4-dien-1-ol (460 mg, 1.6 mmol) in dichloromethane (2 mL) was added dropwise and the reaction mixture stirred for 30 min at −78 °C. Triethylamine (1.44 mL, 10.4 mmol) was then added dropwise and the reaction brought to room temperature. After stirring for 1 h at room temperature, water (15 mL) was added to the reaction mixture, and the layers separated. The aqueous layer was extracted with dichloromethane (3×15 mL) and the combined organic phases washed with 1 M hydrochloric acid (2×15 mL), 5% aq. sodium bicarbonate solution (2×15 mL), brine (15 mL), and dried ($MgSO_4$). The solvent was evaporated under reduced pressure, to afford 456 mg (100%) the titled desired product, **41** as an oil. The crude product was used for next step without further purification. ν_{max} (neat)/cm^{-1} 2957, 2857, 1683, 1627, 1606, 1471, 1463, 1386, 1361, 1256, 970, 837; δ_H (250 MHz, $CDCl_3$) 9.59 (d, J=8.0 Hz, 1H), 7.16 (d, J=15.5 Hz, 1H), 6.13 (dd, J=15.5, 8.0 Hz, 1H), 5.83 (brd, J=10.0 Hz, 1H), 3.57 (m, 2H), 2.52 (m, 1H), 1.87 (d, J=1.0 Hz, 3H), 1.62 (m, 1H), 1.32 (m, 1H), 0.91 (s, 9H), 0.89 (t, J=7.5 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); δ_C (50 MHz, $CDCl_3$) 194.3, 157.9, 146.6, 134.5, 127.0, 65.8, 43.7, 25.9, 24.3, 18.3, 13.0, 11.7, −5.4.

1.2.14. (2*E*,4*E*)-6-(*tert*-Butyldimethylsilanyloxymethyl)-1-[5-(*p*-benzyloxyphenyl)-2,4-dimethoxy-pyridine-3-yl]-4-methylocta-2,4-dien-1-ol, 42 and 5-(*p*-benzyloxyphenyl)-2,4-dimethoxy pyridine, 43. A solution of pyridine, **34** (283 mg, 0.71 mmol) in THF (10 mL) was cooled to −78 °C and was then dropwise treated with a 1.5 M solution of *tert*-butyl lithium in hexanes (0.94 mL, 1.4 mmol). After 30 min, a solution of aldehyde, **41** (200 mg, 0.71 mmol) in THF (2 mL) was added and the resulting mixture stirred at −78 °C for 1 h. The reaction was warmed up to room temperature, and stirred for an additional 1 h. Saturated ammonium chloride solution (10 mL) was then added to the reaction mixture, followed by ethyl acetate (10 mL), and water (10 mL). The layers were separated, and the aqueous layer extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 10% ethyl acetate in 30–40 petroleum ether) to afford the desired titled product as an approximately (1:1) mixture of inseparable diastereomers, **42** as an oil, 250 mg (58%) and **43**, 50 mg (22%), as a yellow solid.

Spectral data for **42**. ν_{max} (neat)/cm^{-1} 3555, 2954, 1590, 1515, 1469, 1379, 1246, 1086, 833; δ_H (250 MHz, $CDCl_3$) 8.03 (s, 1H), 7.52–7.35 (m, 7H), 7.09–7.07 (d, J=6.5 Hz, 2H), 6.31 (dd, J=15.5, 3.5 Hz, 1H), 5.94 (dd, J=15.5, 7.0 Hz, 1H), 5.69 (dd, J=12.0, 7.0 Hz, 1H), 5.22 (brd, J=10.0 Hz, 1H), 5.13 (s, 2H), 4.07–4.05 (s, 3H), 3.78–3.71 (m, D_2O exchangeable, 1H), 3.51–3.45 (m, 2H), 3.44–3.42 (2× s, 3H), 2.56–2.42 (m, 1H), 1.80–1.78 (s, 3H), 1.72–1.62 (m, 1H), 1.32–1.11 (m, 1H), 0.88–0.78 (m, 12H), 0.04–0.03 (2×s, 3H), 0.01–0.00 (2×s, 3H); δ_C (50 MHz, $CDCl_3$) 163.2, 161.5, 158.4, 147.0, 136.9, 135.8, 135.5, 135.3, 134.3, 130.0, 128.7, 128.1, 127.9, 127.7, 124.9, 117.6, 115.1, 70.1, 68.1, 66.4, 60.8, 53.9, 43.0, 25.9, 24.6, 18.4, 13.2, 11.7, −5.3; HRMS (CI+) found 604.3463 (MH^+) $C_{36}H_{50}NO_5Si$ requires 604.3458.

Spectral data for **43**. δ_H (250 MHz, $CDCl_3$) 7.99 (s, 1H), 7.42 (m, 7H), 7.06 (d, J=9.0 Hz, 2H), 6.31 (s, 1H), 5.13 (s, 2H), 3.99 (s, 3H),3.86 (s, 3H); *m/z* (CI+) 322 (MH^+, 100%).

1.2.15. (2*E*,4*E*)-6-(*tert*-Butyldimethylsilanyloxymethyl)-1-[5-(*p*-benzyloxyphenyl)-2,4-dimethoxy pyridine-3-yl]-4-methylocta-2,4-dien-1-one, 44. A suspension of allylic alcohol **42** (185 mg, 0.31 mmol) and activated manganese dioxide, (400 mg, 4.60 mmol) in dichloromethane (10 mL) was stirred at room temperature for 2 days. The reaction mixture was then filtered, and the solid residue washed with dichloromethane (25 mL). The combined filtrates were evaporated under vacuum and the crude residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in 30–40 petroleum ether) to afford 175 mg (95%) of the desired pyridine **44** as a clear gum. ν_{max} (neat)/cm^{-1} 2957, 1651, 1588, 1559, 1514, 1466, 1410, 1379, 1325, 1273, 1247, 1177, 1095, 834; δ_H (250 MHz, $CDCl_3$) 8.12 (s, 1H), 7.42 (m, 7H), 7.06 (d, J=15.5 Hz, 1H), 7.04 (d, J=7.0 Hz, 2H), 6.45 (d, J=15.5 Hz, 1H), 5.70 (d, J=10.0 Hz, 1H), 5.14 (s, 2H), 3.95 (s, 3H), 3.50 (s, 3H), 3.49 (m, 2H), 2.61 (m, 1H), 1.88 (s, 3H), 1.57 (m, 1H), 1.23 (m, 1H), 0.89 (s, 9H), 0.83 (t, J=7.0 Hz, 3H), 0.03 (s, 6H); δ_C (50 MHz, $CDCl_3$) 194.1, 163.0, 161.2, 158.5, 151.6, 148.5, 146.4, 136.9, 134.6, 130.1, 128.7, 128.1, 127.5 (2C), 126.5, 124.2, 115.5, 115.0, 70.1, 65.9, 61.1, 54.0, 43.8, 25.9, 24.3, 18.3, 13.0, 11.8, −5.3; HRMS (CI+) found 602.3303 (MH^+) $C_{36}H_{48}NO_5Si$ requires 602.3302.

1.2.16. (2*E*,4*E*)-6-(Hydroxymethyl)-1-[5-(*p*-benzyloxyphenyl)-2,4-dihydroxypyridine-3-yl]-4-methylocta-2,4-dien-1-one, 45. To a −20 °C solution of pyridine, **44** (50 mg, 0.083 mmol) in acetonitrile (10 mL) was added anhydrous sodium iodide (50 mg, 0.33 mmol) and trimethylsilyl chloride (32 μL, 0.25 mmol) and the reaction slowly brought to room temperature over a period of 4 h.

The reaction was stirred for 3 days at room temperature, and then diluted with ethyl acetate (10 mL) and water (5 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (3×10 mL). The combined organic phases were washed with 5% aq. sodium bicarbonate (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated under vacuum. The crude residue was purified by flash column chromatography (silica gel, 2% methanol in chloroform) to afford 20 mg (53%) of the desired pyridone, **45**, as a yellow solid, mp 199–200 °C. ν_{max} (neat)/cm^{-1} 3340, 2923, 1665, 1628, 1512, 1472, 1406, 1324, 1218, 1177, 1036, 827; δ_H (500 MHz, $CDCl_3$) 10.70 (brs, D_2O exchangeable, 1H), 8.01 (d, J=15.5 Hz, 1H), 7.68 (d, J=15.5 Hz, 1H), 7.39 (m, 8H), 7.04 (d, J=8.0 Hz, 2H), 5.84 (d, J=10.0 Hz, 1H), 5.11 (s, 2H), 3.65 (brs, 1H), 3.53 (t, J=8.5 Hz, 1H), 2.70 (m, 1H), 2.03 (s, 3H), 1.57 (m, 1H), 1.37 (brs, D_2O exchangeable, 1H), 1.31 (m, 1H), 0.94 (t, J=7.0 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 195.1, 178.2, 164.0, 159.1, 150.4, 146.0, 138.5, 137.3 (2C), 130.7, 129.1, 128.5, 127.9, 125.6, 124.3, 115.9, 115.3, 107.2, 70.5, 66.5, 44.4, 24.9, 13.7, 12.1; HRMS (CI+) found 460.2123 (MH^+) $C_{28}H_{30}NO_5$ requires 460.2124.

1.2.17. (2*E*,4*E*)-6-(Hydroxymethyl)-1-[5-(*p*-hydroxyphenyl)-2,4-dihydroxypyridine-3-yl]-4-methylocta-2,4-dien-1-one, pyridovericin, 1. A solution of pyridone, **45** (25 mg, 0.054 mmol) in dichloromethane (10 mL) at −78 °C was treated dropwise with a 1 M solution of boron tribromide in dichloromethane (0.54 mL, 0.54 mmol). The reaction was then stirred at −78 °C for 1 h, before methanol (100 μL) was added, and the mixture kept at −78 °C for 10 min. The reaction was then further quenched by the sequential addition of water (5 mL), and ethyl acetate (5 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with 5% aq. sodium bicarbonate (10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated under vacuum. The crude residue was purified by flash column chromatography (silica gel, 3% methanol in chloroform), to afford 15 mg (75%) of pyridovericin **1**, as a yellow solid, mp 203–206 °C (dec.). ν_{max} (neat)/cm^{-1} 3335, 2963, 1665, 1610, 1588, 1489, 1452, 1261, 1225, 1101, 1035, 799; δ_H (500 MHz, DMSO) 17.56 (brs, D_2O exchangeable, 1H), 11.61 (brs, D_2O exchangeable, 1H), 9.48 (s, 1H), 8.00 (d, J=15.5 Hz, 1H), 7.54 (s, 1H), 7.51 (d, J=15.5 Hz, 1H), 7.27 (d, J=8.5 Hz, 2H), 6.78 (d, J=8.5 Hz, 2H), 5.97 (d, J=10.0 Hz, 1H), 4.56 (t, J=5.5 Hz, D_2O exchangeable, 1H), 3.37 (m, 2H), 2.53 (m, 1H), 1.86 (s, 3H), 1.59 (m, 1H), 1.22 (m, 1H), 0.82 (t, J=7.5 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 194.6, 177.7, 162.6, 157.6, 150.3, 148.4, 141.5, 135.4, 130.9, 124.3, 123.9, 115.8, 113.6, 106.7, 64.7, 44.4, 24.9, 13.7, 12.5; HRMS found 370.1664 (MH^+) $C_{21}H_{24}NO_5$ requires 370.1654.

Acknowledgements

We are very indebted to Professor Akira Nakagawa (Teikyo University) for generous amounts of an authentic sample of pyridovericin **1**. We thank the EPSRC for funding to A.C. N.R.I thanks the Dr. Reddy's Research Foundation (DRF), Hyderabad, India for their support and financial assistance.

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