ELSEVIER

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Contents

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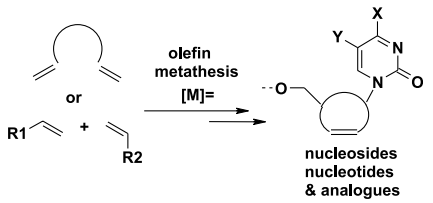
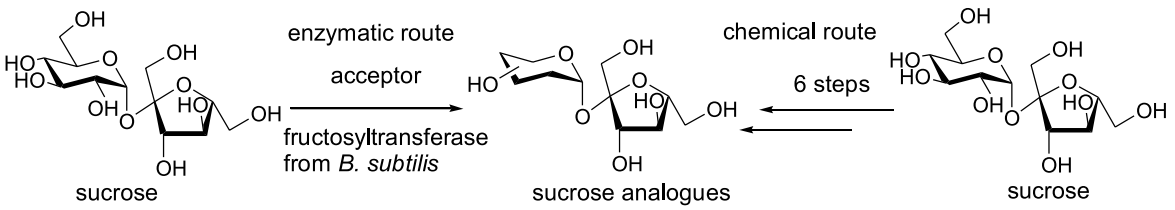
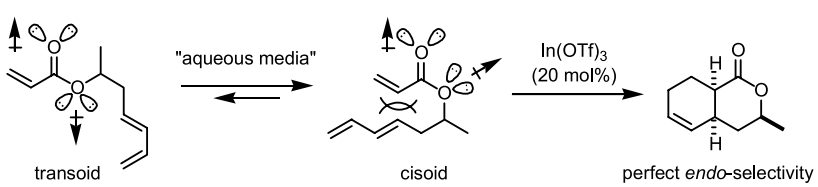
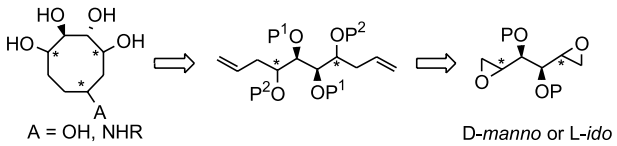


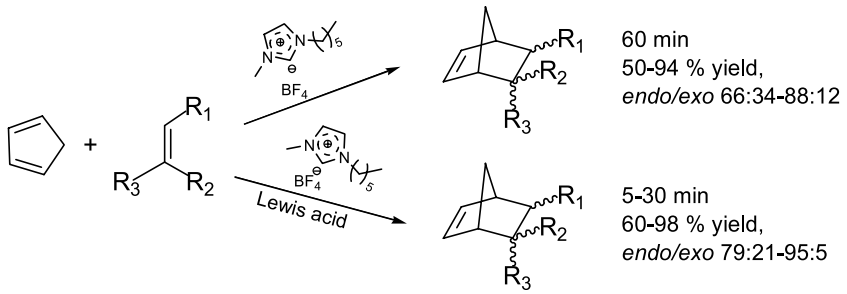
The applications of the olefin metathesis reaction for the synthesis of nucleosides and analogues are reviewed.

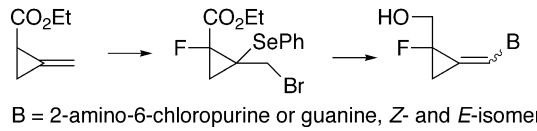
ARTICLES

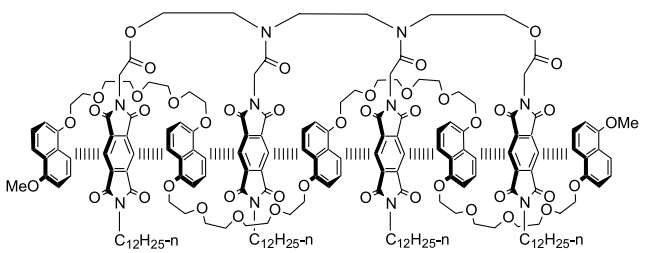


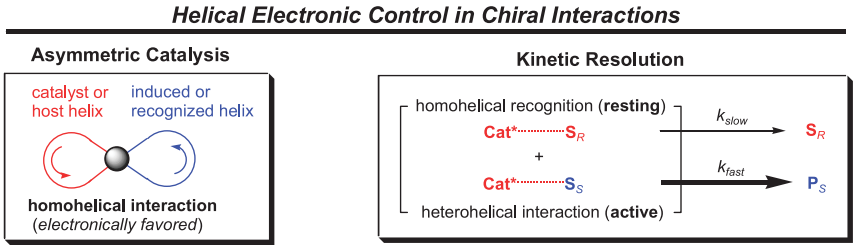




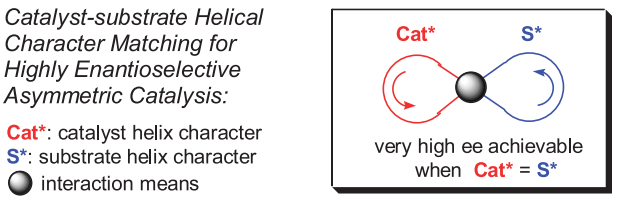




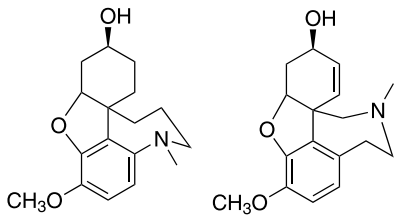


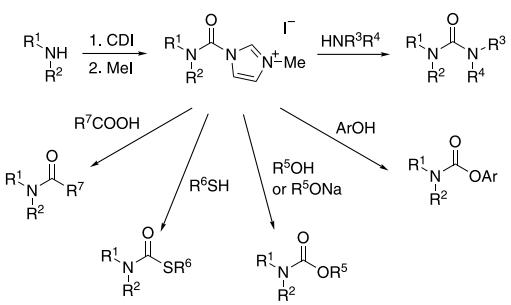


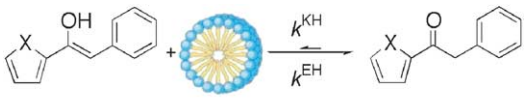
An electronic theory for chiral interactions shows that, in explaining stereoselections in chiral recognition and induction, those effects conventionally attributed to steric hindrances might instead have an electronic basis, and further it shows how a new electronic effect, which we call homohelical interaction, generally controls the stereochemical course of chiral processes.



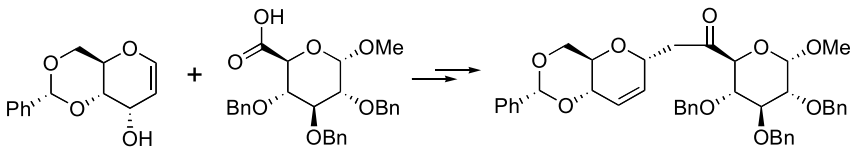
In the framework of a helix theory recently developed for molecular chiralities and chiral interactions, it is further shown that for an asymmetric reaction to be highly enantioselective, the helical characters of the catalyst and the substrate complexed with it in the corresponding enantioselection-determining step must be matched.

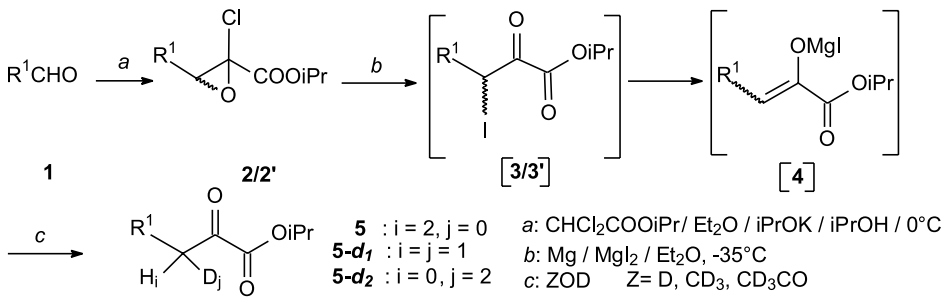


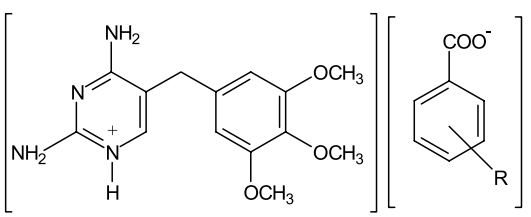




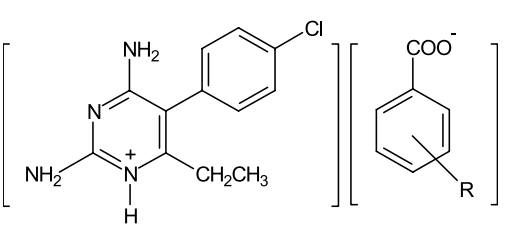
X = O (**2PAF**), S (**2PAT**)



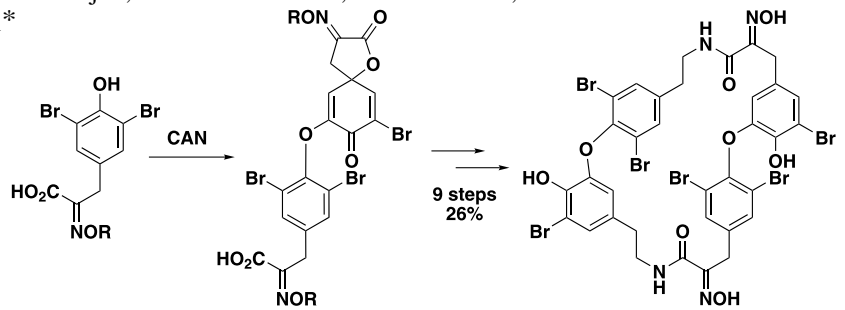


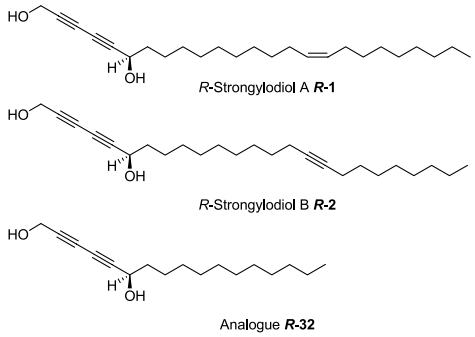


1 (R=*m*-NO_2) and **2** (R=*p*-NO_2)

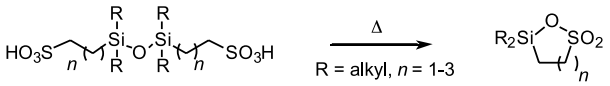


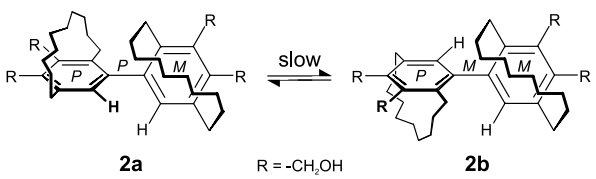
3 (R=*o*-NO_2), **4** (R=*m*-NO_2) and **5** (R=*p*-NO_2)

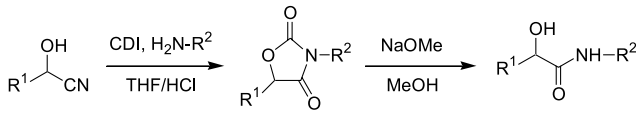


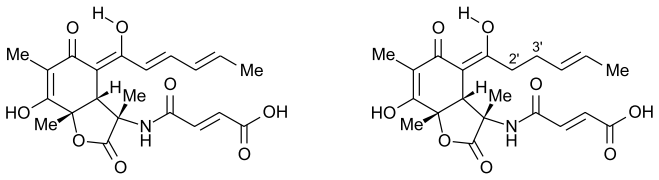


The asymmetric synthesis of *R*-strongylodiols A and B, and an analogue, is described.

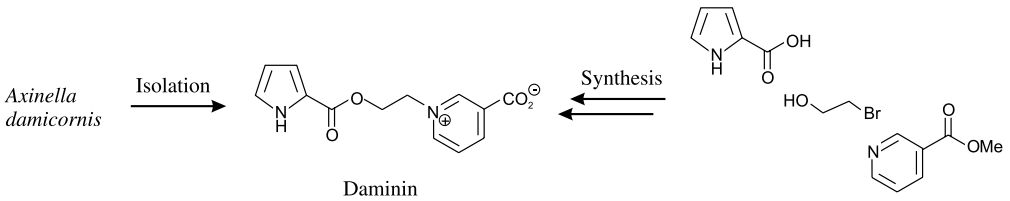


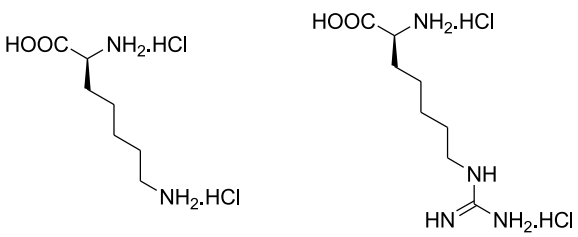


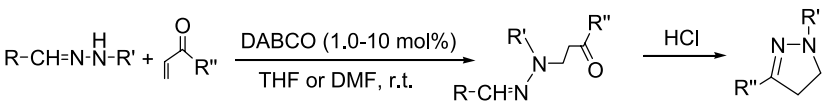




1 Sorbicillactone A **2** Sorbicillactone B

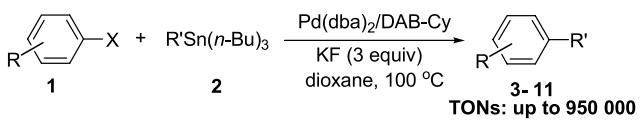


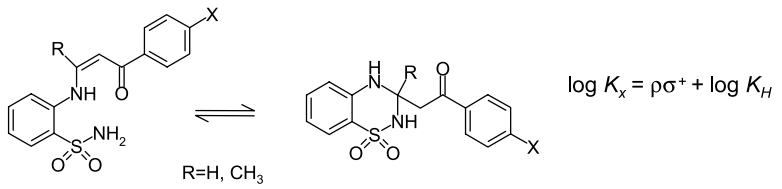


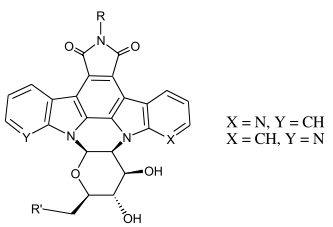


R= aromatic or aliphatic group, R'= Ts or PhC(O),
R"= Me, CN, OMe, Ph.

DABCO-catalyzed aza-Michael addition reactions of hydrazones with activated olefins proceeded smoothly under mild conditions in most cases. Upon treatment with HCl, the cyclized products can be obtained in high yields.







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Metathesis strategy in nucleoside chemistry

Franck Amblard,[a] Steven P. Nolan[b] and Luigi A. Agrofoglio[a,*]

[a]*ICOA UMR CNRS 6005, BP 6759, 45067 Orleans Cedex 2, France*
[b]*Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA*

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Contents

1. Introduction

The study of nucleosides and their phosphorylated derivatives as biologically active molecules has been a fundamental pursuit since, the 1940s and 1950s.[1] It was then that the nature of nucleic acids in cells was established, ultimately resulting in the identification of the double helix structure of DNA and the explanation of the genetic code. As the metabolic processes by, which these materials were manipulated in vivo became understood, so the investigation of close analogs of the components on nucleic acids grew, with the expectation that they might interfere in some way with the natural pathways and perhaps have utility as drugs. Early work focused on traditional nucleoside analogs in which the base was linked to one of the naturally occurring sugars. Some of these were indeed shown to possess anti-metabolic properties but it became apparent that their usefulness was severely limited due to instability and poor selectivity. Since, the discovery of the first successful antiviral drug, acyclovir (**1**),[2] in 1974, interests have been refocused on compounds where the heterocycle and sugar components of the nucleoside have departed significantly from the natural form.

Some of this activity has resulted in structures containing unusual substituents, such as ribavirin (**2**), AZT (**3**), ddC (**4**), BVDU (**5**) and showdomycin (**6**) (Fig. 1). Those novel types of nucleosides act as anticancer, antiviral or antibacterial drugs. The intense search for clinically useful nucleoside derivatives has resulted in a wealth of new approaches for their synthesis. In this context, a powerful reaction has emerged over the past decade that has fundamentally changed the outlook on nucleoside chemistry: the olefin metathesis reaction.[3,4]

Keywords: Olefin metathesis; Nucleosides.
* Corresponding author. Tel.: +33 2 3849 4582; fax: +33 2 3841 7281; e-mail: luigi.agrofoglio@univ-orleans.fr

doi:10.1016/j.tet.2005.04.040

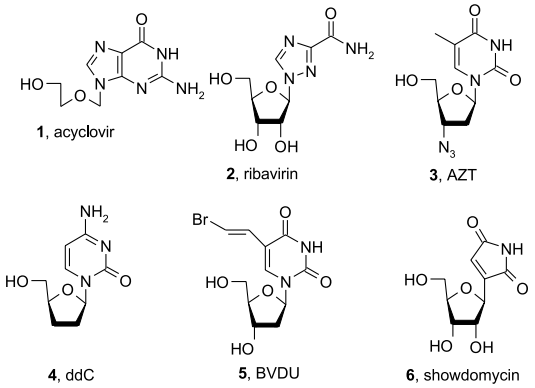


Figure 1. Antiviral drugs.

2. Metathesis

The olefin metathesis reaction was first reported in 1955 by Anderson and Merckeling describing the polymerization of norbornene by titanium(II) species,[5] but it was not until the early 1990s that this transformation became an important tool in organic chemistry. Indeed, despite its widespread use in industry as a method for producing higher olefins and polymers, the generalization in organic synthesis has been driven by the discovery of well-defined and functional-group-tolerant catalysts by Schrock,[6] Nolan[7] and Grubbs.[8]

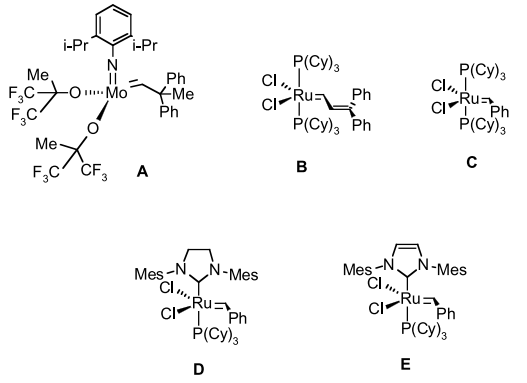


Figure 2. Most commonly used metathesis catalysts.

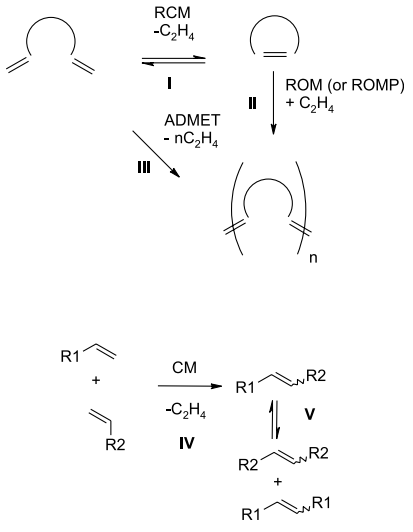
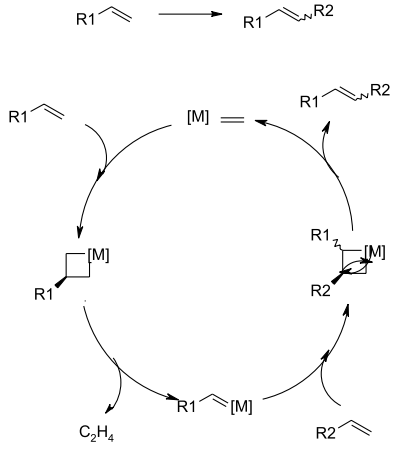


Figure 3. A variety of olefin metathesis reactions.

The most commonly used metathesis catalysts **A–E** are shown in Figure 2.

As shown in Figure 3, this transformation has a variety of forms: (**I**) ring-closing metathesis (RCM), (**II**) ring-opening metathesis polymerization (ROMP) or ring-opening metathesis, (**III**) acyclic diene metathesis polymerization (ADMET), (**IV**) and (**V**) cross-metathesis (CM).

In all cases, olefin metathesis can be formally described as the inter- or intramolecular exchange of alkylidenes promoted by metal–carbene complexes (Scheme 1).



Scheme 1. Basic catalytic cycle for metathesis.

As a carbon–carbon bond-forming tool, metathesis has numerous advantages in that it is a catalytic process (typically 1–5 mol%), provides high yields under mild condition and displays tolerance for a wide range of functional groups, necessitating minimal protecting group manipulation. Moreover, the only byproduct is usually gaseous ethylene, (which is an important consideration in industrial applications).

A number of reviews[9] on olefin metathesis have been published to date, but none of these focuses on the application of olefin RCM and CM for the formation of nucleosidic structures. This review, which covers the literature until January 2005, is not intended to be comprehensive. Rather, it is designed to illustrate typical examples and situations where olefin metathesis was, and can be, used to construct various nucleosides.

3. Introduction of bases in nucleoside chemistry

All syntheses of nucleosides are carried out first, by the formation of a functionalized sugar or analogue (cyclopentane, ….) followed by coupling the latter to a purine or pyrimidine heterocycle or some grouping, which can be elaborated to it. Several well-known approaches can be used to couple a purine or a pyrimidine to a sugar or pseudo-sugar:

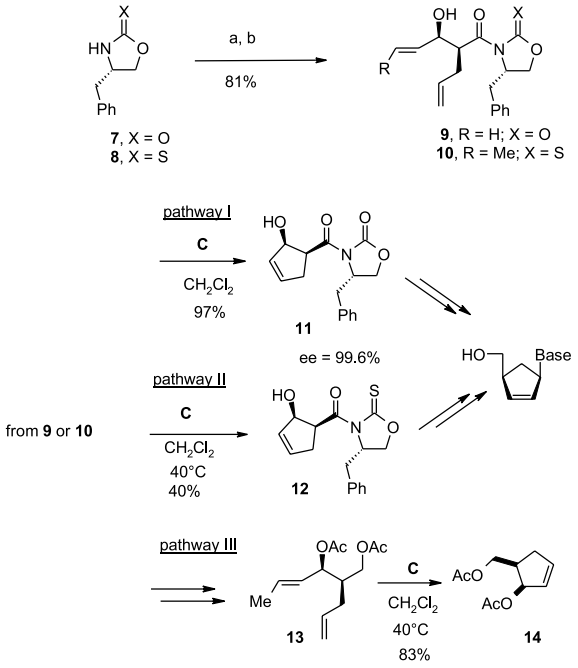
- Direct introduction of a heterocycle under Vorbrüggen conditions;[10]
- Construction of the heterocyclic ring from a 1′-β-amino function or a 1′-β acidic function on the pseudo-sugar;[11]

- Displacement of an activated α hydroxyl group (MsO, TsO);[12]
- Ring opening of a cyclopentane epoxide;[13]
- Displacement of a hydroxyl group under Mitsunobu conditions;[14]
- Tsuji–Trost allylic methodology;[15,16]

4. Formation of carbocyclic nucleosides

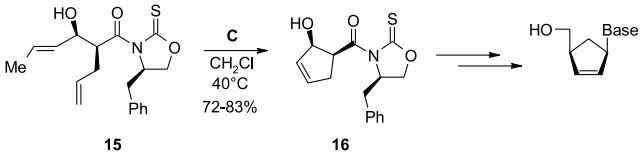
4.1. Using chiral auxiliaries

Historically, the first synthesis of nucleoside analogues using metathesis was achieved in 1996 by Crimmins et al.[17] from chiral (*S*)-4-benzyl-2-oxazolidinones through a strategy combining three key transformations: an asymmetric aldol addition to establish the relative and absolute configuration of the pseudo-sugar (Scheme 2), an RCM to construct the carbocyclic ring and a Trost-type palladium(0) substitution to introduce the aromatic base.



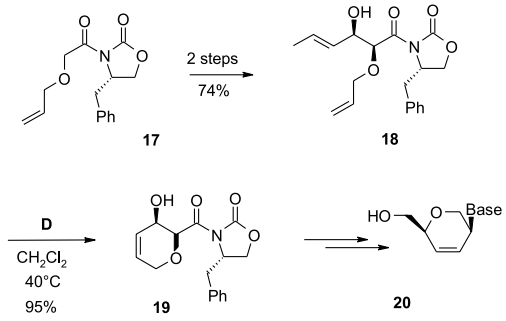
Scheme 2. (a) *n*-BuLi, THF, −78 °C, $CH_2{=}CH(CH_2)_2C(O)OPiv$; (b) $TiCl_4$ (−)-sparteine, CH_2Cl_2, R-CH=CH–CHO.

The cyclisation by RCM of diene **9** (or **10**), obtained in two steps from **7** (or **8**), is achieved in the presence of catalyst **C** giving enantiomerically pure (ee=99.6%) cyclopentenol **11** in 97% yield (Scheme 2, pathway I). Crimmins et al.[18] have also investigated the use of the oxazolidinethione **8** as a chiral auxiliary, but observed low yields in the RCM due to poor conversion of the Evans *syn*-aldol adduct **12** (Scheme 2, pathway II). The authors initially suggest that the oxazolinethione can coordinate the catalyst metal center, thus stabilizing the ruthenium alkylidine. This theory can be confirmed by the removal of the auxiliary (to **13**) prior to the olefin metathesis in the presence of the Grubbs catalyst **C**, giving cyclopentene **14** in 83% yield. In a similar approach, the non-Evans *syn*-aldol adduct **15** underwent RCM to **16**, when treated with **C**, suggesting apparently a difference in the ability of the thiocarbonyl function to coordinate to the metal in the intermediate alkylidene in the Evans *syn* and non-Evans *syn* diastereoisomers (Scheme 3).



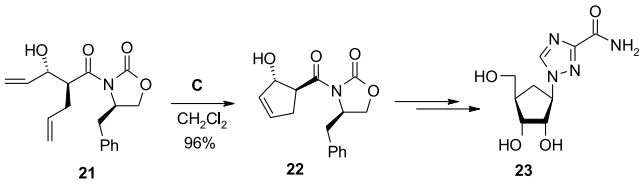
Scheme 3.

Finally, this methodology has been applied to the synthesis of the hex-3′-enopyranosyl nucleoside **20**, by cyclisation of derivative **18**, easily obtained in two steps from **17**, with the more active second-generation Grubbs' catalyst **D** to yield the intermediate **19** in 95% yield (Scheme 4).



Scheme 4.

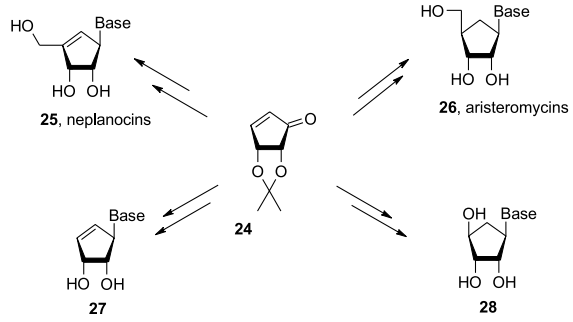
In a similar approach, Kuang et al.[19] have prepared the carbocycle analogue (**23**) of ribavirin starting from the *anti*-aldol **21**, which was submitted to a ring-closing metathesis with catalyst **C** to yield **22** in 96% (Scheme 5).



Scheme 5.

4.2. From sugar derivatives

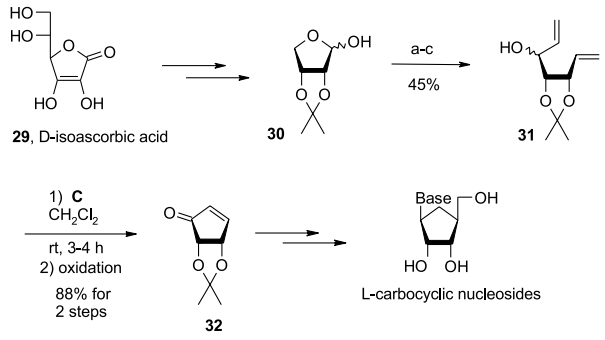
Among the molecules synthesized by metathesis, analogues of neplanocins **25** or aristeromycins **26** represent a major part



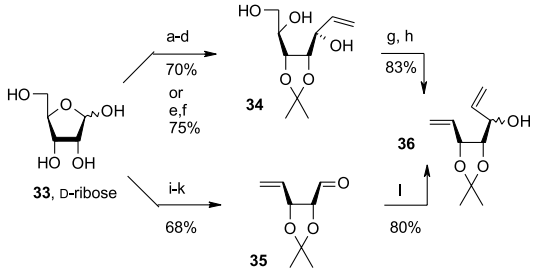
Scheme 6.

of the existing literature. Most of those syntheses involve the key intermediate **24**, which can be a versatile starting point for the preparation of many other carbocyclic nucleosides[20] such as **27** or **28** (Scheme 6).

Access to the cyclopentenone **32** provides a route to L-carbanucleosides by cyclisation of dienes **31**, obtained through the lactol **30** from D-isoascorbic acid[21] (**29**) in the presence of catalyst **C** in dichloromethane, followed by oxidation (Scheme 7). Similar compounds **36** have been obtained starting from the commercially available D-ribose **33**,[22] in order to take advantage of the existing stereogenic centers (Scheme 8), through the allylic alcohol **34** or the unsaturated aldehyde **35**.

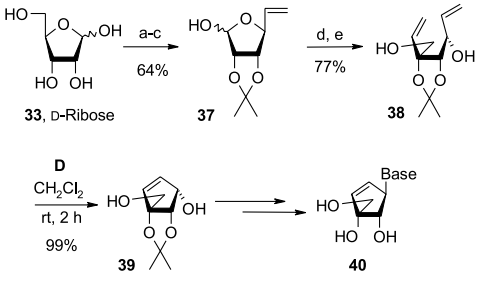


Scheme 7. (a) Ph_3PCH_3Br, NaH, DMSO; (b) Swern oxidation; (c) CH_2=CHMgBr, THF.



Scheme 8. (a) 2,2-Dimethoxypropane, *p*TSA; (b) TBDMSCl, imidazole; (c) vinylMgBr, THF; (d) TBAF, THF; (e) acetone, cat. H_2SO_4; (f) vinylMgBr, THF; (g) $NaIO_4$; (h) Ph_3PMeBr, NaH, DMSO; (i) 2,2-dimethoxypropane; (j) Ph_3P, I_2, imidazole; (k) Zn, MeOH; (l) vinylMgBr, CH_2Cl_2.

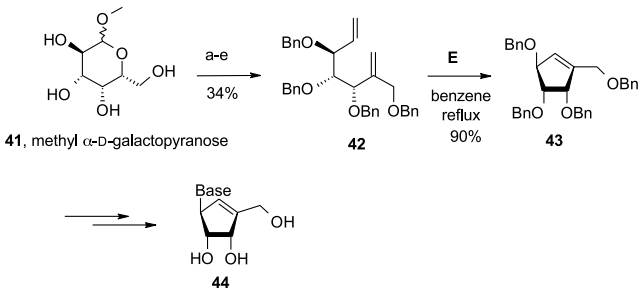
Jeong et al.[23] have also used D-ribose (**33**) as the starting material to synthesize *apio*-neplanocin A (**40**) via a stereoselective hydroxymethylation of **37** to **38** and RCM yielding **39**.



Scheme 9. (a) Acetone, H_2SO_4; (b) CH_2=CHMgBr, THF; (c) $NaIO_4$; (d) K_2CO_3, 37% CH_2O; (e) Ph_3PMeBr, KO*t*-Bu.

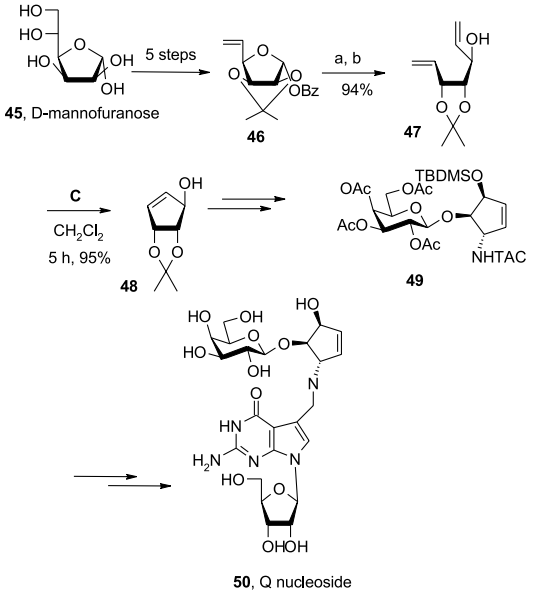
Diene **38** underwent metathesis using catalyst **D** in quantitative yields, to afford the cyclopentene **39**, which was easily converted into the unsaturated carbonucleoside **40** (Scheme 9).

Analogs of L-neplanocins **44** (Scheme 10) have been synthesized by our group[24] starting from methyl α-D-galactopyranoside (**41**) using two Wittig reactions to introduce the double bonds. The obtained diene **42**, which bears the three asymmetric centers of the final molecule, was then cyclized by RCM with catalyst **E** in refluxing benzene to afford cyclopentenyl moiety **43** in 90% yield. The heterocycles were introduced under Tsuji–Trost allylic amination.



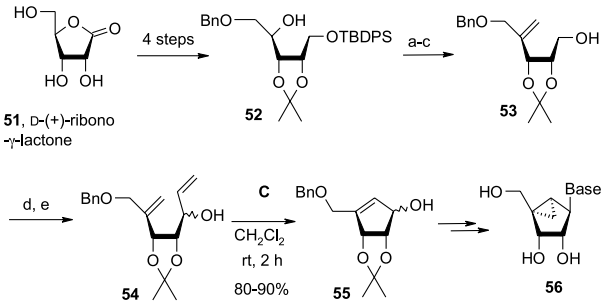
Scheme 10. (a) NaH, BnBr; (b) AcOH, H_2SO_4 3 M; (c) Ph_3PCH_3Br, *n*-BuLi; (d) PCC; (e) Ph_3PMeBr, *n*-BuLi.

Van Boom et al.[25] prepared the molecule **49**, a precursor of nucleoside Q (**50**), as shown in Scheme 11. Starting from D-mannofuranose (**45**), the diene **47** is obtained in a few steps from **46** following a well-established sequence. It was then cyclized under RCM metathesis conditions in the presence of catalyst **C** and the cyclopentenol **48** was isolated in quantitative yields.



Scheme 11. (a) KO*t*-Bu, MeOH; (b) Ph_3PMeBr, *n*-BuLi.

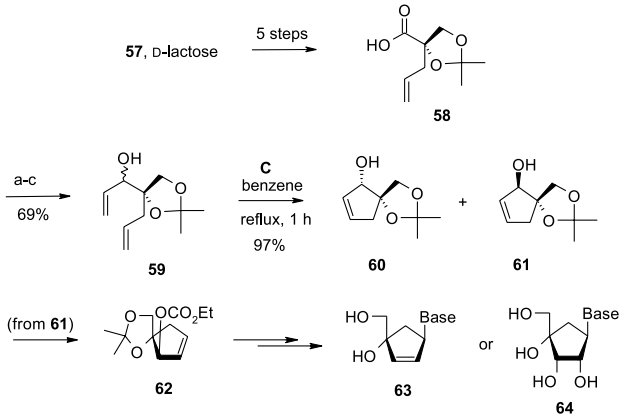
The synthesis of *N*-methanocarbanucleosides **56** has been realized by Jacobson et al.[26] (Scheme 12). Starting from the commercially available D-(+)-ribono-γ-lactone (**51**), the alcohol **52** is synthesized in four steps. After a sequence,



Scheme 12. (a) $(COCl)_2$, DMSO; (b) Ph_3PMeBr, *n*-BuLi; (c) TBAF; (d) $(COCl)_2$, DMSO; (e) vinylmagnesium bromide, THF.

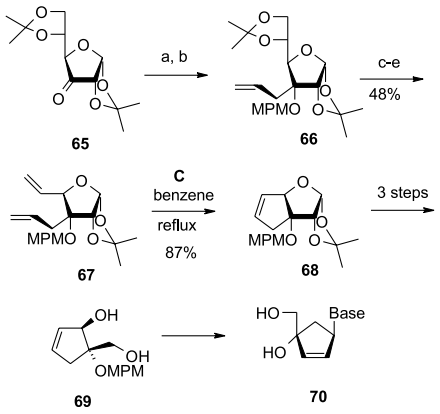
which includes a Wittig reaction (to **53**) and vinyl Grignard addition, the diene intermediate **54** was submitted to an RCM using 0.2 equiv of the Grubbs' catalyst **C** to provide the cyclopentenyl derivative **55**, a key intermediate of functionalized carbocycles **56**.

In addition, to the synthesis of these compounds, more hydroxylated cyclopentenyl nucleosides were obtained by the application of RCM methodology, giving carbovir and aristeromycin analogues, respectively. Hong et al.[27] used D-lactose (**57**) as a chiral carbohydrate template to synthesize the novel carbocyclic nucleosides **63** and **64**, respectively (Scheme 13). The acid derivative **58** was readily synthesized from D-lactose in five steps by a well-known procedure. **58** was then converted through a Weinreb amide to the allylic alcohol **59**. A direct cyclisation of **59** to the cyclopentenols **60** and **61** was found to be a high-yielding reaction under usual Grubbs' RCM conditions with **C** as a catalyst. The β diastereomer **61** was activated as an allylic carbonate **62**, onto, which various heterocycles were introduced under Tsuji–Trost conditions. Several 4′-hydroxy-carbocyclic nucleosides **63** and **64** were subsequently obtained.



Scheme 13. (a) *N*,*O*-Dihydroxymethyl-amine hydrochloride, DCC, DMAP; (b) $LiAlH_4$, THF; (c) CH_2═$CHMgBr$, THF.

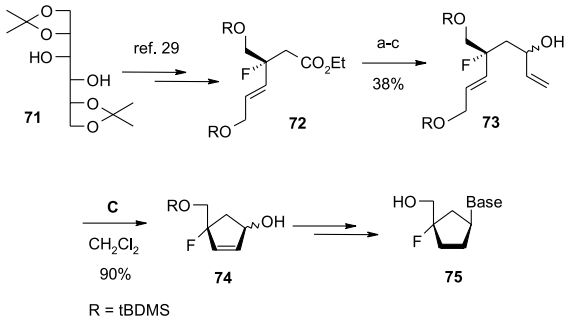
Some 4′-hydroxy-carbocyclic nucleosides **70** were synthesized by Gurjar et al.[28] from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**65**) (Scheme 14). After the introduction of the two double bonds (**66** then **67**), using vinyl Grignard derivatives, ring-closing metathesis of **67** using catalyst **C** at rt gave the bicyclic derivative **68** in 87% yield. Hydrolysis of the isopropylidene group and then



Scheme 14. (a) Allylmagnesium bromide, THF; (b) MPM-Br, NaH, THF; (c) 0.8% H_2SO_4, MeOH; (d) $MeSO_2Cl$, Et_3N, DMAP; (e) NaI, EtCOMe.

oxidative cleavage follow by an $NaBH_4$ reduction afforded the diol **69**, onto, which heterocycles were introduced using Tsuji–Trost conditions.

Carbocyclic 4′-fluoro-2′,3′dideoxynucleosides **75** were synthesized by Chu et al.[29] through the fluoro derivative **74** (Scheme 15). Starting from the carbohydrate **71**, the β-fluoro ester **72** was converted into the diene **73**. Thus, an RCM reaction, catalyzed by **C**, afforded the cyclopentenols **74** in 90% yields.

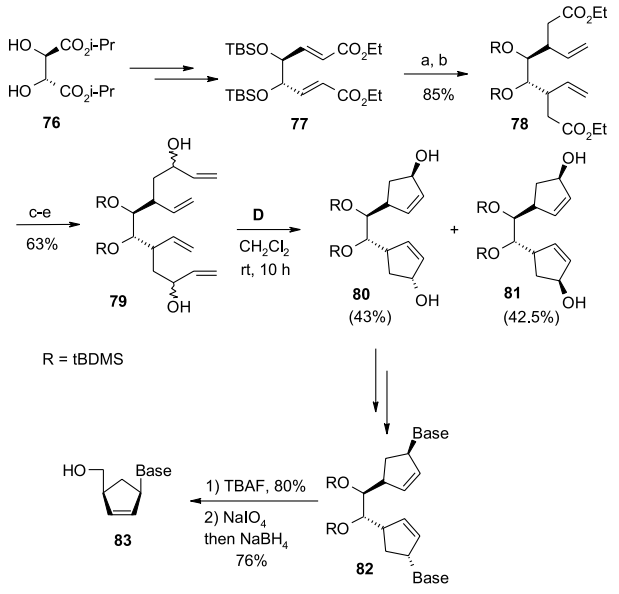


Scheme 15. (a) LAH, THF; (b) PCC, CH_2Cl_2; (c) vinylmagnesium bromide, THF.

4.3. Other approaches

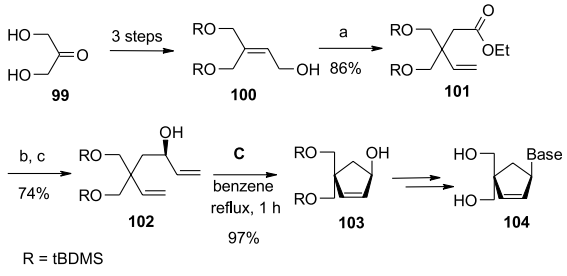
An elegant synthesis of carbovir analogues **83** was achieved by Hong et al.[30] from the L-tartrate derivative **76** (Scheme 16). The dienes **78** were obtained through a double [3,3]-sigmatropic rearrangement of α,β-unsaturated ester **77** followed by a double RCM in the presence of catalyst **D** under mild condition (CH_2Cl_2, rt) afforded the unsaturated C_2-symmetric bis(cyclopentenols) **80** and **81**, respectively. Introduction of heterocyclic bases on **80**, under Pd(0) Tsuji–Trost methodology, afforded **82**, which, after desilylation and treatment with $NaIO_4$, gave the desired carbanucleosides **83**.

Hong et al.[31] have described a very efficient route to novel 4′α-*C*-hydroxymethyl-branched carbocyclic nucleosides **88** starting from the simple 1,3-dihydroxy acetone **83**. The stereocontrolled synthesis of diene precursor **85** was successfully achieved by a Johnson orthoester-Claisen rearrangement on compound **84**. The cyclisation of **86** under normal RCM conditions using catalyst **C** afforded



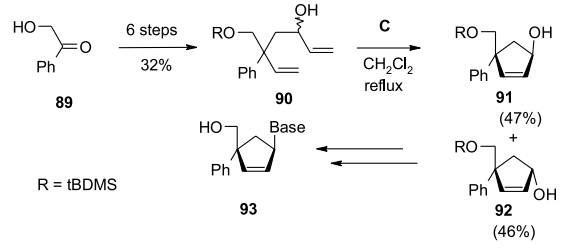
Scheme 16. (a) DIBALH, CH_2Cl_2; (b) triethylorthoacetate, propionic acid, 135 °C; (c) DIBALH, CH_2Cl_2; (d) PCC, CH_2Cl_2; (e) CH_2=CHMgBr, THF.

the cyclopentenol **87** in 97% yield. The introduction of heterobases was finally achieved under a Pd(0)-catalyzed allylic amination under Tsuji–Trost conditions (Scheme 17).



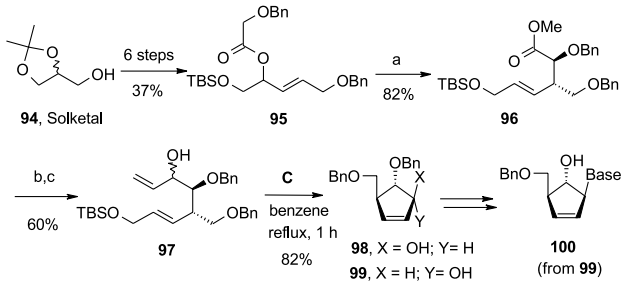
Scheme 17. (a) Triethyl orthoacetate, propionic acid, 130 °C; (b) DIBALH, toluene; (c) vinylMgBr, THF.

Hong et al.[32] applied a similar strategy to the synthesis of 4′α-*C*-phenyl carbocyclic nucleosides **93** starting from **89** (Scheme 18). Since, the diene precursor **90** is not enantiomerically pure, compounds **91** and **92** are obtained in a global yield of 93% after RCM. The allylic cyclopentenol **91** can be converted into carbanucleosides, after activation, through the Tsuji–Trost procedure, meanwhile, the heterocycle could be condensed on **92** under Mitsunobu conditions.



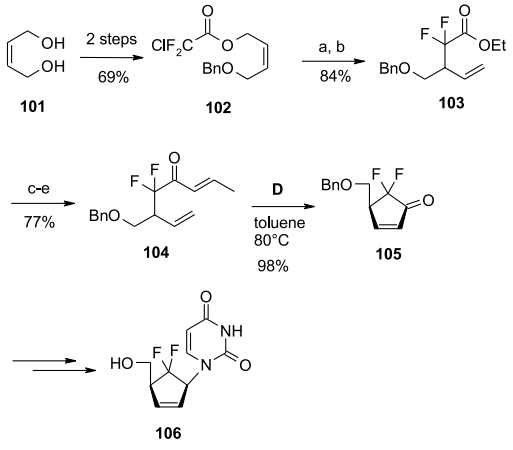
Scheme 18.

The synthesis of 6′(α)-hydroxy-carbovir **100** has been reported by Hong et al.[33] starting from a simple acyclic precursor, solketal (**94**). The relative stereochemistry of the target nucleosides was successfully controlled by a sequential stereoselective Claisen rearrangement of **95** to **96**. An RCM of diene **97** afforded a diastereomeric mixture of cyclopenenols **98** and **99**, in 56 and 26% yield, respectively (Scheme 19).



Scheme 19. (a) LHMDS, TMSCl/TEA then CH_3I, Triton-B, MeOH; (b) DIBALH, CH_2Cl_2; (c) vinylMgBr, THF.

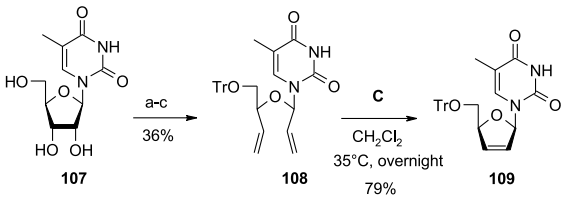
2′,3′-Dideoxy-6′,6′-diflurouracil (**106**), which belongs to a novel series of *gem*-difluoromethylenated carbocyclic nucleosides, was synthesized from (*Z*)-but-2-ene-1,4-diol (**101**) in 14 steps by Yang et al.[34] (Scheme 20). A notable step was the incorporation of a *gem*-difluoromethylene group by way of a silicon-induced Reformatsky–Claisen reaction of the chlorodifluoroacetic ester **102**, yielding **103** in 84% yield. This reaction was followed by a reduction and an addition of an allylmagnesium bromide and gave the diene **104**, which was cyclized via RCM using the second-generation Grubbs' catalyst **D** in refluxing toluene in 98% yield. It is interesting to note that initial treatment of the diene **104** in the presence of the first-generation Grubbs' catalyst did not afford the excepted fluorinated cyclopentenone **105**. The heterocycle was then introduced onto **105** using an undisclosed procedure.



Scheme 20. (a) Zinc dust, TMSCl, MeCN, 100 °C; (b) cat. H_2SO_4, EtOH; (c) *N*,*O*-dimethylhydroxylamine, $AlMe_3$; (d) allylMgBr, THF; (e) Et_3N, THF.

5. Formation of 2′,3′-didehydro-2′,3′-dideoxynucleosides

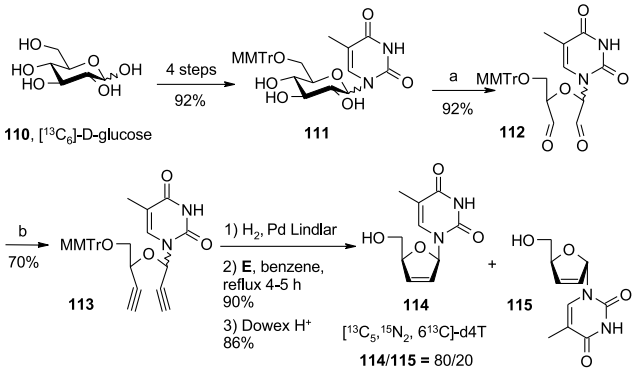
In 2002, Ewing et al.[35] described a novel route to d4T from 5-methyluridine **107** (Scheme 21). The periodinane cleavage



Scheme 21. (a) TrCl, pyr.; (b) $NaIO_4$, EtOH/H2O; (c) Ph_3PMeBr, *t*-BuOK.

of **107** followed by a double Wittig reaction gave the precursor **108**. Treatment of **108** with the first-generation Grubbs' catalyst **C** afforded the desired protected d4T **109** in 79% yield. Nevertheless, the double Wittig step has a low reproducibility and it is the rate-limiting step of this synthetic pathway.

At the same time, our own team[36] reported a similar and optimized strategy for the synthesis of isotopically stable (^{13}C and ^{15}N)-d4T **114** from ^{13}C-labeled α-D-glucose (**110**) (Scheme 22). The key step of this chemical pathway is the formation starting from the hexonucleoside **111** of the dialdehyde **112** and its conversion into the diyne **113**. After a partial reduction of the triple bonds, the resulting diene was submitted to an RCM in presence of catalyst **E**. In the course of this synthesis, the α and β isomers (**114** and **115**) were finally separated after deprotection of the primary alcohol. The global yield starting from **110** was 33%.

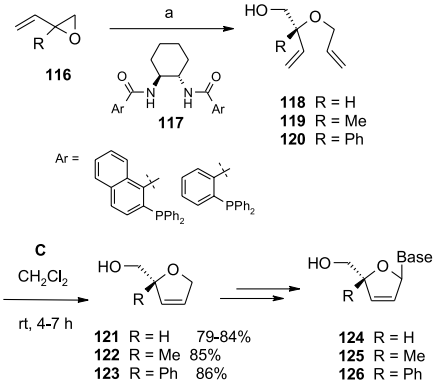


Scheme 22. (a) $Pb(OAc)_4$; (b) $MeCOC(N_2)P(O)(OMe)_2$, K_2CO_3.

Various analogues of d4T (**124–126**) were synthesized by Trost et al.[37] using an RCM step with Grubbs' ruthenium benzylidene catalyst. The bis-olefin key precursors (**118–120**) were obtained from the butadiene mono-epoxide **116** through a palladium-catalyzed asymmetric transformation with a chiral ligand **117**. Treatment of the dienes **118–120** in the presence of catalyst **C** afforded the corresponding cyclized derivatives **121–123** in 79 to 86% yields, respectively, without loss of stereochemical integrity (Scheme 23).

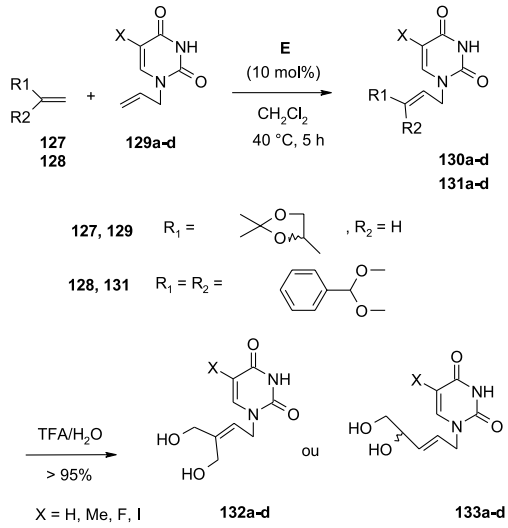
6. Formation of acyclonucleosides

Novel unsaturated acyclonucleosides **132–133** have been synthesized easily in three steps by our team[38] using CM as the key sequence. Thus, the reaction between the terminals olefins **127** (or **128**) and various allylic pyrimidine derivatives **129a–d** in the presence of catalyst **E** in refluxing



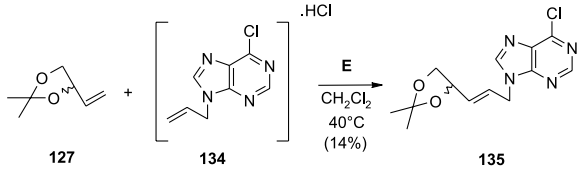
Scheme 23. (a) Allylic alcohol, $[Pd_2(dba)_3]\cdot CHCl_3$, chiral ligand **132**, Et_3B, CH_2Cl_2.

dichloromethane afforded **130a–d** (or **131a–d**) in good to moderate yields (Scheme 24). No self-metathesis products were observed and the metathetical coupling reactions all proceeded with high or exclusive *trans* selectivity.



Scheme 24.

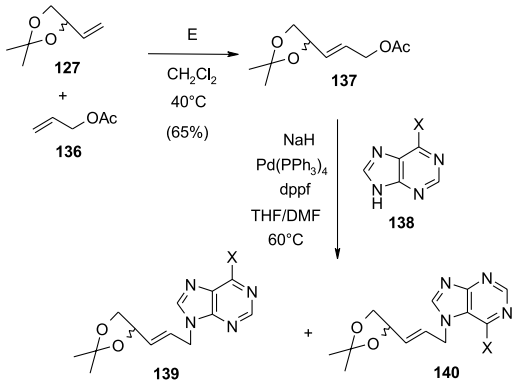
We have also reported the first example, of metathesis in the presence of a purine, but, due to steric hindrance and the presence of several tertiary basic nitrogens of allylic purines, which can be problematic in CM by coordination to the ruthenium center, the CM must be conducted with the hydrochloride salt (**134**) to afford **135**, but only in 14% yield (Scheme 25).



Scheme 25.

This low yield led us to investigate an alternative synthetic route, utilizing first, the cross-metathesis of **127** with allyl acetate **136** in the presence of catalyst **E** affording allylic acetate **137** in 65% yield. Here, again, no homodimeric

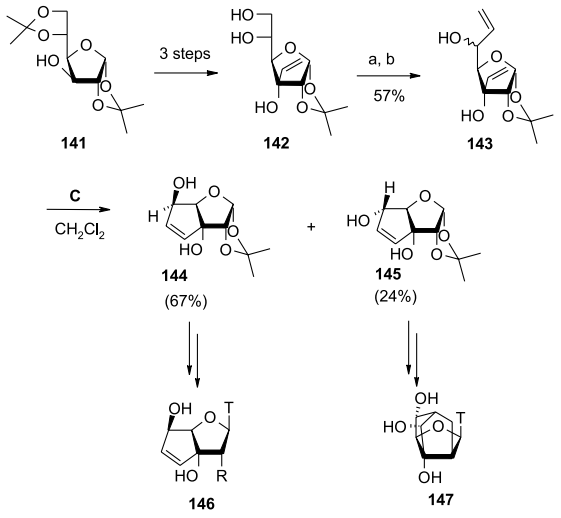
compounds from self-metathesis were isolated. Finally, the purine bases **138** were introduced via Pd(0) Tsuji–Trost allylation (Scheme 26) to afford a mixture of regioisomers **139** and **140**.



Scheme 26.

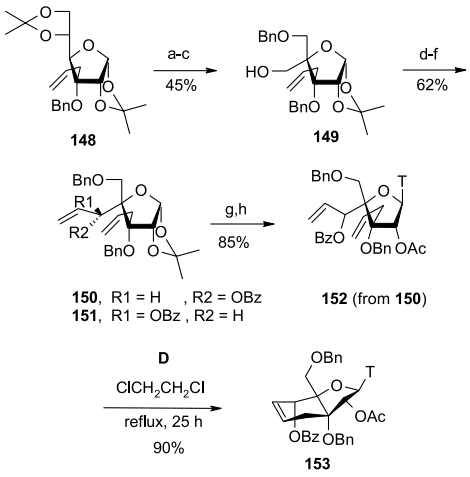
7. Formation of polycyclic nucleosides

Bicyclic[39] (**146**) and tricyclic[40] (**147**) nucleosides (locked nucleosides analogues) have been prepared by Nielsen et al. from the common protected glucofuranose **141** (Scheme 27). The RCM precursor **143** was obtained in two steps from the compound **142**. In the presence of catalyst **C**, diene **143** underwent RCM in 91% global yield for both isomers **144** and **145**. Due to the presence of ruthenium catalyst, these compounds were not isolated in a pure form, but required benzylation in order to isolate them pure. Thymine was introduced under Vorbrüggen conditions onto **144** and **145**, respectively, and the bicyclic thymidine **146** and the tricyclic analogue **147** were, respectively, isolated.



Scheme 27. (a) $NaIO_4$; (b) vinylMgBr, THF.

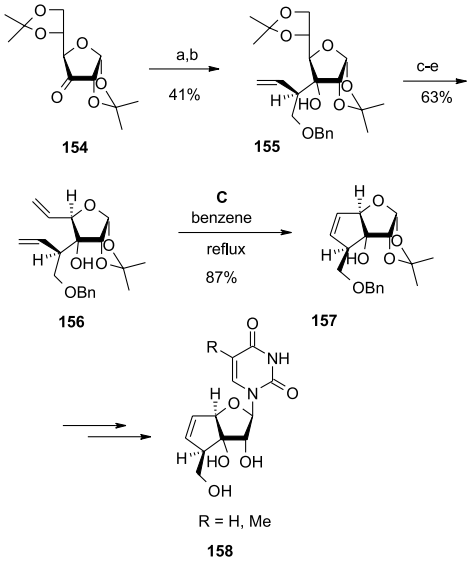
The synthesis of the bicyclic thymidine nucleoside **153** locked in *S*-type conformations has been realized by Nielsen et al.[41] (Scheme 28). Starting from **148**, the main chemical steps involved a Cannizzaro reaction (to **149**), a Grignard addition (to **150** or **151**) and the introduction of the methyluracil under Vorbrüggen conditions (to **152**); the



Scheme 28. (a) H_5IO_6, EtOAc; (b) H_2CO, NaOH then $NaBH_4$; (c) BnBr, NaH; (d) PCC, CH_2Cl_2; (e) vinylMgBr, THF; (f) Bzcl, pyr.: (g) 80% aq AcOH then Ac_2O, pyr.; (h) thymine, *N*,*O*-bis(trimethylsilyl)acetamide, TMSOTf.

diene **152** has been synthesized in eight steps from **148** in 24% overall yield. Finally, an RCM was performed on **152** using precatalyst **D** to afford the bicyclic locked nucleoside **153** in 90% yield.

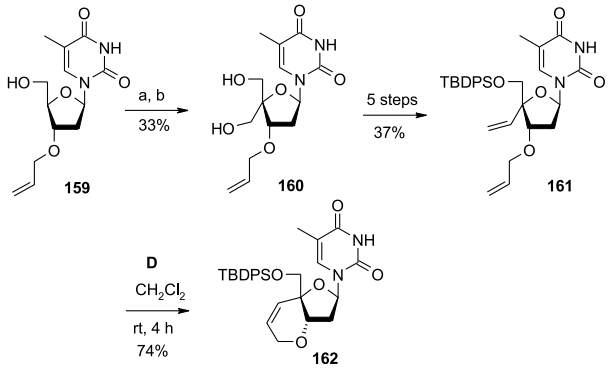
Other bicyclic locked nucleosides **158** have been synthesized by Gurjar et al.[42] (Scheme 29). Starting from the known ketone glucofuranose **154**, the stereochemistry of the diene precursor **156** was successfully achieved by a vinylogous Reformatsky reaction on **155**. The RCM on **156** was achieved in the presence of catalyst **C** (4 mol%) in refluxing benzene and provided the bicyclic derivative **157** in 87% yield. In a few more steps, the heterocycle was introduced under Vorbrüggen conditions.



Scheme 29. (a) Methyl 4-bromocrotonate, Zn–Cu; (b) $LiAlH_4$ then BnBr, Ag_2O; (c) 0.8% H_2SO_4, MeOH; (d) MsCl, *i*-Pr_2EtN; (e) NaI, Et-CO-Me.

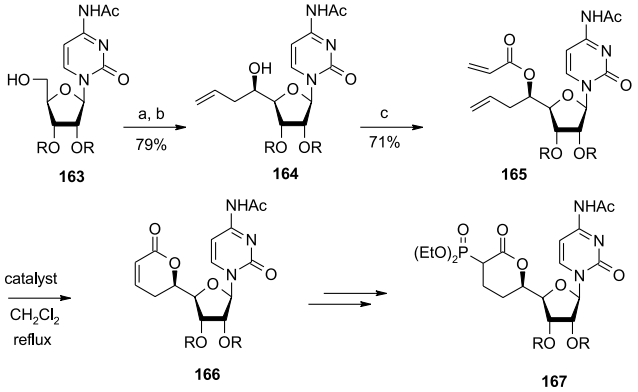
In parallel, Lebreton and co-workers[43] developed a route to the synthesis of new six-membered ring bicyclic nucleoside analogs using RCM. The key diene **161** was produced from **160** obtained starting from the 3′-allyloxythymidine **159**

according to the route outlined in Scheme 30 and then subjected to an RCM reaction in dichloromethane with the second-generation catalyst **D** at rt to give the cyclized derivative **162** in 74% yield.



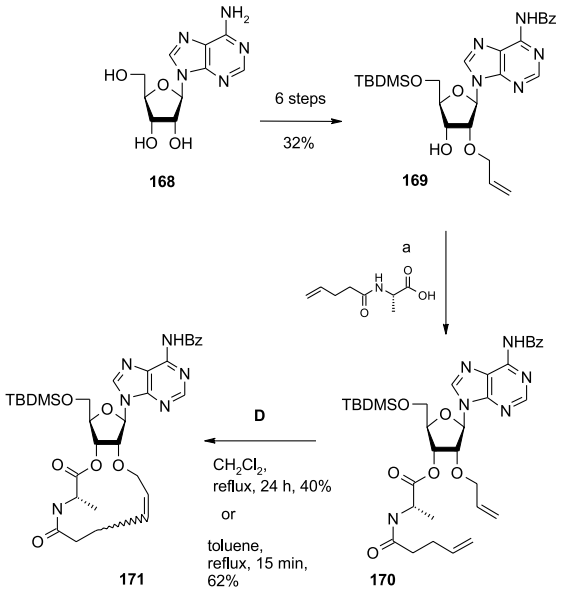
Scheme 30. (a) DCC, pyridinium trifluoroacetate; (b) HCHO, NaOH then $NaBH_4$.

Starting from a protected cytidine analogue, Chen et al.[44] described the synthesis of α-phosphonolactone derivatives of cytosine **167** through a reaction sequence that included RCM (Scheme 31). The precursor **165** was easily obtained from the cytidine derivative **163** through a stereoselective allylation of the 5′ position of the carbohydrate moiety followed by alkylation of the resulting alcohol **164** with acryloyl chloride. The diene **165** was then subjected to RCM under various conditions. The authors reported that the use of catalyst **C** gave 34% of the desired α,β-unsaturated cyclic ether **166**, with 22% recovered starting material. The presence of $Ti[O(i\text{-}Pr)]_4$, which was reported to be able to destabilize unproductive complexes and result in effective cyclization, did not improve the conversion. In return, catalyst **D** permitted the formation of **166** in 85% yield.



Scheme 31. (a) DMSO, EDC, pyr. TFA; (b) $CH_2CHCH_2SnBu_3$, 5.0 M LPDE; (c) acryloyl chloride, Et_3N, DMAP.

RCM has also been used for the preparation of a 13-membered ring bicyclic adenosine analogue (Scheme 32). Etheve-Quelquejeu et al.[45] described the preparation of the diene intermediate **170** through a peptidic coupling of alcohol ribosyl analogue **169** with *N*-pentenoyl-L-alanine. **169** was obtained in six steps from adenosine **168** through a well-known procedure. The cyclisation of diene **170** in the presence of catalyst **D** in dichloromethane as solvent afforded

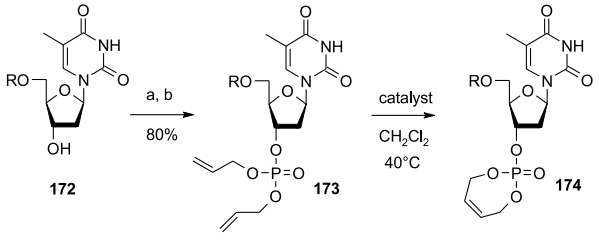


Scheme 32. (a) EDCI, DMAP, CH_2Cl_2.

171 in 40% yield, but the yield can be increased to 62% in toluene at 110 °C. Compound **171** was obtained as a mixture of *Z* and *E* stereoisomers in the ratio 49/51. It is interesting to note that the ring-closing metathesis occurred even in the presence of a purine heterocycle. We can hypothesize that this is mainly due to the protecting group at the C6–NH_2, but also because of the environment around the site of the RCM on, which the steric and electronic effects brought about by the purine cycle have low (or no) effect.

8. Formation of nucleoside and/or nucleotide dimers or trimers

In their efforts to generate conformationally restricted dinucleotides, Nielsen and co-workers[46] described the first examples of RCM to produce cyclic phosphates **174** (Scheme 33). The acyclic phosphate **173** served as a model system for RCM and was produced from the thymidine-derived secondary alcohol **172** using phosphoramidate coupling chemistry. The authors showed that the ring closure was more significantly facile using catalyst **D** (45 min, 97%),



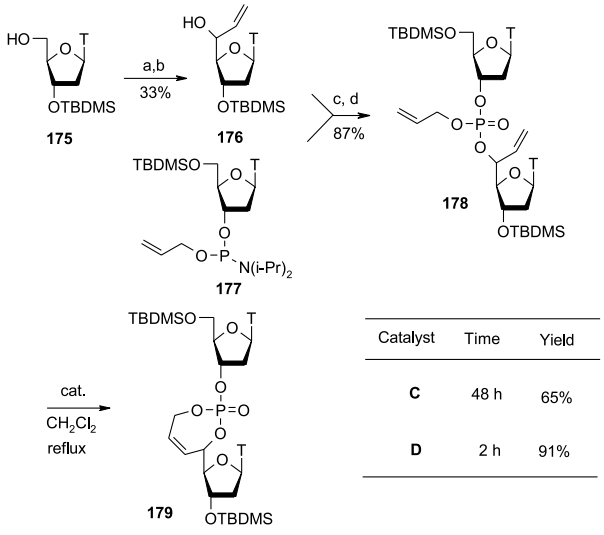
R = tBDMS

Catalyst	Time	Yield
C	20 h	52%
D	45 min	97%

Scheme 33. (a) $(CH_2{=}CHCH_2O)_2PN(i\text{-}Pr)_2$, tetrazole, $(i\text{-}Pr)_2NH$, MeCN; (b) *t*-BuOOH, toluene, CH_2Cl_2.

when compared to cyclisation under the same conditions with catalyst **C** (20 h, 52%).

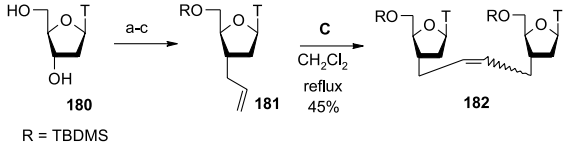
Phosphoramidate **177** was coupled with the allylic thymidine derivative **176**, produced in 35% yield from 3′-*O*-protected thymidine **175**, to afford the dinucleotide **178**, which was then submitted to an RCM with catalyst **D**, which proved again to be more efficient in yielding conformationally restricted dinucleotide **179** (Scheme 34).



Catalyst	Time	Yield
C	48 h	65%
D	2 h	91%

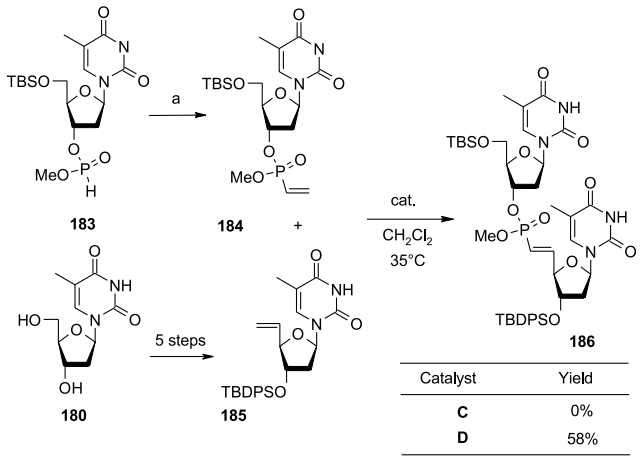
Scheme 34. (a) Dess-Martin periodinane, CH_2Cl_2; (b) vinylMgBr, THF; (c) tetrazole, $(i\text{-Pr})_2NH$, MeCN; (d) *t*-BuOOH, toluene, CH_2Cl_2.

In 2001, Krausz et al.[47] presented the first example of nucleoside dimerization by cross-metathesis (Scheme 35). The reaction between 3′-allylic thymidine **181**, easily obtained in three steps from thymidine **180**, permitted the formation of unsaturated chain-linked dimers. Thus, compound **182** is obtained in 45% yield as a 55/45 mixture of *Z*/*E* isomers after CM in dichloromethane in the presence of catalyst **C**. Nevertheless, the authors noted that the cyclisation was less effective in the presence of free 5′-hydroxymethyl (15% yield) and was not efficient to prepare the allylcytidine analog (<10% yield).



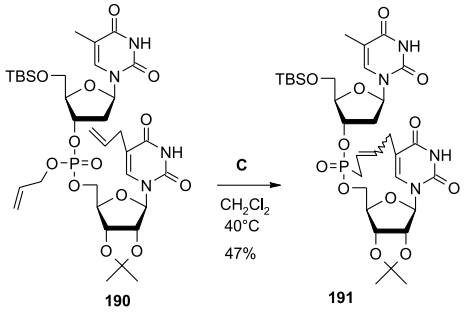
Scheme 35. (a) TBDPSCl, DMAP, pyr.; (b) PhOC(S)Cl, DMAP, MeCN; (c) $Bu_3SnCH_2CH{=}CH_2$, toluene.

The synthesis of vinylphosphonate-linked nucleotide dimers **186** has been achieved by Hayes et al.[48] using an olefin cross-metathesis (Scheme 36). Catalyst **D** was found to be the superior catalyst for the cross-coupling of vinylphosphonate **184**, obtained from the corresponding *H*-phosphonate **183**, with 5′-unsaturated thymidine **185**, affording the (*E*)-vinylphosphonate **186** in 58% yield (Scheme 37). A number of other minor products were formed in this reaction, which were identified as a combination of the products of benzylidene transfer from the catalyst **D** to **187** and **188**,



Catalyst	Yield
C	0%
D	58%

Scheme 36. (a) $Pd(OAc)_2$, dppf, $BrCH{=}CH_2$, propylene oxide, THF.



Scheme 37.

respectively, and the cross-metathesis of **189** with itself (Fig. 4).

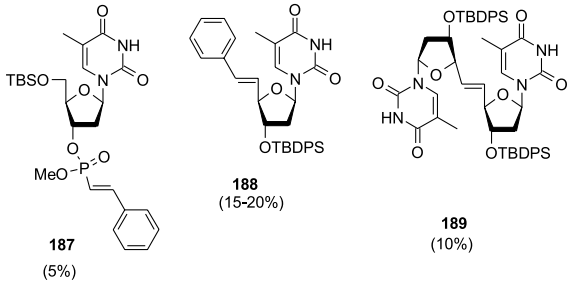
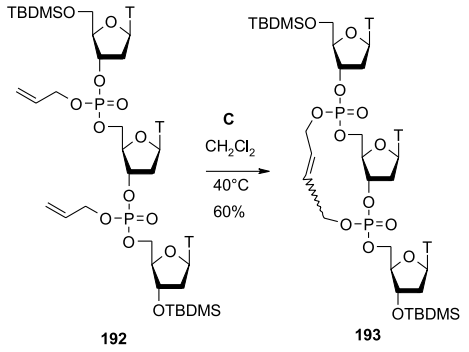


Figure 4. Products from a benzylidene moiety transfer during catalyst activiation and homo-dimer.

Nielsen and co-workers[49] have also produced conformationally restricted di- and trinucleotides using RCM. Thus, the formation of an allylic linkage on diallyl derivative **190** has been achieved using catalyst **C** (Scheme 37). Compound **191** was finally isolated as a diastereoisomeric mixture *E*/*Z* (10/1) in 47% yield.

The bis-phosphate **192** also underwent metathesis using 10 mol% of catalyst **C** to afford 13-membered trinucleotide **193** in 60% yield (Scheme 38).

Recently, Nielsen and co-workers[50] investigated dinucleotides **U**–**X** possessing terminal double bonds at four different positions as substrates for RCM (Fig. 5).



Scheme 38.

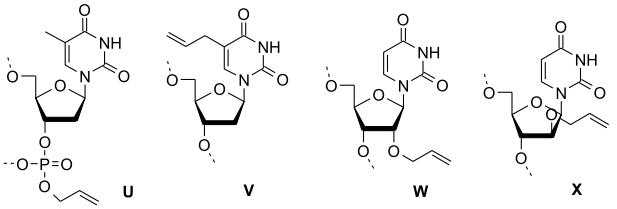
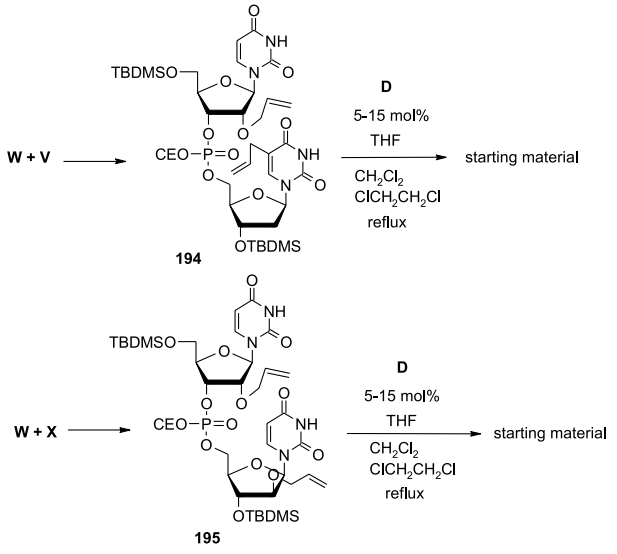


Figure 5. The four different positions for allyl groups.

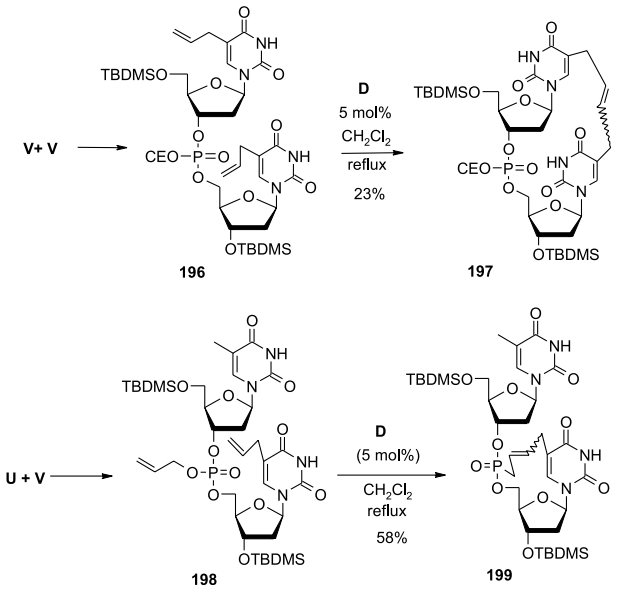
Neither **194** nor **195** dinucleotides were good substrates for RCM reactions using 5–15 mol% of the second-generation catalyst **D** in dichloromethane, 1,2-dichloroethane or THF under reflux (Scheme 39).



Scheme 39.

On the other hand, the dinucleotide **196** was slowly converted into a ring-closed product **197** in 23% yield as a mixture of four stereoisomers in an approximate 1:1:4:6 ratio, as deduced from the ^{31}P NMR spectrum (Scheme 40). This indicates that both *E*- and *Z*-configured products were obtained, that the ratios are dependent on the configuration of the phosphorus and that the two isomers in the substrate reacted at different rates. Thus, 27% of the starting material was recovered with an approximate 1:10 ratio of phosphorus epimers.

Finally, the dinucleotide **198** turned out to be the most



Scheme 40.

efficient substrate for RCM. Thus, treatment with 5 mol% of catalyst **D** in dichloromethane afforded **199** in 58% yield as a mixture of two phosphorus epimers in an equimolar ratio.

9. Conclusions

Less than a decade has elapsed since Crimmins reported on the first use of ring-closing metathesis for nucleoside synthesis. Although, metathesis of alkenes will remain at the core of this area, recent developments, especially in catalysis, point to the notion that metathesis of other π systems may also fertilize nucleoside chemistry. This refers in particular, to enyne-alkyne derivatives. From the work described here, it is apparent that metathesis has played, and will most likely continue to play, a major role in the synthesis of new nucleosides.

Acknowledgements

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References and notes

1. (a) Yokoyama, M.; Momotake, A. *Synthesis* **1999**, 1541. (b) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (c) Agrofoglio, L. A.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (d) Akella, L. B.; Vince, R. *Tetrahedron* **1996**, *52*, 2789. (e) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319. (f) Zemlicka, J. *Pharmacol. Ther.* **2000**, *85*, 251. (g) Agrofoglio, L. A.; Challand, S. R. *Acyclic, Carbocyclic and L-Nucleosides*; Kluwer Academic: Dordrecht, 1998. (h) Ichikawa, E.; Kato, K. *Synthesis* **2002**, 1. (i) Ichikawa, E.; Kato, K. *Curr. Med. Chem.*

2001, *8*, 385. (j) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745.
2. (a) Schaeffer, J. H.; Beauchamp, L.; De Miranda, P.; Elion, G.; Bauer, D. J.; Collins, P. *Nature* **1978**, *272*, 583. (b) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; De Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716. (c) Furman, P. A.; St. Clair, M. H.; Fyfe, J. A.; Rideout, J. L.; Keller, P. M.; Elio, G. B. *J. Virol.* **1979**, *32*, 72.
3. Reviews on applications of RCM: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1883. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Furstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37. (e) Schrock, R. R. *Top. Organomet. Chem.* **1998**, *1*, 1. (f) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141. (g) Blechert, S. *Pure Appl. Chem.* **1999**, *71*, 1393. (h) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (i) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (j) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 30123. (k) Roy, R.; Das, K. *Chem. Commun.* **2000**, 519. (l) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (m) Walters, M. A. In Joule, J. A., Gribble, G. W., Eds.; Progress in Heterocyclic Chemistry; Pergamon: New York, 2003; Vol. 15, p 1. Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.
4. Review on Ru-catalysts development and comparison of various catalysts: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.
5. Anderson, A. W.; Merckling, M. G. *Dupont Nemours U.S.A.* **1955**, *271*, 189. (*Chem. Abstr.* **1955**, *50*, 3008).
6. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.
7. Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678.
8. (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426. (b) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (c) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.
9. (a) Schuster, M.; Blechert, S. *Angew Chem., Int. Ed.* **1997**, *36*, 2036. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (d) Schürer, S. C.; Gessler, S.; Buschmann, N.; Blechert, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3898.
10. Niedballa, U.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 461.
11. (a) Shealy, Y.; O'Dell, C.; Arnett, G. *J. Med. Chem.* **1987**, *30*, 1090. (b) Peterson, M.; Vince, R. *J. Med. Chem.* **1990**, *34*, 1214. (c) Ben Cheikh, A.; Zemlicka, J. *Nucleosides and Nucleotides* **1987**, *6*, 265. (d) Shealy, Y.; O'Dell, C. *J. Heterocycl. Chem.* **1976**, *13*, 1015. (e) Shaw, G.; Warrener, R. *J. Chem. Soc.* **1958**, 153. (f) Shaw, G.; Warrener, R. *J. Chem. Soc.* **1958**, 157. (g) Shung, W. L. *J. Org. Chem.* **1982**, *47*, 3623.
12. (a) Marquez, V.; Lim, M.; Tseng, C.; Markovac, A.; Priest, M.; Khan, M.; Kaskar, B. *J. Org. Chem.* **1988**, *53*, 5709. (b) Tseng, C.; Marquez, V. *Tetrahedron Lett.* **1985**, *26*, 3669. (c) Jones, M.; Roberts, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2927. (d) Tseng, C.; Marquez, V.; Fuller, R.; Goldstein, B.; Haines, D.; McPherson, H.; Parsons, J.; Shannon, W.; Arnett, G.; Hollingshead, M.; Driscoll, J. *J. Med. Chem.* **1989**, *32*, 1442. (e) Marquez, V.; Bodenteich, M.; Copp, R.; Lim, B. *Nucleic Acids Res. Symp. Ser.* **1990**, *22*, 35. (f) Wolfe, M.; Anderson, B.; Borcherding, D.; Borchardt, R. *J. Org. Chem.* **1990**, *5*, 4712.
13. (a) Kondo, K.; Sato, T.; Takemoto, K. *Chem. Lett.* **1973**, 967. (b) DiMenna, W.; Piantadosi, C.; Lamb, R. *J. Med. Chem.* **1978**, *21*, 1073. (c) Martin, J.; Smee, D.; Verheyden, J. *J. Org. Chem.* **1985**, *50*, 755. (d) Bindu Madhavan, G.; Martin, J. *J. Org. Chem.* **1986**, *51*, 1287. (e) Palmer, C.; Parry, K.; Roberts, S. *Tetrahedron Lett.* **1990**, *31*, 279.
14. (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Toyota, A.; Katagiri, N.; Kaneko, C. *Synth. Commun.* **1993**, *23*, 1295. (c) Rosenquist, A.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1996**, *61*, 6282.
15. Trost, B. M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621.
16. For overviews on Pd(0)-catalyzed allylic substitution, see: (a) Frost, C. G.; Howarth, J.; Williams, J. M. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (b) Starý, I.; Zájíček, J.; Kočovský, P. *Tetrahedron* **1992**, *48*, 7229. (c) Williams, J. M. *Synlett* **1996**, 705. (d) Trost, B. M.; Verhoeven, T. R. In Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Comprehensive Organometallic Chemistry; Pergamon: New York, 1982; Vol. 8. (e) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (f) Tsuji, J. Palladium Reagents and Catalysts: Innovations in Organic Synthesis Wiley: Chichester, UK, 1995. (g) Agrofoglio, L. A., Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875.
17. Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192.
18. Crimmins, M. T.; King, B. W.; Zuercher, W. J.; Choy, A. L. *J. Org. Chem.* **2000**, *65*, 8499.
19. Kuang, R.; Ganguly, A. K.; Chan, T. -M.; Pramanik, B. N.; Blythin, D. J.; McPhail, A. T.; Saksena, A. K. *Tetrahedron Lett.* **2000**, *41*, 9575.
20. (a) Bestmann, H. J.; Roth, D. *Synlett* **1990**, 751. (b) Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem.* **1987**, *52*, 5457.
21. Choi, W. J.; Park, J. G.; Yoo, S. J.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jung, Y. H.; Jeong, L. S. *J. Org. Chem.* **2001**, *66*, 6490.
22. (a) Moon, H. R.; Choi, W. J.; Kim, H. O.; Jeong, L. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1189. (b) Jin, Y. H.; Liu, P.; Wang, J.; Baker, R.; Huggins, J.; Chu, C. K. *J. Org. Chem.* **2003**, *68*, 9012. (c) Yang, M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, *69*, 3993.
23. Moon, H. R.; Kim, H. O.; Lee, K. M.; Chun, M. W.; Kim, J. H.; Jeong, L. S. *Org. Lett.* **2002**, *4*, 3501.
24. (a) Gillaizeau, I.; Charamon, S.; Agrofoglio, L. A. *Tetrahedron Lett.* **2001**, *42*, 8817. (b) Agrofoglio, L. A.; Amblard, F.; Nolan, S. P.; Charamon, S.; Gillaizeau, I.; Zevaco, T. A.; Guenot, P. *Tetrahedron* **2004**, *60*, 8397.
25. Ovaa, H.; Codée, J. D. C.; Lastdrager, B.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 7987.
26. Lee, K.; Cass, C.; Jacobson, K. A. *Org. Lett.* **2001**, *4*, 597.
27. Hong, J. H.; Shim, M. J.; Ro, B. O.; Ko, O. H. *J. Org. Chem.* **2002**, *67*, 6837.
28. Gurjar, M. K.; Maheshwar, K. *J. Org. Chem.* **2001**, *66*, 7552.
29. Chong, Y.; Gumina, G.; Chu, C. K. *Tetrahedron: Asymmetry* **2000**, *11*, 4853.
30. Fang, Z.; Hong, J. H. *Org. Lett.* **2004**, *6*, 993.
31. Ko, O. H.; Hong, J. H. *Tetrahedron Lett.* **2002**, *43*, 6399.
32. Hong, J. H.; Ko, O. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 1289.
33. Hong, J. H.; Oh, C.-H.; Cho, J.-H. *Tetrahedron* **2003**, *59*, 6103.
34. Yang, Y.-Y.; Meng, W.-D.; Qing, F.-L. *Org. Lett.* **2004**, *6*, 4257.
35. (a) Ewing, D.; Glaçon, V.; Mackenzie, G.; Postel, D.; Len, C. *Tetrahedron Lett.* **2002**, *43*, 3503. (b) Ewing, D.; Glaçon, V.; Mackenzie, G.; Postel, D.; Len, C. *Tetrahedron* **2003**, *59*, 941.

36. Gillaizeau, I.; Lagoja, I. M.; Nolan, S. P.; Aucagne, V.; Rozenski, J.; Herdewijn, P.; Agrofoglio, L. A. *Eur. J. Org. Chem.* **2003**, 666.
37. Trost, B. M.; Brown, B. S.; McEachern, E. J.; Kuhn, O. *Chem. Eur. J.* **2003**, *9*, 4442.
38. (a) Amblard, F.; Nolan, S. P.; Gillaizeau, I.; Agrofoglio, L. A. *Tetrahedron Lett.* **2003**, *44*, 9177. (b) Amblard, F.; Nolan, S. P.; Schinazi, R. F.; Agrofoglio, L. A. *Tetrahedron* **2005**, *61*, 537.
39. Ravn, J.; Nielsen, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 985.
40. Ravn, J.; Thorup, N.; Nielsen, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1855.
41. (a) Thomasen, H.; Meldgaard, M.; Freitag, M.; Petersen, M.; Wengel, J.; Nielsen, P. *J. Chem. Commun.* **2002**, 1888. (b) Freitag, M.; Thomasen, H.; Christensen, N. K.; Petersen, M.; Nielsen, P. *Tetrahedron* **2004**, *60*, 3775.
42. Gurjar, M. K.; Reddy, D. S.; Bhadbhade, M. M.; Gonnade, R. G. *Tetrahedron* **2004**, *60*, 10269.
43. Montembault, M.; Bourgougnon, N.; Lebreton, J. *Tetrahedron Lett.* **2002**, *43*, 8091.
44. Chen, X.; Wiemer, D. F. *J. Org. Chem.* **2003**, *68*, 6597.
45. Busca, P.; Etheve-Quelquejeu, M.; Valery, J.-M. *Tetrahedron Lett.* **2003**, *44*, 9131.
46. (a) Sorensen, A. M.; Nielsen, P. *Org. Lett.* **2000**, *2*, 4217. (b) Sorensen, A. M.; Nielsen, K. E.; Vogg, B.; Jacobsen, J. P.; Nielsen, P. *Tetrahedron* **2001**, *57*, 10191.
47. Batoux, N.; Benhaddou-Zerrouki, R.; Bressolier, P.; Granet, R.; Laumont, G.; Aubertin, A.-M.; Krausz, P. *Tetrahedron Lett.* **2001**, *42*, 1491.
48. Lera, M.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 2765.
49. (a) Borsting, P.; Nielsen, P. *Chem. Commun.* **2002**, 2140. (b) Borsting, P.; Sorensen, A. M.; Nielsen, P. *Synthesis* **2002**, 797.
50. Borsting, P.; Freitag, M.; Nielsen, P. *Tetrahedron* **2004**, *60*, 10955.

Biographical sketch

Franck Amblard, born in Chateauroux, France (1977), received his PhD degree (2004) in organic chemistry from the University of Orléans (France), working with Dr. L. A. Agrofoglio on the synthesis of new antiviral molecules using olefin metathesis and palladium-catalyzed reactions. In March 2005, he moved to Emory University, USA, as a postdoctoral fellow, working with Professor R. F. Schinazi on antiviral chemistry.

Steven P. Nolan, born in Quebec City, Canada (1962) received his B.Sc (1983) from the University of West Florida and his PhD (1987) from the University of Miami, where he worked under the supervision of Professor Carl Hoff on organometallic thermochemistry. After a postdoctoral fellowship at Northwestern University with Professor Tobin Marks, where he studied homogeneous catalysis involving organolanthanide complexes, he was appointed Assistant Professor of Chemistry at the University of New Orleans in 1990. He now holds the position of University Research Professor at this same institution. His main areas of expertise and interest deal with organometallic chemistry and homogeneous catalysis.

Luigi A. Agrofoglio, born in Antibes, France (1965), received his B.S. (1987) and PhD (1993) degrees in chemistry from the University of Nice Sophia-Antipolis (Fr) working with Professor R. Condom on the synthesis of carbocyclic analogues of nucleosides. Dr. Agrofoglio has held postdoctoral appointments at the University of Alabama at Birmingham, USA, working with Professor J.-P. Sommadossi, as well as at the University of Georgia at Athens (UGA). At UGA, he worked in the laboratory of Professor C. K. Chu. He joined the Institute of Organic and Analytical Chemistry (ICOA), a CNRS research laboratory associated with the University of Orléans (Fr), as Assistant Professor in 1995; he now holds the position of University Professor. At present, he is leader of the 'Chemistry of the Components and Analogues of Nucleic Acids' group in the same institute. His main areas of expertise and interest deal with organic chemistry as well as bioanalysis of nucleosides.

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Biocatalytic and chemical investigations in the synthesis of sucrose analogues

Jürgen Seibel,* Roxana Moraru and Sven Götze

Department for Carbohydrate Technology, Technical University of Braunschweig, Langer Kamp 5, 38106 Braunschweig, Germany

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Abstract—Herein, we report about the synthesis of sucrose analogues, obtained by two different approaches: a chemical and an enzymatic. The one step synthesis of the sucrose analogues with the exo-fructosyltransferase (EC 2.4.1.162) from *Bacillus subtilis* NCIMB 11871, which transfers the fructosyl residue of the substrate sucrose to the monosaccharide acceptors galactose, mannose, xylose and fucose, has been developed. Effects in the fructosylation by variation of the positions of the hydroxyl-groups in glycopyranoside acceptors have been studied in respect to their acceptor properties. In contrast, the chemical equivalent nonenzymatic organic synthesis of galacto-sucrose and manno-sucrose has been achieved including six synthetic steps.

1. Introduction

Oligosaccharides such as galacto-oligosaccharides, xylo-oligosaccharides and lactosucrose have been produced in industrial scale[1] and developed as bulking sugar substitutes that have beneficial health effects.[2] For example, the sucrose analogue sucralose has been examined for its usefulness as noncariogenic sweeting agent. It is 600 times sweeter than sucrose and inhibits certain oral bacterial species including *mutans streptococci* (MS).[3] More recently, these compounds have been demonstrated to exhibit immunomodulatory effects on systemic immune response. Thus, the life sciences industry has an increasing demand in oligosaccharides, because these biomolecules have potential application as therapeutics.[4] Some studies have concluded that fucose and mannose appeared to be the most effective of the essential sugars when it came to slowing the growth of cancer cells.[5] Fucose studies are also showing, that it plays a significant role in many diseases, including cancer and its spread and neuron transmission in the brain.[6]

However, the degree of molecular diversity that can be generated from glycosidic linkage assembly is enormous and the synthesis of specific glycosidic linkages is difficult, as carbohydrates are highly functionalized with hydroxyl groups of similar reactivity.[7] To obtain relatively simple oligosaccharides, a wide range of selective protecting-group strategies has to be planed in synthetic routes.[8] In nature, there are hundreds of different enzymes involved in the synthesis of oligosaccharides. We are recently interested in the synthesis of oligosaccharides by enzymes called non Leloir-glycosyltransferases, which utilize the substrate sucrose.[9] The binding energy of substrates, preserved in sucrose analogues, is used in further/subsequent synthesis, as synthons. In our studies, we present the chemical and enzymatic synthesis of the galactose, xylose, mannose and fucose analogues of sucrose.

2. Results and discussion

2.1. Synthetic approach

The chemistry of sucrose is limited due to the eight hydroxyl groups of similar reactivity. Thus, regioselective protection is difficult.[10] For the synthesis, we started a synthetic classical approach and a parallel enzymatic route. Chemical synthesis of sucrose analogues has been studied by Lichtentaler et al.[11] According to their previous work, we got access to the sucrose analogue β-D-fructofuranosyl-α-D-mannopyranoside, which was obtained in 26% overall yield, respectively.

Inspired by this work, a new route for the synthesis of β-D-fructofuranosyl-α-D-galactopyranoside (Gal-Fru) **6** was investigated (Scheme 1). Thus, isopropylidenation of commercially and cheap available sucrose **1** using 2,2′-dimethoxypropane (DMP) afforded 4,6-mono-*O*-isopropylidenesucrose **2** in

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* Corresponding author. Tel.: +49 531 3917262; fax: +49 531 3917263; e-mail: j.seibel@tu-bs.de

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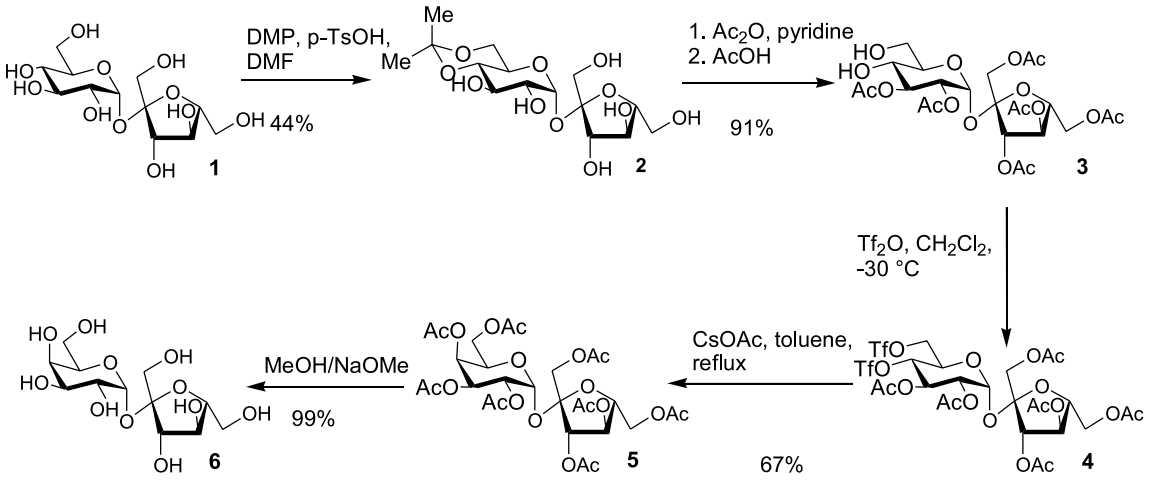


Scheme 1.

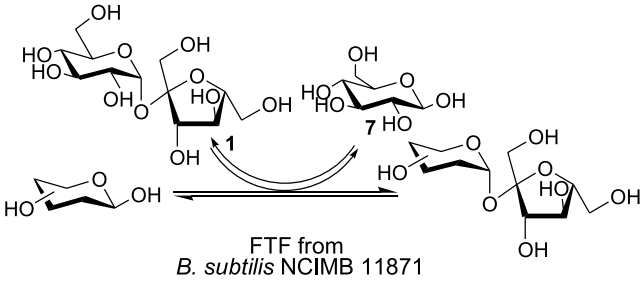
44% yield.[12] Peracetylation, followed by deacetylation using acetic acid, gave 1,3,4,6-tetra-*O*-acetyl-β-D-fructofuranosyl 2,3-di-*O*-acetyl-α-D-glucopyranoside **3** in excellent yield. The free diol was converted in the corresponding ditriflate **4**, which was highly unstable. Thus, refluxing **4** in toluene with caesium acetate gave 1′,2,3,3′,4,4′,6,6′-octa-*O*-acetyl-β-D-fructofuranosyl-α-D-galactopyranoside **5**, which upon deactetylation afforded Gal-Fru **6** in 66% overall yield.

2.2. Enzymatic synthesis

The sucrose analogue synthesis is a time-consuming process, due to the protective group manipulations and the isolation of the intermediates, which decreases overall efficiency. Recently, Römer et al. reported on the synthesis of the sucrose analogue β-D-fructofuranosyl-α-D-xylopyranoside **12** from the donor substrate UDP-α-D-xylose and D-fructose as acceptor by a recombinant sucrose synthase (SuSy1) from potato, respectively.[13] In contrast, in our studies we used an enzyme for a transfructosylation process, which does not require sugar nucleotides, as do all glycosyltransferases of the Leloir pathway, with respect for industrial purposes.

The FTF produced by *Bacillus subtilis* NCIMB 11871[14,15] was tested for its ability to synthesize sucrose analogues by fructosyltransfer from sucrose in the presence of glycopyranosides as in acceptors (Scheme 2). In the presence of D-galactose **8** (400 g/L) and sucrose **1** (400 g/L) the FTF formed the disaccharide Gal-Fru **6**. Optimization of the media and temperature revealed, that the yield of the desired Gal-Fru **6** was maximized at 54%, because an equilibrium is formed,[9] which relies on two transfer reactions: the transfer of the fructosyl residue from sucrose **1** to the acceptor D-galactose **8**, and the reverse reaction the transfer of the fructosyl residue from Gal-Fru **6** to the D-glucose **7**. We also observed the hydrolysis of Gal-Fru **6**. Consequently, the acceptor spectrum for the transfructosylation reaction was expanded. In contrast to D-galactose **8** the acceptor D-mannose **9** demonstrated to be a weak acceptor. The reason should be addressed to its axial position of the hydroxyl group at C-2. Only a maximum yield of 25 g/L manno-sucrose **10** was observed even by variation of the reaction conditions. In addition, the formation of xylosyl-sucrose **12** using D-xylose **11** as acceptor was observed in maximum concentrations of 226 g/L, respectively. The results indicate that the hydroxyl groups of D-glycopyranosides in position 4 and 6 are not crucial for the transfructosylation, in contrast to the position 2. Very recently, Kalovidouris et al. demonstrated that Fuc-α-(1–2)-Gal carbohydrates are capable of modulating neuronal outgrowth and morphology.[16]

This observation prompted us to investigate the acceptor properties of L-fucose **13**. Surprisingly in our studies, the L-fucose **13** was also fructosylated by the enzyme in a concentration of 54 g/L^{-1} (Fig. 1). Because the



Scheme 2.

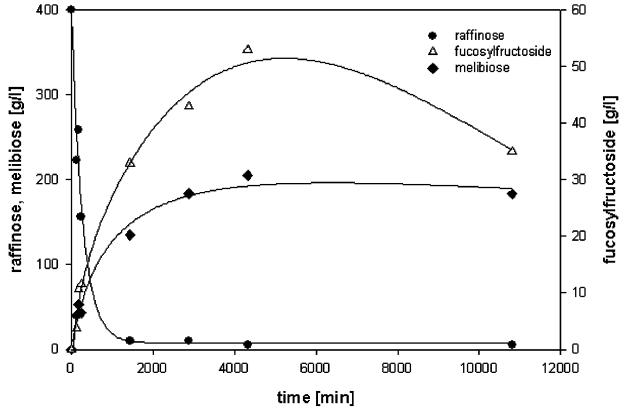
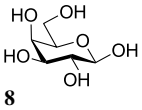
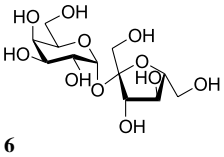
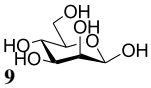
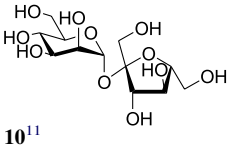
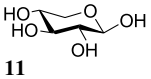
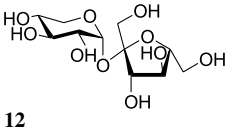
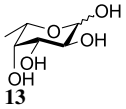
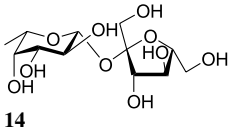


Figure 1.

Table 1. Biocatalytic and chemical synthesis of sucrose analogues

Donor	Product	Organic synthesis	Biocatalysis	
		Yield (%) (synthetic steps)	Yield (%) (enzymatic steps)	Product concentration ($g\,l^{-1}$)
 **8**	 **6**	27 (6)	54 (1)[a]	256
 **9**	 **10**[11]	26 (6)[11]	4 (1)[a]	25
 **11**	 **12**	—	62 (1)[a]	226
 **13**	 **14**	—	21 (1)[b]	53

[a] Yields are calculated from sucrose.
[b] Yields are calculated from raffinose.

fructosylated fucose **14** (Fuc-Fru) had nearly the same polarity as glucose the separation was difficult. Thus, raffinose was used as main substrate for this acceptor, which does not produce glucose, but instead melibiose (Fig. 1). Structural evidence for all sucrose analogues were confirmed by the ^{1}H and ^{13}C NMR spectroscopy. The elucidation of the sucrose analogue structures (galacto-sucrose, xylo-sucrose and fuco-sucrose) were possible only by the combination of all the data acquired from the ^{1}H, ^{13}C and 2D NMR spectra. The doublets at δ_H 5.40 ppm (galacto-sucrose) and 5.36 ppm (xylo-sucrose) exhibited the expected anomeric coupling constants $J_{1,2}$ of 3.9 and 3.6 Hz, characteristic for the anomeric protons of an α-(1-2)-glycosidic linkage. According to ^{1}H NMR spectra we observed, that Fuc-Fru **14** has a β-(1-2)-glycosidic linkage. It is assumed that the L-configuration ($^{1}C_4$) of fucose effects a different orientation of the acceptor in the active side of the FTF. The 2-H resonance of the fucose residue at δ_H 3.45 had $J_{2,1}=8.04$ Hz. In the 2D NMR spectra correlations were observed between H-1 and H-3 of the fructose residue in the ^{1}H, ^{1}H NOESY spectrum, indicating that the fructosyl residue has a β-furanosidic conformation and is bound to fucose through a β-2,1 linkage. The main peaks in the ^{1}H NMR spectrum were assigned using 2D-COSY spectroscopy. It was possible to measure most of the coupling constants. The values observed for the couplings of proton H-3 ($J_{3,2}=9.9$ Hz, $J_{3,4}=3.6$ Hz) showed a fucopyranose residue. The complete interpretation of the ^{13}C spectrum was performed using 2D $^{1}H/^{13}C$ correlation spectroscopy (HMBC, HMQC). Therefore, it can be concluded that the transfructosylation product is a β-D-Fructofuranosyl-β-L-fucopyranoside **14** (Table 1).

In conclusion, we have demonstrated, that a levansucrase from *B. subtilis* NCIMB 11871 is a remarkable catalyst for the synthesis of sucrose analogues. For the production of the oligosaccharide Gal-Fru **6** and further analogues we were able to replace a six step synthetic route (yield 26%) by using this enzyme. The biocatalyst takes just one step and is able to produce a wide repertoire of oligosaccharides, indicating the power of enzymes in oligosaccharide synthesis. Downstream processing for the isolation has been developed.[9]

The application of this biocatalyst in the oligosacchariode synthesis represents an opportunity for the development of industrial chemical and pharmaceutical processes. In addition, sucrose analogues like Gal-Fru, Man-Fru, Xyl-Fru and Fuc-Fru present interesting oligosaccharides, which will be tested in future for biological activity, prebiotic effects and as sweeteners. The structural similarities of the sugars to sucrose may endow them with an ability to inhibit the cariogenicity of sucrose.

3. Experimental

3.1. General

All reactions requiring anhydrous conditions were conducted in flame- or oven-dried apparatus under an atmosphere of Ar. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P_2O_5 before use. CH_2Cl_2, toluene and DMF were distilled from CaH_2 under Ar. External reaction temperatures are reported unless stated otherwise. Reactions were monitored by TLC using commercially available plates, precoated with a 0.25 mm layer of silica containing a fluorescent indicator (Merck) and compounds were sprayed with anisaldehyde reagent followed by heating. Organic

layers were dried over $MgSO_4$ unless stated otherwise. Column chromatography was carried out on Kieselgel 60 (40–63 μm). Petroleum ether refers to the fraction with bp 40–60 °C. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ and D_2O unless stated otherwise using a Bruker AM-400 instrument, operating at 400 MHz for ^1H and at 100 MHz for ^{13}C. Chemical shifts are reported relative to $CHCl_3$ [δ_H 7.26, δ_C (central of triplet) 77.0] or CH_3OH [δ_H 3.35, δ_C (central of septet) 49.0]. Melting points were determined on a Melt-Temp 2 microscope. Electrospray-ionization mass spectra (ESIMS) were recorded with a Finnigan MAT 8340 on samples suspended in CH_3OH. IR spectra in pressed KBr discs were recorded on a Bio-Rad FTS-25 spectrometer. Optical rotation values were measured with a Dr. Kernchen sucromat polarimeter.

The enzymatic reactions were analyzed by high-performance liquid chromatography (HPLC). HPLC was performed with a RCM Monosaccharide Ca^{2+} column (300×7.8 mm, Phenomenex®, Germany) operated at 80 °C and an Ion Chromatograph (IC) (Metrohm, Germany) with refractive index detector (ERC-7512, Erma, Germany), using a refractive index detector and an eluent of bidistilled water at 0.8 ml min^{-1}.

Standard solutions were prepared in the range of 0.1–10 g l^{-1}. The monosaccharides D-fructose, D-galactose, D-glucose, D-xylose, L-fucose, the disaccharide sucrose, melibiose, the trisaccharides raffinose, 1-kestose and the tetrasaccharide nystose were used as external standards for peak identification and quantification. The relative standard deviation of this system is of approx. 3%.

The aliquots from enzymatic reactions were also analyzed using TLC. The solvent system ethylacetate/isopropanol/water in a ratio of 6/3/1 (v/v/v) (rt) was used as mobile phase.

The reaction samples were applied on silica thin-layer plates (TLC aluminium sheets 20×20 cm, silica gel 60 F_{254} with concentrating zone 20×2.5 cm—MERCK, Germany) after appropriate dilution (final concentration between 0.05 and 1 g l^{-1}).

The carbohydrates were separated by using four ascents (4×90 min). Spots were detected by dipping the plates into the detecting reagent (0.3% (w/v) of *N*-(1-naphtyl)-ethylenediamine (Fluka, Germany) and 5% (v/v) concentrated sulfuric acid in methanol using a CAMAG Chromatogram Immersion Device III (speed 2, time 4) (MERCK, Germany), followed by heating in an oven at 120 °C for 15 min. The sugars were visualized as dark spots on a pale pink background. The quantitative determination of the sugars was performed by scanning densitometry (50–2000 ng) using a Bio-Rad Imaging Densitometer utilizing Quantity One® Software (Version 4.2).

3.2. Chemical synthesis of Gal-Fru

3.2.1. 4,6-Mono-*O*-isopropylidensucrose 2. To a stirred solution of sucrose **1** (4.00 g, 11.7 mmol) in DMF (20 ml) was added 2,2-dimethoxypropane (15.0 ml, 122.4 mmol) and catalytic amounts of *para*-toluenesulfonic acid monohydrate (25 mg) at rt. After 2 h the reaction mixture was neutralized with triethylamine and concentrated. Purification by column chromatography (9:1 $CHCl_3$/MeOH, R_f 0.20) gave the title compound as a white solid (2.0 g, 5.2 mmol, 44%).

^1H and ^{13}C NMR spectra data are in accordance with lit.[12]

3.2.2. 1′,2,3,3′,4′,6′-Hexa-*O*-acetylsucrose 3. To a stirred solution of 4,6-mono-*O*-isopropylidensucrose **2** (1.50 g, 3.9 mmol) in pyridine (10 ml) was added acetic anhydride (3.2 ml, 33.3 mmol) at rt. After 12 h methanol (1 ml) was added and evaporated. The residue was added acetic acid (60%, 15 ml). The mixture was stirred at 80 °C for 15 min and concentrated. Purification by column chromatography (1:2 cyclohexane/EtOAc) gave the title compound (2.11 g, 3.5 mmol, 91%) as a colourless oil.

$[\alpha]_D$ +55.0 (*c* 1.0, $CHCl_3$), lit.[17] $[\alpha]_D$ +57.5 (*c* 1.0, $CHCl_3$); R_f 0.20 (1:2 cyclohexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.63–5.64 (d, $J_{1,2}=3.6$ Hz, 1H, H-1), 5.44–5.46 (d, $J_{3',4'}=6.0$ Hz, 1H, H-3′), 5.37–5.40 (t, $J_{3',4'}=J_{4',5'}=6.0$ Hz, 1H, H-4′), 5.32–5.37 (t, $J_{3,4}=J_{3,2}=9.9$ Hz, 1H, H-3), 4.76–4.79 (dd, $J_{2,1}=3.6$ Hz, $J_{2,3}=9.9$ Hz, 1H, H-2), 4.26–4.30 (dd, $J_{5',6'a}=3.6$ Hz, $J_{5',4'}=8.0$ Hz, 1H, H-5′), 4.11–4.17 (m, 2H, H-1_a′, H-1_b′), 4.20–4.25 (m, 1H, H-6_b′), 4.01 (m, 1H, H-5), 3.89–3.93 (dd, $J_{6a,5}=3.0$ Hz, $J_{6b,a}=8.9$ Hz, 1H, H-6a), 3.80–3.85 (dd, $J_{5',6b'}=4.9$ Hz, $J_{6a',b'}=7.2$ Hz, 1H, H-6b′), 2.10–2.18 (m, 18H, 6OAc), 3.67 (t, $J_{4,3}=J_{4,5}=9.9$ Hz, 1H, H-4). ESIMS: *m*/*z* 617.0 100% [M+Na^+].

3.2.3. 1′,2,3,3′,4,4′,6,6′-Octa-*O*-acetyl-β-D-fructofuranosyl-α-D-galactopyranoside 5. To a stirred solution of 1′,2,3,3′,4′,6′-hexa-*O*-acetylsucrose **3** (1.00 g, 1.68 mmol) in CH_2Cl_2 (50 ml) was added on molecular sieves (4 Å) pyridine (560 μl, 6.9 mmol), followed by trifluoromethanesulfonic anhydride (860 μl, 7.0 mmol) at −30 °C. After 12 h the reaction was quenched by the addition of sat. aqueous $NaHCO_3$ (100 ml). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×50 ml). The combined organic layers were dried ($MgSO_4$) and filtered. The filtrate was concentrated to afford the triflate **4** (1.31 g, 1.53 mmol, 91%) as a yellow oil, which was used without further purification in the next step.

To a stirred solution of the triflate **4** (1.31 g, 1.53 mmol) in toluene (100 ml) on molecular sieve (4 Å) was added cesium acetate (1.50 g, 7.81 mmol) and tetrabutylammonium acetate (1.50 g, 5.0 mmol) at rt. The suspension was heated at reflux for 2 h. After cooling at rt H_2O (100 ml) was added. The layers were separated, and the aqueous layer was extracted with DCM (3×50 ml). The combined organic layers were washed with brine (1×50 ml), dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (4:1 diethyl ether/petroleum ether) gave the title compound as a foamy solid (767 mg, 1.13 mmol, 67% overall).

R_f 0.20 (4:1 diethyl ether/petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 5.73–5.72 (d, $J_{1,2}=3.7$ Hz, 1H, 1-H), 5.50–5.48 (d, $J_{3',4'}=6.6$ Hz, 1H, 3′-H), 5.48–5.40 (dd, $J_{5,4}=0.9$ Hz, $J_{5,6}=6.4$ Hz, 1H, 5-H), 5.40–5.36 (t, $J_{3',4'}=J_{4',3'}=6.6$ Hz, 4-H), 5.36–5.32 (dd, $J_{3,2}=11.0$ Hz, $J_{3,4}=3.3$ Hz, 1H,

3-H), 5.18–5.14 (dd, $J_{2,3}=11.0$ Hz, $J_{2,1}=3.7$ Hz, 1H, 2-H), 4.51–4.48 (t, $J=6.60$ Hz, 1H, 5′-H), 4.35–4.05 (m, 7H, 1′-H_2, 4-H, 6′-H_2, 6-H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.46, 170.34, 170.10, 169.93, 169.87, 169.72 (7×*C*OCH$_3$), 103.58 (C-2′), 90.41 (C-1), 78.72 (C-5′), 75.46 (C-3′), 74.63 (C-4′), 68.00 (C-5), 67.47, 67.41, 67.12 (C-2, C-3, C-4), 63.90 (C-1′), 63.08 (C-6′), 61.69 (C-6), 20.67, 20.62, 20.57, 20.54 (CO*C*H$_3$).

3.2.4. β-D-Fructofuranosyl-α-D-galactopyranoside (Gal-Fru) 6. To a stirred solution of **5** (100 mg, 147 μmol) in MeOH (5 ml) was added NaOMe (200 μl of a 5 M solution in MeOH, 1 mmol) dropwise at rt. After 10 min the solution was neutralized to pH 7 with amberlite IR-120 H^+, filtered and concentrated. Purification by column chromatography (6:1 CH_3CN/H_2O) gave the title compound (50.0 mg, 99%) as a white solid.

White solid, mp: 160 °C, lit[18] mp: 174–177 °C; $[\alpha]_D$ +81.2 (*c* 1.0, H_2O), lit.[19] $[\alpha]_D$ +79.0 (*c* 1.0, H_2O); R_f 0.42 (6:3:1 EtOAc/isopropanol/H_2O, 3 ascends); IR (cm^{-1}): 3428, 1132, 1087, 1049, 1017; ^{1}H NMR (400 MHz, D_2O) δ 5.40–5.39 (d, $J_{1,2}=3.9$ Hz, 1H, 1-H), 4.18–4.15 (d, $J_{3',4'}=8.7$ Hz, 1H, 3′-H), 4.11–4.07 (dt, $J_{5,4}=0.9$ Hz, $J_{5,6}=6.4$ Hz, 1H, 5-H), 4.04–4.00 (t, 1H, $J_{3',4'}=J_{4',3'}=8.7$ Hz, 4′-H), 3.99–3.98 (dd, $J_{4,5}=0.9$ Hz, $J_{4,3}=3.20$ Hz, 1H, 4-H), 3.89–3.86 (dd, $J_{3,2}=10.5$ Hz, $J_{4,3}=3.20$ Hz, 1H, 3-H), 3.85–3.76 (m, 3H, 2′-H, 5′-H, 6′-H_2), 3.70–3.68 (t, $J=6.4$ Hz, 2H, 6-H_2), 3.64 (s, 2H, 1′-H_2). ^{13}C NMR (100 MHz, D_2O) δ 106.2 (C-1′), 94.87 (C-1), 83.86 (C-5′), 79.12 (C-3′), 76.72 (C-4′), 73.99 (C-5), 71.70 (C-3), 71.67 (C-4), 70.55 (C-2), 64.93 (C-6′), 64.08 (C-1′), 63.44 (C-6). ESIMS: *m/z* 365.0 100% [M+Na^+].

3.3. Enzymatic synthesis of sucrose analogues

3.3.1. General description of the fructosylation reaction. For the cultivation of *B. subtilis* NCIMB 11871 a liquid mineral salt medium containing 2.5% sucrose (w/v) was prepared. The mineral salt medium contained (in mg/100 ml): KH_2PO_4-136; $Na_2HPO_4\cdot 2H_2O$-267; $(NH_4)_2SO_4$-60; $MgSO_4\cdot 7H_2O$-20; $CaCl_2\cdot 2H_2O$-1; $FeSO_4\cdot 7H_2O$-0.5; $MnSO_4\cdot H_2O$-0.18 and $Na_2MoO_4\cdot 2H_2O$-0.25. Shaken culture was incubated at 30 °C and 150 rpm for 48 h.

When reaching the stationary phase, the cells were separated by centrifugation at 5000×*g* for 15 min at 4 °C (SORVAL® Centrifuge, USA) and then discarded. The supernatant obtained was analyzed undiluted, as crude enzyme solution for the characterisation but also as concentrated solution (ultrafiltration).

To a reaction mixture containing 40% (w/v) sucrose as substrate and 40% (w/v) glycopyranoside as acceptor in 5.0 ml phosphate buffer (pH 6) was added the equivalent volume of FTF supernatant (25 mU FTF per 5.0 ml supernatant). The sucrose analogue formation was investigated by discontinuous analysis of aliquots from the reaction mixture at suitable time intervals up to 48 h.

The enzyme was inactivated by boiling the samples in a water-bath for 10 min. After cooling, the inactivated samples were filtered through a 0.22 μm nitrocellulose membrane filter (Millipore, Germany) and analyzed, after appropriate dilution. Analysis of the samples was carried out using several chromatographic systems.

3.3.2. Preparative chromatography. Prior to preparative chromatographic separation, the sucrose analogue solution was subjected to an enzymatic treatment with a wild type glycosyltransferase (Gtf) from *Streptococcus oralis* cloned in *Escherichia coli*, kindly provided by Dr. Hofer (GBF mbH, Germany). By this step, sucrose was converted into dextran and fructose, which can be separated easily by chromatography. The pH of the crude product solution was adjusted to 5.4 and the reaction was started by adding 1 U Gtf ml^{-1} solution at 30 °C. After 2 h, the reaction was stopped by heat denaturation.

Separation of sucrose analogues from the reaction mixture was carried out with the PCR 6 in Na^+ form (300–330 μm, Purolite, France), packed in a 2 m glass column (∅=3.9 cm) (Borosilicat 3.3, QVF, Germany) and thermostated at 70 °C.

Fifteen millilitre of Gtf (from *S. oralis*) reaction mixture with a total sugar concentration of maximal 400 g l^{-1} was subjected on the column and eluted with a flow rate of 4 ml min^{-1} distilled water. Equal fractions of 12 ml were collected after measurement by differential refractometry.

3.3.3. β-D-Fructofuranosyl-α-D-mannopyranoside (Man-Fru) 10. $[\alpha]_D$ +18.2 (*c* 1.0, H_2O), lit.[11] $[\alpha]_D$ +19.1 (*c* 1.2, H_2O); R_f 0.40 (6:3:1 EtOAc/isopropanol/H_2O, 3 ascends); ^{1}H NMR (400 MHz, D_2O) δ 5.30–5.29 (d, $J_{1,2}=1.9$ Hz, 1H, 1-H), 4.14–4.12 (d, $J_{3',4'}=8.7$ Hz, 1H, 3′-H), 4.02–3.99 (t, $J_{4',3'}=J_{4',5'}=8.7$ Hz, 1H, 4′-H), 3.86–3.67 (m, 9H, 2-H, 3-H, 4-H, 5-H, 6-H_2, 5′-H, 6′-H_2), 3.61 (s, 1′-H_2). ^{13}C NMR (100 MHz, D_2O) δ 106.55 (C-2′), 96.18 (C-1), 83.93 (C-5′), 78.58 (C-3′), 76.51 (C-4′), 75.91, 73.68, 72.70 (C-2, C-3, C-5), 69.02 (C-4), 64.98 (C-6′), 63.55 (C-1′), 63.21 (C-6). ESIMS: *m/z* 365.0 100% [M+Na^+].

3.3.4. β-D-Fructofuranosyl-α-D-xylopyranoside (Xyl-Fru) 12. White solid, mp 120 °C; $[\alpha]_D$ +59.5 (*c* 1.1, H_2O), lit.[20] $[\alpha]_D$ +62 (*c* 1.0, H_2O); R_f 0.46 (6:3:1 EtOAc/isopropanol/H_2O, 2 ascends); IR (cm^{-1}): 3412, 1121, 1046; ^{1}H NMR (400 MHz, D_2O) δ 5.30–5.29 (d, $J_{1,2}=3.6$ Hz, 1H, 1-H), 4.17–4.15 (d, $J_{3',4'}=8.9$ Hz, 1H, 3′-H), 4.07–4.02 (t, $J_{4',3'}=J_{4',5'}=8.9$ Hz, 1H, 4′-H), 3.85–3.81 (dt, $J_{5',4'}=8.9$ Hz, $J_{5',6'}=2.8$ Hz, 1H, 5′-H), 3.78–3.74 (2d, $J_{6a',5'}=J_{6b',5'}=2.8$ Hz, 2H, 6_a′-H, 6_b′-H), 3.68–3.60 (m, 2H, 3-H, 5-H), 3.60 (s, 2H, 1′-H_2), 3.56–3.54 (m, 1H, 4-H), 3.50–3.46 (dd, $J_{2,3}=9.9$ Hz, $J_{2,1}=3.6$ Hz, 1H, 2-H). ^{13}C NMR (100 MHz, D_2O) δ 106.35 (C-2′), 94.97 (C-1), 84.01 (C-5′), 78.83 (C-3′), 76.26 (C-4′), 75.40 (C-3), 73.67 (C-2), 71.82 (C-4), 64.45 (C-6′), 64.38 (C-5), 63.48 (C-1′). ESIMS: *m/z* 335.0 100%, [M+ Na^+].

3.3.5. β-D-Fructofuranosyl-β-L-fucopyranoside (Fuc-Fru) 14. White solid, mp 120 °C; $[\alpha]_D$ −18.8 (*c* 0.6, H_2O); R_f 0.42 (6:3:1 EtOAc/isopropanol/H_2O, 2 ascends); IR (cm^{-1}): 3440, 1117, 1046, 1012; ^{1}H NMR (400 MHz, D_2O) δ 4.74–4.71 (d, $J_{1,2}=8.0$ Hz, 1-H), 4.20–4.16 (m, 1H, 4′-H), 4.18–4.16 (d, $J_{3',4'}=7.8$ Hz, 1H, 3′-H), 3.87–3.84 (m, 1H, 5′-H), 3.82–3.77 (m, 2H, 6_a′-H, 5-H), 3.73–3.70 (m, 2H,

$6_b'$-H, 4′-H), 3.68–3.65 (d, $J_{1a'}=12.6$ Hz, 1H, $1'_a$-H), 3.64–3.60 (dd, $J_{3,2}=9.9$ Hz, $J_{3,4}=3.6$ Hz, 1H, 3-H), 3.60–3.57 (d, $J_{1'b}=12.6$ Hz, 1H, $1'_b$-H), 3.48–3.43 (d, $J_{2,1}=8.0$ Hz, $J_{2,3}=9.9$ Hz, 1H, 2-H), 1.21–1.20 (d, $J_{6,5}=6.6$ Hz, 3H, 6-H_3). ^{13}C NMR (100 MHz, D_2O) δ 106.60 (C-2′), 98.28 (C-1), 84.17 (C-5′), 78.65 (C-3′), 75.21 (C-4′), 75.13 (C-3), 73.79 (C-5), 73.69 (C-4), 72.74 (C-2), 63.51 (C-1′, C-6′), 17.98 (C-6). ESIMS: *m/z* 349.0 100%, [M + Na^+].

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References and notes

1. Nakakuki, T. *Pure Appl. Chem.* **2002**, *74*, 1245–1251.
2. Oku, T.; Nakamura, S. *Pure Appl. Chem.* **2002**, *74*, 1253–1261.
3. Hough, L.; Khan, R. *Trends Biochem. Sci.* **1978**, *3*, 61–63.
4. Buchholz, K.; Seibel, J. Isomaltooligosaccharides. In *Oligosaccharides in Food and Agriculture*; Eggleston, G., Coté, G. L., Eds.; ACS Publication, Oxford University Press: Washington, 2003.
5. Haltiwanger, R. S.; Lowe, J. B. *Annu. Rev. Biochem.* **2004**, *73*, 491–537.
6. Becker, J.; Lowe, J. B. *Glycobiology* **2003**, *13*, 41–53.
7. Varki, A. *Glycobiology* **1993**, *3*, 97–130.
8. (a) *Carbohydrates as Organic Raw Materials*; Lichtenthaler, F. W., Ed.; VCH: Weinheim, 1991. (b) *Carbohydrates as Organic Raw Materials II*; Descotes, G., Ed.; VCH: Weinheim, 1991. (c) Lichtenthaler, F. W. *Carbohydr. Res.* **1998**, *313*, 69–89.
9. Baciu, I. E.; Jördening, H. J.; Seibel, J.; Buchholz, K. *J. Biotechnol.* **2005**, *116*, 347–357.
10. Jarosz, S.; Mach, M. *Eur. J. Org. Chem.* **2002**, 769–780.
11. Lichtenthaler, F. W.; Mondel, S. *Carbohydr. Res.* **1997**, *303*, 293–302.
12. Fanton, E.; Gelas, J.; Horton, D.; Karl, H.; Khan, R.; Lee, C.-K.; Patel, G. *J. Org. Chem.* **1981**, *46*, 4057–4060.
13. Römer, U.; Rupprath, C.; Elling, L. *Adv. Synth. Catal.* **2003**, *345*, 684–686.
14. Cheetham, P. S. J.; Hacking, A. J.; Vlitos, M. *Enzyme Microb. Technol.* **1989**, *11*, 212–219.
15. Rathbone, E. B.; Hacking, A. J.; Cheetham, P. S. J. EP 0130054, 1990.
16. Kalovidouris, S. A.; Gama, C. I.; Lee, L. W.; Hsieh-Wilson, L. C. *J. Am. Chem. Soc.* **2005**, *127*, 1340–1341.
17. Ong, G.-T.; Chang, K.-Y.; Wu, S.-H.; Wang, K.-T. *Carbohydr. Res.* **1993**, *241*, 327–334.
18. Feingold, D. S.; Avigad, G.; Hestrin, S. *J. Biol. Chem.* **1957**, *224*, 295–307.
19. Hough, L.; Mufti, K. S. *Carbohydr. Res.* **1973**, *29*, 291–296.
20. Avigad, G.; Feingold, D. S.; Hestrin, S. *Biochim. Biophys. Acta* **1956**, *20*, 129–131.

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Intramolecular Diels–Alder reaction of 1,7,9-decatrienoates catalyzed by indium(III) trifluoromethanesulfonate in aqueous media

Hikaru Yanai, Akio Saito and Takeo Taguchi*

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

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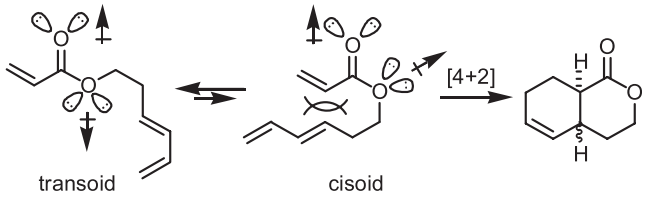
Abstract—The intramolecular Diels–Alder reaction of ester-tethered 1,7,9-decatrienoate derivatives in a mixture of water and 2-propanol was catalyzed by indium(III) triflate to give the cycloadducts in good yield with perfect *endo*-selectivity.

1. Introduction

Nowadays, the use of aqueous media or water as a sole solvent has been attracting much interest not only from the viewpoint of green chemistry, but also due to a number of examples of highly regio- and/or stereoselective reactions achieved specifically in aqueous solvent.[1] These involves synthetically important carbon–carbon bond forming reactions such as allylation of carbonyl compounds,[2] aldol reaction,[3] Diels–Alder reaction[4] and the transition metal catalyzed cross-coupling reactions.[5,6] Furthermore, during these days extensive efforts have been made to develop a variety of Lewis acid catalyzed reactions using rare earth metal triflates[7,8] such as $Sc(OTf)_3$ and $Yb(OTf)_3$ or indium(III) salts[9] which are found to work efficiently in aqueous media or in water.

Study on the intramolecular Diels–Alder (IMDA) reactions of ester-tethered trienoate derivatives is one of our ongoing research projects. It is well documented that contrary to hydrocarbon substrates or amide-tethered substrates, ester-tethered triene compounds show lower reactivity in the IMDA reaction due to the conformational preference of the transoid form over the cisoid form in which the diene and dienophile are in close proximity required for the reaction to proceed. This fact is explained by repulsive dipole interaction between the two oxygen atoms in ester moiety and steric repulsion between the two alkyl substituents existing in the carboxylic acid part and in the alcohol part (Scheme 1).[10,11] Towards to this issue, we have reported that bis-aluminated triflic amide $TfN[Al(Me)Cl]_2$, a novel bidentate Lewis acid, efficiently promoted the IMDA reaction of 1,7,9-decatrienoate derivatives presumably due to the restriction to the cisoid conformation in some extent and decrease in LUMO level of dienophile part through the bidentate coordination of the ester group,[12,13] although in some cases stoichiometric amount of this aluminated triflic amide was essentially needed for the smooth reaction. Continuously, we have focused our attention to find out more efficient Lewis acid. It was demonstrated by several examples that in a highly polar solvent such as water or DMSO, repulsive dipole interaction between the two oxygen atoms in the ester moiety may be weakened, thereby the energy difference between the transoid geometry and the cisoid geometry in polar solvent should be smaller than that in non-polar solvent. For example, Jung et al. reported that the IMDA reaction of the ester-tethered trienoate derivatives in DMSO[14] and Oshima et al. reported the intramolecular radical addition reaction of alkenyl iodoacetate in water.[15] Both reactions were found to efficiently proceed by using such polar solvent. Taking into account this polar solvent effect on the conformation of ester compounds, we examined the IMDA reaction of 1,7,9-



Scheme 1. IMDA reaction of ester-tethered trienoate derivative.

Keywords: Intramolecular Diels–Alder reaction; 1,7,9-Decatrienoates; Indium(III)triflate; Aqueous media.
* Corresponding author. Tel./fax: +81 426 76 3257; e-mail: taguchi@ps.toyaku.ac.jp

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decatrienoates in aqueous media using various water-compatible Lewis acids and as a result, $In(OTf)_3$ (20 mol%) was found to nicely catalyze the reaction. Detail is reported in this paper.

2. Results and discussion

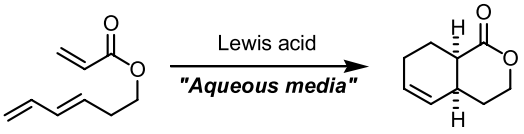
The IMDA reaction of (3*E*)-3,5-hexadienyl acrylate **1a** was conducted to examine the efficiency of various water-compatible Lewis acids. Results are summarized in Table 1. In a mixture of water and 2-propanol (6:1 v/v) reaction of **1a** in the presence of stoichiometric amount of $Sc(OTf)_3$ at 60 °C for 24 h gave the IMDA product **2a** in low yield (8% yield, entry 1). $Yb(OTf)_3$ also gave similar result (11% yield, entry 2). Any appreciable improvement in the yield of **2a** was not realized by the use of $Gd(OTf)_3$, $Ho(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, AgOTf. On the other hand, $InCl_3$ promoted the reaction efficiently to give **2a** in 51% yield with complete *endo*-selectivity after 12 h at 60 °C, although 100 mol% $InCl_3$ was used (entry 3). As shown in entries 4–6, with catalytic amount of $In(OTf)_3$ the reaction proceeded smoothly. That is, the use of 20 mol% $In(OTf)_3$ at 70 °C for 12 h resulted in the isolation of **2a** in 82% yield (entry 5), while in the cases of either 100 or 10 mol% of $In(OTf)_3$ yields of **2a** were lowered to 56 and 60%, respectively and in the latter case the reaction rate significantly decreased (entries 4 and 6).

Concerning the co-solvent, 2-propanol gave the best result (entry 5), while the product yield lowered to 39 and 52%, respectively when methanol or 2-methyl-2-propanol was used (entries 7 and 8). It should be noted that in the $In(OTf)_3$ catalyzed IMDA reaction of **1a** aqueous media is crucial to obtain the product **2a** in good yield. For example, reaction in 2-propanol under the similar conditions provided **2a** in low yield (39%, entry 9). Reaction in aprotic solvent such as 1,2-dichloroethane failed to obtain **2a**, but gave a complex mixture (entry 10). To check if a trace amount of trifluoromethanesulfonic acid (TfOH) liberated from $In(OTf)_3$ acts as a Brønsted acid catalyst, reaction was conducted in the presence of 0.6 M equiv of TfOH, but the yield of **2a** was only 47% (entry 11). This result should indicate that the IMDA reaction is catalyzed by $In(OTf)_3$ in this aqueous media.

Next, we examined the effect of the ratio of water on the product yield. Results are shown in Figure 1 by plotting the yield of **2a** on *y* axis and the water-content (H_2O in 2-propanol, vol%) on *x* axis. The best result was obtained when the ratio of H_2O–^{i}PrOH was 6:1 (85.7 v/v%, 82% yield, entry 6). Increase in water content resulted in a remarkable drop of the product yield and without 2-propanol, namely in water **2a** was formed only in 20% yield (entries 7 and 8). As the water content decreased to 80, 75 and 50 v/v%, the yield of **2a** was also gradually lowered to 71, 64 and 34%, respectively (entries 3–5), and when the water content was between 50 and 0 v/v%, very little difference in the product yield was observed keeping in a range of 35–40% yield (entries 1–3).

To see the scope and limitation of the $In(OTf)_3$ catalyzed IMDA reaction in aqueous media, we examined the IMDA reaction of 1,7,9-decatrienoates **1b–g** having a different substituent pattern. Results are summarized in Table 2. Compared to the model substrate **1a**, 5-methyl derivative **1b** (R^1=Me, R^{2-5}=H) showed a similar reactivity to give the *endo*-adduct **2b** as a single isomer after 8 h at 70 °C (76% yield, entry 1). The IMDA reaction of 6,10-dimethylated substrate **1c** ($R^{2,4}$=Me, $R^{1,3,5}$=H) and 8-methylated substrate **1d** (R^3=Me, $R^{1,2,4,5}$=H) gave products **2c** and **2d** in 71 and 83% yield, respectively (entries 2 and 3). The IMDA adduct **2c** was a mixture of two diastereomers, and the stereochemistry of the major one was determined to have *cis*-relationship between angular hydrogen and 6-methyl group (*cis*/*trans*=4.9:1). The reaction of 10-methyl derivative **1e** (R^4=Me, $R^{1-3,5}$=H) required longer time (24 h) and higher temperature (80 °C) to give the IMDA product **2e** in moderate yield (68%, entry 4), and the reaction of more lipophilic 10-propyl derivative **1f** required much longer reaction time even at higher temperature (under reflux condition) to give **2f** in only 18% yield (entry

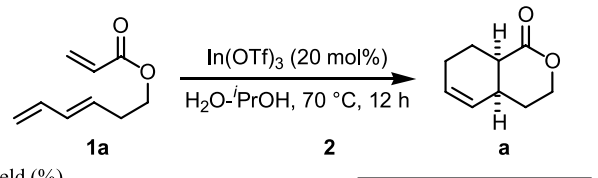
Table 1. Effect of Lewis acids on IMDA reaction of (3*E*)-3,5-hexadienyl acrylate (**1a**)

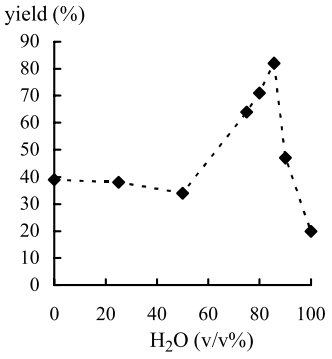


1a **2a**

Entry	Lewis acid (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	$Sc(OTf)_3$ (100)	H_2O–^{i}PrOH (6:1)	60	24	8
2	$Yb(OTf)_3$ (100)	H_2O–^{i}PrOH (6:1)	60	24	11
3	$InCl_3$ (100)	H_2O–^{i}PrOH (6:1)	60	12	51
4	$In(OTf)_3$ (100)	H_2O–^{i}PrOH (6:1)	70	12	56
5	$In(OTf)_3$ (20)	H_2O–^{i}PrOH (6:1)	70	12	82
6[b]	$In(OTf)_3$ (10)	H_2O–^{i}PrOH (6:1)	70	12	60
7	$In(OTf)_3$ (20)	H_2O–MeOH (6:1)	70	12	39
8	$In(OTf)_3$ (20)	H_2O–^{t}BuOH (6:1)	70	12	52
9	$In(OTf)_3$ (20)	^{i}PrOH	70	12	39
10[c]	$In(OTf)_3$ (20)	$ClCH_2CH_2Cl$	70	12	—
11	TfOH (60)	H_2O–^{i}PrOH (6:1)	70	12	47

[a] Isolated yield.
[b] 87% conversion.
[c] Complex mixture was obtained.





Entry	H_2O (v/v%)	Yield[a] (%)
1	0	39
2	25	38
3	50	34
4	75	64
5	80	71
6	85.7	82
7	90	47
8	100	20

[a] Isolated yield.

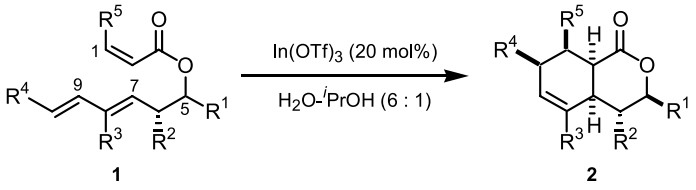
Figure 1. The plots of the yield and the water-content (H_2O in 2-propanol, volume %) on the IMDA reaction of **1a**.

5). The reaction of reactive maleic monoester **1g** proceeded at room temperature to give the product **2g** in 78% yield as a single isomer (entry 6).

Since the present $In(OTf)_3$ catalyzed IMDA reaction smoothly proceeded with the 1,7,9-decatrienoate derivative having active hydrogen as in the case of carboxylic acid **1g**, the reaction of the substrate having C6-hydroxyl group **1h** was conducted (Scheme 2).[16] In this case the IMDA reaction and the simultaneous ring-contraction from the six membered lactone to the five membered lactone occurred to give the *cis*-fused oxabicyclo[4.3.0]nonene compound **2h** in 55% yield as a mixture of diastereomers in a ratio of *cis*/*trans*=2.8:1. Since the relative configuration between the angular hydrogen atom and the hydroxymethyl group in the major diastereomer was confirmed to be *cis*, this major isomer **2h**-*cis* was possibly formed through the IMDA reaction via *endo*-boat axial transition state leading to the *cis*-fused oxabicyclo[4.4.0]decene derivative **B**, which, in turn, re-lactonized stereospecifically to the thermodynamically stable five membered ring system **2h**-*cis*.[17] Likewise, the formation of the minor isomer **2h**-*trans*, which has the *trans* configuration between the hydroxymethyl group and the angular hydrogen atom, can be explained by considering the *endo*-boat equatorial transition state in the IMDA reaction steps followed by the re-lactonization. Since it was reported that diastereo (*endo*/*exo*) control in the IMDA reaction of 1,6,8-nonatrienoate derivatives is quite difficult, our present result provides a highly *endo*-selective and convenient mean for oxabicyclo[4.3.0]nonene system.[18]

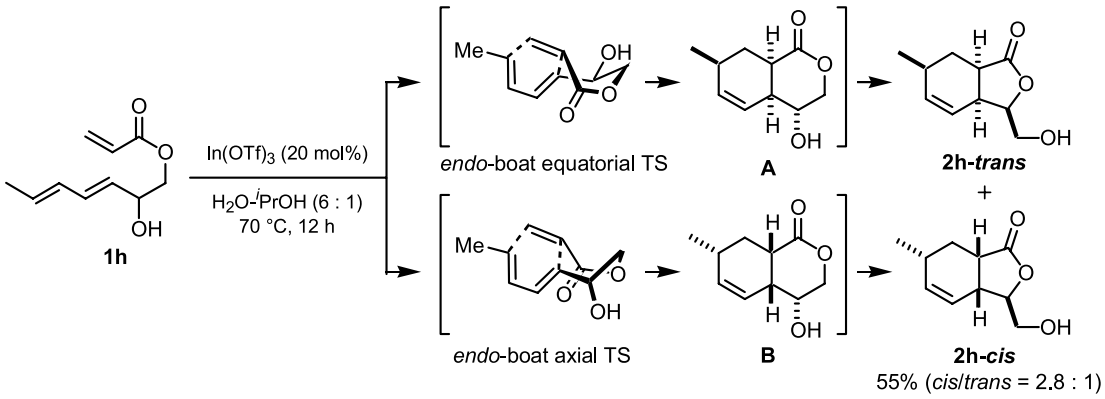
Since certain examples demonstrated that indium(III) salts were recyclable Lewis acids,[9] we also examined recycling experiment of $In(OTf)_3$ used in the IMDA reaction of trienoate **1d** as a model substrate (Scheme 3). Extraction of the reaction mixture of the first run with diethyl ether left the aqueous phase, which without any modification was used for the second run giving rise to the IMDA product **2d** in the comparable yield (78%) to that obtained in the first run.

Table 2. IMDA reaction of 1,7,9-decatrienoate derivatives in aqueous media

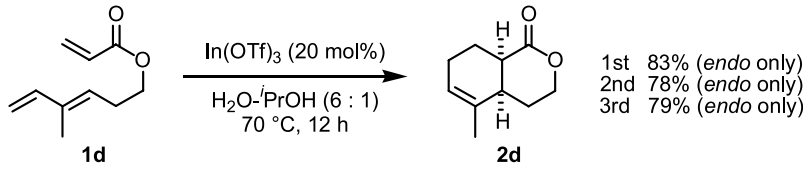


Entry	**1**	R^1	R^2	R^3	R^4	R^5	Temp. (°C)	Time (h)	Products **2**	Yield (%)[a]
1	**1b**	Me	H	H	H	H	70	8	**2b**	76
2	**1c**	H	Me	H	Me	H	70	14	**2c**	71[b]
3	**1d**	H	H	Me	H	H	70	12	**2d**	83
4	**1e**	H	H	H	Me	H	80	24	**2e**	68
5	**1f**	H	H	H	*n*-Pr	H	Reflux	24	**2f**	18
6	**1g**	H	H	H	H	CO_2H	rt	24	**2g**	78

[a] Isolated yield.
[b] *cis*/*trans*=4.9:1 based on isolated yield.



Scheme 2. IMDA reaction of 6-hydroxy substrate (**1h**).



Scheme 3. Recycling experiment of $In(OTf)_3$.

Likewise, in the third run **2d** was also isolated in essentially similar yield (79%), indicating that $In(OTf)_3$ was recyclable catalyst for the present IMDA reaction.

Finally, the effect of $In(OTf)_3$ on the IMDA reaction of acrylamide derivative **1i** was examined (Scheme 4). The IMDA reaction of amide-tethered substrate **1i** under thermal conditions was reported by Martin et al.[19] to proceed in toluene at 85 °C for 12 h to give a mixture of **2i**-*endo* and **2i**-*exo* in 63% yield (*endo*/*exo*=6.9:1). 20 mol% $In(OTf)_3$ catalyzed reaction in a mixture of water and 2-propanol (6:1 v/v) proceeded at lower temperature (50 °C, 12 h) to give the cycloadduct **2i**-*endo* as a sole stereoisomer (74% yield). On the other hand, the use of bidentate Lewis acid $TfN[Al(Me)Cl]_2$ reduced the yield of product **2i** (41% yield).

3. Conclusion

We have demonstrated that catalytic amount of $In(OTf)_3$ in a mixture of water and 2-propanol can promote the IMDA reaction of the various 1,7,9-decatrienoate derivatives to give the corresponding cycloadducts in good yield with perfect *endo*-selectivity. Since the present reaction proceeds quite nicely in water and 2-propanol as environmentally friendly solvents and $In(OTf)_3$ used as the catalyst is recyclable without troublesome purification, these results provide useful examples from a viewpoint of green chemistry.

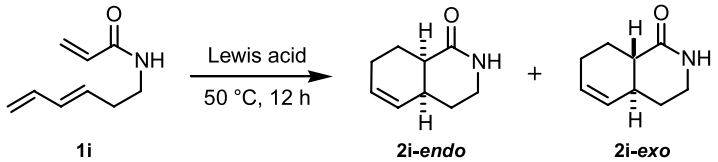
4. Experimental

4.1. General

Indium(III) trifluoromethanesulfonate is available commercially. All reactions were carried out under argon atmosphere. ^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a 400 MHz spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^1H NMR, and $CDCl_3$ (77.01 ppm) for ^{13}C NMR as an internal standard, respectively. Mass spectra (MS) were obtained by EI or ESI technique. Medium pressure liquid chromatography (MPLC) was performed using pre-packed column (silica gel, 50 μm) with UV or RI detector.

4.2. General procedure for preparation of 1,7,9-decatrienoate derivatives: (3*E*,5*E*)-3,5-heptadienyl acrylate (1e)

After a suspension of (3-hydroxypropyl)triphenyl-phosphonium bromide[20] (7.06 g, 17.0 mmol) in THF (25 mL)



Scheme 4. IMDA reaction of N–H acrylamide derivative (**1i**).

was treated with lithium bis(trimethylsilyl)amide (LHMDS, 35 mL, 1.0 M in THF) for 1 h at 0 °C, crotonaldehyde (2.80 g, 40.0 mmol) was added at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. After usual work-up (extracted with Et_2O, dried over $MgSO_4$, and concentrated under reduced pressure), the residue was purified by flash column chromatography on silica gel (hexane/Et_2O=15:1) to give (3*E*,5*E*)-3,5-heptadien-1-ol (1.03 g, 9.18 mmol, 54% yield) as colorless oil. ^{1}H NMR spectrum of this compound was identical with that reported in the literature.[21] To a solution of this dienyl alcohol (561 mg, 5.0 mmol) in CH_2Cl_2 (10 mL), acryloyl chloride (0.45 mL, 5.5 mmol) and triethylamine (0.83 mL, 6.0 mmol) were added at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was quenched by H_2O and extracted with Et_2O (10 mL×3). The organic layer was washed with brine and dried over $MgSO_4$. Purification by column chromatography (hexane/Et_2O=50:1) gave the product **1e** (689 mg, 85% yield). Colorless oil. IR (neat) ν cm^{-1}; 1726. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (3H, d, J=6.9 Hz), 2.42 (2H, q, J=6.8 Hz), 4.18 (2H, t, J=6.9 Hz), 5.45–5.55 (1H, m), 5.57–5.68 (1H, m), 5.81 (1H, dd, J=10.4, 1.5 Hz), 5.96–6.14 (2H, m), 6.12 (1H, dd, J=17.3, 10.4 Hz), 6.39 (1H, dd, J=17.3, 1.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.0, 31.9, 63.9, 126.1, 128.3, 128.5, 130.6, 131.2, 132.9, 166.2. EI-MS *m*/*z*: 166 [M]$^+$. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.17; H, 8.24.

The substrates **1a–d**, **1h**[12a,b] and **1i**[19] were prepared according to the reported procedure. The physical data of **1a–d**, **1h** and **1i** were reported previously.

4.2.1. (3*E*,5*E*)-3,5-Nonadienyl acrylate (1f). In a similar manner for the preparation of (3*E*,5*E*)-3,5-heptadien-1-ol, reaction of (3-hydroxypropyl)triphenylphosphonium bromide (7.06 g, 17.0 mmol) with LHMDS (35 mL, 1.0 M in THF) and *E*-2-hexenal (4.60 mL, 40 mmol), and the subsequent purification by flash column chromatography on silica gel (hexane/EtOAc=25:1) gave (3*E*,5*E*)-3,5-nonadien-1-ol (1.19 g, 8.5 mmol, 50% yield) as colorless oil. IR (neat) ν cm^{-1}; 3340, 3016, 1653, 986. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J=7.4 Hz), 1.42 (2H, qt, J=7.4, 7.2 Hz), 2.04 (2H, q, J=7.2 Hz), 2.29–2.39 (2H, m), 3.66 (2H, bs), 5.48–5.68 (2H, m), 5.97–6.18 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.7, 22.5, 34.6, 36.0, 62.1, 127.2, 130.0, 133.6, 133.7. EI-MS *m*/*z*: 140 [M]$^+$. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.16; H, 11.63. To a solution of this dienyl alcohol (701 mg, 5.0 mmol) in CH_2Cl_2 (10 mL), acryloyl chloride (0.45 mL, 5.5 mmol) and triethylamine (0.83 mL, 6.0 mmol) were added at 0 °C. After being stirred at room temperature for 2.5 h, the reaction mixture was quenched by H_2O and extracted with Et_2O (10 mL×3). The organic layer was washed with brine and dried over $MgSO_4$. Purification by column chromatography on silica gel (hexane/Et_2O=50:1) gave the product **1f** (93% yield). Colorless oil. IR (neat) ν cm^{-1}; 1727. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J=7.4 Hz), 1.42 (2H, qt, J=7.4, 7.2 Hz), 2.04 (2H, q, J=7.2 Hz), 2.43 (2H, q, J=6.9 Hz), 4.19 (2H, t, J=6.9 Hz), 5.49–5.67 (2H, m), 5.82 (1H, dd, J=10.4, 1.5 Hz), 5.97–6.15 (2H, m), 6.12 (1H, dd, J=17.3, 10.4 Hz), 6.40 (1H, dd, J=17.3, 1.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.7, 22.5, 31.9, 34.7, 63.9, 126.3, 128.5, 130.1, 130.6, 133.1, 133.7, 166.2. ESI-MS *m*/*z*: 195 [M+H]$^+$. HRMS Calcd for $C_{12}H_{19}O_2$ [M+H]$^+$: 195.1385, Found: 195.1400.

4.2.2. (*Z*)-4-[(3*E*)-3,5-Hexadienyloxy]-4-oxo-2-butenoic acid (1g). After a solution of 3,5-hexadien-1-ol (981 mg, 10.0 mmol) in CH_2Cl_2 (25 mL) was treated with maleic anhydride (981 mg, 10.0 mmol) and 4-dimethylaminopyridine (DMAP, 24.5 mg, 0.20 mmol) for 3 h at 0 °C, the reaction mixture was extracted with EtOAc (10 mL×3). The organic layer was washed with brine, dried over $MgSO_4$, and purified by silica gel column chromatography (hexane/EtOAc=3:1) to give **1g** (746 mg, 3.8 mmol, 38% yield) and 3,5-hexadien-1-ol (549 mg, 5.6 mmol). Colorless oil. IR (neat) ν cm^{-1}; 3025, 1731, 1712. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (2H, t, J=6.7 Hz), 4.33 (2H, t, J=6.7 Hz), 5.05 (1H, d, J=10.1 Hz), 5.16 (1H, d, J=14.8 Hz), 5.69–5.74 (1H, m), 6.14 (1H, dd, J=14.8, 10.4 Hz), 6.24–6.35 (1H, m), 6.37 (1H, d, J=12.7 Hz), 6.47 (1H, d, J=12.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 31.4, 66.1, 116.8, 128.2, 128.9, 134.2, 136.4, 137.1, 167.0, 171.2. ESI-MS *m*/*z*: 197 [M+H]$^+$. HRMS Calcd for $C_{10}H_{13}O_4$ [M+H]$^+$: 197.0798, Found: 197.0814.

4.3. Typical procedure for IMDA reaction of 1,7,9-decatrienoate derivatives in aqueous media: (4a*S**,7*S**,8a*R**)-7-methyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one (2e)

To a solution of indium(III) triflate (56.0 mg, 0.1 mmol) in H_2O (6.0 mL), a solution of 1,7,9-decatrienoate **1e** (83.1 mg, 0.5 mmol) in 2-propanol (1.0 mL) was added at room temperature and then the reaction mixture was stirred at 80 °C for 24 h. After the resulting mixture was extracted with Et_2O (5 mL×3), the organic layer was washed with brine and dried over $MgSO_4$. Purification by column chromatography on silica gel (hexane/EtOAc=3:1) gave the product **2e** (56.5 mg, 68% yield) as colorless oil. IR (neat) ν cm^{-1}; 1732. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, d, J=7.1 Hz), 1.38 (1H, ddd, J=12.7, 10.3, 10.2 Hz), 1.67–1.80 (1H m), 1.81–1.89 (1H, m), 2.10 (1H, dt, J=12.7, 4.3 Hz), 2.24–2.37 (1H, m), 2.47–2.58 (1H, m), 2.77–2.86 (1H, m), 4.26 (1H, td, J=11.5, 3.3 Hz), 4.41 (1H, ddd, J=11.5, 4.6, 2.8 Hz), 5.53–5.58 (1H, m), 5.64 (1H, bd, J=10.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.2, 27.3, 30.7, 32.2, 32.4, 40.2, 69.2, 126.9, 134.8, 174.1. EI-MS *m*/*z*: 166 [M]$^+$. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.16; H, 8.20.

The cycloadducts **2a–d**, **2h**[12a,b] and **2i**[19] were reported previously.

4.3.1. (4a*S,7*S**,8a*R**)-7-Propyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one (2f).** Yield 18%. Colorless crystals. Mp 31–32 °C. IR (KBr) ν cm^{-1}; 1731. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J=6.7 Hz), 1.19–1.46 (6H, m), 1.67–1.80 (1H, m), 1.81–1.89 (1H, m), 2.08–2.26 (2H, m), 2.49–2.59 (1H, m), 2.67–2.76 (1H, m), 4.27 (1H, td, J=11.6, 3.3 Hz), 4.41 (1H, ddd, J=11.6, 4.6, 2.5 Hz), 5.58 (1H, ddd, J=10.0, 4.2, 2.5 Hz), 5.68 (1H, bd, J=10.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 19.7, 27.3, 30.1, 32.8, 35.4, 38.1, 40.1, 69.2, 127.1, 133.7, 174.3. ESI-MS *m*/*z*: 195 [M+H]$^+$. HRMS Calcd for $C_{12}H_{19}O_2$ [M+H]$^+$: 195.1385, Found: 195.1402.

4.3.2. (4a*S,8*R**,8a*S**)-1-Oxo-3,4,4a,7,8,8a-hexahydro-1*H*-isochromene-8-carboxylic acid (2g).** Yield 78%. Colorless crystals. Mp 177–178 °C. IR (KBr) ν cm^{-1}; 3023, 1734, 1709, 946. ^1H NMR (400 MHz, $CDCl_3$) δ 1.70–1.81 (1H, m), 2.18–2.29 (1H, m), 2.30–2.53 (2H, m), 2.62–2.72 (1H, m), 2.96 (1H, bs), 3.41–3.49 (1H, m), 4.16–4.25 (1H, m), 4.26–4.35 (1H, m), 5.54 (1H, bd, $J=10.0$ Hz), 5.79–5.88 (1H, m), 11.2 (1H, bs, CO_2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.9, 28.5, 32.6, 40.1, 40.9, 66.3, 128.0, 128.2, 171.5, 178.7. ESI-MS *m/z*: 197 $[M+H]^+$. HRMS Calcd for $C_{10}H_{13}O_4$ $[M+H]^+$: 197.0814, Found: 197.0810. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.01; H, 6.19.

4.4. Recycling procedure of $In(OTf)_3$: IMDA reaction of 1-methyl-3,5-hexadienyl acrylate (1d)

To a solution of indium(III) triflate (56 mg, 0.1 mmol) in H_2O (6.0 mL), a solution of 1,7,9-decatrienoate **1d** (83 mg, 0.5 mmol) in 2-propanol (1.0 mL) was added at room temperature, and then the whole was stirred at 70 °C for 12 h. When the consumption of **1d** was confirmed by monitoring the reaction mixture by TLC, the reaction mixture was carefully extracted with Et_2O (5 mL×2). Usual work-up of the organic extracts (washed with brine, dried over $MgSO_4$ and evaporated) and purification by column chromatography gave the cycloadduct **2d** (68.7 mg, 83% yield). To the aqueous layer (ca. 6 mL), a solution of substrate **1d** (83 mg, 0.5 mmol) in 2-propanol (1.0 mL) was added and the mixture was stirred under the similar conditions for the first run. After extractive work-up and purification by column chromatography on silica gel, the organic phase gave the product **2d** (64.7 mg, 78% yield). In a similar manner, the resulting aqueous layer was used for the third reaction (**1d**; 83 mg, 0.5 mmol) to obtain **2d** (65.3 mg) in 79% yield.

References and notes

1. For reviews, see: (a) Li, C. *Chem. Rev.* **1993**, *93*, 2023. (b) Lubineau, A. *Chem. Ind.* **1996**, 123. (c) Engberts, J. B. N.; Feringa, B. L.; Keller, E.; Otto, S. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 457. (d) Cornils, B.; Herrmann, W. A.; Eckl, R. W. *J. Mol. Catal., A* **1997**, *116*, 27. (e) Li, C.; Chen, T.-H. *Organic Synthesis in Water*; Wiley: New York, 1997. (f) Grieco, P. A. *Organic Reaction in Aqueous Media*; Blackie Academic and Professinal: London, 1998.
2. For recent examples of the allylation of carbonyl compounds mediated by indium, see: (a) Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 2958. (b) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823. Bismuth mediated reactions, see: (c) Smith, K.; Lock, S.; El-Hiti, G. A.; Wada, M.; Miyoshi, N. *Org. Biomol. Chem.* **2004**, *2*, 935. (d) Xu, X.; Zha, Z.; Miao, Q.; Wang, Z. *Synlett* **2004**, 1171. Other metal salts mediated reactions, see: (e) Wang, Z.; Yuan, S.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5097. (f) Fukuma, T.; Lock, S.; Miyoshi, N.; Wada, M. *Chem. Lett.* **2002**, 376.
3. For recent examples, see: (a) Tian, H.-Y.; Chen, Y.-J.; Wang, D.; Bu, Y.-P.; Li, C.-J. *Tetrahedron Lett.* **2001**, *42*, 1803. (b) Darbre, T.; Machuqueiro, M. *Chem. Commun.* **2003**, 1090. (c) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891. (d) Iimura, S.; Manabe, K.; Kobayashi, S. *Tetrahedron* **2004**, *60*, 7673.
4. For recent examples, see: (a) Loh, T.-P.; Pei, J.; Lin, M. *Chem. Commun.* **1996**, 2315. (b) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 6798. (c) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 9263.
5. Reviews on Pd-catalyzed cross coupling reactions in water, see: (a) Pierre Genet, J.; Savignac, M. *J. Organometal. Chem.* **1999**, *576*, 305. (b) Beletskaya, I. P.; Cheprakov, A. V. In Negishi, E., Ed.; Handbook of organopalladium chemistry for organic synthesis; Wiley: New York, 2002; Vol. 2, pp 2957–3006. (c) Uozumi, Y. *J. Synth. Org. Chem., Jpn.* **2002**, *60*, 1063.
6. Recent examples, see: (a) Morin Deveau, A.; MacDonald, T. L. *Tetrahedron Lett.* **2004**, *45*, 803. (b) Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147. (c) Friesen, R. W.; Trimble, L. A. *Can. J. Chem.* **2004**, *82*, 206. (d) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. *J. Org. Chem.* **2004**, *69*, 7919.
7. For reviews on synthetic utility of lanthanoid triflates, see: (a) Kobayashi, S.; Ishitani, H. *J. Synth. Org. Chem., Jpn.* **1998**, *56*, 357. (b) Kobayashi, S. In Yamamoto, H., Ed.; Lewis Acids in Organic Synthesis; Wiley: Weinheim, Germany, 2000; Vol. 2, pp 883–910. (c) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227.
8. For some examples, see: (a) Kobayashi, S.; Iwamoto, S.; Nagayama, S. *Synlett* **1997**, 1099. (b) Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049. (c) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, 19.
9. (a) Kobayashi, S.; Busujima, T.; Nagayama, S. *Tetrahedron Lett.* **1998**, *39*, 1579. (b) Munoz-Muniz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 1622. (c) Ding, R.; Zhang, H. B.; Chen, Y. J.; Liu, L.; Wang, D.; Li, C. J. *Synlett* **2004**, 555.
10. For a review on conformation and stereoelectronic effect of ester compounds, see: Deslongchamps, P. *Stereoelectric Effects in Organic Chemistry*; Pergamon: Oxford, 1983; pp 54–100.
11. Cain, D.; Pawar, D. M.; Stewart, M.; Billings, H., Jr.; Noe, E. A. *J. Org. Chem.* **2001**, *66*, 6092.
12. For examples of IMDA reaction, see: (a) Saito, A.; Ito, H.; Taguchi, T. *Org. Lett.* **2002**, *4*, 4619. (b) Saito, A.; Yanai, H.; Taguchi, T. *Tetrahedron* **2004**, *60*, 12239.(c) Saito, A.; Yanai, H.; Sakamoto, W.; Takahashi, K.; Taguchi, T. *J. Fluorine Chem.* **2005**, *126*, 709.
13. For example of intermolecular version, see: Saito, A.; Yanai, H.; Taguchi, T. *Tetrahedron Lett.* **2004**, *45*, 9439.
14. (a) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469. (b) Jung, M. E. *Synlett* **1990**, 186. (c) Giessner-Prettre, C.; Hückel, S.; Maddaluno, J.; Jung, M. E. *J. Org. Chem.* **1997**, *62*, 1439. (d) Jung, M. E. *Synlett* **1999**, 843.
15. (a) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604. (b) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041. (c) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674.
16. The reaction of 6-hydroxy substrate **1h** with $TfN(AlMe_2)_2$ resulted in decomposition of the substrate **1h**.
17. We have already reported that stereoselective construction of oxabicyclo[4.3.0]nonene derivatives was achieved by the

IMDA reaction of 6-silyloxy derivative followed by the desilylation reaction of the cycloadducts with fluoride ion. In these cases, re-lactonization reactions also proceeded in stereospecificic manner. See, Ref. 12b.

18. White, J. D.; Nolen, E. G., Jr.; Miller, C. H. *J. Org. Chem.* **1986**, *51*, 1150.
19. Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170.
20. Page, P. C. B.; Vahedi, H.; Batchelor, K. J.; Hindley, S. J.; Edgar, M.; Beswick, P. *Synlett* **2003**, 1022.
21. Snider, B. B.; Phillips, G. B.; Cordova, R. *J. Org. Chem.* **1983**, *48*, 3003.

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Synthesis and glycosidase inhibitory activity of new penta-substituted C8-glycomimetics

Olivia Andriuzzi,[a] Christine Gravier-Pelletier,[a,*] Pierre Vogel[b] and Yves Le Merrer[a,*]

[a]*Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, Université René Descartes, UMR 8601 CNRS, 45 rue des Saints-Pères, 75270 Paris Cedex 06, France*
[b]*Institut des Sciences et Ingéniérie Chimiques, Ecole Polytechnique Fédérale de Lausanne, BCH, CH-1015 Lausanne, Switzerland*

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Abstract—The syntheses of new C8-carbasugars and -aminocyclitols related to miglitol and voglibose are described. The key step involves the ring closing metathesis of 1,9-dienes derived from D-mannitol. Chemical transformations of the newly created double bond of the resulting cyclooctenes involved notably hydroboration and reductive amination. The inhibitory activity of the glycomimetics so-obtained has been evaluated towards 24 commercially available glycosidases.

1. Introduction

The biological importance of oligosaccharides was first recognized for their role in metabolism and energy storage. More recently, it became clear that complex oligosaccharides also regulate a large number of biological processes. Most important are the oligosaccharides formed on the surface of cells and their role on protein and glycoprotein conformation. The cell-surface oligosaccharides are the 'words' used by cells to communicate with the outer world.[1–4] They guide their social behavior such as cell/cell interactions, cell/invader interactions, including HIV/cell penetration.[5] These oligosaccharides are conjugated with proteins (*N*-linked, *O*-linked glycoproteins), with phosphatidylinositol (GPI-anchored proteins) or with glycolipids.[5–10] Carbohydrate mimetics are potential tools to study the mechanisms of cellular interactions, the biosynthesis of glycoproteins, the catabolism of glycoconjugates,[11,12] and the mechanisms of digestions.[13,14] Inhibition of intestinal α-glucosidases can be used to treat diabetes through the lowering of blood glucose levels, and α-glucosidase inhibitors[1–3] are being marketed against type 2 (non-insulinodependent mellitus) diabetes (Fig. 1).[15–17]

The naturally occurring acarbose (**1**)[18] and voglibose (or AO-128) (**2**),[19] the synthetic piperidine derivatives such as **3** (miglitol)[20] and **4** (1-deoxynojirimycin)[21] or pyrrolidine derivatives such as **5** (nectrisine)[22,23] can have their amino moiety protonated. The corresponding ammonium ions mimick the charge of the presumed transition states or intermediates of the enzymatic glycoside hydrolyses.[21,22]

Furthermore, it has to be pointed out that carbasugars such as valienamine (**6**) and its derivative **7**[24] (Fig. 2), or polyol **8**[25] and C7-aminocyclitols **9**[26] (Fig. 2) can also present potent glycosidase inhibitory activity.

In that context, new C8-glycomimetics[27] have been targeted

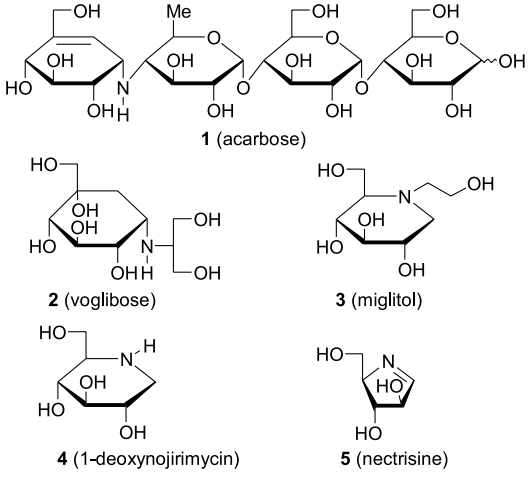

Figure 1. Examples of glycosidase inhibitors.

Keywords: Carbasugars; Aminocyclitols; Glycomimetics; Ring closing metathesis; Reductive amination; Glycosidases.
* Corresponding authors. Tel.: +33 142862181; fax: +33 42868387 (C.G-P.); tel.: +33 142862176; fax: +33 42868387 (Y.Le M.); e-mail addresses: christine.gravier-pelletier@univ-paris5.fr; yves.le-merrer@univ-paris5.fr

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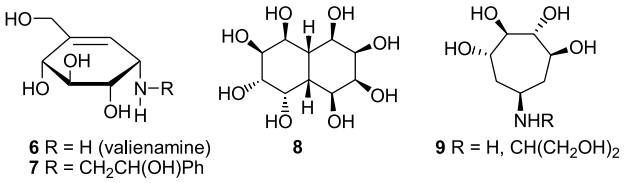


Figure 2. Examples of glycosidase inhibitors.

in order to study the effect of the enhanced flexibility and of the new spatial distribution displayed by these structures on their adaptability in the active site of the enzymes.

2. Results and discussion

Our retrosynthetic analysis (Fig. 3) involves the carbacyclisation of enantiomerically pure polyhydroxylated C_2-symmetric 1,9-dienes **13** by ring closing metathesis (RCM) leading to a cyclooctenic structure **11**.[28] The synthetic potentialities of the newly created double bond are then explored to reach pentasubstituted C8-carbasugars and their apparented aminocyclitols (**10**). Due to the different configurations available, (D-*manno* and L-*ido*) of corresponding presented bis-epoxides **14**, the approach allows access to various glycomimetics. Furthermore, the pinacolic coupling (PC) of 1,8-dialdehyde **12**, resulting from oxidative cleavage of dienes **13**, is proposed as a complementary approach towards related hexasubstitued C8-carbasugars of type **10**.

Ring closing metathesis is a widespread method[29] to reach carba- or hetero-cyclic compounds and has been largely applied to the synthesis of five to seven-membered rings. It is less used for the preparation of eight-membered ring systems,[30] perhaps due to unfavorable thermodynamic factors.[31]

The synthesis of protected polyhydroxylated cyclooctenes is outlined in Scheme 1. First, the double opening of the C_2-symmetrical 3,4-*O*-methylethylidene-L-*ido*-bis-epoxide **15**[32] by an excess of lithium divinylcyanocuprate[33] at −78 °C cleanly afforded diene **16** in 92% yield. Thanks to the stability of commercially available ruthenium Grubbs catalyst and to its potential compatibility with free hydroxyl groups, the RCM was first applied to unprotected diene-diol **16**. Thus, up to 13 mol% of ruthenium catalyst

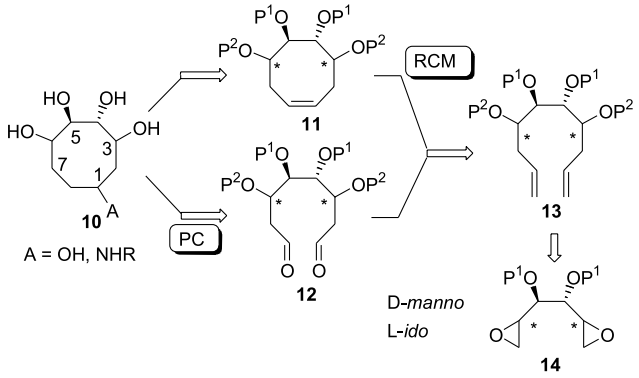
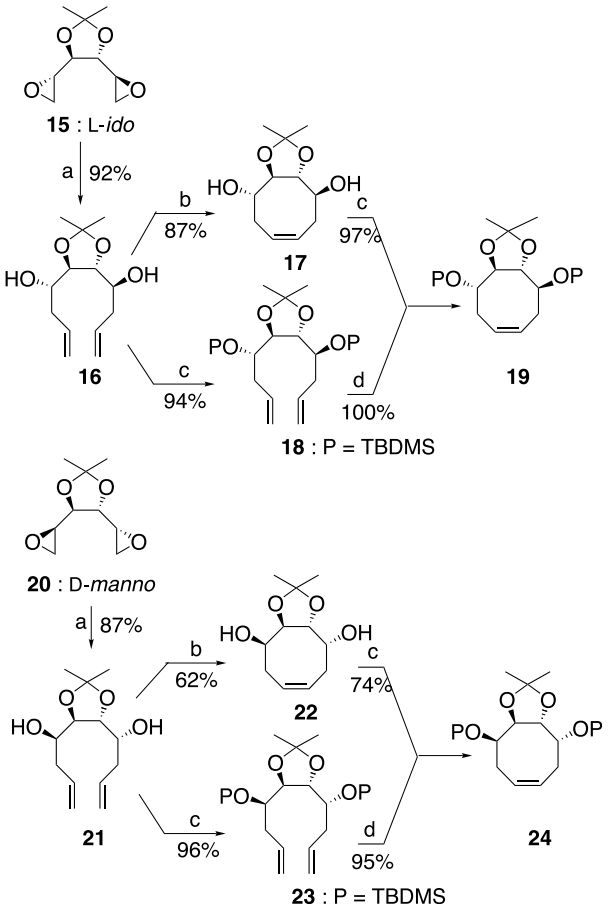


Figure 3. Retrosynthetic analysis.

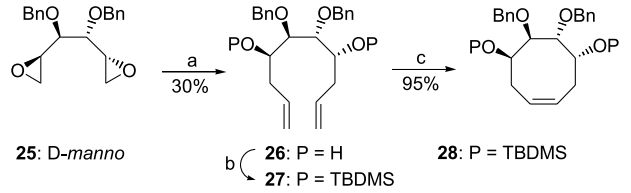


Scheme 1. Reagents and conditions: (a) $(CH_2{=}CH)_2CuCNLi_2$, THF, −78 °C to 20 °C; (b) Grubbs I cat. 13 mol%, CH_2Cl_2, rt, 96 h; (c) TBDMSCl, DMF, ImH, 50 °C; (d) Grubbs I cat. 2 mol%, CH_2Cl_2, rt, 30 min.

[$(PCy_3)_2Cl_2Ru{=}CHPh$] in dichloromethane (20 °C, 96 h) gave the expected cyclooctene **17** in 87% yield. In order to avoid subsequent side reactions of the free alcohol functions, they were protected as their *O*-silylated derivative **19**. The alternative way involving double-*O*-protection prior to RCM was also carried out. In that case, the cyclisation involving the di-*O*-silylated dienetetrol **18** was realized in quantitative yield with 2 mol% of catalyst in much shorter time (20 °C, 30 min).

The same sequence of reactions was applied to the D-manno bis-epoxide **20** and afforded the protected cyclooctenetetrol **24**. However, it has to be pointed out that the route involving protection of the diol (**21**→**23**) followed by RCM (**23**→**24**) was both more efficient and easier to carry out than that involving first RCM (**21**→**22**→**24**) due to incomplete reaction.

We explored further the efficiency of RCM with diene **26** and with the alcohol protected derivative **27** (Scheme 2) resulting from opening of 3,4-di-*O*-benzyl-D-manno-bis-epoxide **25**[34] by lithium divinylcyanocuprate (30% yield)[35] and subsequent *O*-silylation. Under the same reaction conditions as above the expected cyclooctene **28** was obtained in 95% yield.

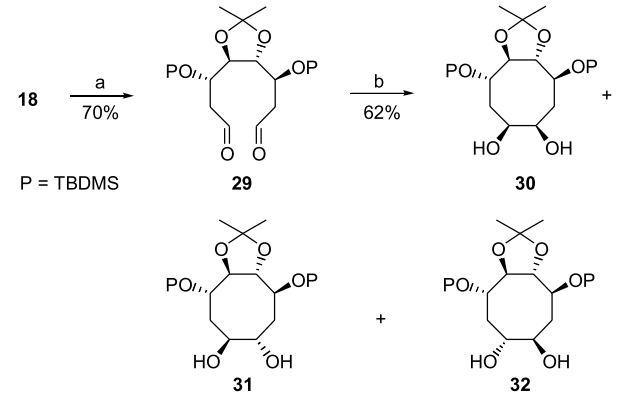


Scheme 2. Reagents and conditions: (a) $(CH_2{=}CH)_2CuCNLi_2$, THF, −78 °C to rt; (b) TBDMSCl, DMF, ImH, 50 °C, 70%; (c) Grubbs I cat. 2 mol%, CH_2Cl_2, rt.

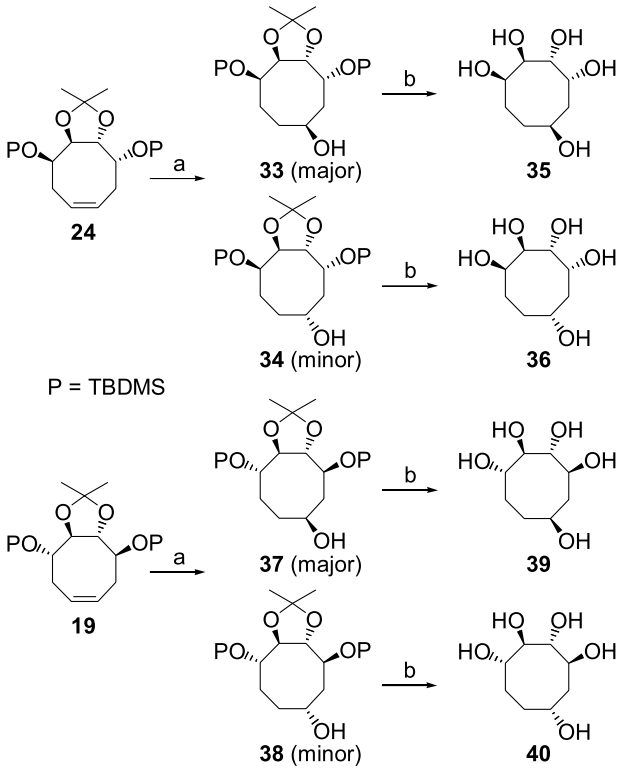
We next turned to the second proposed pathway that involves the pinacolic coupling of 1,8-dialdehyde **29** (Scheme 3). For that purpose ozonolysis of both double bonds of **18** in dichloromethane and methanol, followed by the decomposition of the resulting ozonide by trimethylphosphite, furnished the expected dialdehyde **29** in 70% yield. Samarium diiodide (0.1 M in THF) reductive coupling of the dialdehyde **29** in the presence of *tert*-butanol and HMPA[36] led to cyclization. However, a 1:1 diastereoisomeric mixture of polyhydroxylated cyclooctanes **30** and **31**+**32** was obtained. The poor diastereoselectivity and the difficulty in separating the *cis* derivative **30** from the two *trans* derivatives **31** and **32** led us to only perform the synthesis of glycomimetics from the key cyclooctenes **19** and **24** obtained by RCM.

The first goal was the obtention of C8-carbasugars. Thus, hydroboration of the protected D-*manno*-configurated cyclooctenetetrol **24** by borane tetrahydrofuran complex[37] in diethyl ether and subsequent oxidative cleavage by alkaline hydrogen peroxide (Scheme 4) afforded a mixture of the two epimers **33** and **34** in a 2:1 ratio[38] in 92% overall yield and that were separated by column chromatography.

Subsequent trifluoroacetic acid catalyzed hydrolysis of **33** and **34** gave the expected C8-carbasugar analogs **35** and **36**, respectively. In a similar manner, hydroboration of the L-*ido* **19**, followed by oxidative cleavage and then acidic hydrolysis led to the corresponding carbasugars **39** and **40**. In the latter case, diastereoselectivity was only 3:2 ratio for **37** and **38**, and these compounds could be separated by flash chromatography. The structures of **33**, **34**, **37** and **38** were unambiguously assigned by 2D ^{1}H NMR studies and NOE measurements. In each case the major isomer results from the favored hydroboration of the face of the alkene



Scheme 3. Reagents and conditions: (a) O_3, CH_2Cl_2, −78 °C then $P(OMe)_3$, rt; (b) SmI_2, HMPA, *t*BuOH, −40 °C to rt.



Scheme 4. Reagents and conditions: (a) $BH_3{\cdot}THF$, Et_2O then NaOH, EtOH, H_2O_2, 62, 30, 51 and 38% yield for **33**, **34**, **37** and **38**; (b) TFA, H_2O, rt, 95–100%.

moieties of **19** and **24** *anti* with respect to the oxygen atom of the 1,3-dioxolane in γ position. On one hand, the ^{1}H NMR spectrum of **33** showed relatively large coupling constants between H1 and H8 (*proS*),[39] H1 and H2 (*proS*), H8 (*proS*) and H7 (*proS*) as expected for protons in pseudo-axial positions. On the other hand, small $^3J_{1H,1H}$ coupling constants were observed between H1 and H8 (*proR*), H1 and H2 (*proR*), as expected for protons in pseudo-equatorial positions. Furthermore, prochiral H2 (*proS*) and H8 (*proS*) both displayed strong NOEs with H4 and with each other, thus indicating that these protons are close together and are located on the same (upper) face. The ^{1}H NMR signal of H7 (*proS*) displayed strong NOEs with H5 and H1. This shows that these protons are on the other (lower) face of the C8 cycle (Fig. 4). These data allowed the structural determination of compound **33** which implies a (*S*)-configurated alcohol moiety of the newly created stereogenic center.

We next turned to the obtention of the corresponding aminocyclitols. Their preparation was first attempted by hydroboration of **19** and **24**, followed by aminolysis with sulfamic acid,[40] but this reaction failed. Alternatively, activation of the hydroxyl group of **33** or **37** as their triflate derivatives, followed by in situ nucleophilic substitution with sodium azide or ethanolamine (DMF, −78 °C to room temperature) resulted in β-elimination and, consequently, to recover the starting cyclooctene. To circumvent this difficulty we have studied the reductive amination of ketones resulting from oxidation of the alcohols **33**, **34**, **37** and **38**. Treatment of the mixture **33** and **34** by Dess–Martin periodinane[41] in CH_2Cl_2/pyridine at room temperature yielded ketone **41** (85% yield, Scheme 5). Alternatively,

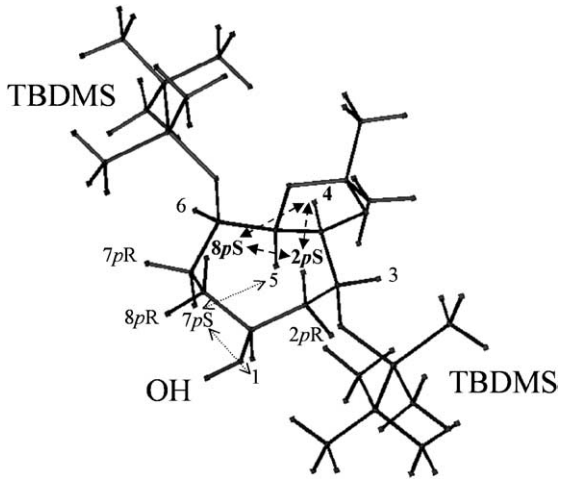
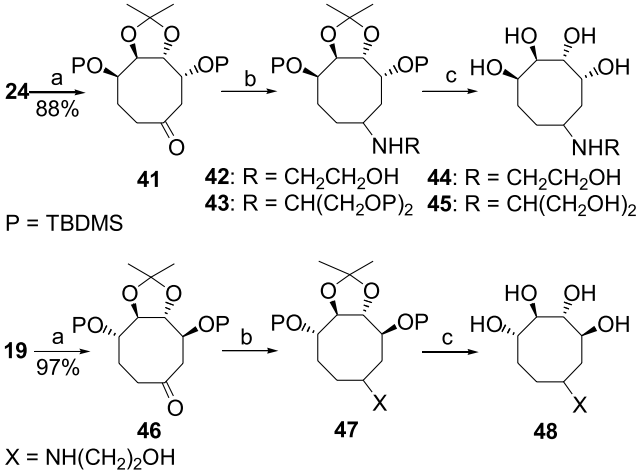


Figure 4. Schematic representation of the NOEs (indicated with arrows) found to deduce structure **33**. Prochiral ^1H of the CH_2 groups are labelled *p*R or *p*S.



Scheme 5. Reagents and conditions: (a) $BH_3\cdot THF$, Et_2O then PCC, rt; (b) $Ti(OiPr)_4$, $H_2NCH_2CH_2OH$ or $H_2NCH(CH_2CH_2OTBDMS)_2$, CH_2Cl_2 then $NaBH_3CN$, EtOH; (c) TFA, H_2O, rt, 60, 63 and 31% overall yield for **44**, **45** and **48** from **41** and **46**, respectively.

this ketone can be obtained in an one-pot reaction from the cyclooctene **24** by hydroboration and in situ oxidation[42] by pyridinium chlorochromate (88% overall yield from **24**). Reductive amination to introduce either the aglycon part of miglitol or voglibose was further performed by ethanolamine or bis-*O*-*tert*-butyldimethylsilylserinol[43] in the presence of titanium(IV) tetra-isopropoxide[44] in dichloromethane followed by cyanoborohydride reduction of the resulting imine intermediate. The expected aminocyclitols **42** and **43** were isolated in good yield (84 and 96%) as unseparable 4:1 mixtures of 1*S*:1*R* epimers, respectively. Simultaneous acidic hydrolysis of protected groups led to the corresponding aminocyclitols **44** and **45**. Similarly, the aminocyclitol **48** displaying the aglycon part of miglitol was obtained from the L-*ido* cyclooctene **19** by successive hydroboration, oxidative cleavage, reductive amination with ethanolamine and acidic hydrolysis (30% overall yield from **19**). In that sequence, the reductive amination led to an unseparable mixture of epimers in a 3:1 ratio in favor of the 1*S* stereoisomer.

The new C8-carbasugars **35**, **36**, **39** and **40** and C8-aminocyclitols **44**, **45** and **48** have been assayed for their inhibitory activity towards 24 commercially available glycosidases.[45] They did not inhibit the following enzymes at 1 mM concentration and optimal pH: α-glucosidase (maltase) from yeast and rice, amyloglucosidase from *Aspergillus niger*, β-glucosidase from *Caldocellum saccharolyticum*, α-L-fucosidases from bovine epididymis and human placenta, α-galactosidases from coffee beans and *Escherichia coli*, β-galactosidases from *Escherichia coli*, bovine liver, *Aspergillus niger* and *Aspergillus orizae*, α-*N*-acetylgalactosaminidase from chicken liver, β-*N*-acetylglucosaminidases from Jack bean, bovine epididymis A and bovine epididymis B, α-mannosidase from almonds, β-mannosidase from *Helix pomatia*, and β-xylosidase from *Aspergillus niger*. For other enzymes: amyloglucosidase *Rhizopus* mold, α-D-glucosidase from *Bacillus stearothermophilus*, β-D-glucosidase from almonds, α-D-mannosidase from Jack beans and α-L-fucosidase from bovine kidney, the results are shown in Table 1. These new compounds revealed weak inhibitions of the tested enzymes with a percentage of inhibition not exceeding 33%. These results show that the enhanced flexibility displayed by C8-glycomimetics is not correlated with an increase of glycosidase inhibitory activity. Indeed, we had previously shown that the C7-aminocyclitol (see Fig. 2, (**9**) R=$CH(CH_2OH)_2$) exhibited interesting activity towards amyloglucosidases from *Aspergillus niger* and *Rhizopus* mold (K_i=35 and 18 μM, respectively), while the corresponding aminocyclitol **45** was almost inactive towards the same enzymes.

Table 1. Inhibitory activities for C8-carbasugars **35**, **36**, **39** and **40**, and for C8-aminocyclitols **44** and **45**

Enzyme[a]	**35**	**36**	**39**	**40**	**44**[b]	**45**[b]
α-D-Glu						
- *Bac. Stearotherm.*[c]	15%	13%	23%	n.i.[a]	17%	15%
- *Rhizopus* mold	n.i.[d]	n.i.[d]	n.i.[d]	20%	32%	n.i.[d]
β-D-Glu[c]	n.i.[d]	n.i.[d]	n.i.[d]	5%	n.i.[d]	n.i.[d]
α-D-Man[c]	12%	8%	n.i.[d]	7%	17%	12%
α-L-Fuc[c]	6%	29%	16%	n.i.[d]	27%	33%

Percentage of inhibitions at 1 mM.
[a] See text.
[b] Tested as a mixture of epimers.
[c] See Ref. 46.
[d] No inhibition detected.

3. Conclusion

We have realized efficient and versatile syntheses of new C8-glycomimetics using RCM methodology as the key step to afford enantiomerically pure tetrahydroxylated cyclooctenes with D-*manno* or L-*ido* configuration. Further transformation of the cyclic double bond involved hydroboration and alkaline oxidation, followed by oxidation to a ketone and reductive amination, then acidic hydrolysis. According to this strategy and depending on the nature of the amine involved in the reductive amination, various aminocyclitols could be obtained. Thus, in this study, four carbasugars and three aminocyclitols displaying the aglycon part of miglitol or voglibose were obtained. These compounds were evaluated for their inhibitory activity towards 24 commercially available glycosidases. In the case of the aminopolyols **44** and **45**, spatial disposition of the four hydroxy groups and the amino moiety departs probably too much from that realized in glycomimetics such as valiolamine, vogliobose and valienamine. The even weaker inhibitory activities of pentols **35**, **36**, **39** and **40** can be attributed to the fact that they lack a function (amino group) that can imitate the glycosyl cation intermediate generated during the glycosidase-catalyzed hydrolysis.

4. Experimental

^{1}H NMR (250 or 500 MHz) and ^{13}C NMR (63 MHz) spectra were recorded on a Bruker AM250 in $CDCl_3$ (unless indicated). Chemical shifts (δ) are reported in ppm and coupling constants are given in Hz. Optical rotations were measured on a Perkin-Elmer 241C polarimeter with sodium (589 nm) or mercury (365 nm) lamp. Mass spectra, chemical ionization (CI), and high resolution (HRMS) were recorded by the Service de Spectrométrie de Masse, Ecole Normale Supérieure, Paris. All reactions were carried out under an argon atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Flash chromatography was performed with Merck Kieselgel 60 (0.2–0.5 mm); the solvent system were given v/v spectroscopic (^{1}H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

4.1. General procedure for bis-epoxides opening

To a solution of vinylbromide (48.4 mmol) in diethyl ether (12 mL) at −78 °C was slowly added *tert*-butyllithium (1.7 M in pentane, 96.8 mmol, 2 equiv). The temperature was then raised from −78 °C to 20 °C. This solution was slowly added to a suspension of copper(I) cyanide (2.16 g, 24.2 mmol) in THF (24 mL) at −78 °C. The temperature was then slowly raised from −78 to 0 °C. After addition of a solution of bis-epoxide (5.38 mmol) in THF (10 mL) at −78 °C, the temperature was allowed to raise to 20 °C overnight. A saturated NH_4Cl aqueous solution containing 10% of NH_4OH (250 mL) was added and after stirring for 30 min, the mixture was filtered through celite. After extraction of the mixture with diethyl ether, the combined organic layers were washed with a saturated NH_4Cl aqueous solution, dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the crude led to pure diene derivatives.

4.1.1. (4*S*,5*R*,6*R*,7*S*)-5,6-*O*-Methylethylidene-deca-1,9-diene-4,5,6,7-tetrol (16). Isolated yield: 92%; R_f 0.3 (cyclohexane/EtOAc 7:3); $[\alpha]_D$ +4 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 5.83 (dddd, 2H, $J_{2,1a}$=17.2 Hz, $J_{2,1b}$=10.1 Hz, $J_{2,3a}$=$J_{2,3b}$=7.1 Hz, $H_{2,9}$), 5.12 (dd, 2H, $J_{1a,2}$=17.2 Hz, $J_{1a,1b}$=1.1 Hz, $H_{1a,10a}$), 5.10 (dd, 2H, $J_{1b,1a}$=1.1 Hz, $J_{1b,2}$=10.1 Hz, $H_{1b,10b}$), 4.00–3.90 (m, 2H, $H_{5,6}$), 3.57 (ddd, 2H, $J_{4,OH}$=8.1 Hz, $J_{4,3a}$=$J_{4,3b}$=6.9 Hz, $H_{4,7}$), 2.30 (AA′, XX′, 4H, $J_{3a,2}$=$J_{3b,2}$=7.1 Hz, $J_{3a,4}$=$J_{3b,4}$=6.9 Hz, $H_{3a,3b,8a,8b}$), 1.41 (s, 6H, CH_3); ^{13}C NMR δ 134.2 ($C_{2,9}$), 118.0 ($C_{1,10}$), 109.4 (*C*Me$_2$), 79.1, 69.3 ($C_{4,5,6,7}$), 39.3 ($C_{3,8}$), 27.2 (C*Me*$_2$). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.31; H, 9.35.

4.1.2. (4*R*,5*R*,6*R*,7*R*)-5,6-*O*-Methylethylidene-deca-1,9-diene-4,5,6,7 tetrol (21). Isolated yield: 87%; R_f 0.2 (cyclohexane/EtOAc 8:2); $[\alpha]_D$ +13 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 5.88 (dddd, 2H, $J_{2,1a}$=17.1 Hz, $J_{2,1b}$=10.3 Hz, $J_{2,3a}$=6.4 Hz, $J_{2,3b}$=7.9 Hz, $H_{2,9}$), 5.17 (d, 2H, $J_{1a,2}$=17.1 Hz, $H_{1a,10a}$), 5.16 (d, 2H, $J_{1b,2}$=10.3 Hz, $H_{1b,10b}$), 3.78–3.58 (m, 4H, $H_{4,5,6,7}$), 2.58 (ddd, 2H, $J_{3a,3b}$=14.2 Hz, $J_{3a,2}$=6.4 Hz, $J_{3a,4}$=3.0 Hz, $H_{3a,8a}$), 2.22 (ddd, 2H, $J_{3b,3a}$=14.2 Hz, $J_{3b,2}$=$J_{3b,4}$=7.9 Hz, $H_{3b,8b}$), 1.36 (s, 6H, CH_3); ^{13}C NMR δ 134.2 ($C_{2,9}$), 118.3 ($C_{1,10}$), 108.9 (CMe_2), 82.5 ($C_{5,6}$), 72.0 ($C_{4,7}$), 38.5 ($C_{3,8}$), 26.8 (CMe_2); HRMS for $C_{13}H_{23}O_4$ (M^++1): calcd 243.1596; found 243.1600.

4.1.3. (4*R*,5*R*,6*R*,7*R*)-5,6-Di-*O*-benzyl-deca-1,9-diene-4,5,6,7-tetrol (26). Isolated yield: 30%; R_f 0.3 (cyclohexane/EtOAc 7:3); $[\alpha]_{Hg}$ −10 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 7.37–7.24 (m, 10H, H_{Ar}), 5.88 (dddd, 2H, $J_{2,1a}$=17.2 Hz, $J_{2,1b}$=10.0 Hz, $J_{2,3a}$=6.2 Hz, $J_{2,3b}$=8.1 Hz, $H_{2,9}$), 5.13 (d, 2H, $J_{1a,2}$=17.2 Hz, $H_{1a,10a}$), 5.12 (d, 2H, $J_{1b,2}$=10.0 Hz, $H_{1b,10b}$), 4.66 (s, 4H, CH_2Ph), 4.02 (ddd, 2H, $J_{4,3a}$=1.2 Hz, $J_{4,3b}$=7.8 Hz, $J_{4,5}$=6.1 Hz, $H_{4,7}$), 3.68 (d, 2H, $J_{5,4}$=6.1 Hz, $H_{5,6}$), 2.49 (ddd, 2H, $J_{3a,2}$=6.2 Hz, $J_{3a,3b}$=14.1 Hz, $J_{3a,4}$=1.2 Hz, $H_{3a,8a}$), 2.28 (ddd, 2H, $J_{3b,2}$=8.1 Hz, $J_{3b,3a}$=14.1 Hz, $J_{3b,4}$=7.8 Hz, $H_{3b,8b}$); ^{13}C NMR δ 137.3 ($C_{2,9}$), 134.7, 128.5, 128.3, 128.1 (C_{Ar}), 117.9 ($C_{1,10}$), 79.5, 70.3 ($C_{4,5,6,7}$), 73.1 (CH_2Ph), 38.3 ($C_{3,8}$); HRMS for $C_{24}H_{31}O_4$ (M^++1): calcd 383.2222; found 383.2222.

4.2. General procedure for ring closing metathesis of diene-diols

To a solution of diene-diol (4.42 mmol) in CH_2Cl_2 (800 mL) was added Grubbs' catalyst (0.22 mmol, 5.0 mol %). After stirring at 20 °C for 24, 48 and 72 h, 2.5 mol % of catalyst (0.11 mmol) were successively added. After stirring for 4 days, DMSO (1.96 mL, 27.6 mmol, 50 equiv relative to the catalyst) was added and the mixture was stirred overnight before concentration in vacuo. Flash chromatography of the crude led to pure cyclooctene derivatives.

4.2.1. (*Z*)-(1*S*,2*R*,3*R*,4*S*)-2,3-*O*-Methylethylidene-cyclooct-6-ene-1,2,3,4-tetrol (17). Isolated yield: 87%; R_f 0.3 (cyclohexane/EtOAc 5:5); mp 102 °C; $[\alpha]_D$ +60 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 5.78–5.73 (m, 2H, $H_{1,8}$), 3.80 (dd, 1H, $J_{4,3}$=$J_{4,5}$=5.9 Hz, H_4), 3.76 (dd, 1H, $J_{5,4}$=$J_{5,6}$=5.9 Hz,

H_5), 3.71–3.57 (m, 2H, $H_{3,6}$), 2.41 (ddd, 2H, $J_{2a,1}=5.4$ Hz, $J_{2a,2b}=13.9$ Hz, $J_{2a,3}=3.5$ Hz, $H_{2a,7a}$), 2.30 (ddd, 2H, $J_{2b,1}=6.8$ Hz, $J_{2a,2b}=13.9$ Hz, $J_{2b,3}=6.8$ Hz, $H_{2b,7b}$), 1.34 (s, 6H, CH_3); ^{13}C NMR δ 127.7 ($C_{1,8}$), 108.9 (*C*Me$_2$), 82.2 ($C_{4,5}$), 72.5 ($C_{3,6}$), 30.3 ($C_{2,7}$), 26.8 (C*Me*$_2$). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.48; H, 8.66.

4.2.2. (*Z*)-(1*R*,2*R*,3*R*,4*R*)-2,3-*O*-Methylethylidene-cyclooct-6-ene-1,2,3,4-tetrol (22). Isolated yield: 62%; R_f 0.2 (cyclohexane/EtOAc 6:4); $[\alpha]_D$ −87 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 5.81–5.67 (m, 2H, $H_{1,8}$), 4.23 (s*l*, 2H, $H_{4,5}$), 4.14 (dd, 2H, $J_{3,2a}=4.6$ Hz, $J_{3,2b}=7.6$ Hz, $H_{3,6}$), 2.50–2.31 (m, 4H, $H_{2a,2b,7a,7b}$), 1.42 (s, 6H, CH_3); ^{13}C NMR δ 128.0 ($C_{1,8}$), 108.2 (*C*Me$_2$), 77.0 ($C_{4,5}$), 67.4 ($C_{3,6}$), 29.0 ($C_{2,7}$), 27.2 (C*Me*$_2$); HRMS for $C_{11}H_{19}O_4$ ($M^+ +1$): calcd 215.1283; found 215.1278.

4.3. General procedure for silylation of alcohols

To a solution of diol (4.46 mmol) in DMF (6 mL) at 20 °C were successively added imidazole (23.2 mmol, 5.2 equiv) and *tert*-butyldimethylsilyl chloride (11.2 mmol, 2.5 equiv). The temperature was then raised to 50 °C and the mixture was stirred for 4 h. After cooling at 20 °C, a saturated NH_4Cl aqueous solution was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were then dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the crude led to pure silylated derivatives.

4.3.1. (*Z*)-(1*S*,2*S*,3*S*,4*S*)-1,4-Di-*O*-*tert*-butyldimethylsilyl-2,3-*O*-methylethylidene-cyclooct-6-ene-1,2,3,4-tetrol (19). Isolated yield: 97%; R_f 0.3 (cyclohexane/CH_2Cl_2 8:2); mp 44 °C; $[\alpha]_D$ +76 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 5.78–5.64 (m, 2H, $H_{1,8}$), 3.75 (dd, 1H, $J_{4,3}=J_{4,5}=5.8$ Hz, H_4), 3.72 (dd, 1H, $J_{5,4}=J_{5,6}=5.8$ Hz, H_5), 3.68–3.52 (m, 2H, $H_{3,6}$), 2.45–2.20 (m, 4H, $H_{2a,2b,7a,7b}$), 1.31 (s, 6H, CH_3), 0.88 (s, 18H, Si*t*Bu), 0.06 (s, 12H, $SiMe_2$); ^{13}C NMR δ 127.6 ($C_{1,8}$), 107.4 (*C*Me$_2$), 82.3 ($C_{4,5}$), 73.6 ($C_{3,6}$), 32.8 ($C_{2,7}$), 26.9 (C*Me*$_2$), 25.9 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), −4.3, −5.1 (Si*Me*$_2$); HRMS for $C_{23}H_{47}O_4Si_2$ ($M^+ +1$): calcd 443.3013; found 443.3013.

4.3.2. (*Z*)-(1*R*,2*S*,3*S*,4*R*)-1,4-Di-*O*-*tert*-butyldimethylsilyl-2,3-*O*-methylethylidene-cyclooct-6-ene-1,2,3,4-tetrol (24). Isolated yield: 74%; R_f 0.25 (cyclohexane/CH_2Cl_2 8:2); mp 87 °C; $[\alpha]_D$ −126 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 5.70–5.55 (m, 2H, $H_{1,8}$), 4.26 (s*l*, 2H, $H_{4,5}$), 4.14 (dd, 2H, $J_{3,2a}=4.5$ Hz, $J_{3,2b}=7.9$ Hz, $H_{3,6}$), 2.40–2.28 (m, 4H, $H_{2a,7a}$), 2.23 (ddd, 2H, $J_{2b,1}=2.4$ Hz, $J_{2b,2a}=16.0$ Hz, $J_{2b,3}=7.8$ Hz, $H_{2b,7b}$), 1.36 (s, 6H, CH_3), 0.89 (s, 18H, Si*t*Bu), 0.08, 0.06 (2 s, 12H, $SiMe_2$); ^{13}C NMR δ 127.9 ($C_{1,8}$), 108.5 (*C*Me$_2$), 77.6 ($C_{4,5}$), 68.7 ($C_{3,6}$), 31.7 ($C_{2,7}$), 27.6 (C*Me*$_2$), 26.0 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), −4.2, −5.0 (Si*Me*$_2$). Anal. Calcd for $C_{23}H_{46}O_4Si_2$: C, 62.39; H, 10.48. Found: C, 62.39; H, 10.57.

4.3.3. (4*S*,5*S*,6*S*,7*S*)-4,7-Di-*O*-*tert*-butyldimethylsilyl-5,6-*O*-methylethylidene-deca-1,9-diene-4,5,6,7-tetrol (18). Isolated yield: 94%; R_f 0.25 (cyclohexane/CH_2Cl_2 8:2); $[\alpha]_D$ +18 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 5.78 (dddd, 2H, $J_{2,1a}=17.2$ Hz, $J_{2,1b}=10.0$ Hz, $J_{2,3a}=J_{2,3b}=7.1$ Hz, $H_{2,9}$), 5.09 (d, 2H, $J_{1a,2}=17.2$ Hz, $H_{1a,10a}$), 5.03 (d, 2H, $J_{1b,2}=10.0$ Hz, $H_{1b,10b}$), 3.98 (s*l*, 2H, $H_{5,6}$), 3.62 (dd, 2H, $J_{4,3a}=6.1$ Hz, $J_{4,3b}=7.3$ Hz, $H_{4,7}$), 2.45 (ddd, 2H, $J_{3a,3b}=13.5$ Hz, $J_{3a,4}=6.1$ Hz, $J_{3a,2}=7.1$ Hz, $H_{3a,8a}$), 2.24 (ddd, 2H, $J_{3b,3a}=13.5$ Hz, $J_{3b,4}=7.3$ Hz, $J_{3b,2}=7.1$ Hz, $H_{3b,8b}$), 1.38 (s, 6H, CH_3), 0.88 (s, 18H, Si*t*Bu), 0.06, 0.04 (2 s, 12H, $SiMe_2$); ^{13}C NMR δ 134.7 ($C_{2,9}$), 117.5 ($C_{1,10}$), 108.8 (*C*Me$_2$), 78.4 ($C_{5,6}$), 71.9 ($C_{4,7}$), 39.1 ($C_{3,8}$), 27.4 (C*Me*$_2$), 25.9 (SiC(*C*H$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), −4.1, −4.3 (Si*Me*$_2$); HRMS for $C_{25}H_{51}O_4Si_2$ ($M^+ +1$): calcd 471.3326; found 471.3321.

4.3.4. (4*R*,5*S*,6*S*,7*R*)-4,7-Di-*O*-*tert*-butyldimethylsilyl-5,6-*O*-methylethylidene-deca-1,9-diene-4,5,6,7-tetrol (23). Isolated yield: 96%; R_f 0.3 (cyclohexane/CH_2Cl_2 9:1); $[\alpha]_D$ −8 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 5.85 (dddd, 2H, $J_{2,1a}=17.2$ Hz, $J_{2,1b}=10.3$ Hz, $J_{2,3a}=6.7$ Hz, $J_{2,3b}=7.4$ Hz, $H_{2,9}$), 5.07 (d, 2H, $J_{1a,2}=17.2$ Hz, $H_{1a,10a}$), 5.06 (d, 2H, $J_{1b,2}=10.3$ Hz, $H_{1b,10b}$), 4.00 (dd, 1H, $J_{5,6}=3.8$ Hz, $J_{5,4}=4.8$ Hz, H_5), 3.99 (dd, 1H, $J_{6,5}=3.8$ Hz, $J_{6,7}=4.8$ Hz, H_6), 3.82 (ddd, 2H, $J_{4,5}=4.8$ Hz, $J_{4,3a}=5.4$ Hz, $J_{4,3b}=5.1$ Hz, $H_{4,7}$), 2.41 (ddd, 2H, $J_{3a,2}=6.7$ Hz, $J_{3a,3b}=14.2$ Hz, $J_{3a,4}=5.4$ Hz, $H_{3a,8a}$), 2.28 (ddd, 2H, $J_{3b,2}=7.4$ Hz, $J_{3b,3a}=14.2$ Hz, $J_{3b,4}=5.1$ Hz, $H_{3b,8b}$), 1.36 (s, 6H, CH_3), 0.88 (s, 18H, Si*t*Bu), 0.08, 0.07 (2 s, 12H, $SiMe_2$); ^{13}C NMR δ 134.6 ($C_{2,9}$), 117.4 ($C_{1,10}$), 109.0 (*C*Me$_2$), 79.8 ($C_{5,6}$), 71.9 ($C_{4,7}$), 37.7 ($C_{3,8}$), 28.4 (C*Me*$_2$), 25.9 (SiC(*C*H$_3$)$_3$), 18.1 (Si*C*(CH$_3$)$_3$), −4.2, −4.4 (Si*Me*$_2$). Anal. Calcd for $C_{25}H_{50}O_4Si_2$: C, 63.77; H, 10.70. Found: C, 63.84; H, 10.69.

4.3.5. (4*R*,5*S*,6*S*,7*R*)-5,6-Di-*O*-benzyl-4,7-di-*O*-*tert*-butyldimethylsilyl-deca-1,9-diene-4,5,6,7-tetrol (27). Isolated yield: 70%; R_f 0.3 (cyclohexane/CH_2Cl_2 8:2); $[\alpha]_D$ +21 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 7.55–7.20 (m, 10H, CH_2Ph), 5.89 (dddd, 2H, $J_{2,1a}=17.2$ Hz, $J_{2,1b}=9.9$ Hz, $J_{2,3a}=J_{2,3b}=7.1$ Hz, $H_{2,9}$), 5.07 (d, 2H, $J_{1a,2}=17.2$ Hz, $H_{1a,10a}$), 5.06 (d, 2H, $J_{1b,2}=9.9$ Hz, $H_{1b,10b}$), 4.85, 4.68 (AB, $J_{AB}=11.1$ Hz, CH_2Ph), 3.80 (d, 2H, $J_{4,3a}=7.0$ Hz, $J_{4,3b}=5.1$ Hz, $H_{4,7}$) 3.62 (s*l*, 2H, $H_{5,6}$), 2.55 (ddd, 2H, $J_{3a,2}=7.1$ Hz, $J_{3a,3b}=14.2$ Hz, $J_{3a,4}=7.0$ Hz, $H_{3a,8a}$), 2.28 (ddd, 2H, $J_{3b,2}=7.1$ Hz, $J_{3b,3a}=14.2$ Hz, $J_{3b,4}=5.1$ Hz, $H_{3b,8b}$), 0.91 (s, 18H, Si*t*Bu), 0.07 (s, 12H, $SiMe_2$); ^{13}C NMR δ 139.3, 128.2, 127.8, 127.3 (CH_2Ph), 136.1 ($C_{2,9}$), 116.8 ($C_{1,10}$), 84.4 ($C_{5,6}$), 75.0 (*C*H$_2$Ph), 74.0 ($C_{4,7}$), 37.1 ($C_{3,8}$), 26.0 (SiC(*C*H$_3$)$_3$), 18.1 (Si*C*(CH$_3$)$_3$), −4.2, −4.4 (Si*Me*$_2$); HRMS for $C_{36}H_{58}O_4Si_2$ ($M^+ +1$): calcd 611.3952; found 611.3945.

4.4. General procedure for ring closing metathesis of dienes-diols silylated derivatives

To a solution of diene (2.12 mmol) in CH_2Cl_2 (10 mL) was added Grubbs' catalyst (0.04 mmol, 2.0 mol %). After stirring at 20 °C for 30 min was added lead tetraacetate[47] (0.06 mmol, 1.5 equiv relative to the catalyst). After stirring overnight, the mixture was filtered through celite and concentrated in vacuo. Flash chromatography of the crude led to pure cyclooctene derivatives.

4.4.1. (*Z*)-(1*S*,2*S*,3*S*,4S)-1,4-Di-*O*-*tert*-butyldimethylsilyl-2,3-*O*-methylethylidene-cyclooct-6-ene-1,2,3,4-tetrol (19). Isolated yield: 100%. Physical data: see Section 4.3.1.

4.4.2. (*Z*)-(1*R*,2*S*,3*S*,4*R*)-1,4-Di-*O*-*tert*-butyldimethylsilyl-2,3-*O*-methylethylidene-cyclooct-6-ene-1,2,3,4-tetrol (24). Isolated yield: 95%. Physical data: see Section 4.3.2.

4.4.3. (*Z*)-(1*R*,2*S*,3*S*,4*R*)-2,3-Di-*O*-benzyl-1,4-di-*O*-*tert*-butyldimethylsilyl-cyclooct-6-ene-1,2,3,4-tetrol (28). Isolated yield: 95%; R_f 0.3 (cyclohexane/CH_2Cl_2 8:2); $[\alpha]_D$ +21 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 7.35–7.15 (m, 10H, CH_2*Ph*), 5.75–5.55 (m, 2H, $H_{1,8}$), 4.86, 4.45 (AB, $J_{A,B}$= 10.9 Hz, CH_2Ph), 4.30–4.13 (m, 2H, $H_{3,6}$), 3.90 (*sl*, 2H, $H_{4,5}$), 2.40–2.15 (m, 4H, $H_{2a,2b,7a,7b}$), 0.91 (s, 18H, Si*t*Bu), 0.10, 0.09, 0.07 (3 s, 12H, $SiMe_2$); ^{13}C NMR δ 140.0, 128.3, 127.9, 127.5 (CH_2*Ph*), 126.8 ($C_{1,8}$), 77.6 ($C_{4,5}$), 73.8 (*C*H_2Ph), 72.4 ($C_{3,6}$), 32.7 ($C_{2,7}$), 26.0 (SiC(*C*H_3)$_3$), 18.3 (Si*C*$(CH_3)_3$), 1.0, –4.0, –5.0 (Si*Me*$_2$); HRMS for $C_{34}H_{55}O_4Si_2$ (M^++1): calcd 583.3639; found 583.3633.

4.5. 2,5-Di-*O*-*tert*-butyldimethylsilyl-1,6-didesoxy-1,6-diformyl-3,4-*O*-methylethylidene-L-iditol (29)

By using an ozone generator, a stream of O_3/O_2 was passed through a solution of diene (1.62 mmol) in CH_2Cl_2 (24 mL) and methanol (4 mL) at −78 °C, until a slight blue color developed. After 30 min, O_3 in excess was removed by a stream of argon in the solution until decoloration. Trimethylphosphite (14.6 mmol, 9 equiv) was then added at −78 °C and the mixture was stirred for 10 min from −78 °C to 20 °C, then overnight at 20 °C. After concentration in vacuo, flash chromatography of the crude led to pure dialdehyde derivative. Isolated yield: 70%; R_f 0.2 (cyclohexane/CH_2Cl_2 1:9); $[\alpha]_D$ +16 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 9.81 (dd, 2H, $J_{1,2a}$=1.5 Hz, $J_{1,2b}$=2.3 Hz, $H_{1,8}$), 4.23 (ddd, 2H, $J_{3,4}$=1.2 Hz, $J_{3,2a}$=6.6 Hz, $J_{3,2b}$=4.8 Hz, $H_{3,6}$), 4.03 (dd, 2H, $J_{4,3}$=1.2 Hz, $J_{4,5}$=1.8 Hz, $H_{4,5}$), 2.81 (ddd, 2H, $J_{2a,1}$=1.5 Hz, $J_{2a,2b}$=14.2 Hz, $J_{2a,3}$=6.6 Hz, $H_{2a,7a}$), 2.55 (ddd, 2H, $J_{2b,1}$=2.3 Hz, $J_{2b,2a}$=14.2 Hz, $J_{2b,3}$=4.8 Hz, $H_{2b,7b}$), 1.37 (s, 6H, CH_3), 0.88 (s, 18H, Si*t*Bu), 0.09, 0.08 (2 s, 12H, $SiMe_2$); ^{13}C NMR δ 200.6 ($C_{1,8}$), 110.0 (*C*Me_2), 79.6 ($C_{4,5}$), 67.7 ($C_{3,6}$), 48.3 ($C_{2,7}$), 27.2 (C*Me*$_2$), 25.8 (SiC(*C*H_3)$_3$), 18.1 (Si*C*$(CH_3)_3$), −4.5 (Si*Me*$_2$); HRMS for $C_{23}H_{47}O_6Si_2$ (M^++1): calcd 475.2911; found 475.2917.

4.6. General procedure for oxidative hydroboration

To a solution of cyclooctene (1.03 mmol) in diethyl ether (4 mL) was added at 0 °C BH_3·THF complex (1 M in THF, 1 mmol, 1 equiv). After stirring at 20 °C for 1 h 30 min the mixture was oxidized by adding successively ethanol (1.2 mL), 3 M NaOH (0.25 mL) and 30% hydrogen peroxide (0.25 mL). After stirring overnight at 20 °C, water (20 mL) was added and the reaction mixture was extracted with diethyl ether. The combined organic layer were washed with water, then with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the crude led to pure cyclooctanol derivatives.

4.6.1. (1*R*,2*S*,3*S*,4*R*,6*S*)-1,4-Di-*O*-*tert*-butyldimethylsilyl-2,3-*O*-methylethylidene-cyclooctane-1,2,3,4,6-pentol (33). Isolated yield: 62%; R_f 0.15 (cyclohexane/EtOAc 9:1); $[\alpha]_D$ −28 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 4.27 (d, 1H, $J_{3,2a}$= 7.8 Hz, H_3), 4.15 (dd, 1H, $J_{6,5}$=1.5 Hz, $J_{6,7a}$=7.7 Hz, H_6), 4.11 (d, 1H, $J_{4,5}$=8.5 Hz, H_4), 4.01 (dd, 1H, $J_{5,4}$=8.5 Hz, $J_{5,6}$=1.5 Hz, H_5), 3.90 (dddd, 1H, $J_{1,2a}$=1.9 Hz, $J_{1,2b}$= 9.8 Hz, $J_{1,8a}$=9.6 Hz, $J_{1,8b}$=1.0 Hz, H_1), 2.12 (dddd, 1H, $J_{2a,1}$=1.9 Hz, $J_{2a,2b}$=14.1 Hz, $J_{2a,3}$=7.8 Hz, $^4J_{2a,8b}$= 1.9 Hz, H_{2a}), 2.00 (dddd, 1H, $J_{8a,1}$=9.6 Hz, $J_{8a,7a}$= 5.4 Hz, $J_{8a,7b}$=10.0 Hz, $J_{8a,8b}$=13.4 Hz, H_{8a}), 1.96 (dddd, 1H, $J_{7a,6}$=7.7 Hz, $J_{7a,7b}$=15.0 Hz, $J_{7a,8a}$=5.4 Hz, $J_{7a,8b}$= 10.1 Hz, H_{7a}), 1.74 (dd, 1H, $J_{2b,1}$=9.8 Hz, $J_{2b,2a}$=14.1 Hz, H_{2b}), 1.64 (dddd, 1H, $J_{8b,1}$=1.0 Hz, $^4J_{8b,2a}$=1.9 Hz, $J_{8b,7a}$=10.1 Hz, $J_{8b,8a}$=13.4 Hz, H_{8b}), 1.56 (dd, 1H, $J_{7b,7a}$=15.0 Hz, $J_{7b,8a}$=10.0 Hz, H_{7b}), 1.34 (s, 6H, CH_3), 0.92, 0.91, 0.90 (3 s, 18H, Si*t*Bu), 0.09, 0.07, 0.05, 0.04 (4 s, 12H, $SiMe_2$); ^{13}C NMR δ 106.1 (*C*Me_2), 78.3, 78.2 ($C_{4,5}$), 69.1 (C_1), 68.3, 68.2 ($C_{3,6}$), 45.0 (C_2), 31.4 (C_8), 31.0 (C_7), 27.3 (C*Me*$_2$), 26.0 (SiC(*C*H_3)$_3$), 18.1 (Si*C*$(CH_3)_3$), −4.5, −4.6, −4.8, −4.9 (Si*Me*$_2$). Anal. Calcd for $C_{23}H_{48}O_5Si_2$: C, 59.95; H, 10.50. Found: C, 59.79; H, 10.66.

4.6.2. (1*R*,2*S*,3*S*,4*R*,6*R*)-1,4-Di-*O*-*tert*-butyldimethylsilyl-2,3-*O*-methylethylidene-cyclooctane-1,2,3,4,6-pentol (34). Isolated yield: 30%; R_f 0.2 (cyclohexane/EtOAc 9:1); mp 55–60 °C; $[\alpha]_D$ −36 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 4.35 (dd*l*, 1H, $J_{3,2a}$=6.8 Hz, $J_{3,4}$=1.7 Hz, H_3), 4.20 (dd*l*, 1H, $J_{6,5}$=1.3 Hz, $J_{6,7a}$=6.9 Hz, H_6), 4.16 (dd, 1H, $J_{5,4}$=8.6 Hz, $J_{5,6}$=1.3 Hz, H_5), 4.06 (dd, 1H, $J_{4,3}$=1.7 Hz, $J_{4,5}$=8.6 Hz, H_4), 4.11–4.01 (m, 1H, H_1), 2.29 (ddd, 1H, $J_{2a,1}$=7.4 Hz, $J_{2a,2b}$=14.8 Hz, $J_{2a,3}$=6.8 Hz, H_{2a}), 2.03–1.86 (m, 2H, $H_{8a,8b}$), 1.80–1.60 (m, 3H, $H_{2b,7a,7b}$), 1.35, 1.34 (2 s, 6H, CH_3), 0.90, 0.89 (2 s, 18H, Si*t*Bu), 0.13, 0.12, 0.07, 0.05 (4 s, 12H, $SiMe_2$); ^{13}C NMR δ 106.2 (*C*Me_2), 78.6, 77.3 ($C_{4,5}$), 70.9 (C_3), 68.4 (C_1), 68.2 (C_6), 39.3 (C_2), 27.3 (C*Me*$_2$), 27.2 (C_7), 26.0, 25.9 (SiC(*C*H_3)$_3$), 25.6 (C_8), 18.2, 18.0 (Si*C*$(CH_3)_3$), −4.4, −4.8 (Si*Me*$_2$); HRMS for $C_{23}H_{49}O_5Si_2$ (M^++1): calcd 461.3119; found 461.3116.

4.6.3. (1*S*,2*S*,3*S*,4*S*,6*S*)-1,4-Di-*O*-*tert*-butyldimethylsilyl-2,3-*O*-methylethylidene-cyclooctane-1,2,3,4,6-pentol (37). Isolated yield: 51%; R_f 0.35 (cyclohexane/EtOAc 9:1); mp 62–65 °C; $[\alpha]_D$ +37 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 4.10 (dd, 1H, $J_{4,3}$=7.6 Hz, $J_{4,5}$=8.0 Hz, H_4), 4.03 (ddd, 1H, $J_{3,2a}$=5.8 Hz, $J_{3,2b}$=2.3 Hz, $J_{3,4}$=7.4 Hz, H_3), 3.87–3.74 (m, 1H, H_1), 3.67 (ddd, 1H, $J_{6,5}$=8.2 Hz, $J_{6,7a}$=4.3 Hz, $J_{6,7b}$=8.3 Hz, H_6), 3.58 (dd, 1H, $J_{5,4}$=8.0 Hz, $J_{5,6}$=8.2 Hz, H_5), 2.17 (dd, 1H, $J_{8a,7b}$=6.5 Hz, $J_{8a,8b}$=13.6 Hz, H_{8a}), 2.10 (ddd, 1H, $J_{2a,1}$=4.8 Hz, $J_{2a,2b}$=15.0 Hz, $J_{2a,3}$= 5.8 Hz, H_{2a}), 1.91 (ddd, 1H, $J_{2b,1}$=2.2 Hz, $J_{2b,2a}$= 15.0 Hz, $J_{2b,3}$=2.3 Hz, H_{2b}), 1.80 (dd, 1H, $J_{7a,6}$=4.3 Hz, $J_{7a,7b}$=13.6 Hz, H_{7a}), 1.39–1.22 (m, 2H, $H_{7b,8b}$), 1.34, 1.31 (2 s, 6H, CH_3), 0.88, 0.86 (2 s, 18H, Si*t*Bu), 0.12, 0.11, 0.07, 0.06 (4 s, 12H, $SiMe_2$); ^{13}C NMR δ 107.7 (*C*Me_2), 81.8, 81.7 ($C_{4,5}$), 77.2, 76.1 ($C_{3,6}$), 70.4 (C_1), 35.4 (C_2), 31.1 (C_8), 29.6 (C_7), 27.0, 26.7 (C*Me*$_2$), 25.9, 25.8 (SiC(*C*H_3)$_3$), 18.2, 18.0 (Si*C*$(CH_3)_3$), −4.3, −4.4, −5.0, −5.3 (Si*Me*$_2$). Anal. Calcd for $C_{23}H_{48}O_5Si_2$: C, 59.95; H, 10.50. Found C, 59.92; H, 10.54.

4.6.4. (1*S*,2*S*,3*S*,4*S*,6*R*)-1,4-Di-*O*-*tert*-butyldimethylsilyl-2,3-*O*-methylethylidene-cyclooctane-1,2,3,4,6-pentol (38). Isolated yield: 38%; R_f 0.25 (cyclohexane/EtOAc 9:1); $[\alpha]_D$ +26 (*c*1.0, CH_2Cl_2); ^{1}H NMR δ 4.23–4.13 (m, 1H, H_1), 3.88–3.78 (m, 2H, $H_{3,4}$), 3.68–3.53 (m, 2H, $H_{5,6}$), 1.93–1.53 (m, 6H, $H_{2a,2b,7a,7b,8a,8b}$), 1.32, 1.30 (2 s, 6H, CH_3), 0.87 (3 s, 18H, Si*t*Bu), 0.07, 0.06 (4 s, 12H, $SiMe_2$); ^{13}C NMR δ 107.5 (*C*Me_2), 81.7, 81.6 ($C_{4,5}$), 76.4 (C_6), 73.3 (C_3), 65.9 (C_1), 38.2 (C_2), 30.2 (C_8), 27.0, 26.7 (C*Me*$_2$), 26.9 (C_7), 25.9, 25.8 (SiC(*C*H_3)$_3$), 18.3, 18.1 (Si*C*$(CH_3)_3$), −4.3, −4.5, −5.0, −5.2 (Si*Me*$_2$); HRMS for $C_{23}H_{49}O_5Si_2$ (M^++1): calcd 461.3119; found 461.3121.

4.7. General procedure for ketone formation

To a solution of cyclooctene (1.0 mmol) in diethylether (6 mL) was added at 0 °C $BH_3 \cdot THF$ complex (1 M in THF, 1 mmol, 1 equiv). After stirring at 20 °C for 2 h the mixture was oxidized by adding pyridinium chlorochromate (36 mg, 0.17 mmol, 6 equiv). After stirring overnight at 20 °C the mixture was filtered through celite and concentrated in vacuo. Flash chromatography of the crude led to pure ketone derivatives.

4.7.1. (3*R*,4*S*,5*S*,6*R*)-3,6-Di-*O*-*tert*-butyldimethylsilyl-4,5-*O*-methylethylidene-3,4,5,6-tetrahydroxy cyclooctanone (41). Isolated yield: 88%; R_f 0.4 (cyclohexane/EtOAc 9:1); mp 69 °C; $[\alpha]_D$ −59 (*c*1.0, CH_2Cl_2); ^1H NMR δ 4.31 (ddd, 1H, $J_{3,2a}=J_{3,2b}=5.6$ Hz, $J_{3,4}=1.1$ Hz, H_3), 4.26–4.20 (m, 1H, H_6), 4.21 (dd, 1H, $J_{4,3}=1.1$ Hz, $J_{4,5}=8.2$ Hz, H_4), 4.10 (dd, 1H, $J_{5,4}=8.2$ Hz, $J_{5,6}=1.0$ Hz, H_5), 2.76–2.56 (m, 3H, $H_{2a,2b,8a}$), 2.31 (ddd, 1H, $J_{8b,7a}=7.5$ Hz, $J_{8b,7b}=3.8$ Hz, $J_{8b,8a}=15.0$ Hz, H_{8b}), 2.08–1.88 (m, 2H, $H_{7a,7b}$), 1.36, 1.35 (2 s, 6H, CH_3), 0.90 (s, 18H, Si*t*Bu), 0.10, 0.08, 0.04 (3 s, 12H, $SiMe_2$); ^{13}C NMR δ 210.4 (C_1), 107.7 (*C*Me_2), 78.0 (C_5), 77.0 (C_4), 68.6 (C_6), 68.2 (C_3), 47.0 (C_2), 36.8 (C_8), 30.4 (C_7), 27.5, 27.3 (C*Me*$_2$), 26.0 (SiC(*C*H_3)$_3$), 18.1 (Si*C*$(CH_3)_3$), −4.4, −4.8, −4.9 (Si*Me*$_2$); HRMS for $C_{23}H_{47}O_5Si_2$ ($M^+ +1$): calcd 459.2962; found 459.2958.

4.7.2. (3*S*,4*S*,5*S*,6*S*)-3,6-Di-*O*-*tert*-butyldimethylsilyl-4,5-*O*-methylethylidene-3,4,5,6-tetrahydroxy cyclooctanone (46). Isolated yield: 97%; R_f 0.6 (cyclohexane/EtOAc 9:1); mp 99–100 °C; $[\alpha]_D$ +26 (*c*1.0, CH_2Cl_2); ^1H NMR δ 3.90–3.80 (m,1H, H_6), 3.82 (ddd, 1H, $J_{3,2a}=10.9$ Hz, $J_{3,2b}=4.5$ Hz, $J_{3,4}=8.2$ Hz, H_3), 3.72 (dd, 1H, $J_{4,3}=J_{4,5}=8.2$ Hz, H_4), 3.44 (dd, 1H, $J_{5,4}=J_{5,6}=8.2$ Hz, H_5), 2.95 (dd, 1H, $J_{2a,2b}=11.1$ Hz, $J_{2a,3}=10.9$ Hz, H_{2a}), 2.75 (ddd, 1H, $J_{8a,7a}=13.0$ Hz, $J_{8a,7b}=2.9$ Hz, $J_{8a,8b}=16.2$ Hz, H_{8a}), 2.41 (dd, 1H, $J_{2b,2a}=11.1$ Hz, $J_{2b,3}=4.5$ Hz, H_{2b}), 2.27 (ddd, 1H, $J_{7a,7b}=15.2$ Hz, $J_{7a,8a}=13.0$ Hz, $J_{7a,8b}=2.2$ Hz, H_{7a}), 2.13 (ddd, 1H, $J_{8b,7a}=2.2$ Hz, $J_{8b,7b}=5.9$ Hz, $J_{8b,8a}=16.2$ Hz, H_{8b}), 1.89 (ddd, 1H, $J_{7b,7a}=15.2$ Hz, $J_{7b,8a}=2.9$ Hz, $J_{7b,8b}=5.9$ Hz, H_{7b}), 1.32, 1.29 (2 s, 6H, CH_3), 0.86, 0.85 (2 s, 18H, Si*t*Bu), 0.09, 0.03 (2 s, 12H, $SiMe_2$); ^{13}C NMR δ 210.4 (C_1), 108.7 (*C*Me_2), 81.9 (C_4), 80.1 (C_5), 74.9 (C_3), 74.0 (C_6), 46.3 (C_2), 39.0 (C_8), 28.9 (C_7), 26.9 (C*Me*$_2$), 25.8 (SiC(*C*H_3)$_3$), 18.2, 18.1 (Si*C*$(CH_3)_3$), −4.3, −5.0, −5.2 (Si*Me*$_2$); Anal. Calcd for $C_{23}H_{46}O_5Si_2$: C, 60.21; H, 10.11; found C, 59.89; H, 10.40.

4.8. Reductive amination

To the cycloalkanone (0.33 mmol) at 20 °C, were successively added titanium(IV) tetra-isopropoxide (0.41 mmol, 1.25 equiv) and the primary amine (0.66 mmol, 2 equiv). After stirring for 2 h, absolute ethanol (0.3 mL) and sodium cyanoborohydride (1.75 mmol, 5.3 equiv) were added and the mixture was stirred overnight at 20 °C. Addition of water (0.2 mL) resulted in the formation of a white precipitate which was filtered and washed with absolute ethanol. Concentration of the filtrate was followed by extraction of the residue with ethyl acetate, filtration and concentration in vacuo. The oily residue was then dissolved in CH_2Cl_2, stirred in the presence of sodium hydrogencarbonate, filtered and concentrated in vacuo. Flash chromatography of the crude led to a mixture of two epimers.

4.8.1. (1*R*,2*S*,3*S*,4*R*)-1,4-Di-*O*-*tert*-butyldimethylsilyl-6-(2-hydroxyethylamino)-2,3-*O*-methylethylidene-cyclooctane-1,2,3,4-tetrol (42). Isolated yield: 84% (unseparable 4:1 mixture of 6*S*:6*R* epimers); R_f 0.2 (CH_2Cl_2/MeOH 9:1); ^1H NMR δ 4.30–3.96 (m, 4H, $H_{3,4,5,6}$), 3.66–3.52 (m, 2H, $H_{2'a,2'b}$), 2.82–2.65 (m, 3H, $H_{1,1'a,1'b}$), 2.06–1.42 (m, 6H, $H_{2a,2b,7a,7b,8a,8b}$), 1.34 (s, 6H, CH_3), 0.90 (s, 18H, Si*t*Bu), 0.09, 0.07, 0.03 (3 s, 12H, $SiMe_2$); ^{13}C NMR δ 106.1 (*C*Me_2), 78.6, 78.1 ($C_{4,5}$), 68.6, 68.4 ($C_{3,6}$), 60.9 ($C_{2'}$), 54.3 (C_1), 48.5 ($C_{1'}$), 37.7 (C_2), 32.5 (C_8), 27.9 (C_7), 27.3 (C*Me*$_2$), 26.0 (SiC(*C*H_3)$_3$), 18.2 (Si*C*$(CH_3)_3$), −4.5, −4.8 (Si*Me*$_2$); HRMS for $C_{25}H_{54}NO_5Si_2$ ($M^+ +1$): calcd 504.3541; found 504.3537.

4.8.2. (1*R*,2*S*,3*S*,4*R*)-1,4-Di-*O*-*tert*-butyldimethylsilyl-6-[2-silyloxy-1-silyloxymethylethylamino]-2,3-*O*-methylethylidene-cyclooctane-1,2,3,4-tetrol (43). Isolated yield: 96% (unseparable 4:1 mixture of 6*S*:6*R* epimers); R_f 0.2 (CH_2Cl_2/MeOH 9:1); ^1H NMR δ 4.30–4.02 (m, 4H, $H_{3,4,5,6}$), 3.65–3.40 (m, 4H, $H_{1'a,1'b,3'a,3'b}$), 2.91–2.82 (m, 1H, H_1), 2.70–2.60 (m, 1H, $H_{2'}$), 2.00–1.40, 1.29–1.18 (m, 6H, $H_{2a,2b,7a,7b,8a,8b}$), 1.34, 1.33 (2 s, 6H, CH_3), 0.90, 0.88, 0.87 (3 s, 18H, Si*t*Bu), 0.10, 0.09, 0.06, 0.05, 0.04, 0.03 (6 s, 24H, $SiMe_2$); ^{13}C NMR δ 106.1 (*C*Me_2), 78.0 ($C_{4,5}$), 68.6 ($C_{3,6}$), 64.5, 62.2 ($C_{1',3'}$), 54.3 (C_1), 52.0 ($C_{2'}$), 37.7 (C_2), 29.7 (C_8), 28.1 (C_7), 27.4, 27.3 (C*Me*$_2$), 26.0, 25.9 (SiC(*C*H_3)$_3$), 18.2 (Si*C*$(CH_3)_3$), −4.5, −4.9, −5.5 (Si*Me*$_2$); SM (CI, NH_3) 763 ($M^+ +1$).

4.8.3. (1*S*,2*S*,3*S*,4*S*)-1,4-Di-*O*-*tert*-butyldimethylsilyl-6-(2-hydroxyethylamino)-2,3-*O*-methylethylidene-cyclooctane-1,2,3,4-tetrol (47). Isolated yield: 61% (unseparable 3:1 mixture of 6*S*:6*R* epimers); R_f 0.2 (CH_2Cl_2/MeOH 9:1); ^1H NMR δ 3.91–3.50 (m, 6H, $H_{3,4,5,6,2'a,2'b}$), 2.80–2.65 (m, 2H, $H_{1'a,1'b}$), 2.65–2.41 (m, 1H, H_1), 2.22–2.02 (m, 1H, H_{8a}), 1.90–1.38 (m, 4H, $H_{2a,2b,7a,8b}$), 1.30, 1.29 (2 s, 6H, CH_3), 1.17–0.98 (m, 1H, H_{7b}), 0.85 (s, 18H, Si*t*Bu), 0.09, 0.05, 0.03 (3 s, 12H, $SiMe_2$); ^{13}C NMR δ 107.6 (CMe_2), 81.9, 81.5 ($C_{4,5}$), 76.3, 75.3 ($C_{3,6}$), 60.9 ($C_{2'}$), 54.2 (C_1), 48.7 ($C_{1'}$), 36.5 (C_2), 29.4 (C_7), 29.0 (C_8), 27.0, 26.8 (CMe_2), 25.9 (SiC(CH_3)$_3$), 18.2 (SiC(CH_3)$_3$), −4.4, −4.8, −5.1 ($SiMe_2$); HRMS for $C_{25}H_{54}NO_5Si_2$ ($M^+ +1$): calcd 504.3541; found 504.3537.

4.9. Deprotection of the cyclooctanols

The substrate (0.43 mmol) was stirred in a 9:1 solution of trifluoroacetic acid/H_2O at 20 °C for 15 h. After concentration in vacuo, the resulting oily residue was triturated in diethyl ether and the supernatant was discarded to afford a brownish solid which was then purified by reverse phase chromatography (Sep-Pak® Cartridges, H_2O/MeOH 1:1 to 1:5).

4.9.1. (1*R*,2*R*,3*R*,4*R*,6*S*)-Cyclooctane-1,2,3,4,6-pentol (35). Isolated yield: 100%; $[\alpha]_{Hg}$ −12 (*c*1.0, MeOH); ^1H NMR (D_2O) δ 4.35 (ddd, 1H, $J_{3,2a}=8.7$ Hz, $J_{3,2b}=2.3$ Hz, $J_{3,4}=2.4$ Hz, H_3), 4.18–4.06 (m, 2H, $H_{1,6}$), 3.97 (dd, 1H, $J_{4,3}=2.4$ Hz, $J_{4,5}=8.2$ Hz, H_4), 3.77 (dd, 1H, $J_{5,4}=8.2$ Hz,

$J_{5,6}=1.9$ Hz, H_5), 2.18 (ddd, 1H, $J_{2a,1}=2.8$ Hz, $J_{2a,2b}=15.3$ Hz, $J_{2a,3}=8.7$ Hz, H_{2a}), 2.10–1.60 (m, 5H, $H_{2b,7a,7b,8a,8b}$); ^{13}C NMR (D_2O) δ 76.4 (C_5), 75.9 (C_4), 74.1 (C_1), 69.5 (C_6), 68.8 (C_3), 40.6 (C_2), 31.9, 29.1 ($C_{7,8}$); HRMS for $C_8H_{17}O_5$ ($M^+ +1$): calcd 210.1341; found 210.1345.

4.9.2. (1*R*,2*R*,3*R*,4*R*,6*R*)-Cyclooctane-1,2,3,4,6-pentol (36). Isolated yield: 100%; $[\alpha]_{Hg}$ −15 (*c*1.0, MeOH); ^{1}H NMR (D_2O) δ 4.17–4.07 (m, 1H, H_1), 4.11 (ddd, 1H, $J_{3,2a}=8.4$ Hz, $J_{3,2b}=2.8$ Hz, $J_{3,4}=2.6$ Hz, H_3), 4.01–3.91 (m, 1H, H_6), 3.87 (dd, 1H, $J_{4,3}=2.6$ Hz, $J_{4,5}=8.8$ Hz, H_4), 3.83 (dd, 1H, $J_{5,4}=8.8$ Hz, $J_{5,6}=2.0$ Hz, H_5), 2.13–1.92 (m, 3H, $H_{2a,7a,8a}$), 1.91 (ddd, 1H, $J_{2b,1}=3.7$ Hz, $J_{2b,2a}=14.6$ Hz, $J_{2b,3}=2.8$ Hz, H_{2b}), 1.71–1.45 (m, 2H, $H_{7b,8b}$); ^{13}C NMR (D_2O) δ 76.0, 75.6 ($C_{5,4}$), 74.0 (C_1), 72.5, 69.7 ($C_{3,6}$), 42.0 (C_2), 34.0, 29.4 ($C_{7,8}$); HRMS for $C_8H_{17}O_5$ ($M^+ +1$): calcd 210.1341; found 210.1344.

4.9.3. (1*S*,2*R*,3*R*,4*S*,6*S*)-Cyclooctane-1,2,3,4,6-pentol (39). Isolated yield: 100%; $[\alpha]_{Hg}=+11$ (*c*1.0, MeOH); ^{1}H NMR (D_2O) δ 3.97 (ddd, 1H, $J_{1,2a}=3.8$ Hz, $J_{1,8a}=5.6$ Hz, $J_{1,8b}=9.4$ Hz, H_1), 3.76 (ddd, 1H, $J_{6,5}=7.8$ Hz, $J_{6,7a}=3.0$ Hz, $J_{6,7b}=7.1$ Hz, H_6), 3.67 (ddd, 1H, $J_{3,2a}=8.4$ Hz, $J_{3,2b}=4.8$ Hz, $J_{3,4}=8.4$ Hz, H_3), 3.43 (dd, 1H, $J_{4,3}=J_{4,5}=8.4$ Hz, H_4), 3.40 (dd, 1H, $J_{5,4}=8.4$ Hz, $J_{5,6}=7.8$ Hz, H_5), 2.10 (dddd, 1H, $J_{8a,1}=5.6$ Hz, $J_{8a,8b}=14.4$ Hz, $J_{8a,7a}=13.0$ Hz, $J_{8a,7b}=2.8$ Hz, H_{8a}), 2.03–1.94 (m, 2H, $H_{2a,2b}$), 1.93 (dddd, 1H, $J_{7a,6}=3.0$ Hz, $J_{7a,7b}=15.8$ Hz, $J_{7a,8a}=13.0$ Hz, $J_{7a,8b}=3.4$ Hz, H_{7a}), 1.71 (dddd, 1H, $J_{7b,6}=7.1$ Hz, $J_{7b,7a}=15.8$ Hz, $J_{7b,8a}=2.8$ Hz, $J_{7b,8b}=6.0$ Hz, H_{7b}), 1.44 (dddd, 1H, $J_{8b,1}=9.4$ Hz, $J_{8b,8a}=14.4$ Hz, $J_{8b,7a}=3.4$ Hz, $J_{8b,7b}=6.0$ Hz, H_{8b}); ^{13}C NMR (D_2O) δ 77.1 (C_4), 76.2 ($C_{5,6}$), 75.7 (C_3), 70.1 (C_1), 42.4 (C_2), 32.4 (C_8), 29.4 (C_7); HRMS for $C_8H_{17}O_5$ ($M^+ +1$): calcd 210.1341; found 210.1339.

4.9.4. (1*S*,2*R*,3*R*,4*S*,6*R*)-Cyclooctane-1,2,3,4,6-pentol (40). Isolated yield: 95%; $[\alpha]_{Hg}$ +16 (*c*1.0, MeOH); ^{1}H NMR (D_2O) δ 4.20–4.06 (m, 1H, H_1), 3.93–3.80 (m, 1H, H_3), 3.72–3.55 (m, 1H, H_6), 3.60 (dd, 1H, $J_{4,3}=J_{4,5}=8.4$ Hz, H_4), 3.48 (dd, 1H, $J_{5,4}=J_{5,6}=8.4$ Hz, H_5), 2.16–1.65 (m, 6H, $H_{2a,2b,7a,7b,8a,8b}$); ^{13}C NMR (D_2O) δ 77.0 (C_4), 76.2 (C_5), 75.9 (C_6), 74.6 (C_3), 68.8 (C_1), 39.0 (C_2), 32.0 (C_7), 28.9 (C_8); HRMS for $C_8H_{17}O_5$ ($M^+ +1$): calcd 210.1341; found 210.1344.

4.10. Deprotection of the aminocyclooctanols

The substrate (0.43 mmol) was stirred in a 9:1 solution of trifluoroacetic acid/H_2O at 20 °C for 15 h. After concentration in vacuo, the resulting oily residue was triturated in diethyl ether and the supernatant was discarded to afford a brownish solid which was then purified by ion-exchange chromatography (Dowex® 50×8-100, 1% aqueous ammonium hydroxide).

4.10.1. (1*R*,2*R*,3*R*,4*R*)-6-(2-Hydroxyethylamino)-cyclooctane-1,2,3,4-tetrol (44). Isolated yield: 60% (unseparable 4:1 mixture of 6*S*:6*R* epimers); ^{1}H NMR (D_2O) δ 4.30 (ddd, 1H, $J_{3,2a}=8.6$ Hz, $J_{3,2b}=J_{3,4}=2.5$ Hz, H_3), 4.12 (ddd, 1H, $J_{6,5}=1.7$ Hz, $J_{6,7a}=5.5$ Hz, $J_{6,7b}=6.8$ Hz, H_6), 3.90 (dd, 1H, $J_{4,3}=2.5$ Hz, $J_{4,5}=7.7$ Hz, H_4), 3.83 (dd, 1H, $J_{5,4}=7.7$ Hz, $J_{5,6}=1.7$ Hz, H_5), 3.72 (dd, 1H, $J_{2',1'a}=J_{2',1'b}=5.6$ Hz, $H_{2'}$), 3.03–2.97 (m, 1H, H_1), 2.91–2.81 (m, 2H, $H_{1'}$), 2.06 (ddd, 1H, $J_{2a,1}=3.5$ Hz, $J_{2a,2b}=14.5$ Hz, $J_{2a,3}=8.6$ Hz, H_{2a}), 1.89–1.70 (m, 3H, $H_{7a,7b,8a}$), 1.74 (ddd, $J_{2b,1}=9.1$ Hz, $J_{2b,2a}=14.5$ Hz, $J_{2b,3}=2.5$ Hz, H_{2b}), 1.70–1.60 (m, 1H, H_{8b}); ^{13}C NMR (D_2O) δ 76.4 ($C_{4,5}$), 74.3 (C_6), 71.2 (C_3), 62.7 ($C_{2'}$), 58.5 (C_1), 50.3 ($C_{1'}$), 38.0 (C_7), 31.7, 29.9 ($C_{1,8}$); HRMS for $C_{10}H_{22}NO_5$ ($M^+ +1$): calcd 236.1498; found 236.1492.

4.10.2. (1*R*,2*R*,3*R*,4*R*)-6-(2-Hydroxy-1-hydroxymethyl-ethylamino)-cyclooctane-1,2,3,4-tetrol (45). Isolated yield: 63% (unseparable 4:1 mixture of 6*S*:6*R* epimers); ^{1}H NMR (D_2O) δ 4.38–4.30 (m, 1H, H_3), 4.22–4.12 (m, 1H, H_6), 3.96 (dd, 1H, $J_{4,3}=1.7$ Hz, $J_{4,5}=7.8$ Hz, H_4), 3.88 (dd, 1H, $J_{5,4}=7.8$ Hz, $J_{5,6}=1.4$ Hz, H_5), 3.80–3.60 (m, 4H, $H_{1',3'}$), 3.12–3.00 (m, 1H, H_1), 2.98–2.88 (m, 1H, $H_{2'}$), 2.13–1.98 (m, 1H, H_{2a}), 1.83–1.60 (m, 5H, $H_{2b,7a,7b,8'a,8'b}$); ^{13}C NMR (D_2O) δ 76.5, 76.2 ($C_{4,5}$), 74.3 (C_6), 71.1 (C_3), 64.5, 63.7 ($C_{1',3'}$), 59.4 ($C_{2'}$), 52.3 (C_1), 38.7 (C_7), 31.8, 30.9 ($C_{1,8}$); HRMS for $C_{11}H_{24}NO_6$ ($M^+ +1$): calcd 265.1604; found 265.1600.

4.10.3. (1*S*,2*R*,3*R*,4*S*)-6-(2-Hydroxyethylamino)-cyclooctane-1,2,3,4-tetrol (48). Isolated yield: 31% (unseparable 3:1 mixture of 6*S*:6*R* epimers); ^{1}H NMR (D_2O) δ 3.88–3.50 (m, 4H, $H_{3,4,5,6}$), 3.50–3.30 (m, 1H, $H_{2'}$), 2.95–2.73 (m, 3H, $H_{1,1'}$), 2.28–2.08 (m, 1H, H_{2a}), 2.08–1.80 (m, 4H, $H_{2b,7a,7b,8a}$), 1.80–1.60 (m, 1H, H_{8b}); ^{13}C NMR (D_2O) δ 78.3, 77.4 ($C_{4,5}$), 77.1, 76.6 ($C_{3,6}$), 63.2 ($C_{2'}$), 57.3 (C_1), 50.4 ($C_{1'}$), 39.1 (C_7), 30.1, 29.4 ($C_{1,8}$); HRMS for $C_{10}H_{22}NO_5$ ($M^+ +1$): calcd 236.1498; found 236.1492.

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References and notes

1. Varki, S. A. *Glycobiology* **1993**, *3*, 97–130.
2. Roth, J. *Chem. Rev.* **2002**, *102*, 285–303.
3. Chrispeels, M.; Hindsgaul, O.; Paulson, J. C.; Lowe, J.; Manzi, A.; Powell, L.; van Halbeek, H. In *Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G. G., Marth, J., Eds.; Cold Spring Harbor Laboratory: Cold Spring Harbor, New York, 1999.
4. Puri, A.; Rawat, S. S.; Lin, H-M. J. ; Finnegan, C. M.; Mikovits, J.; Ruscetti, F. W.; Blumenthal, R. *AIDS* **2004**, *18*, 849–858.
5. Feizi, T. In Earnst, B., Hart, G. W., Sinay, P., Eds.; Glycobiology of AIDS in Carbohydrates in Chemistry and Biology; Wiley-VCH Verlag GmbH: D-69469 Weinheim, 2000; 52, Chapter 52, pp 851–866.
6. Rudd, P. M.; Dwek, R. A. *Crit. Rev. Biochem. Mol. Biol.* **1997**, *32*, 1–100.
7. Van den Steen, P.; Rudd, P. M.; Dwek, R. A.; Opddenakker, G. *Crit. Rev. Biochem. Mol. Biol.* **1998**, *33*, 151–208.

8. Lis, H.; Sharon, N. *Eur. J. Biochem.* **1993**, *218*, 1–27.
9. Bill, R.; Revers, L.; Wilson, I. B. H. *Protein Glycosylation*; Klumer Academic: Boston, 1998.
10. Hirschberg, C. B.; Snider, M. D. *Annu. Rev. Biochem.* **1987**, *56*, 63–87.
11. Kornfeld, R.; Kornfeld, S. *Annu. Rev. Biochem.* **1985**, *54*, 631–664.
12. Lal, A.; Pang, P.; Kalelkar, S.; Romero, P. A.; Herscovics, A.; Moremen, K. W. *Glycobiology* **1998**, *8*, 981–995 and ref. cited therein.
13. Marshall, J. J. *Adv. Carbohydr. Chem. Biochem.* **1974**, *30*, 257–370.
14. Schmidt, D. D.; Frommer, W.; Junge, B.; Müller, L.; Wingender, W.; Truscheit, E.; Schefer, D. *Naturwissenschaften* **1977**, *64*, 535–536.
15. Truscheit, E.; Hillebrand, I.; Junge, B.; Müller, L.; Puls, W.; Schmidt, D. *Prog. Clin. Biochem. Med.* **1988**, *7*, 17–23.
16. Treadway, J. L.; Mendys, P.; Hoover, D. J. *Expert Opin Invest-Drugs* **2001**, *10*, 439–454.
17. Johnson, P. S.; Coniff, R. F.; Hoogwerf, B. J.; Santiago, J. V.; Pi-Sunyer, F. X.; Krol, A. *Diabetes Care* **1994**, *17*, 20–29.
18. (a) Schoffling, K.; Hillebrand, I. *Deutsche med. Wochenschrift* **1981**, *106*, 1083–1084. (b) Chiasson, J. L.; Josse, R. G.; Hunt, A. H.; Palmason, C.; Roger, N. W.; Ross, S. A.; Ryan, E. A.; Tan, M. H.; Wolever, T. M. S. *Ann. Interm. Med.* **1994**, *121*, 928–935.
19. (a) Kobatake, T.; Matsuzawa, Y.; Tokunaga, K.; Fujioka, S.; Kawamoto, T.; Keno, Y.; Inui, Y.; Odaka, H.; Matsuo, T.; Tarui, S. *Int. J. Obesity* **1989**, *13*, 147–154. (b) Matsuo, T.; Odaka, H.; Ikeda, H. *Am. J. Clin. Nutr.* **1992**, *55*, 3145–3175. (c) Holman, R. R.; Cull, C. C.; Tyrner, R. C. *Diabetes Care* **1999**, *22*, 960–964.
20. (a) Lembcke, B.; Folsch, U. R.; Creutzfeldt, W. *Digestion* **1985**, *31*, 120–127. (b) Hillebrand, I.; Boehme, K.; Graefe, K. H.; Wehling, K. *Klinische Wochenscrift* **1985**, *64*, 393–396. (c) Matsumoto, K.; Yano, M.; Miyake, S.; Ueki, Y.; Yamaguchi, Y.; Akazawa, S.; Tominaga, Y. *Diabetes Care* **1998**, *21*, 256–260.
21. (a) Stütz, A. E. *Iminosugars as Glycosidane Inhibitors*; Wiley-VCH: Weinheim, 1999. (b) Chapleur, Y. *Carbohydrates Mimics, Concepts and Methods*; Wiley-VCH: Weinheim, 1998.
22. Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553 and ref. cited therein.
23. (a) Shibata, T.; Nakayama, O.; Tsurumi, Y.; Okuhara, M.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1988**, *41*, 296–301. (b) Kayakiri, H.; Nakamura, K.; Takase, S.; Setoi, H.; Uchida, I.; Terano, H.; Hashimoto, M.; Tada, T.; Koda, S. *Chem. Pharm. Bull.* **1991**, *39*, 2807–2812. (c) Tsuji, E.; Muroi, M.; Shiragami, N.; Takatsuki, A. *Biochem. Biophys. Res. Commun.* **1996**, *220*, 459–466.
24. Chen, X.; Fan, Y.; Zheng, Y.; Chen, Y. *Chem. Rev.* **2003**, *103*, 1955–1977.
25. Mehta, G.; Ramesh, S. S. *Chem. Commun.* **2000**, 2429–2430.
26. Gravier-Pelletier, C.; Maton, W.; Dintinger, T.; Tellier, C.; le Merrer, Y. *Tetrahedron* **2003**, *59*, 8705–8720.
27. For C8-cyclitols or analogs synthesis, see for example: (a): Hanna, I.; Ricard, L. *Org. Lett.* **2000**, *2*, 2651–2654. (b) Wang, W.; Zhang, Y.; Sollogoub, M.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2466–2467. (c) van Hooft, P. A. V.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 1769–1772. (d) van Hooft, P. A. V.; Litjens, E. J. N.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Org. Lett.* **2001**, *3*, 731–733. (e) McNulty, J.; Grunner, V.; Mao, J. *Tetrahedron Lett.* **2001**, *42*, 5609–5612. (f) Boyer, F.-D.; Hanna, I.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 4094–4096. (g) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2002**, *67*, 3705–3717. (h) Blériot, Y.; Giroult, A.; Mallet, J.-M.; Rodriguez, E.; Vogel, P.; Sinaÿ, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2553–2565. (i) Mehta, G.; Pallavi, K. *Chem. Commun.* **2002**, 2828–2829. (j) Paquette, L. A.; Zhang, Y. *Org. Lett.* **2005**, *7*, 511–513.
28. Preliminary results (a): Gravier-Pelletier, C.; Andriuzzi, O.; Le Merrer, Y. *Tetrahedron Lett.* **2002**, *43*, 245–248. b Andriuzzi, O.; Gravier-Pelletier, C.; Le Merrer, Y. *Tetrahedron Lett.* **2004**, *45*, 8043–8046.
29. For recent reviews on olefin metathesis, see (a): Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043.
30. For cyclooctene by RCM synthesis, see for example Ref. 11a, b,e–h and: (a) : Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 725–728. (b) Krafft, M. E.; Cheung, Y. Y.; Abboud, K. A. *J. Org. Chem.* **2001**, *66*, 7443–7448. (c) Kariuki, B. M.; Owton, W. M.; Percy, J. M.; Pintat, S.; Smith, C. A.; Spencer, N. S.; Thomas, A. C.; Watson, M. *Chem. Commun.* **2002**, 228–229. (d) Michaut, A.; Miranda-Garcia, S.; Menédez, J. C.; Rodriguez, J. *Org. Lett.* **2004**, *6*, 3075–3078. (e) Braddock, D. C.; Cansell, G.; Hermitage, S. A.; White, A. J. P. *Tetrahedron: Asymmetry* **2004**, *15*, 3123–3129. (f) Michalak, K.; Michalak, M.; Wicha, J. *Tetrahedron Lett.* **2005**, *46*, 1149–1153.
31. Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109.
32. Le Merrer, Y.; Duréault, A.; Greck, C.; Micas-Languin, D.; Gravier, C.; Depezay, J.-C. *Heterocycles* **1987**, *25*, 541–547.
33. Sanière, M.; Le Merrer, Y.; Barbe, B.; Koscielniak, T.; Micas-Languin, D.; Dumas, J.; Depezay, J.-C. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 614–616.
34. Poitout, L.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1995**, *36*, 6887–6890.
35. The low yield obtained for this reaction is due to competitive *O*-cyclisation involving the alcoholate resulting from the nucleophilic opening of a single epoxide moiety, see Ref. 34.
36. Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 5382–5390.
37. Brown, J. M.; Kim, K.-W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc* **1986**, *108*, 6761–6763.
38. A modification of the diastereoselectivity was tentatively carried out in the presence of bulky borane such as 9-BBN or catechol borane, but revealed unsuccessful.
39. The NMR description are related to numbering of the corresponding compounds 10 shown in Figure 2.
40. Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem. Eur. J.* **2000**, *6*, 1840–1846.
41. Araki, K.; Suenaga, K.; Sengoku, T.; Uemura, D. *Tetrahedron* **2002**, *58*, 1983–1995.
42. Jones, T. H.; Blum, M. S. *Tetrahedron Lett.* **1981**, *22*, 4373–4377.
43. The bis-*O*-TBDMS-serinol was prepared from commercially available serinol: TBDMSCl, Et_3N, DMAP, CH_2Cl_2.
44. Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *53*, 2552–2554.
45. A known protocol was applied (a) : Saul, R.; Chambers, J. P.; Molyneux, R. J.; Elbein, A. D. *Arch. Biochem. Biophys.* **1983**, *221*, 593–597. Brandi, A.; Cicchi, S.; Codero, F. M.; Frignoli,

B.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806–6812. We verified that the delay of inhibitor/enzyme incubation did not affect the inhibition measurements. Under standard conditions optimal inhibitory activities were measured after five minutes of incubation.

46. For these enzymes, the biological tests have been carried out as explained in: Gavier-Pelletier, C.; Maton, W.; Dintinger, I.; Tellier, C.; Le Merrer, Y. *Tetrahedron* **2003**, *59*, 8705–8720.
47. Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Méndez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259–1261.

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An in-depth look at the effect of Lewis acid catalysts on Diels–Alder cycloadditions in ionic liquids

Guadalupe Silvero,[a,*] María José Arévalo,[b] José Luis Bravo,[a] Martín Ávalos,[b] José Luis Jiménez[b] and Ignacio López[b]

[a]*Departamento de Química Orgánica, Universidad de Extremadura, Cáceres E-10071, Spain*
[b]*Departamento de Química Orgánica, Universidad de Extremadura, Badajoz E-06071, Spain*

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Abstract—The present work explores in detail the Diels–Alder reaction between cyclopentadiene and a series of dienophiles, performed in an innovative medium such as an ionic liquid. The potential activation of different Lewis acid catalysts and their load effect when used in combination with this solvent have been explored, in order to settle the improvement on rates and selectivities.

1. Introduction

Cycloadditions and, especially the Diels–Alder reaction, represent the favourite protocol to synthesise six-membered carbo- or heterocycles, which are otherwise ubiquitous in natural products. It is not by chance that the Diels–Alder reaction has emerged as the most versatile tool in organic synthesis and its robustness proved with a large and heterogeneous variety of solvents, catalysts, and reaction conditions, which often lead to significant accelerations and selectivity changes.[1]

For more than a decade, cycloaddition reactions have been a dominant research topic in our laboratories,[2] although our interest has increasingly moved forward and upward to the research of cleaner methodologies. Thus, both Diels–Alder and Michael reactions have been studied under microwave activation,[3,4] often catalysed by clays and other non-pollutant minerals under solventless conditions.[3–5] Likewise, we have now turned our attention to room-temperature ionic liquids (RTILs), which have experienced an impressive development in a record time.[6]

In recent years, RTILs have emerged as exciting reaction media for a wide variety of organic processes.[6]

There is a certain controversy on the non-innocent nature of ionic liquids, particularly those containing $AlCl_4$ and PF_6 anions.[7] Thus, it has been reported that, under certain conditions, hydrolysis of the PF_6 anion produces hydrogen fluoride.[8] Moreover, under basic conditions some RTILs may likely form carbenes and, in high-energy conditions such as those provided by thermal or sonochemical activation, haloalkanes can also be generated.[9] Despite the above considerations, and when compared with most organic solvents, RTILs are certainly greener.[6h,10,11] This is due to some key properties: (a) their negligible vapour pressure, and (b) the usual potentiality of recovering and recycling.

Although some ionic liquids (ILs) have already been utilised in cycloaddition chemistry,[12] most studies simply suggest that they constitute a suitable medium in terms of reaction rates and practical work-up. Herein, we describe the effect of a series of Lewis acids on Diels–Alder reactions performed in a typical alkyl imidazolium ionic liquid. In a subsequent paper, we also report on the synergic effect of that ionic liquid with mineral supports and, especially, when activated by microwave irradiation.

2. Results and discussion

For this study, 1-hexyl-3-methylimidazolium tetrafluoroborate, [HMI][BF_4], was chosen as a representative ionic liquid. The various reasons for this choice are: (a) it has no Lewis acid character, hence it would not interfere with the catalyst study, (b) it is moisture stable, thus simplifying its handling, (c) it allows simple and quantitative extraction of the products with diethyl ether, and, (d) it is accessible in terms of both ease and cost of preparation. Moreover, it is

Keywords: Lewis acid; Diels–Alder cycloaddition; Ionic liquids.
* Corresponding author. Tel.: +34 927 257 158; fax: +34 927 257 110; e-mail: gsilvero@unex.es

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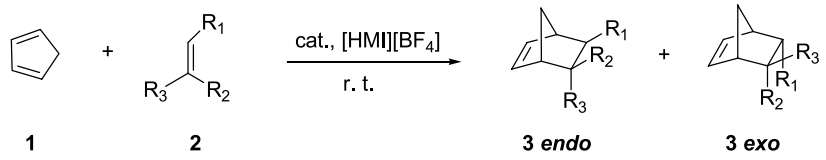


Scheme 1.

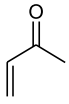
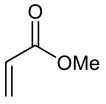
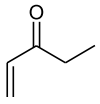
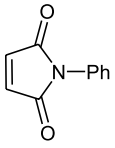
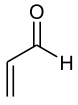
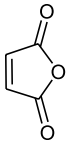
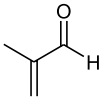
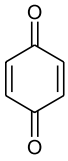
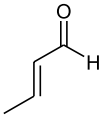
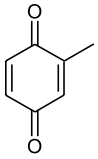
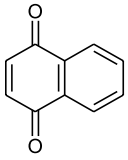
synthesised in a simple two-step procedure; the first step being the alkylation of an amine to obtain the halide salt, and the second an anion metathesis.

In previous works, it has been established that not only Lewis acidic ionic liquids,[13] but also non-Lewis acidic RTILs exert a catalytic effect on Diels–Alder reactions.[12] Even a catalytic amount of an ionic liquid is capable of inducing activation.[12b] In the light of the results reported, we studied the Diels–Alder reaction between cyclopentadiene (CPD) and several dienophiles encompassing the use of [HMI][BF_4] with the addition of Lewis acid catalysts (Scheme 1).

At a first stage of this research, several dienophiles were reacted with cyclopentadiene (CPD) in the ionic liquid, with no catalyst added. The results obtained are summarised in Table 1.

The two ketones tested (exp. 1 and 2) gave moderate results, while among the aldehydes, acrolein reacted similarly (exp. 3), but methacrolein and crotonaldehyde did not react at all (exp. 4 and 5 respectively). Acrylonitrile and methyl acrylate underwent low transformations in one hour (exp. 6 and 7). For *N*-phenylmaleimide, maleic anhydride and 2-methyl-1,4-benzoquinone (exp. 8, 9 and 11), the results were excellent, for such reactions were completed in 5 min

Table 1. Reaction of CPD and dienophiles in [HMI][BF_4] at rt[a]

Exp.[b]	Dienophile	*t* (min)	Yield (%)[c]	*endo*:*exo*[d]	Exp.[b]	Dienophile	*t* (min)	Yield (%)[c]	*endo*:*exo*[d]
1		60	52	85:15	**7**		60	16[e]	79:21
2		60	54	88:12	**8**		5	94	100:0
3		120	59	77:23	**9**		5	90	100:0
4		120	0	—	**10**		30	80	97:3[f]
5		120	0	—	**11**		5	88	100:0
6		60	17[e]	66:34	**12**		30	81	100:0

[a] 2.2 mmol of CPD +2.0 mmol of dienophile in 2 mL [HMI][BF_4].
[b] Experiment number. All different experiments in this paper are given one number, regardless the Table in which they appear, for the ease of comparison. Results correspond to, at least, duplicate runs.
[c] Isolated yield.
[d] Determined by ^{1}H NMR (400 MHz).
[e] Not isolated, estimated by ^{1}H NMR (400 MHz).
[f] Monoadduct and bisadduct ratio.

Table 2. Reaction of CPD and MVK with catalyst (0.5 mol%) in [HMI][BF_4] at rt[a]

Exp.	Catalyst (0.5 mol%)	5 min		60 min	
		Conversion (%)[b]	*endo*:*exo*[b]	Conversion (%)[b]	*endo*:*exo*[b]
13	Li(OTf)	15	82:18	64	86:14
14	Li(NTf_2)	15	82:18	66	86:14
15	ZnI_2	24	89:11	73	91:9
16	$AlCl_3$	24	88:12	68	84:16
17	BF_3	15	94:6	68	88:12
18	HOTf	67	90:10	>99	93:7
19	$HNTf_2$	84	93:7	>99	94:6
20	$Ce(OTf)_4 \cdot 5H_2O$[14]	>99	94:6	[c]	[c]
21	$Y(OTf)_3$	95	93:7	>99[d]	95:5
22	$Sc(OTf)_3$	95	93:7	>99[d]	95:5
23	$Sc(NTf_2)_3$	95	94:6	>99[d]	95:5
1	None	[e]	[e]	52	85:15

[a] 2.2 mmol of CPD+2.0 mmol of MVK+0.5 mol% of catalyst in 2 mL [HMI][BF_4].
[b] Determined by ^{1}H NMR (400 MHz) on, at least, two runs.
[c] Not measured, reaction was completed in 5 min.
[d] Results after 15 min.
[e] Not measured.

yielding only the *endo* isomer. Interestingly, methylbenzoquinone reacted with 100% selectivity; this is thought to be provoked by the steric hindrance caused on one side by the methyl group. 1,4-Benzoquinone produced the *endo*-monoadduct in high yield (exp. 10). 1,4-Naphthoquinone (exp. 12) gave also very good results, with a reaction time of thirty minutes and with the *endo* isomer as the sole product. For 1,2-naphthoquinone (not shown in the table), the reaction medium showed decomposition and was not further analysed.

It is well known that Diels–Alder reactions can be accelerated by Lewis acids.[1] For this reason, and at this point, we decided to study the combined influence of both an ionic liquid and a Lewis acid on these cycloadditions. The reaction between cyclopentadiene and methyl vinyl ketone (MVK) was chosen as a model due, on one hand, to the moderate yield and selectivity shown in the reaction with the ionic liquid, so any potential improvement could easily be observed (Table 1, exp. 1). On the other hand, for comparative purposes, as Lewis acid-catalysed reactions are widely referenced in the literature. This reaction was tested with several Lewis acid catalysts, loaded initially in a 0.5 mol% ratio, in [HMI][BF_4] (Table 2).

The reactions proceeded smoothly at room temperature and were monitored until completion or 60 min, whichever first, by ^{1}H NMR. All the tested catalysts accelerated the reaction, remarkably with no loss of stereoselection. The ability of Lewis acids to increase both the reaction rate and the selectivity of the cycloaddition is known.[15] It can be seen that the cerium trifluoromethanesulphonate-catalysed reaction was quantitative in 5 min (exp. 20). *endo*:*exo* Selectivity was very good for this experiment as well (94:6, *endo*:*exo*). Also with the scandium or yttrium salts tested, reactions came to completion in a short time (15 min) with high stereoselection (exp. 21–23). Cerium, scandium and yttrium triflates (or trifluoromethanesulphonates) are strong Lewis acids known to be quite effective catalysts in the cycloadditions of cyclopentadiene with acyclic aldehydes, ketones, quinones and cycloalkenones.[1,16] These compounds are expected to act as strong Lewis acids because of their hard character and the electron-withdrawing triflate group.

Table 3. Reaction of CPD and MVK with catalyst (0.2 mol%) in [HMI][BF_4] at rt[a]

Exp.	Catalyst (0.2 mol%)	60 min		180 min	
		Conversion (%)[b]	*endo*:*exo*[b]	Conversion (%)[b]	*endo*:*exo*[b]
24	Li(OTf)	60 (64)	84:16	93	86:14
25	Li(NTf_2)	58 (66)	87:13	85	86:14
26	ZnI_2	68 (73)	86:14	93	87:13
27	$AlCl_3$	67 (68)	88:12	89	90:10
28	BF_3	68 (68)	84:16	84	84:16
29	HOTf	61 (>99)	82:18	87	85:15
30	$HNTf_2$	72 (>99)	86:14	87	88:12
31	$Ce(OTf)_4 \cdot 5H_2O$[14]	> 99 (>99[c])	94:6	[d]	[d]
32	$Y(OTf)_3$	90 (>99[e])	93:7	[f]	[f]
33	$Sc(OTf)_3$	96 (>99[e])	92:8	[f]	[f]
34	$Sc(NTf_2)_3$	95 (>99[e])	93:7	[f]	[f]
1	None	52	85:15	78	83:17

[a] 2.2 mmol of CPD +2.0 mmol of MVK +0.2 mol% of catalyst in 2 mL [HMI][BF_4].
[b] Determined by ^{1}H NMR (400 MHz) on, at least, two runs; results with 0.5 mol% shown into brackets for comparison.
[c] Result after 5 min.
[d] Not measured, reaction was completed in 5 min.
[e] Results after 15 min.
[f] Not measured, reaction was completed in 15 min.

Table 4. Isolated yields after work up of reactions of CPD and MVK

Entry	Catalyst	Load (mol%)	t (min)	Isolated yield %	*endo*:*exo*[a]
a	$Ce(OTf)_4 \cdot 5H_2O$	0.5	5	98	94:6
b	$Ce(OTf)_4 \cdot 5H_2O$	0.2	60	97	94:6
c	$Y(OTf)_3$	0.5	15	96	95:5
d	$Y(OTf)_3$	0.2	60	85	93:7
e	$Sc(OTf)_3$	0.5	15	98	95:5
f	$Sc(OTf)_3$	0.2	60	92	92:8
g	$Sc(NTf_2)_3$	0.5	15	98	95:5
h	$Sc(NTf_2)_3$	0.2	60	90	93:7

[a] Determined by ^{1}H NMR on the isolated product.

On the other hand, it took one hour for complete transformation when either triflic or triflamic acids were used, resulting also in a good *endo*:*exo* ratio, (exp. 18 and 19). The rest of the Lewis acids tested (exp. 13–17), showed catalytic activity, yet not as good as the ones previously described. Enhancement of *endo*:*exo* ratio was achieved in some cases, compared with exp. 1. It is known that traditional Lewis acids are sensitive to water, and therefore they turn inactive when used in lower quantity than the residual water content of the reaction medium. This could account for the poor catalytic activity shown in some experiments.

At this stage, we turned our attention to the catalyst load. Although a catalyst loading of 0.5 mol% is quite low, and typical $Sc(OTf)_3$ loadings range from 5 to 15 mol%, we checked the activity of a 0.2 mol% load (Table 3). Eventually, this set of experiments would also allow us to distinguish among some of the catalysts that showed similar results in the previous experiments. Results obtained with 0.5 mol% load after 60 min have been included into brackets for comparative purposes.

At first glance, it is clear that the presence of the catalyst in either load does affect the reaction rates (compare with the run without catalyst, experiment 1). Although both loads accelerate the processes, this acceleration is higher with the 0.5 mol% load. For the rest of the catalysts studied the *endo*:*exo* ratio values are within the same experimental range.

Again, cerium triflate was the most active catalyst (exp. 31), with a reaction time of 60 min along with a good *endo*:*exo* ratio of 94:6. Scandium-based catalysts were next in line, with conversions over 95% in one hour, accompanied by *endo*:*exo* selectivities around 93:7 (exp. 33 and 34); yttrium triflate was a bit less active a catalyst, with 90% conversion and 93:7 *endo*:*exo* outcome in one hour (exp. 32).

It can be noted that little difference was found when comparing the two loads tested of lithium, zinc, aluminium and boron catalysts, which reinforce the idea of a possible partial deactivation due to residual water content in the ionic liquid. However since they showed some catalytic activation, compared with exp. 1, this fact suggests that some remain of the catalyst is still active in the medium.

Isolation of cycloadducts was accomplished for the best results for the two sets of reactions. Work-up consisted of the extraction of the products from the reaction media with diethyl ether and further purification by flash chromatography. This protocol afforded pure cycloadducts in excellent yields, as shown in Table 4. Isolation of the final products, following this simple procedure, proved to be quantitative for both stereoisomers.

At this point, the activity of the best reaction media found was tested against a choice of dienophiles, to broaden the scope of the protocol. As for the reaction media, two of them were selected: scandium triflate or cerium triflate, loaded in 0.5 mol% in the ionic liquid. The chosen dienophiles were representatives of three families of compounds. Hence, acrolein, acrylonitrile, and methyl acrylate were tested. Furthermore, we decided to use the two aldehydes that did not react at all in the ionic liquid; that is, methacrolein and crotonaldehyde (experiments 4 and 5, shown in Table 1). Reactions of *N*-phenylmaleimide, maleic anhydride and 2-methyl-1,4-benzoquinone were not tested with catalysts, since they gave excellent results with the ionic liquid only as solvent. Table 5 summarises the experiments undertook (methyl vinyl ketone run showed as reference). These reactions were also monitored by ^{1}H NMR until completion or 60 min, and then processed.

Table 5. Reaction of CPD and dienophile with catalyst (0.5 mol%) in $[HMI][BF_4]$ at rt[a]

Dienophile	Exp.[b]	$Ce(OTf)_4 \cdot 5H_2O$			Exp.[b]	$Sc(OTf)_3$		
		Time	Yield[c]	*endo*:*exo*[d]		Time	Yield[c]	*endo*:*exo*[d]
Methyl vinyl ketone	**20**	5 min	98	94:6	**22**	15 min	98	95:5
Acrolein	**35**	5 min	96	82:18	**40**	15 min	95	85:15
Acrylonitrile	**36**	24 h	40	63:37	**41**	24 h	50	67:33
Methyl acrylate	**37**	24 h	52	84:16	**42**	24 h	56	84:16
Methacrolein	**38**	5 min	98	87:13	**43**	30 min	97	87:13
Crotonaldehyde	**39**	30 min	60	79:21	**44**	30 min	72	79:21

[a] 2.2 mmol of CPD + 2.0 mmol of dienophile + 0.5 mol% of catalyst in 2 mL $[HMI][BF_4]$.
[b] Experiment number.
[c] Isolated yield (%).
[d] *endo*:*exo* Ratio determined by ^{1}H NMR (400 MHz) on the isolated product.

Table 6. Best results reported for the reaction of CPD and MVK in different conditions

Entry	Conditions	Time	Temperature	Yield (%)	*endo*:*exo*	Reference
a	$Sc(OTf)_3$ 10 mol%/CH_2Cl_2	12 h	0 °C	96	89:11	16c,d
b	$InCl_3$ (20 mol%)/H_2O	4 h	rt	84	87:13	17
c	CH_3ReO_3 (1%)/$CHCl_3$	1 h	rt	95	>99:1	18
d	$Sc(OSO_2C_4F_9)_3$ (5 mol%) /MS5 Å/CH_2Cl_2	3 h	−20 °C	100[a]	98:2	19

[a] Determined by GC analysis.

The most outstanding results in these experiments are those of methacrolein and crotonaldehyde; these substrates, which gave no reaction in the absence of catalyst (Table 1), are dramatically activated by either catalytic system tested. Scandium or cerium triflates gave excellent results for methyl vinyl ketone and acrolein as well. It should be noted that even acrylonitrile and methyl acrylate are catalysed under these conditions.

For the sake of comparison, Table 6 shows some of the best results published for the reaction of CPD and MVK in conditions similar to those tested in this research.

Finally, the recyclability of the medium was examined. In processes with no Lewis acid catalyst added, the ionic liquid [HMI][BF_4] was recovered and reused up to six times without loss of activity nor selectivity, after extraction with diethyl ether and drying under vacuum.

The catalytic systems using $Ce(OTf)_4 \cdot 5H_2O$ or $Sc(OTf)_3$ were also recycled and reused, extracting the products with petroleum ether. No drop of activity was observed until five runs for reactions with cerium triflate (72% transformation and 90:10 *endo*/*exo* selectivity after 5 min reaction in the fifth cycle), and ten runs for reactions with scandium triflate (89% transformation and 93:7 *endo*/*exo* selectivity after 15 min reaction in the tenth cycle), this meaning that catalyst remained within the IL after simple work-up.

3. Conclusions

In summary, several catalysts have been successfully used in the Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone in an ionic liquid. We have shown that, among several Lewis-acid catalysts, those based on Ce^{IV}, Sc^{III} or Y^{III} salts are extraordinarily active when used in [HMI][BF_4] in Diels–Alder reactions. In fact, cerium triflate performs better than any other catalyst tested, although scandium triflate is usually considered the most active in the literature.

The scope of this procedure has been extended to a wide variety of dienophiles. The combination of 1-hexyl-3-methylimidazolium tetrafluoroborate with cerium triflate, as well as with scandium triflate, gave excellent results not only in terms of reaction rates, but also in enhanced stereoselection. This protocol competes favourably with others reported previously.

It is possible to recycle IL medium up to six runs without any loss of activity. Catalytic systems consisting on $Sc(OTf)_3$ plus [HMI][BF_4] and $Ce(OTf)_4 \cdot 5H_2O$ plus [HMI][BF_4] can also be recycled and reutilised after extraction of the products for at least five times without loss of activity and *endo*/*exo* selectivity.

Further investigation on the application of this novel methodology along with non-conventional activation technologies is currently under way in our lab. A series of preliminary results obtained with other techniques are to be presented in a future paper.

4. Experimental

4.1. General

All organic solvents were purchased from commercial sources and used as received or dried using standard procedures. All chemicals were used as purchased from Aldrich or Acros except cyclopentadiene that was cracked from dicyclopentadiene (Aldrich) and then freshly distilled before use. Melting points were determined on Gallenkamp and/or Electrothermal apparatus. Analytical TLC were performed on precoated Merck 60 GF_{254} silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. Flash chromatography[20] was performed on Merck 60 silica gel (230–400 mesh). IR spectra were recorded in the range 4000–600 cm^{-1} on an FT-IR MIDAC spectrophotometer. Solid samples were recorded on KBr (Merck) pellets and liquid samples as a film between NaCl plates (Spectra-Tech). ^1H and ^{13}C NMR spectra were recorded on a Bruker AM400 instrument at 400 and 100 MHz, respectively in $CDCl_3$. TMS was used as the internal standard ($\delta = 0.00$ ppm). Ionic chromatographic analysis were recorded on an Ion Chromatograph DIONEX, DX-120 with suppressor column ASRS-ULTRA (4 mm), equipped with an AS-HC anion analytical column (4 mm) and an AG-9-HC guard column (4 mm) and performed by CTAEX Laboratories, Badajoz (Spain) following a previously described procedure.[21]

4.1.1. Preparation of 1-hexyl-3-methylimidazolium chloride [HMI][Cl]: the Menschutkin reaction.[22] The amine, 1-methylimidazol, (1 equiv) is mixed with 1-chlorohexane (1.2 equiv) and the homogeneous phase is heated to 80 °C under stirring for 2 days. After completion, the excess of haloalkane is decanted and the halide salt obtained is washed thoroughly with dry diethyl ether. The solvent is decanted and the liquid salt then dried under vacuum. The product is a yellowish liquid of a yield of ca. 80%. IR (liquid film) ν_{max} 3139, 2931, 2859, 1634, 1571, 1465, 1168 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 10.85 (s, 1H, H-2), 7.49 (s, 1H, H-4), 7.35 (s, 1H, H-5), 4.32 (t, 2H,

$J=8.0$ Hz, N–CH_2), 4.14 (s, 3H, N–CH_3), 1.91 (m, 2H, CH_2), 1.31 (m, 6H, CH_2), 0.88 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.11 (C2), 123.43 (C4), 121.61 (C5), 49.52 (C1′), 36.06 (N–CH_3), 30.60 (C2′), 29.78 (C3′), 25.38 (C4′), 21.86 (C5′), 13.46 (C6′).

4.1.2. Preparation of 1-hexyl-3-methylimidazolium tetrafluoroborate [HMI][BF_4]: the Finkelstein reaction.[22] A solution of the [HMI][Cl] (1 equiv), $NaBF_4$ (1 equiv) and water (14 equiv) is stirred at room temperature for 48 h. The product is extracted into CH_2Cl_2 and the organic phase is then washed with successive small portions of deionised water, until no chloride ions are detected by testing with $AgNO_3$. The collected organic layer is dried over $MgSO_4$, filtered and CH_2Cl_2 is then removed on a rotary evaporator. The ionic liquid is dried by heating under vacuum for 48 h. The product is obtained in 79% yield. The water content in the ionic liquid was determined using a Karl–Fischer titrator (Aquapal(R) III, CSC Scientific Co. Inc.) and showed a value of 1000 ppm for the melt used.[23] Purity was examined using ion chromatography to check for residual chloride ion impurities.[21] The residual chloride concentration was 217 ppm. IR (liquid film) ν_{max} 3161, 3121, 2958, 2933, 2862, 1573, 1467, 1170, 1059 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.74 (s, 1H, H-2), 7.42 (s, 1H, H-4), 7.38 (s, 1H, H-5), 4.17 (t, 2H, $J=7.6$ Hz, N–CH_2), 3.94 (s, 3H, N–CH_3), 1.86 (m, 2H, CH_2), 1.32 (m, 6H, CH_2), 0.86 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.84 (C2), 123.62 (C4), 122.13 (C5), 49.80 (C1′), 35.93 (N–CH_3), 30.81 (C2′), 29.78 (C3′), 25.56 (C4′), 22.14 (C5′), 13.70 (C6′).

4.2. Typical procedure for cycloaddition reactions

A typical experimental procedure. In a flat-bottomed vial of 25 mL capacity, 2.2 mmol of freshly distilled cyclopentadiene and 2.0 mmol of dienophile were added to a mixture of 2 mL of [HMI][BF_4] and, if applicable, 0.2 or 0.5 mol% catalyst. The reaction is stirred for a given reaction time. All processes were monitored by ^{1}H NMR and/or TLC. After reported reaction time, the crude was extracted with diethyl ether (5×4 mL). The ethereal solution was reduced to half volume in a rotavapor and then filtered through a 3 cm-silica gel bed, to avoid contamination of the ionic liquid. The final adducts were isolated by evaporation of the crude mixture and, if necessary, purified by chromatography or crystallization.

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References and notes

1. Fringuelli, F.; Taticchi, A. The Diels–Alder Reaction In *Selected Practical Methods*; Wiley: Chichester, 2002.
2. (a) Areces, P.; Ávalos, M.; Babiano, R.; Cintas, P.; González, L.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C.; Silvero, G. *Eur. J. Org.* **2001**, 2135. (b) Arévalo, M. J.; Ávalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C. *Tetrahedron Lett.* **1999**, *40*, 8675. (c) Ávalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C. *Chem. Commun.* **1999**, 1589. (d) Ávalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C.; Silvero, G. *Chem. Eur. J.* **2001**, *7*, 3033. (e) Arévalo, M. J.; Ávalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C. *Tetrahedron* **2000**, *56*, 1247. (f) Arévalo, M. J.; Ávalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *Tetrahedron: Asymmetry* **2002**, *13*, 223.
3. Ávalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron Lett.* **1998**, *39*, 9301.
4. Ávalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *Green Chem.* **2001**, *3*, 26.
5. Ávalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Ranu, B. C. *Tetrahedron Lett.* **1998**, *39*, 2013.
6. (a) Zhao, H.; Malhotra, S. V. *Aldrichim. Acta* **2002**, *35*, 75. (b) Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A: Chem.* **2002**, *419*, 182–183. (c) Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, *74*, 157. (d) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667. (e) Gordon, C. M. *Appl. Catal. A* **2001**, *222*, 101. (f) Brennecke, J. F.; Maginn, E. J. *AIChE J.* **2001**, *47*, 2384. (g) Sheldon, R. *Chem. Commun.* **2001**, 2399. (h) *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH: Weinheim, 2003.
7. Dupont, J.; Spencer, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5296.
8. Swatkoski, R. P.; Holbrey, J. D.; Rogers, R. D. *Green Chem.* **2003**, *5*, 361.
9. (a) Oxley, J. D.; Prozorov, T.; Suslick, K. S. *J. Am. Chem. Soc.* **2003**, *125*, 11138. (b) Kumar Sur, U.; Marken, F.; Coles, B. A.; Compton, R. G.; Dupont, J. *Chem. Commun.* **2004**, 2816.
10. Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3772.
11. Wasserscheid, P.; van Hal, R.; Bösmann, A. *Green Chem.* **2002**, *4*, 400.
12. (a) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785. (b) Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097. (c) Lee, C. W. *Tetrahedron Lett.* **1999**, *40*, 2461. (d) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793. (e) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, *1*, 23. (f) Song, C. E.; Shim, W. H.; Roh, E. J.; Lee, S.; Choi, J. H. *Chem. Commun.* **2001**, 1122. (g) Ludley, P.; Karodia, N. *Tetrahedron Lett.* **2001**, *42*, 2011. (h) Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Green Chem.* **2002**, *4*, 24. Meracz, I.; Oh, T. *Tetrahedron Lett.* **2003**, *44*, 6465. (i) Xiao, Y.; Malhotra, S. V. *Tetrahedron Lett.* **2004**, *45*, 8339. (j) Doherty, S.; Goodrich, P.; Hardacre, C.; Luo, H.-K.; Rooney, D. W.; Seddon, K. R.; Styring, P. *Green Chem.* **2004**, *6*, 63.

13. (a) Lee, C. W. *Tetrahedron Lett.* **1999**, *40*, 2461. (b) Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Green Chem.* **2002**, *4*, 24.
14. The water content for commercial (Aldrich) samples of $Ce(OTf)_4 \cdot nH_2O$ was determined to be $5 \leq n \leq 6$ by Laali et al.: Laali, K. K.; Herbert, M.; Cushnyr, B.; Bhatt, A.; Terrano, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 578.
15. (a) Branchadell, V.; Oliva, A.; Bertran, J. *J. Mol. Struct. (Theochem)* **1986**, *138*, 117. (b) Epiotis, N. D.; Shaik, S. *J. Am. Chem. Soc.* **1978**, *100*, 1.
16. (a) Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815. (b) Keshevaraja, A.; Hegde, V. R.; Pandey, B.; Ramaswamy, A. V.; Kumar, P.; Rabindranathan, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2143. (c) Kobayashi, S. *Synlett* **1994**, 689. (d) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755.
17. (a) Loh, T.-P.; Pei, J.; Lin, M. *Chem. Commun.* **1996**, 2315. Corrigendum: (b) *Chem. Commun.* **1996**, 2315.
18. Zhu, Z.; Espenson, J. H. *J. Am. Chem. Soc.* **1997**, *119*, 3507.
19. Kobayashi, S.; Tsuchiya, T.; Komoto, I.; Matsuo, J. *J. Organomet. Chem.* **2001**, *624*, 392.
20. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
21. Villagrán, C.; Deetlefs, M.; Pitner, W. R.; Hardacre, C. *Anal. Chem.* **2004**, *76*, 2118.
22. This synthesis was accomplished by a method adapted from the general procedure described in Ref. 6h (pp 7–19).
23. Mendam, J.; Dennery, R. C.; Barnes, J. D.; Thomas, M. *Vogel's Textbook of Quantitative Chemical Analysis*, 6th ed.; Prentice Hall: Harlow, 2000.

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A new alkylation–elimination method for synthesis of antiviral fluoromethylenecyclopropane analogues of nucleosides

Shaoman Zhou and Jiri Zemlicka*

Developmental Therapeutics Program, Department of Chemistry, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI 48201-1379, USA

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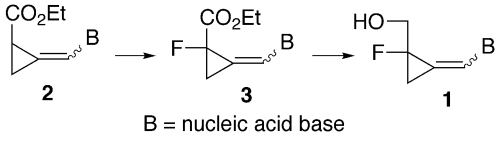
Abstract—A new method for the synthesis of fluoromethylenecyclopropane nucleosides by alkylation–elimination procedure is described. Fluorination of methylenecyclopropane carboxylate **6** gave fluoroester **7**. Treatment of **7** with phenylselenenyl bromide afforded the desired ethyl (*E*)-2-bromomethyl-1-fluoro-2-phenylselenenylcyclopropane-1-carboxylate **11** in 85% yield. DIBALH reduction of **11** gave **13**, which after acetylation to **14** was reacted with 2-amino-6-chloropurine to give the 9-alkylated product **15** in 87% yield. Se-oxidation of **15** with hydrogen peroxide afforded **16**, which underwent smooth elimination in a mixture of THF–DMF at 60 °C giving rise to a *Z*,*E* mixture of protected nucleosides **17**. Deacetylation gave *Z*-**1a** and *E*-**1a** which were separated on a silica gel column. Both *Z*-**1a** and *E*-**1a** were converted into the respective guanine analogues *Z*-**1b** and *E*-**1b**.

1. Introduction

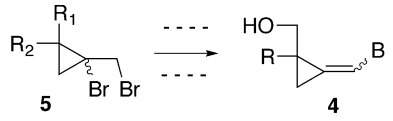
Methylenecyclopropane analogues of nucleosides are potent antivirals effective especially against human cytomegalovirus (HCMV) and Epstein Barr virus (EBV).[1,2] The anti-HCMV activity resides in the *Z*-isomers of purine analogues but both *Z*- and *E*-isomers are effective anti-EBV agents. Recently, we have described the synthesis of antiviral fluoroanalogues of methylenecyclopropanes **1** by a direct fluorination of carbanions of the respective carboxylic esters **2** and subsequent reduction of the resultant fluoroesters **3** (Scheme 1).[3] The need to prepare methylenecyclopropane esters[4,5] from individual nucleic acid bases or corresponding precursors is a substantial drawback of this procedure. In addition, the preparation of the 2-amino-6-chloropurine fluoroester **3a** from **2a** failed.[3] The presence of a reactive 2-amino-6-chloropurine moiety[6] would be of considerable advantage for the synthesis of a series of 2-amino-6-substituted purine fluoromethylenecyclopropane analogues.



Scheme 1.

2. Results and discussion

An alkylation–elimination approach proved successful for synthesis of non-fluorinated methylenecyclopropane analogues[1,2,4,5,7–10] of nucleosides **4a** and **4b** (Scheme 2). The *gem*-difluoromethylenecyclopropane analogues were obtained in a similar fashion.[11] A major advantage of this procedure is that reagents **5a**–**5c** can be used for reaction with any nucleic acid base or suitable precursor. Therefore, we became interested in applying of this approach to fluoromethylenecyclopropanes **1**. Methylenecyclopropane carboxylate[12] **6** was fluorinated with *N*-fluorobenzenesulfonimide (NFSI) via the corresponding carbanion to give



5a: $R_1 = CO_2Et$, $R_2 = H$ **4a**: R = H
5b: $R_1 = CH_2OAc$, $R_2 = H$ **4b**: $R = CH_2OH$
5c: $R_1 = R_2 = CH_2OAc$

Scheme 2.

Keywords: Alkylation–elimination; Fluoromethylenecyclopropane nucleoside analogues; Methylenecyclopropanes.
* Corresponding author. Tel.: +1 313 833 0715x2452; fax: +1 313 832 7294; e-mail: zemlicka@kci.wayne.edu

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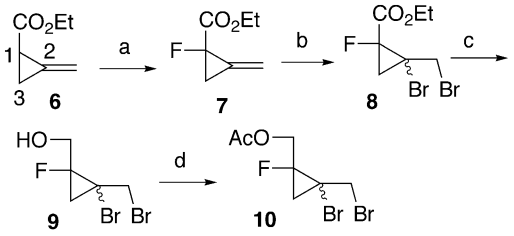
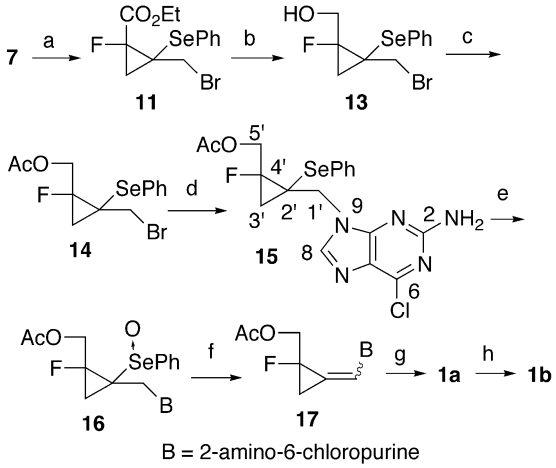


a. LDA, NFSI, LiCl, THF, -78 °C.
b. Br_2, CCl_4, 0 °C. c. DIBALH, hexanes, 0 °C.
d. Ac_2O, $NEtMe_2$.

Scheme 3.

fluoroester **7** in 62% yield[22] following the protocol for a similar fluorination[3] of esters **2** (Scheme 3). Compound **7** was successfully converted to alkylation–elimination reagents **8** and **10** using procedures described[4,5,7–9] previously for non-fluorinated methylenecyclopropanes via addition of bromine (**8**, 83%), reduction (**9**, 87%) and acetylation (**10**, 83%). Nevertheless, alkylation–elimination with adenine and reagents **8** or **10** under a variety of conditions gave either none or $<10\%$ of the expected methylenecyclopropane.

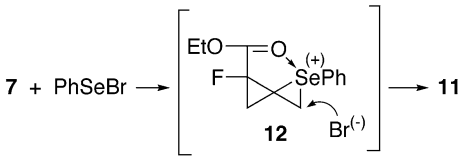
We reasoned that a strategy separating the alkylation and elimination steps could overcome this obstacle. The presence of a less reactive leaving group activated just before the elimination was considered an important requisite for success. A similar approach was employed in the synthesis of methylenecyclobutane nucleoside analogues but several steps had to be performed with intermediates containing a nucleic acid base.[13,14] The 1,2 electrophilic additions of phenylselenenyl chloride to alkenes are well-established[15,16] although they usually proceed with a limited regioselectivity.[17,18] Additions to allylic acetates which were highly regioselective form an important exception.[17] Reaction of phenylselenenyl bromide, generated in situ from NBS and diphenyl diselenide in analogy to the corresponding chloride,[19] with fluoroester **7** gave selenide **11** in 85% yield (Scheme 4). The addition was



B = 2-amino-6-chloropurine

a. NBS, Ph_2Se_2, CH_2Cl_2. b. DIBALH, THF.
c. Ac_2O, pyridine. d. 2-Amino-6-chloropurine, K_2CO_3, DMF.
e. H_2O_2, THF. f. THF - DMF (10 : 1), Δ.
g. K_2CO_3, MeOH-H_2O (9:1). h. 1. HCO_2H, Δ. 2. NH_4OH.

Scheme 4.

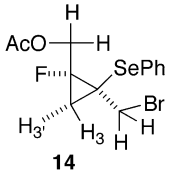


Scheme 5.

regioselective and the presence of a single stereoisomer of **11** was established by NMR. To the best of our knowledge, this is the first stereoselective addition of phenylselenenyl halide to a methylenecyclopropane system. The episelenonium ion **12** is a likely intermediate in this transformation (Scheme 5), with the carboxylic ester function playing a role similar to the acetoxy group in allylic acetates[17] by directing the addition of phenylselenenyl group to the *syn* face of double bond of fluoroester **7**. A nucleophilic attack of bromide then gave the *E* isomer of selenide **11** and reduction of **11** with DIBALH afforded the hydroxymethyl derivative **13** (88% yield). Acetylation provided acetate **14** (95%). The *E*(*trans*)-isomeric structure of **14** was confirmed by NOE. As expected, the NOE enhancements were observed between the H_3 and CH_2OAc or $H_{3'}$ and CH_2Br (Table 1).

As indicated at the outset, a direct fluorination of 2-amino-6-chloropurine ester **2a** failed. Therefore, 2-amino-6-chloropurine was chosen as a precursor of nucleobase for alkylation with acetate **14** (K_2CO_3 in DMF at rt) to give intermediate **15** in 87% yield. Oxidation with H_2O_2 in THF provided selenoxide **16** as two stereoisomers (ratio 2.4:1) in 95% yield. Mild thermolysis in THF–DMF (10:1) at 60 °C furnished (*Z*,*E*)-methylenecyclopropane acetate (76%) and deacetylation followed by chromatography afforded the *Z*- and *E*-isomers of **1a** in 45 and 41% yield, respectively. Hydrolysis of the individual isomers with formic acid gave the *Z*- and *E*-guanine analogues of **1b** (78 and 73%) which were identical with compounds prepared by a different procedure.[3] Overall yields of the *Z*- and *E*-isomers of **1b** (10.2 and 8.7% from ester **6**) are significantly improved over those obtained previously[3] (4.1 and 2.5%).

Table 1. Selected NOE data[a] of compound **14**



14

H_{irr} (δ)	H_{obs} (δ)	% NOE
H_3 (1.28)	CH_2OAc (4.57)	1.31
	CH_2OAc (4.89)	0.7
$H_{3'}$ (1.52)	CH_2Br (3.67)	0.95
	CH_2Br (3.88)	1.08
CH_2OAc (4.60)	H_3 (1.52)	1.61
CH_2Br (3.89)	H_3 (1.28)	1.41

[a] Assignments of H_3 and $H_{3'}$ were based on coupling constants $J_{H,F}$ ($J_{H,F\text{-}cis} > J_{H,F\text{-}trans}$),[20,21] see Section 4.

3. Conclusion

A method for the synthesis of fluoromethylenecyclopropane analogues based on a novel alkylation–elimination approach is reported. The yields of guanine analogues *Z*-**1b** and *E*-**1b** were improved by a factor of 2–3 over the previous protocol. It is likely that the differential reactivity of 1,2-haloselenides in alkylation–elimination will find general use in the synthesis of methylenecyclopropane analogues, especially in cases where the reaction products are less stable toward bases. The regio- and stereoselective addition of phenylselenyl halide to methylenecyclopropane carboxylate **7** may then find application in areas other than nucleoside analogues.

4. Experimental

4.1. General methods

The UV spectra were measured in ethanol and NMR spectra were determined at 300 or 400 MHz (^{1}H), 75 or 100 MHz (^{13}C) and 376 MHz (^{19}F) in CD_3SOCD_3 unless stated otherwise. For ^{19}F NMR $CFCl_3$ was used as a reference. Mass spectra were determined in electron-impact (EI-MS) or electrospray ionization (ESI-MS, methanol–NaCl) mode.

4.1.1. Ethyl 1-fluoro-2-methylenecyclopropane-1-carboxylate (7). A suspension of dried[1] LiCl and ester **6** (750 mg, 6.0 mmol) in THF (30 mL) was cooled to −78 °C. After 10 min, LDA (4.0 mL, 7.2 mmol) was added dropwise with stirring which was continued for 40 min. *N*-Fluorobenzenesulfonimide (NFSI, 2.24 g, 7.2 mmol) in THF (3 mL) was then added and, after 10 min, the reaction was quenched with aqueous NH_4Cl (15 mL). Pentane (100 mL) was added, the organic phase was washed with 5% HCl (3×25 mL) and 5% $NaHCO_3$ (3×25 mL) whereupon it was dried ($MgSO_4$). The solvents were evaporated at atmospheric pressure and the residue was chromatographed on a silica gel column (pentane–Et_2O=100:1 to 40:1) to give product **7** (540 mg, 62%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J=7.2 Hz, Me), 2.00 (tt, 1H, J=12.0, 3.2 Hz), 2.24 (dt, 1H, J=12.0, 2.8 Hz, H_3), 4.25 (m, 2H, CH_2 of Et), 5.68 (t, 1H, J=3.2 Hz), 5.86 (t, 1H, J=3.2 Hz, =CH_2). ^{13}C NMR 14.3 (CH_3), 19.6 (d, J=13.5 Hz, C_3), 62.1 (CH_2 of Et), 72.3 (d, J=236.5 Hz, C_1), 109.2 (=CH_2), 130.1 (d, J=4.5 Hz, C_2), 168.8 (d, J=27.7 Hz, C=O). ^{19}F NMR −189.9 (d, J=10.5 Hz). EI-MS 144 (M, trace), 116 (M−C_2H_4, 100.0). EI-HRMS calcd for $C_5H_5FO_2$ (M−C_2H_4) 116.0274, found 116.0277.

4.1.2. Ethyl (*Z*,*E*)-2-bromo-2-bromomethyl-1-fluorocyclopane-1-carboxylate (8). A solution of ester **7** (145 mg, 1.0 mmol) in CCl_4 (5 mL) was treated with bromine (320 mg, 2.0 mmol) at 0 °C. The reaction mixture was allowed to stand at rt for 30 min. It was diluted with EtOAc (30 mL) and washed with saturated $Na_2S_2O_3$-$NaHCO_3$ solution and water. The organic phase was dried over Na_2SO_4, solvent was evaporated and the crude product was purified by chromatography on silica gel (hexane–EtOAc = 30:1) to give product **8** as a colorless oil (254 mg, 83%). ^{1}H NMR ($CDCl_3$) δ 1.37 (2 overlapped t, 3H, J=7.2 Hz, Me), 1.83 (dd, J=19.6, 9.0 Hz), 2.05 (dd, J=15.2, 9.0 Hz) and 2.21 (dd, J=19.2, 11.6 Hz, total 2H, H_3), 3.83 (dd, J=12.8, 8.8 Hz), 3.91 (dd, J=10.4, 2.8 Hz), 4.01 (dd, J=12.4, 2.4 Hz, total 2H, CH_2Br), 4.36 (2 overlapped q, 2H, J=7.2 Hz, CH_2 of Et). ^{19}F NMR −181.6 (m), −193.9 (dd, J=18.4, 9.0 Hz). EI-MS 302, 304, 306 (1.0, 2.0, 1.0, M), 195 (100.0). EI-HRMS calcd for $C_7H_9O_2F^{79}Br_2$ (M) 301.8953, found 301.8956.

4.1.3. (*Z*,*E*)-2-Bromo-2-bromomethyl-1-fluoro-1-hydroxymethylcyclopropane (9). A solution of 1 M DIBALH in hexane (1 mL, 1 mmol) was added to ester **8** (145 mg, 0.47 mmol) in hexane (5 mL) at 0 °C under N_2. The stirring was continued at rt for 3 h. The reaction was quenched by a dropwise addition of 5% HCl (10 mL) and then it was extracted with Et_2O (4×20 mL). The organic phase was washed successively with saturated $NaHCO_3$ (2×10 mL) and water (2×10 mL) and it was dried over $MgSO_4$. The solvent was evaporated and the residue was chromatographed on a silica gel column in hexane–EtOAc=5:1 to give compound **9** as a colorless oil (106 mg, 87%). ^{1}H NMR ($CDCl_3$) δ 1.45–1.79 (m, 2H, H_3), 2.39 (bs, 1H, OH), 3.71–4.32 (m, 4H, CH_2Br, CH_2OH). ^{19}F NMR −172.9, −193.4 (2m). EI-MS 73 (100.0), 242, 244, 246 (0.007, 0.014, 0.007, M−OH). ESI-MS 283, 285, 287 (47.9, 100.0, 38.6, M+Na). EI-HRMS calcd for $C_5H_6F^{79}Br_2$ (M−OH) 242.8820, found 242.8819.

4.1.4. (*Z*,*E*)-1-Acetoxymethyl-2-bromo-2-bromomethyl-1-fluorocyclopropane (10). Acetic anhydride (1 mL) was added dropwise with stirring to a solution of compound **9** (106 mg, 0.87 mmol) in *N*,*N*-dimethyl-*N*-ethylamine (3 mL) at rt. The stirring was continued for 5 h whereupon the volatile components were evaporated in vacuo and the residue was chromatographed on a silica gel column (hexanes–EtOAc=20:1) to give product **10** as a colorless oil (100 mg, 82%). ^{1}H NMR ($CDCl_3$) δ 1.47–1.82 (m, 2H, H_3), 2.13, 2.14 (2s, 3H, Me), 3.62–3.91 (m, 2H, CH_2Br), 4.37–4.81 (m, 2H, CH_2O). ^{19}F NMR −169.9, −190.5 (2m). ESI-MS 325, 327, 329 (50.6, 100.0, 49.1, M+Na).

4.1.5. Ethyl (*E*)-2-bromomethyl-1-fluoro-2-phenylselenenylcyclopropane-1-carboxylate (11). NBS (3.07 g, 17.27 mmol) and Ph_2Se_2 (5.38 g, 17.27 mmol) were added to a solution of fluoroester **7** (2.26 g, 15.7 mmol) in CH_2Cl_2 (100 mL) at −5 to 0 °C with stirring. After 35 min, the reaction was quenched with aqueous NH_4Cl (20 mL), EtOAc (200 mL) was added and the organic phase was washed with saturated $Na_2S_2O_3$–$NaHCO_3$ solution and water. The organic phase was dried over Na_2SO_4, solvent was evaporated and the residue was chromatographed on a silica gel column (hexanes–Et_2O=20:1) to give product **11** (5.1 g, 85%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3H, J=7.0 Hz, Me), 1.65 (dd, 1H, J=18.8, 8.0 Hz) and 1.84 (t, 1H, J=8.8 Hz, H_3), 3.65 (d, 1H, J=11.2 Hz), 3.84 (dd, 1H, J=11.2, 2.4 Hz, CH_2Br), 4.82 (dq, 2H, J=7.2, 2.4 Hz, CH_2O), 7.30–7.34 (m, 3H), 7.57 (dd, 2H, J=8.0, 1.6 Hz, Ph). ^{13}C NMR 14.4 (Me), 26.4 (d, J=9.7 Hz, C_3), 34.6 (d, J=9.0 Hz, C_2), 37.4 (d, J=9.7 Hz, CH_2Br), 62.7 (CH_2O), 84.9 (d, J=245.6 Hz, C_1), 127.4, 128.9, 129.6, 135.2 (Ph), 166.3 (d, J=26.2 Hz, C=O). ^{19}F NMR −191.3 (dd, J=18.3, 10.5 Hz). ESI-MS (KOAc) 379, 381, 383 (45.6, 100.0, 79.1, M+H), 417, 419, 421 (44.3,

100.0, 83.5, M+K). Anal. Calcd for $C_{13}H_{14}BrFO_2Se$: C, 41.08; H, 3.71. Found: C, 41.21; H, 3.70.

4.1.6. (*E*)-2-Bromomethyl-1-fluoro-1-hydroxymethyl-2-phenylselenenylcyclopropane (13). DIBALH in hexane (1 M, 30 mL, 30 mmol) was added to a solution of **11** (4.5 g, 11.8 mmol) in hexane (40 mL) at 0 °C with stirring during 10 min under N_2. The stirring was continued at 0 °C for 2.5 h. The reaction was quenched by a dropwise addition of 0.1 N HCl (20 mL) and the mixture was extracted with Et_2O (4×30 mL). The combined organic phase was washed successively with saturated $NaHCO_3$ (2×30 mL) and water (2×30 mL). Solvents were evaporated and the crude product was chromatographed on silica gel (hexanes–Et_2O=10:1 to 5:1) to give **13** as a colorless oil (3.51 g, 88%). ^{1}H NMR ($CDCl_3$) δ 1.24 (dd, 1H, J=10.4, 8.0 Hz), 1.49 (dd, 1H, J=20.4, 8.0 Hz, H_3), 2.08 (bs, 1H, OH), 3.69 (dd, 1H, J=11.2, 2.0 Hz), 3.90 (dd, 1H, J=11.2, 2.0 Hz, CH_2Br), 4.15 (AB, 1H, J=12.8 Hz), 4.33 (AB, 1H, J=13.4 Hz, CH_2O), 7.31–7.35 (m, 3H), 7.58 (dd, 2H, J=8.0, 1.6 Hz, Ph). ^{13}C NMR 25.7 (d, J=11.2 Hz, C_3), 33.4 (d, J=8.2 Hz, C_2), 38.6 (d, J=10.4 Hz, CH_2Br), 65.5 (d, J=23.1 Hz, CH_2O), 88.3 (d, J=232.8 Hz, C_1), 127.7, 128.8, 129.7, 134.8 (Ph). ^{19}F NMR −190.0 (m). ESI-MS 337, 339, 341 (45.6, 100.0, 78.5, M+H), 319, 321, 323 (44.9, 100.0, 78.5, M−OH). Anal. Calcd for $C_{11}H_{12}BrFOSe$: C, 39.08; H, 3.58. Found: C, 39.31; H, 3.52.

4.1.7. (*E*)-1-Acetoxymethyl-2-bromomethyl-1-fluoro-2-phenylselenenylcyclopropane (14). Acetic anhydride (0.5 mL) was added dropwise with stirring to a solution of **13** (340 mg, 1.0 mmol) in pyridine (3 mL) at rt. The stirring was continued for 16 h whereupon the reaction was quenched with water and the mixture was extracted with pentane (50 mL). The combined organic phase was washed successively with saturated $CuSO_4$, 5% HCl, aqueous $NaHCO_3$. It was dried over $MgSO_4$, the solvent was evaporated and the residue was chromatographed on a silica gel column (hexanes - Et_2O, 20:1) to give product **14** as a colorless oil (365 mg, 95%). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 1H, J=9.4 Hz, H_3), 1.52 (dd, 1H, J=19.6, 8 Hz, $H_{3'}$), 2.13 (s, 3H, Me), 3.67 (d, 1H, J=10.4 Hz), 3.88 (dt, 1H, J=10.4, 2.0 Hz, CH_2Br), 4.57 (d, 1H, J=13.2 Hz) and 4.89 (dd, 1H, J=13.2, 1.6 Hz, CH_2O), 7.32 (m, 3H) and 7.55 (dd, 2H, J=7.2, 1.6 Hz, Ph). ^{13}C NMR 21.1 (Me), 25.8 (d, J=11.3 Hz, C_3), 38.0 (d, J=10.5 Hz, CH_2Br), 66.8 (d, J=21.6 Hz, CH_2O), 85.8 (d, J=233.5 Hz), 128.8, 129.7, 134.7 (Ph), 170.9 (C=O). ^{19}F NMR −187.8 (m). EI-MS 301 (M−Br, 100.0). ESI-MS 379, 381, 383 (10.8, 23.1, 13.2, M+H), 401, 403, 405 (45.6, 100.0, 78.8, M+K). EI-HRMS calcd for $C_{13}H_{14}FO_2^{80}Se$ (M−Br) 301.0143, found 301.0145. Anal. Calcd for $C_{13}H_{14}BrFO_2Se$: C, 41.08; H, 3.71. Found: C, 41.30; H, 3.87.

4.1.8. (*E*)-2-Amino-6-chloro-9-[(2-acetoxymethyl-2-fluoro-1-phenylselenenyl)-1-cyclopropylmethyl]purine (15). A mixture of compound **14** (343 mg, 0.9 mmol), 2-amino-6-chloropurine (153 mg, 0.9 mmol) and K_2CO_3 (140 mg, 1.01 mmol) was stirred in DMF (3.5 mL) at rt for 36 h. The solid was filtered off using a silica gel pad and it was washed with DMF (60 mL). DMF was evaporated in vacuo and the residue was chromatographed on a silica gel column (CH_2Cl_2–MeOH=60:1 to 30:1) to give compound 15 as a white solid (353 mg, 87%), mp 154–155 °C. UV max 221 nm (ε 29,500), 243 (ε 7800), 310 (ε 7800). ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 1H, J=9.6 Hz), 1.87 (dd, 1H, J=20.0, 8.4 Hz, $H_{3'}$), 2.16 (s, 3H, Me), 4.10 (d, 1H, J=14.8 Hz), 4.80 (AB, 1H, J=14.4 Hz, 1.6 Hz, $H_{1'}$), 4.56 (dd, 1H, J=31.6, 12.8 Hz), 4.97 (dd, 1H, J=17.4, 13.4 Hz, $H_{5'}$), 5.13 (bs, 2H, NH_2), 7.24–7.32 (m, 3H), 7.42 (d, 2H, J=6.4 Hz, Ph), 7.90 (s, 1H, H_8). ^{13}C NMR 21.1 (Me), 23.7 (J=11.2 Hz, $C_{3'}$), 31.1 (d, J=9.0 Hz, $C_{4'}$), 46.3 (d, J=11.2 Hz, $C_{1'}$), 66.9 (d, J=21.6 Hz, CH_2O), 84.0 (d, J=231.3 Hz, $C_{4'}$), 126.9, 128.9, 129.7, 134.4 (Ph), 125.0, 142.8/split/, 151.3, 154.5, 159.3 (purine), 170.7 (C=O). ^{19}F NMR −185.7 (ddt, J=30.9, 19.9, 10.9 Hz). ESI-MS 468, 470, 472 (47.6, 100.0, 45.2, M+H), 490, 492, 494 (40.5, 81.6, 38.1, M+Na). Anal. Calcd for $C_{18}H_{17}ClFN_5O_2Se$: C, 46.12; H, 3.66; N, 14.94. Found: C, 46.03; H, 3.69; N, 14.72.

4.1.9. (*E*)-2-Amino-6-chloro-9-[(2-acetoxymethyl-2-fluoro-1-phenylselenenyl)-1-cyclopropylmethyl]purine oxide (16). Hydrogen peroxide (30%, 0.15 mL, 1.3 mmol) was added dropwise with stirring to a solution of compound **15** (350 mg, 0.74 mmol) in CH_2Cl_2 (10 mL) at rt. The stirring was continued for 2.5 h whereupon the volatile components were evaporated in vacuo to give selenoxide **16** (341 mg, 95%), mp 139–142 °C (decomp). UV max 222 nm (ε 27,900), 248 (ε 8600), 311 (ε 7500). ^{1}H NMR δ 1.62 (dd, J=20.2, 8.2 Hz), 1.98–2.11 (m, partly overlapped with Me), 2.25 (dd, J=19.2, 8.4 Hz, 2H, $H_{3'}$), 1.71, 2.03 (2s, 3H, Me), 4.17–4.55, 4.67–4.86 (2 clusters of m, 4H, $H_{1'}+H_{5'}$), 6.81, 7.10 (2s, 2H, NH_2), 7.42 (d), 7.58 (d), 7.64 (t), 7.81 (s), 7.96 (m, 6H, Ph+H_8). ^{19}F NMR −175.0 (ddd, J=33.5, 18.1 Hz), −181.1 (ddt, 30.5, 18.4, 12.4 Hz). ESI-MS 484, 486, 488 (47.8, 100.0, 47.8, M+H), 506, 508, 510 (49.8, 100.0, 44.7, M+Na).

4.1.10. (*Z*)- and (*E*)-2-Amino-6-chloro-9-[(4-fluoro-4-hydroxymethyl-cyclopropylidenemethyl]purine (*Z*-1a) and (*E*-1a). Selenoxide **16** (250 mg, 0.51 mmol) was dissolved in THF–DMF (10:1, 6.6 mL) and the mixture was stirred at 60 °C for 12 h. Solvents were removed in vacuo and the product was chromatographed on a silica gel column (CH_2Cl_2–MeOH=40:1) to give a mixture of *Z*,*E*-isomeric acetates **17** (122 mg, 76%), mp 161–165 °C. UV max 202 nm (ε 27,200), 224 (ε 28,200), 310 (ε 7700). ^{1}H NMR ($CDCl_3$) δ 2.09, 2.17 (2s, 3H, Me) overlapped with 1.93–2.21 (m, 2H, $H_{3'}$), 4.30–4.59 (m), 4.75 (dd, 2H, $H_{5'}$), 5.34 (bs, 2H, NH_2), 7.38 (t), 7.81 (bs, 1H, $H_{1'}$), 8.21, 8.26 (2s, 1H, H_8). ^{19}F NMR −179.6 (ddd), −179.8 (m). ESI-MS 312, 314 (M+H, 35.0, 11.7), 334, 336 (M+Na, 57.8, 20.1), 102 (100.0).

A solution of product **17** (353 mg, 1.13 mmol) and K_2CO_3 (125 mg, 0.91 mmol) in MeOH–water (9:1, 40 mL) at rt for 15 h. The solvents were evaporated in vacuo and the product was chromatographed on silica gel (EtOAc–hexanes=2:1 to 100% EtOAc) to give faster moving *Z*-**1a** (129 mg, 42%) and slower moving *E*-**1a** (107 mg, 35%).

Compound Z-**1a**. Mp 218–219 °C, UV max 237 nm (ε 27,200), 274 (ε 5900), 310 (ε 7400). ^{1}H NMR δ 1.94 (td, 1H, J=12.0, 1.6 Hz), 2.00 (td, 1H, J=11.2, 2.4 Hz, $H_{3'}$), 3.65 (dd, 1H, J=29.0, 13.4 Hz), 4.18 (dd, 1H, J=14.8, 12.8 Hz, $H_{5'}$), 5.67 (s, 1H, OH), 7.11 (s, 2H, NH_2), 7.31 (s, 1H, $H_{1'}$),

8.57 (s, 1H, H_8). ^{13}C NMR 15.7 (d, $J=12.7$ Hz, $C_{3'}$), 63.7 (d, $J=24.7$ Hz, $C_{5'}$), 77.8 (d, $J=231.3$ Hz, $C_{4'}$), 112.4 (d, $J=4.5$ Hz, $C_{2'}$), 113.4 ($C_{1'}$), 123.7, 140.2, 150.5, 153.0, 160.9 (purine). ^{19}F NMR −179.4 (ddd, $J=26.0$, 13.6, 10.5 Hz). EI-MS 269, 271 (23.1, 8.2, M), 252, 254 (100.0, 33.0, M−OH), 169, 171 (59.5, 24.4, 2-amino-6-chloropurine). EI-HRMS calcd for $C_{10}H_9^{35}ClFN_5O$ (M): 269.0480, found: 269.0486.

Compound E-**1a**. Mp 212–214 °C, UV max 236 nm (ε 28,100), 274 (ε 6100), 310 (ε 7700). ^1H NMR δ 1.94 (dd, 1H, $J=12.4$, 1.8 Hz), 2.20 (td, 1H, $J=10.8$, 2.4 Hz, $H_{3'}$), 3.77 (dt, 2H, $J=21.2$, 6.4 Hz, $H_{5'}$), 5.32 (t, 1H, $J=6.0$ Hz, OH), 7.10 (s, 2H, NH_2), 7.71 (s, 1H, $H_{1'}$), 8.51 (s, 1H, H_8). ^{13}C NMR 18.1 (d, $J=13.5$ Hz, $C_{3'}$), 63.3 (d, $J=26.1$ Hz, $C_{5'}$), 77.6 (d, $J=229.8$ Hz, $C_{4'}$), 113.4 (d, $J=5.2$ Hz, $C_{2'}$), 114.7 ($C_{1'}$), 123.8, 140.2, 150.5, 153.5, 160.8 (purine). ^{19}F NMR −179.0 (td, $J=21.5$, 10.9 Hz). EI-MS 269, 271 (23.18, 8.11, M), 252, 254 (100.0, 32.7, M−OH), 169, 171 (57.1, 23.2, 2-amino-6-chloropurine). EI-HRMS calcd for ($C_{10}H_9^{35}ClFN_5O$): 269.0480, found: 269.0480.

4.1.11. (*Z*)- and (*E*)-9-{[2-Fluoro-2-(hydroxymethyl) cyclopropylidene]methyl}guanine (*Z*-1b and *E*-1b). Compound *Z*-**1a** (85 mg, 0.32 mmol) was heated in HCO_2H (80%, 10 mL) at 80 °C with stirring for 4 h. After cooling, the volatile components were evaporated in vacuo and the crude product was stirred in NH_3/MeOH (5%, 40 mL) at 0 °C for 4 h. Solvents were removed, the product *Z*-**1b** was recrystallized from methanol (69 mg, 87%). *E*-**1b** was prepared in a similar fashion from *E*-**1a** (80 mg, 0.30 mmol) to yield 71 mg (95%). Both isomers were identical (TLC, UV and ^1H NMR) with authentic compounds.[1]

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References and notes

1. Zemlicka, J. In *Recent Advances in Nucleosides: Chemistry and Chemotherapy*; Chu, C. K., Ed.; Elsevier: Amsterdam, The Netherlands, 2002; pp 327–357.
2. Zemlicka, J.; Chen, X. Methylenecyclopropane Analogues of Nucleosides as Antiviral Agents. In *Frontiers in Nucleosides and Nucleic Acids*; Schinazi, R. F., Liotta, D. C., Eds.; IHL: Tucker, GA, 2004; pp 267–307.
3. Zhou, S.; Kern, E. R.; Gullen, E.; Cheng, Y.-C.; Drach, J. C.; Matsumi, S.; Mitsuya, H.; Zemlicka, J. *J. Med. Chem.* **2004**, *47*, 6964–6972.
4. Qiu, Y.-L.; Ksebati, M. B.; Ptak, R. G.; Fan, B. Y.; Breitenbach, J. M.; Lin, J.-S.; Cheng, Y.-C.; Kern, E. R.; Drach, J. C.; Zemlicka, J. *J. Med. Chem.* **1998**, *41*, 10–23.
5. Qiu, Y.-L.; Ptak, R. G.; Breitenbach, J. M.; Lin, J.-S.; Cheng, Y.-C.; Kern, E. R.; Drach, J. C.; Zemlicka, J. *Antiviral Chem. Chemother.* **1998**, *9*, 341–352.
6. Chen, X.; Kern, E. R.; Drach, J. C.; Gullen, E.; Cheng, Y.-C.; Zemlicka, J. *J. Med. Chem.* **2003**, *46*, 1531–1537.
7. Qiu, Y.-L.; Zemlicka, J. *Synthesis* **1998**, 1447–1452.
8. Chen, X.; Zemlicka, J. *J. Org. Chem.* **2002**, *67*, 286–289.
9. Zhou, S.; Breitenbach, J. M.; Borysko, K. Z.; Drach, J. C.; Kern, E. R.; Gullen, E.; Cheng, Y.-C.; Zemlicka, J. *J. Med. Chem.* **2004**, *47*, 566–575.
10. Guan, H.-P.; Qiu, Y.-L.; Ksebati, M. B.; Kern, E. R.; Zemlicka, J. *Tetrahedron* **2002**, *58*, 6047–6059.
11. Wang, R.; Ksebati, M. B.; Corbett, T. H.; Kern, E. R.; Drach, J. C.; Zemlicka, J. *J. Med. Chem.* **2001**, *44*, 4019–4022.
12. Guan, H.-P.; Ksebati, M. B.; Cheng, Y.-C.; Drach, J. C.; Kern, E. R.; Zemlicka, J. *J. Org. Chem.* **2000**, *65*, 1280–1290.
13. Guan, H.-P.; Ksebati, M. B.; Kern, E. R.; Zemlicka, J. *J. Org. Chem.* **2000**, *65*, 5177–5184.
14. Wang, R.; Kern, E. R.; Zemlicka, J. *Antiviral Chem. Chemother.* **2002**, *13*, 251–262.
15. Back, T. G. Electrophilic Selenium Reactions. In *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987; pp 1–125; loc. cit. p 59.
16. Beaulieu, P. L.; Dezile, R. In *Organoselenium Chemistry*; Back, T. G., Ed.; Oxford University Press: New York, 1999; pp 35–66.
17. Liotta, D.; Zima, G.; Saindane, M. *J. Org. Chem.* **1982**, *47*, 1258–1267.
18. Tunge, J. A.; Mellegard, S. R. *Org. Lett.* **2004**, *6*, 1205–1207.
19. Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4208–4210.
20. Muller, C.; Stier, F.; Weyerstahl, P. *Chem. Ber.* **1977**, *110*, 124–137.
21. Williamson, K. L.; Li, Y.-F.; Hall, F. H.; Swager, S. *J. Am. Chem. Soc.* **1966**, *88*, 5678–5680.
22. In the absence of LiCl, the yield of fluoroester **7** was only 43%. A similar beneficial effect of an excess of LiCl was observed[3] in fluorination of esters **2**.

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Self-assembly of a novel series of hetero-duplexes driven by donor–acceptor interaction

Qi-Zhong Zhou,[a] Mu-Xin Jia,[b] Xue-Bin Shao,[a] Li-Zhu Wu,[c] Xi-Kui Jiang,[a] Zhan-Ting Li[a,*] and Guang-Ju Chen[b,*]

[a]*State Key Laboratory of Bio-Organic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*
[b]*Department of Chemistry, Beijing Normal University, Beijing 100875, China*
[c]*Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100101, China*

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Abstract—The self-assembly of a novel series of donor–acceptor interaction-driven artificial hetero-duplexes in organic media has been described. Four linear compounds **1a**–**1d**, bearing two to five electron rich 1,5-dioxynaphthalene units connected by the tetra(ethylene glycol) linker, respectively, have been prepared and used as donors, while eight compounds **2a**–**2d**, **13**–**16**, bearing one to four electron deficient pyromellitic diimide, 1,4,5,8-naphthalene-tetracarboxydiimide, or perylene-3,4,9,10-tetracarboxydiimide units, respectively, have been used as acceptors. The structure of the hetero-duplexes has been characterized by the ^{1}H NMR, UV–vis spectroscopy and vapor pressure osmometry. It is revealed that the binding stability of the duplexes vary greatly, depending on the length and structure of the monomers and also the solvent, and hetero-duplex **1d**·**2d** displays a maximum association constant of ca. 1.0×10^4 M^{-1} in chloroform.

1. Introduction

Self-assembly of linear molecules into functional complexes is a common phenomenon in biological systems.[1,2] In recent years, there has been intensive interest in constructing duplexes or dimers of defined structures through the self-assembly of synthetic molecules. Most artificial duplexes have been constructed by making use of hydrogen bonding[3,4] and metal ion–ligand coordination[5,6] as the dominant driving forces. Examples of duplexes based on electrostatic interaction between ionic acid and base monomers have also been reported.[7] Although, it has been well-established that cyclophanes incorporating electron rich or deficient aromatic units could, through donor–acceptor interaction, complex linear electron-deficient or rich molecules to give rise to another kind of threading dimeric supramolecular structures[8–10] and supramolecular materials,[11] much less attention has been paid to this non-covalent interaction for constructing duplex architectures probably due to its low directionality.

In 2002, Iverson et al. described the self-assembly of a new class of aromatic stacking-based hetero-duplexes from 1,5-dialkoxynaphthalene (DAN) and 1,4,5,8-naphthalene-tetracarboxydiimide (NDI)-incorporated peptide in aqueous solutions.[12] Although, donor–acceptor interaction between the electron-rich DAN unit and the electron-deficient NDI unit played a significant role in controlling the aromatic stacking pattern, hydrophobic interaction was revealed to be the main driving force for the formation of the peptide-derived duplexes. We previously reported that new zipper-styled hetero-duplexes could be constructed in less polar chloroform from DAN and pyromellitic diimide (PDI)-incorporated monomers by utilizing the cooperative donor–acceptor interaction between DAN and electron-deficient PDI units as the driving force.[13] We herein, describe the self-assembly of a novel series of hetero-duplexes which are driven by the multi-site donor–acceptor interaction between linear DAN and PDI-incorporated oligomers.[14]

2. Results and discussion

Two series of compounds **1a**–**1d** and **2a**–**2d** were designed as monomeric donors and acceptors. Because compounds **1** and **2** possess two different skeletons, it was envisioned that complexation between them would lead to the formation of new series of hetero-duplex architectures. The syntheses of

Keywords: Self-assembly; Donor–acceptor interaction; Aromatic stacking; Dimer; Oligo(glycol).
* Corresponding authors. Tel.: +86 21 5492 5122; fax: +86 21 6416 6128; e-mail: ztli@mailc.sioc.ac.cn

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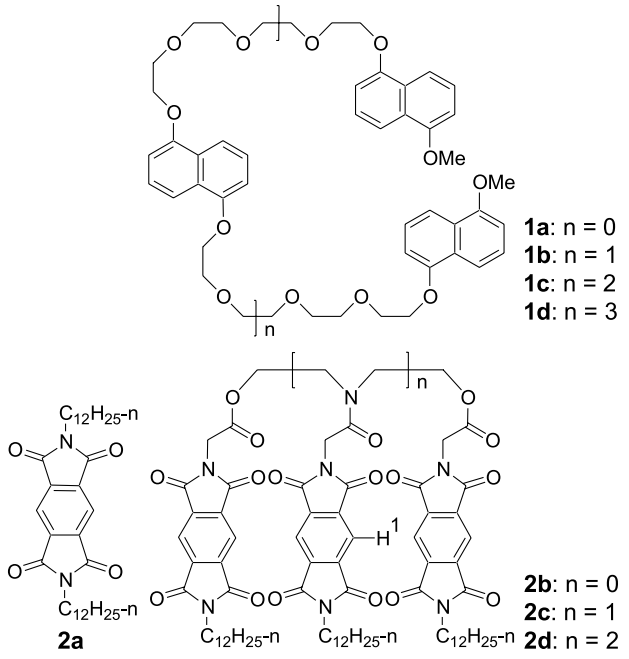
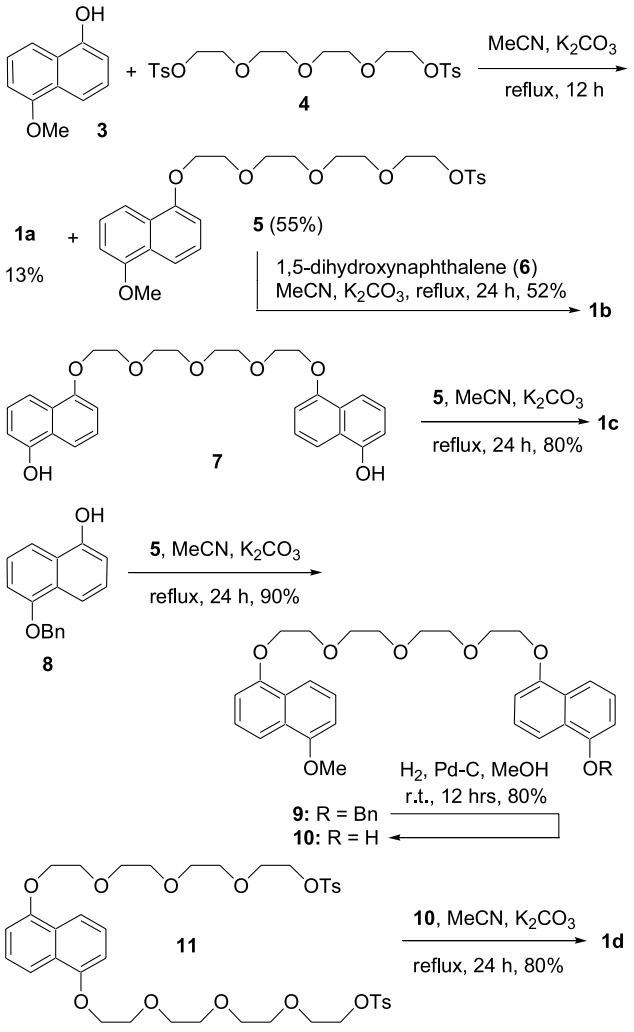
compounds **1a**–**1d** are outlined in Scheme 1.[15] Thus, compound **3** was first, reacted with ditosylate **4** in acetonitrile in the presence of potassium carbonate to give **1a** and **5** in 13 and 55% yield, respectively. Compound **5** was then treated with diol **6** in acetonitrile with potassium carbonate as a base to give **1b** in 52% yield. In a similar way, compound **1c** was prepared in 80% yield from the reaction of **5** and **7**.[16] For the preparation of **1d**, compound **8** was first, treated with **5** to afford **9** in 90% yield, the latter was then hydrogenated in methanol with Pd–C as catalyst to yield compound **10** in 80% yield. Finally, the reaction of **10** with an excessive amount of ditosylate **11** in acetonitrile in the presence of potassium carbonate afforded **1d** in 80% yield. Compounds **2a**[17] and **2b**–**2d**[13] were prepared according to the reported procedures.



^{1}H NMR dilution experiments in $CDCl_3$ from 50 to 1.0 mM revealed no significant chemical shifts ($\leq$0.04 ppm) for compounds **1a**–**1d** (with one of the sharp Ar-H's as probe). This small change of chemical shifts indicates that no important intermolecular aggregation took place in chloroform.[18] Quantitative binding studies were then performed in $CDCl_3$ solutions by titrating compounds **2a**–**2d** with **1a**–**1d**, respectively, with the Ar-H signal of one PDI unit as probe.[13] As examples, the chemical shift summaries for the titration experiments of **1c** with **2c** and **15** (vide infra) are displayed in Figure 1. Association constants K_{assoc}'s for complexes **1**·**2** were obtained by fitting the changing data of the chemical shifts of the probe to a 1:1 binding isotherm and presented in Table 1.[19] Job's plots of the probe signals provide evidence that the complexes follow a 1:1 binding mode,[20] which displayed maximum chemical shift change at the equimolar ratio of **1** and **2** when the total concentration of both compounds was kept unchanged.

The data in Table 1 show that the association improves remarkably with the increase in the donor or acceptor units of both **1** and **2** as a result of the strengthened intermolecular donor–acceptor interaction of the DAN and PDI units of the



Scheme 1.

monomers. It can also be found (notes b–d) that increasing the polarity of the solvent significantly reduces the binding stability of the complexes. Similar results have been observed for the complexes with two comb-shaped monomers.[13] These results suggest that, instead of the hydrophobic interaction, the donor–acceptor interaction is the dominant driving force for the present complexes.[21]

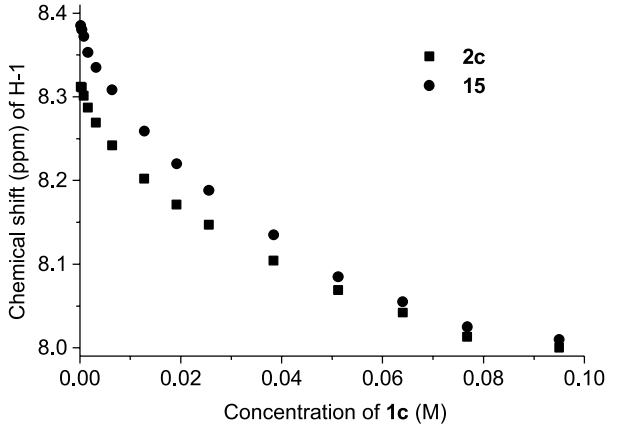


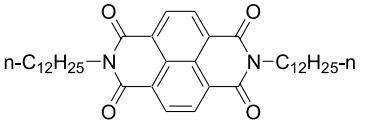
Figure 1. ^{1}H NMR titration results of the H-1 of **2c** (0.5 mM) and **15** (0.5 mM, vide infra) with **1c** in $CDCl_3$ at 25($\pm$1) °C.

Table 1. Association constants K_{assoc}'s of novel series of hetero duplexes **1·2** in $CDCl_3$ at 25 °C[a]

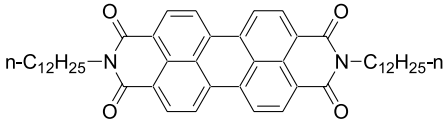
Complex	K_{assoc} (M^{-1})	Complex	K_{assoc} (M^{-1})
1a·2a	12	**1a·2b**	35
1a·2c	124	**1b·2b**	180
1b·2c	430	**1b·2d**	1150
1c·2c	1200	**1c·2d**	4700
1d·2c	1250	**1d·2d**	10200
1b·2b[b]	140	**1b·2b**[c]	115
1b·2b[d]	125	**1c·2d**[e]	4500

[a] With an error ≤20%.
[b] With 10% CD_3OD (v/v).
[c] With 20% CD_3OD (v/v).
[d] With 10% CD_3SOCD_3 (v/v).
[e] Obtained by UV dilution method with the absorption at 451 nm as probe peak.

As expected, the complexes formed from longer monomers displayed stronger electron-transfer absorption band. Quantitative UV dilution studies were also carried out with 1:1 mixture of **1c** and **2d** in chloroform with the maximum charge transfer absorbance as probe, which gave a K_{assoc} of approximately 4.5×10^3 M^{-1} for **1c·2d**.[13] The value is comparable to that obtained by the ^1H NMR titration method. A vapor pressure osmometric (VPO) experiment was performed for the most stable duplex **1d·2d** in chloroform–toluene (4:1, v:v) at 30 °C, which afforded an average molecular mass of 2900(±400) u. The value is agreeable to that calculated mass (3306 u) for the 1:1 binding stoichiometry of the complex.



12



13

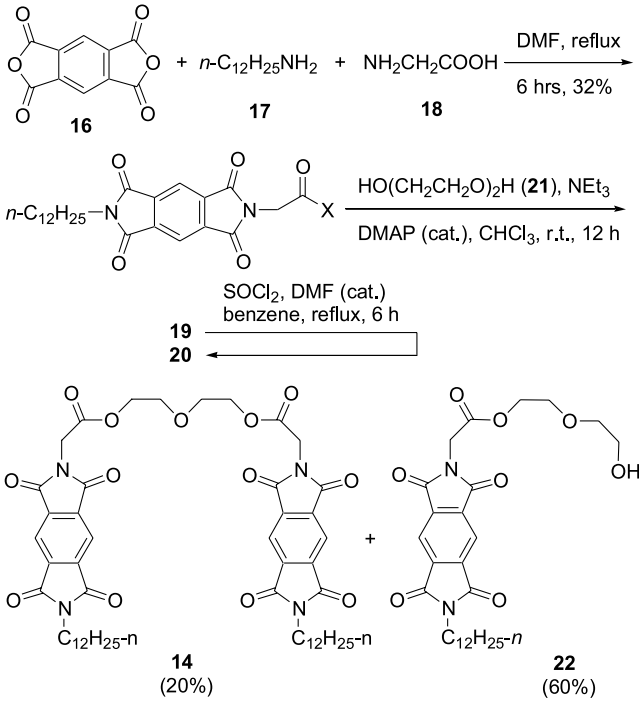
In order to investigate the diversity of this new series of binding mode and also to explore the possibility of developing more stable duplex structures, molecules with the skeletons of **2b** and **2c** but with two or three electron deficient NDI[22] or perylene-3,4,9,10-tetracarboxydiimide unit (PTI)[23] were also designed. However, no pure samples could be synthesized following the procedures to prepare **2b** and **2c** possibly as a result of the poor solubility of the required compounds. Compounds **12** and **13**, which are soluble in chloroform, were then prepared from the reaction of *n*-dodecyl amine with naphthalene-1,4,5,8-tetracarboxylic acid dianhydride or perylene-3,4,9,10-tetracarboxylic acid dianhydride in DMF. Binding study for **12** and **13** towards **1a** was then carried out in $CDCl_3$ by ^1H NMR titration of **12** and **13** with **1a** and the derived association constants K_{assoc} are shown in Table 2. It can be found that K_{assoc} of complex **1a·12** is larger than that of **1a·2a**, which is consistent with the greater electron deficiency of NDI relative to PDI,[22a] and addition of DMSO to the solvent reduced the stability of the complex (note b, Table 2). The K_{assoc} of complex **1a·13** is very low, indicating that PTI unit is only a weak acceptor in non-polar solvent like chloroform.

Table 2. Association constants K_{assoc}'s of donor–acceptor interaction-driven complexes or duplexes in $CDCl_3$ at 25 °C[a]

Complex	K_{assoc} (M^{-1})	Complex	K_{assoc} (M^{-1})
1a·12	42	**1a·13**	<5
1a·14	48	**1b·14**	220
1a·15	410	**1b·15**	950
1c·15	2500	**1d·15**	2650
1a·12[b]	32		

[a] Performed at 25 °C with an error ≤20%.
[b] With 10% CD_3SOCD_3 (v/v).

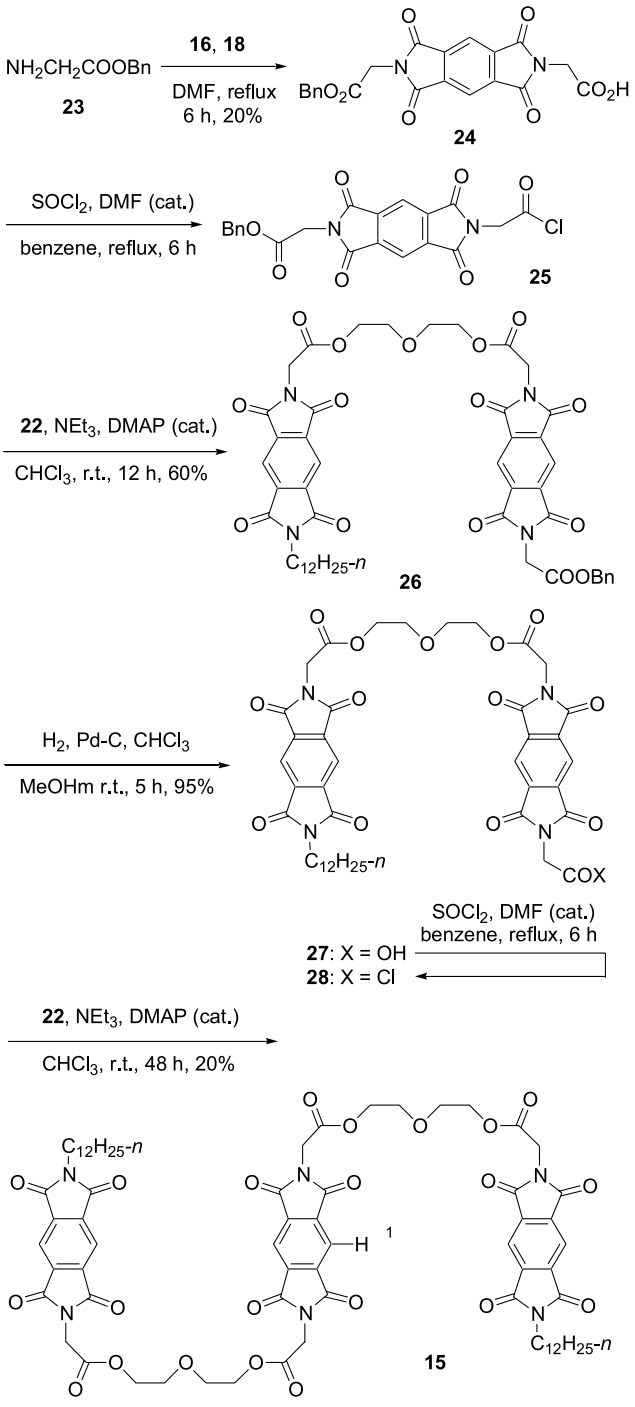
Previously, Iverson et al. had reported that two linear ionic monomers incorporating DAN and NDI units could form stable duplexes in aqueous solution.[12] The successful self-assembly of the new class of duplexes **1·2** prompted us to explore the formation of duplexes from two neutral linear monomers. Therefore, compounds **14** and **15** were designed and synthesized. The synthetic route for **14** is outlined in Scheme 2. In brief, acid **19** was prepared in 32% yield from the reaction of **16**, **17** and **18** in refluxing DMF and then converted into acyl chloride **20** with thionyl chloride. Subsequent reaction of **20** with diol **21** in chloroform afforded **14** and **22** in 20 and 60% yields, respectively.



Scheme 2.

For preparing **15** (Scheme 3),[24] compound **24** was first, produced in 20% yield from the reaction of **16**, **18** and **23** in hot DMF and then treated with thionyl chloride to afford **25**. The later was reacted with **22** in chloroform to give **26** in 60% yield. Chloride **28** was then produced from **26** after Pd–C-catalyzed hydrogenation, followed by the treatment of the intermediate acid **27** with thionyl chloride. Compound **28** was then reacted with **22** to afford **15** in 20% yield. Both **14** and **15** are soluble in organic solvents such as chloroform and dichloromethane.

Quantitative binding study of **14** and **15** towards **1a–1d** in



Scheme 3.

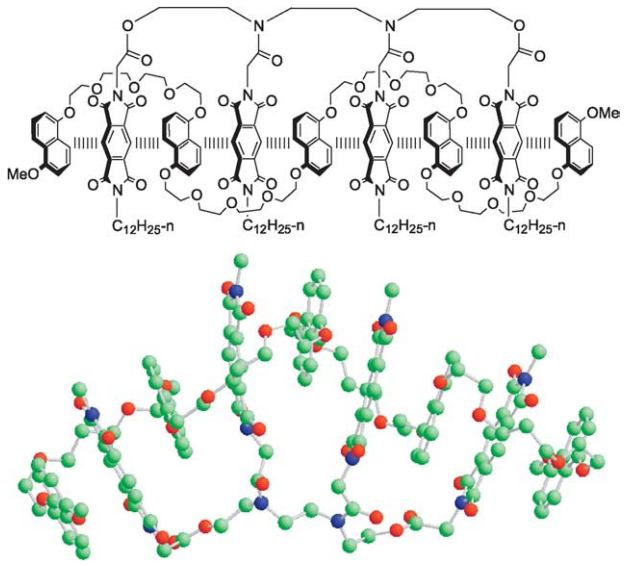


Figure 2. The proposed twine-featured binding motif and the minimized structure for hetero-duplex **1d**·**2d**.

$CDCl_3$ was performed by the ^1H NMR titration method with the PDI proton signal (H-1 for **15**) as the probe. The corresponding association constants K_{assoc} derived by non-linear regression for a 1:1 binding mode are provided in Table 2. It can be found that both **14** and **15** exhibit notably increased binding ability towards the corresponding donor molecules than **2b** and **2c**, respectively.

All the complexes displayed pale to dark orange color in chloroform, depending on their stability and concentration. Consistently, UV–vis investigations revealed broad electron transfer absorbance between 400–600 nm for the new complexes. The corresponding molar extinction coefficient ε's obtained in chloroform at room temperature at a fixed concentration are shown in Table 3. Also, it can be found that the ε's were increased substantially with the increase of the donor or acceptor units. This observation supports that important multiple donor–acceptor interaction exists within the complexes.

Based on the above binding studies, we propose a twine-styled binding mode for the new series of hetero duplexes, as shown in Figure 2 with complex **1d**·**2d** as an example. Although, such a binding mode requires a twining conformation, which would lead to negative entropic effect for the binding, for the longer monomers **1**, it could facilitate multi-site donor–acceptor interactions and

Table 3. Molar extinction coefficients ε's of the 1:1 complexes in chloroform at 25 °C ([monomer]=0.02 M at 25 °C)

Complex	ε (M^{-1} cm^{-1})	λ_{max} (nm)	Complex	ε (M^{-1} cm^{-1})	λ_{max} (nm)
1a·**2a**[a]	10	445	**1a**·**2b**	24	447
1a·**2c**	87	450	**1a**·**12**	25	448
1a·**13**	15	455	**1a**·**14**	110	449
1a·**15**	165	448	**1b**·**2b**	94	448
1b·**2c**	165	450	**1b**·**2d**	210	450
1c·**2c**	220	451	**1c**·**2d**	280	451
1c·**15**	190	450	**1d**·**2d**	320	450
1d·**2d**[b]	130	450			

[a] Obtained at [monomer]=0.05 M. No detectable absorbance was exhibited in the visible range at [**1a**] (=[**2a**])=0.02 M.
[b] Obtained at [monomer]=8.0×10^{-3} M.

consequently increase the stability of hetero duplexes generated from the longer monomers. Comparison of the binding constants of **1a·2a**, **1b·2b**, **1c·2c** and **1d·2d** revealed no favorable cooperativity of binding, indicating that other multiple 'two-points' interactions may also exist.

To obtain more insight for the structural characteristics of this kind of complexes, molecular mechanic calculations were also carried out for **1d–2d**. The dodecyl groups have been substituted with methyl groups for the sake of simplicity. The conformation was optimized and obtained by using the conjugate gradient method with the AMBER force field,[25] and is provided in Figure 2. It can be found that **1d** and **2d** bind each other by means of multiple π–π interactions. The distances between the adjacent donor and acceptor units are about 3.4–3.6 Å. The binding mode of hetero-duplex **1c·15** should be similar to the twined dimeric structure assembled from ionic linear monomers by Iverson et al.[12] and is shown in Figure 3.

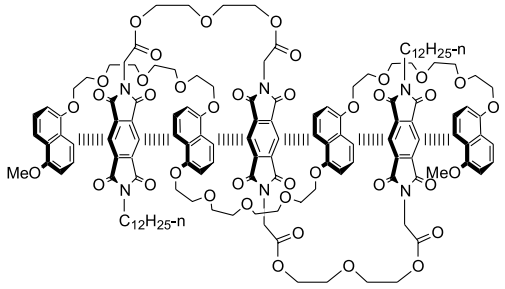


Figure 3. A possible binding mode of hetero-duplex **1c·15**.

3. Conclusion

In conclusion, the multiple donor–acceptor interaction has been successfully utilized for the self-assembly of a new series of twine-styled hetero-duplexes from readily available linear and/or comb-shaped molecules. By modifying the molecular skeletons of the monomers or introducing new and more electron deficient units into the acceptor molecules, it is expected that more stable binding motifs may be generated. Further, applications of the new binding motif in the self-assembly of new generation of supramolecular species are also under investigation.

4. Experimental

4.1. General methods

Melting points are uncorrected. All reactions were performed under an atmosphere of dry nitrogen. The ^{1}H NMR spectra were recorded on 500, 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*. Vapour pressure osmometric experiment was performed on a Knauer K-7000 instrument with sucrose octaacetate for calibration. Elemental analysis was carried out at the SIOC analytical center. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. All solvents were dried before use following standard procedures. The methods for the determination of binding constants have been reported in a previous paper.[13]

4.1.1. Compounds 1a and 5. To a solution of compound **3**[26] (5.22 g, 30.0 mmol) in acetonitrile (300 mL) was added potassium carbonate (17.0 g, 0.12 mol). The suspension was stirred at room temperature for 1 h and a solution of ditosylate **4**[27] (45.2 g, 90.0 mmol) in acetonitrile (100 mL) was added. The suspension was heated under reflux for 12 h and then filtered. The filtrate was concentrated in vacuo, and the resulting residue triturated in chloroform (400 mL). The organic phase was washed with aqueous HCl solution (1 N, 100 mL), water (100 mL), brine (100 mL), and dried over sodium sulfate. After removal of the solvent under reduced pressure, the crude products were subjected to column chromatography (chloroform/AcOEt 20:1) to give compounds **1a** (1.97 g, 13%, colorless solid) and **5** (8.32 g, 55%, oily solid). *Compound* **1a**. Mp 46 °C. ^{1}H NMR ($CDCl_3$): δ 7.84 (t, J=8.4 Hz, 4H), 7.31–7.37 (m, 4H), 6.81 (d, J=7.5 Hz, 4H), 4.26 (t, J=4.8 Hz, 4H), 3.97 (t, J=4.5 Hz, 10H), 3.78–3.81 (m, 4H), 3.70–3.73 (m, 4H). MS (EI): *m/z*: 506 $[M]^+$. Anal. Calcd for $C_{30}H_{34}O_7$: C, 71.13; H, 6.76. Found: C, 70.76; H, 6.78. *Compound* **5**: ^{1}H NMR ($CDCl_3$): δ 7.76–7.86 (m, 4H), 7.26–7.39 (m, 4H), 6.84 (d, J=7.5 Hz, 2H), 4.29 (t, J=4.8 Hz, 2H), 4.12 (t, J=4.5 Hz, 2H), 3.97–4.00 (m, 5H), 3.77–3.80 (m, 2H), 3.63–3.67 (m, 4H), 3.56–3.60 (m, 4H), 2.41 (s, 3H). MS (EI): *m/z*: 504 $[M]^+$. Anal. Calcd for $C_{26}H_{32}SO_8$: C, 61.89; H, 6.39. Found: C, 61.83; H, 6.58.

4.1.2. Compound 1b. A suspension of **5** (2.52 g, 5.00 mmol), **6** (0.40 g, 2.50 mmol), and potassium carbonate (1.38 g, 10.0 mmol) in acetonitrile (50 mL) was heated under reflux for 24 h. After work-up as described for preparing **1a** and **5**, the crude product was purified by column chromatography (chloroform/AcOEt 10:1) to afford compound **1b** as a white solid (1.07 g, 52%). Mp 56–58 °C. ^{1}H NMR ($CDCl_3$): δ 7.81–7.86 (m, 6H), 7.28–7.37 (m, 6H), 6.76–6.82 (m, 6H), 4.22–4.27 (m, 8H), 3.94–3.98 (m, 8H), 3.77–3.80 (m, 8H), 3.70–3.73(m, 8H). MS (EI): *m/z*: 825 $[M+H]^+$. Anal. Calcd for $C_{48}H_{56}O_{12}\cdot 0.5H_2O$: C, 69.13; H, 6.89. Found: C, 69.00; H, 6.89.

4.1.3. Compound 1c. A suspension of compound **5** (0.80 g, 1.59 mmol), **7**[22a] (0.38 g, 0.79 mmol), and potassium carbonate (2.00 g, 14.5 mmol) in acetonitrile (50 mL) was heated under reflux for 24 h. Upon cooling to room temperature, the solid was filtered and the filtrate was concentrated in vacuo. Chloroform (100 mL) was added to the resulting residue and the solution was washed with dilute hydrochloric acid, water, brine, and dried over sodium sulfate. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (chloroform/acetone 25:1) to produce **1c** as a white solid (0.73 g, 80%). Mp 78–80 °C. ^{1}H NMR ($CDCl_3$): δ 7.81–7.86 (m, 8H), 7.24–7.36 (m, 8H), 6.75–6.81 (m, 8H), 4.21–4.25 (m, 12H), 3.90–3.95 (m, 18H), 3.76–3.79 (m, 12H), 3.69–3.72 (m, 12H). MS (ESI): *m/z*: 1160 $[M+NH_3]^+$. Anal. Calcd for $C_{66}H_{78}O_{17}$: C, 69.33; H, 6.88. Found: C, 69.50; H, 7.02.

4.1.4. Compound 9. The title compound was prepared from the reaction of **5** and **8**[28] by using the procedure analogous to **5**. The crude product was purified by column chromatography (*n*-hexane/AcOEt 20:1) to afford **9** as a colorless gel (90%). ^{1}H NMR ($CDCl_3$): δ 7.81–7.93 (m, 4H), 7.31–7.54 (m, 9H), 6.80–6.90 (m, 4H), 5.22 (s, 2H), 4.24–4.28 (m, 4H), 3.97 (t, J=5.4 Hz, 7H), 3.78–3.81 (m, 4H), 3.71–3.74 (m, 4H). Ms (EI): *m/z*: 582 $[M]^+$. HRMS (EI): Calcd for $C_{36}H_{38}O_7$: 582.2618. Found: 582.2612.

4.1.5. Compound 10. The title compound was prepared by hydrogenation of **9** with hydrogen gas (1 atm) in the presence of Pd–C (10%) in methanol. The crude product was purified by column chromatography (chloroform/methanol 20:1) to give **10** as a white gel (80%). ^{1}H NMR ($CDCl_3$): δ 7.71–7.86 (m, 4H), 7.20–7.37 (m, 4H), 6.76–6.82 (m, 4H), 4.22–4.26 (m, 4H), 3.95–3.97 (m, 7H), 3.78–3.81 (m, 4H), 3.71–3.74 (m, 4H). MS (EI): *m/z*: 492 $[M]^+$. HRMS (EI): *m/z*: Calcd for $C_{29}H_{32}O_7$: 492.2148. Found: 492.2143.

4.1.6. Compound 1d. The title compound was prepared from the reaction of **10** and **11**[10] with a method analogous to **1b**. The crude product was purified by column chromatography (chloroform/methanol 20:1) to give the desired compound as a white solid (80%). Mp 50–52 °C. ^{1}H NMR ($CDCl_3$): δ 7.81–7.86 (m, 10H), 7.26–7.37 (m, 10H), 6.79 (t, J=7.8 Hz, 10H), 4.22–4.26 (m, 24H), 3.94–3.96 (m, 32H), 3.77–3.80 (m, 22H), 3.69–3.72 (m, 22H). MS (MALDI): *m/z*: 1483 $[M+Na]^+$. Anal. Calcd for $C_{84}H_{100}O_{22}$: C, 69.02; H, 6.90. Found: C, 69.12; H, 6.61.

4.1.7. Compound 12. The title compound was prepared according to the reported method.[29] Mp 160–162 °C. ^{1}H NMR ($CDCl_3$): δ 8.76 (s, 4H), 4.19 (t, J=7.2 Hz, 4H), 1.72–1.77 (m, 4H), 1.25–1.43 (m, 36H), 0.86 (t, J=6.6 Hz, 6H). MS (MALDI): *m/z*: 603 $[M+H]^+$. Anal. Calcd for $C_{38}H_{54}N_2O_4$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.87; H, 9.05; N, 4.34.

4.1.8. Compound 13. The title compound was prepared according to the reported method.[30] Mp >240 °C. ^{1}H NMR ($CDCl_3$): δ 8.696 (s, 2H), 8.67 (s, 2H), 8.62 (s, 2H), 8.59 (s, 2H), 4.21 (t, J=7.5 Hz, 4H), 1.74–1.79 (m, 4H), 1.26–1.47 (m, 36H), 0.87 (t, J=6.6 Hz, 6H). MS (MALDI): *m/z*: 727 $[M+H]^+$. Anal. Calcd for $C_{48}H_{58}N_2O_4$: C, 79.30; H, 8.04; N, 3.85. Found: C, 79.05; H, 7.98; N, 3.43.

4.1.9. Compound 19. A solution of compounds **16** (21.8 g, 0.10 mol), *n*-$C_{12}H_{25}NH_2$ 17 (18.5 g, 0.10 mol), and glycine **18** (7.50 g, 0.10 mol) in DMF (200 mL) was heated under reflux for 6 h and then poured onto ice (1000 mL). The solids were filtered and washed thoroughly with water, dried in vacuo, and subjected to column chromatography (chloroform/methanol 50:1 to 10:1). *Compound* **19** was obtained as a white solid (12.4 g, 28%). Mp 246–247 °C. ^{1}H NMR ($CDCl_3$): δ 8.32 (s, 2H), 4.55 (s, 2H), 3.74 (t, J=7.5 Hz, 2H), 1.63–1.79 (m, 2H), 1.25–1.33 (m, 18H), 0.88 (t, J=3.0 Hz, 3H). MS (EI): *m/z*: 442 $[M]^+$. Anal. Calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.99; H, 6.80; N, 6.27.

4.1.10. Compound 20. A suspension of compound **19** (1.26 g, 2.84 mmol), oxalyl chloride (5 mL), and DMF (0.05 mL) in benzene (50 mL) was heated under reflux for 6 h and then concentrated in vacuo to give **20** as a white solid. This crude product was used for the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 8.35 (s, 2H), 4.88 (s, 2H), 3.75 (t, J=7.2 Hz, 2H), 1.68–1.70 (m, 2H), 1.25–1.33 (m, 18H), 0.88 (t, J=6.6 Hz, 3H). MS (EI): *m/z*: 460 $[M]^+$.

4.1.11. Compounds 14 and 22. To a solution of compound **21** (1.28 g, 11. 3 mmol), triethylamine (1.50 mL), and DMAP (0.1 g) in chloroform (60 mL) was added with stirring a solution of the above **20** in chloroform (10 mL) at room temperature. Stirring was continued for 12 h and chloroform (40 mL) was added. The solution was washed with dilute hydrochloric acid (1 N, 50 mL×2), water (50 mL×2), brine (50 mL), and dried over sodium sulfate. After removal of the solvent under reduced pressure, the resulting residue was chromatographed (chloroform/acetone 20:1) to give **14** (0.54 g, 20%) and **22** (0.90 g, 60%) both as white solid. *Compound* **14**. Mp 190–191 °C. ^{1}H NMR ($CDCl_3$): δ 8.32 (s, 4H), 4.57 (s, 4H), 4.34–4.37 (m, 4H), 3.71–3.76 (m, 8H), 1.68–1.72 (m, 4H), 1.20–1.33 (m, 36H), 0.88 (t, J=6.9 Hz, 6H). MS (ESI): *m/z*: 955 $[M+H]^+$. Anal. Calcd for $C_{52}H_{66}O_{13}N_4$: C, 65.39; H, 6.96; N, 5.87. Found: C, 65.42; H, 6.95; N, 5.82. **22**. Mp 112–114 °C. ^{1}H NMR ($CDCl_3$): δ 8.32 (s, 2H), 4.54 (s, 2H), 4.36–4.39 (m, 2H), 3.71–3.77 (m, 6H), 3.58–3.61 (m, 2H), 2.13 (t, J=3.6 Hz, 1H), 1.65–1.72 (m, 2H), 1.20–1.33 (m, 18H), 0.88 (t, J=6.6 Hz, 3H). MS (MALDI): *m/z*: 531 $[M+H]^+$. Anal. Calcd for $C_{28}H_{38}O_8N_2$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.33; H, 7.19; N, 5.16.

4.1.12. Compound 24. The title compound was prepared from the reaction of **16**, **18**, and **23** by a method analogous to **19**. The crude product was purified by column chromatography (chloroform/methanol 10:1) to give the desired product as a white solid (20%). Mp >240 °C. ^{1}H NMR ($CDCl_3$–DMSO-d_6 1:1): δ 8.33 (s, 2H), 7.36 (s, 5H), 5.21 (s, 2H), 4.58 (s, 2H), 4.41 (s, 2H). MS (MALDI): *m/z*: 422 $[M]^+$. Anal. Calcd for $C_{21}H_{14}N_2O_8$: C, 59.72; H, 3.34; N, 6.63. Found: C, 59.41; H, 3.21; N, 6.50.

4.1.13. Compound 26. Compound **24** (1.27 g, 3.00 mmol) was first, converted into **25** by treating with oxalyl chloride according to the method described for preparing **20**. The solution of this acyl chloride in chloroform (10 mL) was added to the solution of **22** (1.59 g, 3.00 mmol), triethylamine (1.0 mL), DMAP (0.05 g) in chloroform (50 mL) at room temperature. After stirring for 24 h, the solution was washed with diluted hydrochloric acid, water, brine, and dried over sodium sulfate. Upon removal of the solvent, the crude product was purified by column chromatography (chloroform/methanol 30:1) to give **26** as a white solid (1.68 g, 60%). Mp 178–180 °C. ^{1}H NMR ($CDCl_3$): δ 8.37 (s, 2H), 8.31 (s, 2H), 7.36 (s, 5H), 5.21 (s, 2H), 4.58 (s, 2H), 4.57 (s, 2H), 4.55 (s, 2H), 4.34–4.37 (m, 4H), 3.71–3.76 (m, 6H), 1.68–1.72 (m, 2H), 1.25–1.33 (m, 18H), 0.86 (t, J=6.0 Hz, 3H). MS (MALDI): *m/z*: 952 $[M+NH_4]^+$. HRMS (MALDI): Calcd for $C_{49}H_{50}N_4O_{15}$: 957.3149 $[M+Na]^+$. Found: 957.3165.

4.1.14. Compound 27. A solution of **26** (1.40 g, 1.50 mol)

and Pd–C (10%, 0.30 g) in methanol (30 mL) and chloroform (30 mL) was stirred at 1 atm of hydrogen gas for 5 h. After work-up, the crude product was subjected to flash chromatography (chloroform/methanol 15:1) to give **27** as a white solid (1.20 g, 95%). Mp 184–186 °C. ^{1}H NMR ($CDCl_3$): δ 8.36 (s, 2H), 8.32 (s, 2H), 7.36 (s, 5H), 4.36–4.57 (m, 12H), 3.74–3.76 (s, 6H), 1.70–1.71 (m, 2H), 1.25–1.32 (m, 18H), 0.87 (t, 3H). MS (MALDI): 867 $[M+Na]^+$. HRMS (MALDI): Calcd for $C_{42}H_{44}N_4O_{15}$: 844.2803. Found: 844.2798.

4.1.15. Compound 15. A suspension of compound **27** (0.84 g, 1.00 mmol) in thionyl chloride (10 mL) and benzene (50 mL) was heated under reflux for 6 h and then concentrated in vacuo to give acyl chloride **28**. Without further purification, this crude product was dissolved in chloroform (10 mL) and the solution was added dropwise to a stirred solution of **22** (0.53 g, 1.00 mmol), triethylamine (0.5 mL), DMAP (0.05 g) in chloroform (50 mL). Stirring was continued for 48 h at room temperature and chloroform (50 mL) was added. The solution was washed with dilute hydrochloric acid (1 N, 50 mL×2), water (50 mL), brine (50 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting residue was subjected to column chromatography (chloroform/AcOEt 3:1) to afford compound **15** as a white solid (0.27 g, 20%). Mp 204 °C. ^{1}H NMR ($CDCl_3$): δ 8.38 (s, 2H), 8.32 (s, 4H), 4.58 (d, J=2.7 Hz, 8H), 4.36 (t, J=4.5 Hz, 8H), 3.71–3.76 (m, 12H), 1.68–1.69 (m, 4H), 1.25–1.33 (m, 36H), 0.88 (t, J=6.3 Hz, 6H). MS (MALDI): m/z: 1379 $[M+Na]^+$. HRMS (MALDI): Calcd for $C_{70}H_{80}N_6O_{22}$: 1356.5326. Found: 1356.5320. Anal. Calcd for $C_{70}H_{80}N_6O_{22}$: C, 61.94; H, 5.94; N, 6.19. Found: C, 61.57; H, 5.81; N, 6.02.

4.2. Computational method

The binding patterns were constructed with the Builder program within the package HyperChem.[31] Then they were optimized by the conjugate gradient with the AMBER force field and the RMS derivative criteria of 0.00001 kcal/mol. To explore the lower energy structure, molecular dynamics calculations were performed without constraints. After 100 ps of molecular dynamics simulation, an additional round of energy minimization was again completed. Molecular mechanics and molecular dynamics are used to obtain the geometry of the dimers.[32]

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References and notes

1. Horton, R. H.; Moran, L. A.; Ochs, R. S.; Rawn, D. J.; Scrimgeour, G. K. *Principles of Biochemistry*; Prentice Hall: London, 1992.
2. Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131–3152.
3. (a) Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding* **2000**, *96*, 63–94. (b) Archer, E. A.; Gong, H.; Krische, M. J. *Tetrahedron* **2000**, *57*, 1139–1159. (c) Gong, B. *Synlett* **2001**, *5*, 582–589.
4. (a) Sessler, J. L.; Wang, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1726–1729. (b) Lüning, U.; Kühl, C. *Tetrahedron Lett.* **1998**, *39*, 5735–5738. (c) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761–6767. (d) Gong, B.; Yang, Y.; Zeng, H.; Skrzypczak-Jankunn, E.; Kim, Y. W.; Zhu, J.; Ickes, H. *J. Am. Chem. Soc.* **1999**, *121*, 5607–5608. (e) Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475–10488. (f) Carver, F. J.; Hunter, C. A.; Jones, P. S.; Livingstone, D. J.; McCabe, J. F.; Seward, E. M.; Tiger, P.; Spey, S. E. *Chem. Eur. J.* **2001**, *7*, 4854–4862. (g) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128–15139.
5. Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4763–4768.
6. (a) Taylor, P. N.; Anderson, H. L. *J. Am. Chem. Soc.* **1999**, *121*, 11538–11545. (b) Tanaka, K.; Tengeiji, A.; Kato, T.; Toyama, N.; Shiro, M.; Shionoya, M. *J. Am. Chem. Soc.* **2002**, *124*, 12494–12498. (c) Barboiu, M.; Vaughan, G.; Kyritsakas, N.; Lehn, J.-M. *Chem. Eur. J.* **2003**, *9*, 763–769.
7. (a) Sanchez-Quesada, J.; Seel, C.; Prados, P.; de Mendoza, J.; Dalcol, I.; Giralt, E. *J. Am. Chem. Soc.* **1996**, *118*, 277–278. (b) Schmuck, C.; Wienand, W. *J. Am. Chem. Soc.* **2003**, *125*, 452–459. (c) Schmuck, C.; Geiger, L. *J. Am. Chem. Soc.* **2004**, *126*, 8898–8899.
8. Anelli, P. L.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Delgado, M.; Gandolfi, M. T.; Goodnow, T. T.; Kaifer, A. E.; Philp, D.; Pietraszkiewicz, M.; Prodi, L.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 193–218.
9. (a) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725–2828. (b) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **1996**, *35*, 1154. (c) Fyfe, M. C. T.; Stoddart, J. S. *Acc. Chem. Res.* **1997**, *30*, 393. (d) Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, *99*, 1643–1664.
10. Raehm, L.; Hamilton, D. G.; Sanders, J. K. M. *Synlett* **2002**, 1743–1761.
11. (a) Würthner, F. *Chem. Commun.* **2004**, 1564–1579. (b) Neuteboom, E. E.; Beckers, E. H. A.; Meskers, S. C. J.; Meijer, E. W.; Janssen, R. A. J. *Org. Biomol. Chem.* **2003**, *1*, 198–203. (c) Vignon, S. A.; Jarrosson, T.; Iijima, T.; Tseng, H.-R.; Sanders, J. K. M.; Stoddart, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 9884–9885. (d) Weiss, E. A.; Chernick, E. T.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2004**, *126*, 2326–2327.
12. (a) Guelev, V.; Sorey, S.; Hoffman, D.; Iverson, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 2864–2865. (b) Gabriel, G. J.; Iverson, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 15174–15175.
13. Zhou, Q.-Z.; Jiang, X.-K.; Shao, X.-B.; Chen, G.-J.; Jia, M.-X.; Li, Z.-T. *Org. Lett.* **2003**, *5*, 1955–1958.
14. For recent examples of the application of the donor–acceptor interaction between neutral aromatic units for the self-assembly of other kinds of supramolecular structures, see: (a) Cubberley, M. S.; Iverson, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 7560–7563. (b) Zhao, X.; Jia, M.-X.; Jiang, X.-K.; Wu, L.-Z.; Li, Z.-T.; Chen, G.-J. *J. Org. Chem.* **2004**, *69*, 270–279. (c) Hansen, J. G.; Feeder, N.; Hamilton, D. G.; Gunter, M. J.; Becher, J.; Sanders, J. K. M. *Org. Lett.* **2000**, *2*, 449–452. (d) Wang, X.-Z.; Li, X.-Q.; Chen, Y.-Q.; Shao, X.-B.; Zhao,

X.; Deng, P.; Jiang, X.-K.; Li, Z.-T. *Chem. Eur. J.* **2003**, *9*, 2904–2913. (e) Li, X.-Q.; Feng, D.-J.; Jiang, X.-K.; Li, Z.-T. *Tetrahedron* **2004**, *60*, 8275–8284. (f) Feng, D.-J.; Li, X.-Q.; Wang, X.-Z.; Jiang, X.-K.; Li, Z.-T. *Tetrahedron* **2004**, *60*, 6137–6144.

15. Several linear compounds incorporating two to four 1,5-oxynaphthalene units have been reported, see: Amabilino, D. B.; Ashton, P. R.; Balzani, V.; Boyd, S. E.; Credi, A.; Lee, J. Y.; Menzer, S.; Stoddart, J. F.; Venturi, M.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 4295–4307.
16. Hamilton, D. G.; Davies, J. E.; Prodi, L.; Sanders, J. K. M. *Chem. Eur. J.* **1998**, *4*, 608–620.
17. Otsuki, J.; Okuda, N.; Amamiya, T.; Araki, K.; Seno, M. *Chem. Commun.* **1997**, 311–312.
18. Tung, C.; Wang, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6322–6328.
19. (a) Conners, K. A. Binding Constants: the Measurement of Molecular Complex Stability; Wiley: New York, 1987. (b) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: New York, 1991; p 123.
20. Job, P. *Ann. Chim. Ser.* **1928**, *9*, 113–121.
21. The increase of the solvent polarity usually improves the stability of complexes in polar solvent when the solvophobic interaction is the major driving force, see: (a) Wu, A.; Mukhopadhyay, P.; Chakraborty, A.; Fettinger, J. C.; Isaacs, L. *J. Am. Chem. Soc.* **2004**, *126*, 10035–10043. (b) Mukhopadhyay, P.; Wu, A.; Isaacs, L. *J. Org. Chem.* **2004**, *69*, 6157–6164.
22. (a) Hamilton, D. G.; Montalti, M.; Prodi, L.; Fontani, M.; Zanello, P.; Sanders, J. K. M. *Chem. Eur. J.* **2000**, *6*, 608–617. (b) Zych, A. J.; Iverson, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 8898–8909. (c) Shao, X.-B.; Wang, X.-Z.; Jiang, X.-K.; Li, Z.-T.; Zhu, S.-Z. *Tetrahedron* **2003**, *59*, 4881–4889.
23. Syamakumari, A.; Schenning, A. P. H. J.; Meijer, E. W. *Chem. Eur. J.* **2002**, *8*, 3353–3361.
24. We initially attempted to prepare **15** from the reaction of **22** and *N*, *N*′-di(chlorocarbonylmethyl)pyromellitic diimide (Rhone-Poulenc, S. A. USA Patent 6,515,709, 1964), but did not succeed.
25. (a) Chen, G.-J.; Liu, R.-Z.; Silaghi-Dumitrescu, I.; Espinoza-Perez, G.; Zentella-Dehesa, A.; Lara-Ochoa, F. *Int. J. Quantum Chem.* **2001**, *83*, 60–69. (b) Chen, G.-J.; Su, S.; Liu, R.-Z. *J. Phys. Chem. B* **2002**, *106*, 1570–1575. (c) Tan, H.-W.; Qu, W.; Chen, G.-J.; Liu, R.-Z. *Chem. Phys. Lett.* **2003**, *369*, 556–559.
26. Nishinaka, Y.; Satoh, T.; Miura, M.; Morisaka, H.; Nomura, M.; Matsui, H.; Yamaguchi, C. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1727–1732.
27. Tung, C.-H.; Yuan, Z.-Y.; Wu, L.-Z.; Weiss, R. G. *J. Org. Chem.* **1999**, *64*, 5156–5161.
28. Becher, J.; Matthews, O. A.; Nielsen, M. B.; Raymo, F. M.; Stoddart, J. F. *Synlett* **1999**, 330–333.
29. Green, S.; Fox, M. A. *J. Phys. Chem.* **1995**, *99*, 14752–14757.
30. Struijk, C. W.; Sieval, A. B.; Dakhorst, J. E. J.; van Dijk, M.; Kimkes, P.; Koehorst, R. B. M.; Donker, H.; Schaafsma, T. J.; Picken, S. J.; van de Craats, A. M.; Warman, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 11057–11066.
31. *Hyperchem 5.1 for windows*; Hypercube Inc.: 1115 NW 4th Street, Gainesville, FL 32601-4256.
32. Chen, G.-J.; Cruz, R.; Martinze, M.; Lara-Ochoa, F. *J. Mol. Struct. (THEOCHEM)* **2000**, *496*, 73–80.

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Conservation of helical asymmetry in chiral interactions

David Zhigang Wang*

Department of Chemistry, Columbia University, 3000 Broadway, MC 3151, New York, NY 10027, USA

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Dedicated to Professor Thomas J. Katz on the occasion of his 69th birthday

Abstract—A theory for chiral molecular recognition and induction is presented that attributes enantioselection to electronic interactions. It assigns helicities to chiral molecules and has a chiral host or catalyst preferentially recognize or induce chirality of the same helicity. This principle of conservation of helical asymmetry agrees well with many experiments, accommodates results that conventional steric reasoning cannot, and promises predictive power. The work suggests that helical electronic effects may generally exert greater control than steric effects in enantioselection.

1. Introduction

The phenomena of molecular chirality and chiral interactions are of fundamental importance in a wide range of fields including chemistry, biology, medicine and materials.[1] Enantioselection, that is, the formation of one enantiomer preferentially over its mirror image in an asymmetric reaction, is usually thought to have a geometrical origin thus to favorably develop through a transition state that has less steric hindrance. It is, therefore, often analyzed by means of steric size-based considerations complemented with, in some cases, such electronic factors as hydrogen-bonding, π–π stacking and electrostatics.[2] However, experimental observations contradicting the prevalent steric theories abound in literature. Described here is an alternative, an electronic theory of chiral interactions,[3] which it will be shown accounts successfully for the enantioselection observed in a large number of chiral induction and recognition experiments. The theory is based on identifying the helicities of chiral molecules, including those that at first do not seem helical. Like theories that account for optical activity as a consequence of electron movement on helical paths,[4,5] it views all chiral molecules as helical.

2. Results and discussion

A simple 5-atom chiral molecule, for example, C*HFBrCl, does not appear to be helical since every pair of covalent bonds seems coplanar. However, helical electronic structures can be visualized and analyzed in these and other molecules by supposing that unbalanced electronic repulsions, measured by group polarizabilities that characterize the sensitivity of a group's electron density to distort in an electric field, deform the bonds into helices. This idea is an outgrowth of earlier attempts, long pursued, to identify helical electronic paths in chiral molecules.[5]

Suppose that in C*$abcd$, a point-chiral molecule in which substituents a, b, c, and d are attached to central chiral atom C*, the polarizabilities of the substituents follow the sequence $a>b>c>d$. The helical structures in this molecule are identified in Scheme 1 by a procedure proposed by Yin.[6] Consider, for example, the pair of covalent bonds a–C*–b. The anisotropic electronic fields of c and d should distort a–C*–b from co-planarity into a micro-helical electronic structure.[3b] If, as in electronic theories of optical activity,[5] the distortion increases with group polarizability, it is reasonable to expect the strength of repulsion, represented by the length of the doubly arrowed lines on the left in Scheme 1, to follow the sequences a–$c>b$–c; and a–$d>b$–d. The result should be to twist the a–C* bond up more than the b–C* bond. The bonds will thus be twisted into a right-handed micro-helix. Similar effects, illustrated in Scheme 1, will twist the a–C*–d, b–C*–c, and c–C*–d bonds into right-handed micro-helices and the a–C*–c and b–C*–d bonds into left-handed

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* Tel.: +1 212 854 4964; fax: +1 212 932 1289;
e-mail: zw61@columbia.edu

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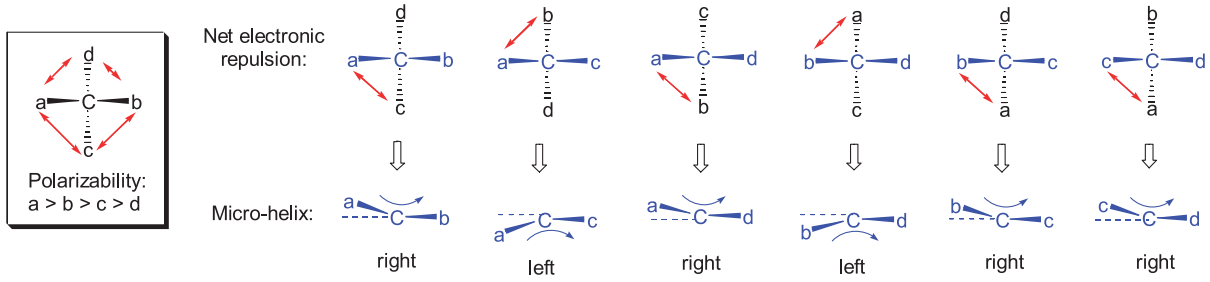
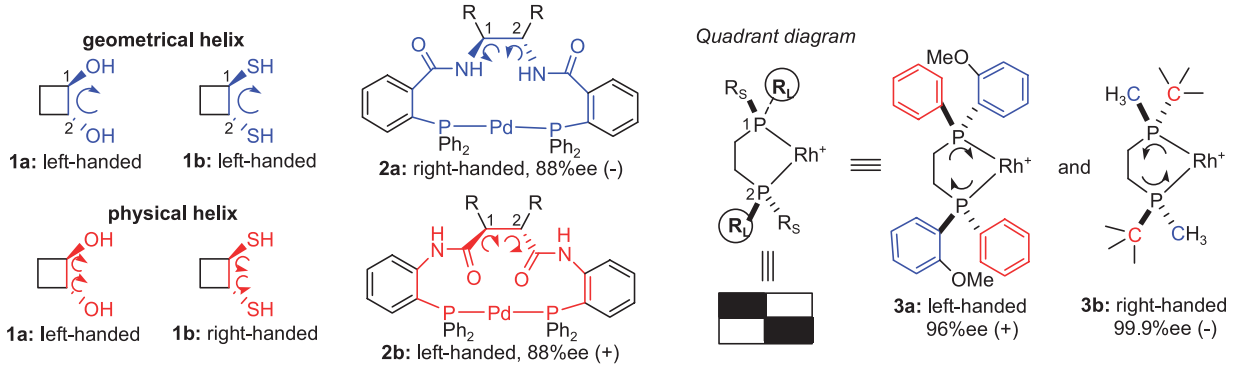


Scheme 1. Helical structures in a typical point-chiral molecule C*abcd* with a group polarizability sequence $a>b>c>d$.

micro-helices. Since there are more right-handed than left-handed structures, the molecule has a net right-handed helicity.[7] A molecule's net electronic helicity, thus its optical activity, would disappear if any two groups are the same.

The polarizabilities of a limited number of common groups can be obtained from measurements of atomic refractive indices ($I>Br>SH>Cl>C{\equiv}N>C_6H_5>C{=}O>CH_3>NH_2>OH>H>D>F$), but not of many other significant groups for which such data are unavailable.[8,9] However, some general ranking principles, which are direct consequences of the polarizability characters and are widely used,[9] make it possible to deduce the sequence of polarizabilities even though precise data are unavailable. These principles include the following: in a group atoms with larger numbers of electron shells > atoms with smaller numbers of electron shells, in a period atoms with lower nuclear charge > atoms with higher nuclear charge, transition metals > organic groups, lone pair electrons > bonding electrons, triple bonds > double bonds > single bonds, aromatic and π-groups > alkyls, strained alkyls > unstrained alkyls, groups with more conjugation > analogous groups with less conjugation, electron-rich groups > electron-poor analogues, and for the central carbon in simple alkyls $CH_3>1^\circ\ CH_2R>2^\circ\ CHR_2>3^\circ\ CR_3$ (because *C*–H > *C*–C).[9] In addition, the electron repulsion responsible for orbital twisting within groups should arise largely from the bonds and atoms that are directly attached to the chiral center. Thus for multi-atom groups, in agreement with Brewster's suggestion, the polarizability ranking should be assigned according to the polarizabilities of the atoms or moieties directly attached to the chiral center (i.e., local polarizability), and not according to the polarizabilities of the whole group.[8a] The above principles serve as general guidelines in group polarizability rankings and will be closely and consistently followed throughout the work. Specifically, polarizability rankings are explicitly shown whenever molecular helicity analyses are needed and also are comprehensively compiled in the Supplementary data of this article.[10]

There is a significant difference between the micro-helical structures described here and those described earlier, notably by Brewster et. al.[5a,11] The former, because of their origins in asymmetric orbital twisting, have electronic properties that the latter, because of their purely geometrical origin, do not. We distinguish the two by calling the former a 'physical helix' and the latter a 'geometrical helix'.[12] Scheme 2 illustrates the difference for two related molecules, **1a** and **1b**. According to Brewster's conformational helix analysis, the HX–C^1*–C^2*–XH fragments define left-handed geometries whether X=O or X=S. However, the group local polarizability sequence around each chiral center is O<C* in **1a** and S>C* in **1b**. Accordingly, when deformed by a CH_2 and an H (the former being more polarizable), the physical helices, which in the HO–C^1*–C^2*–OH moiety are left-handed, in the HS–C^1*–C^2*–SH moiety are right-handed (note that at each chiral center only the local helix that develops along the HX–C^1*–C^2*–XH moiety, that is, –X–C^1*-C^2*– at the C^1* center and –C^1*–C^2*–X– at the C^2* center, but not the total six micro-helices, needs to be considered)! Thus, while as bidentate



Scheme 2. An illustration of the different electronic properties of geometrically similar chiral molecules **1a–b**, and the failure of steric effects and the success of electronic effects to account for the direction of enantioselection in the allylations and hydrogenations catalyzed by Palladium or Rhodium-complexes. Handedness of catalyst ring helices -P-phenyl-amide–C^1*–C^2*-amide-phenyl-P-Pd- in **2a–b** and –P^1*–CH_2–CH_2–P^2*–Rh- in **3a–b**, observed ees and rotation signs of the favored products are shown below each catalyst. The numbers 1 and 2 label the chiral centers. The positions of larger (R_L) and smaller (R_S) substituents in **3a–b** are shown at the left. P-substituents of higher local polarizability are shown in blue and of lower local polarizability in red. R–R = *trans*-9, 10-dihydro-9, 10-ethanoanthracene.

ligands in asymmetric catalysis **1a** and **1b** may resemble each other sterically, electronically they do not. The Supplementary data shows how physical and geometrical helices also can be identified in planar, axial, and other chiralities.[10,13] In small and conformationally flexible point chiral molecules C*abcd*, geometrical helices may be completely absent.

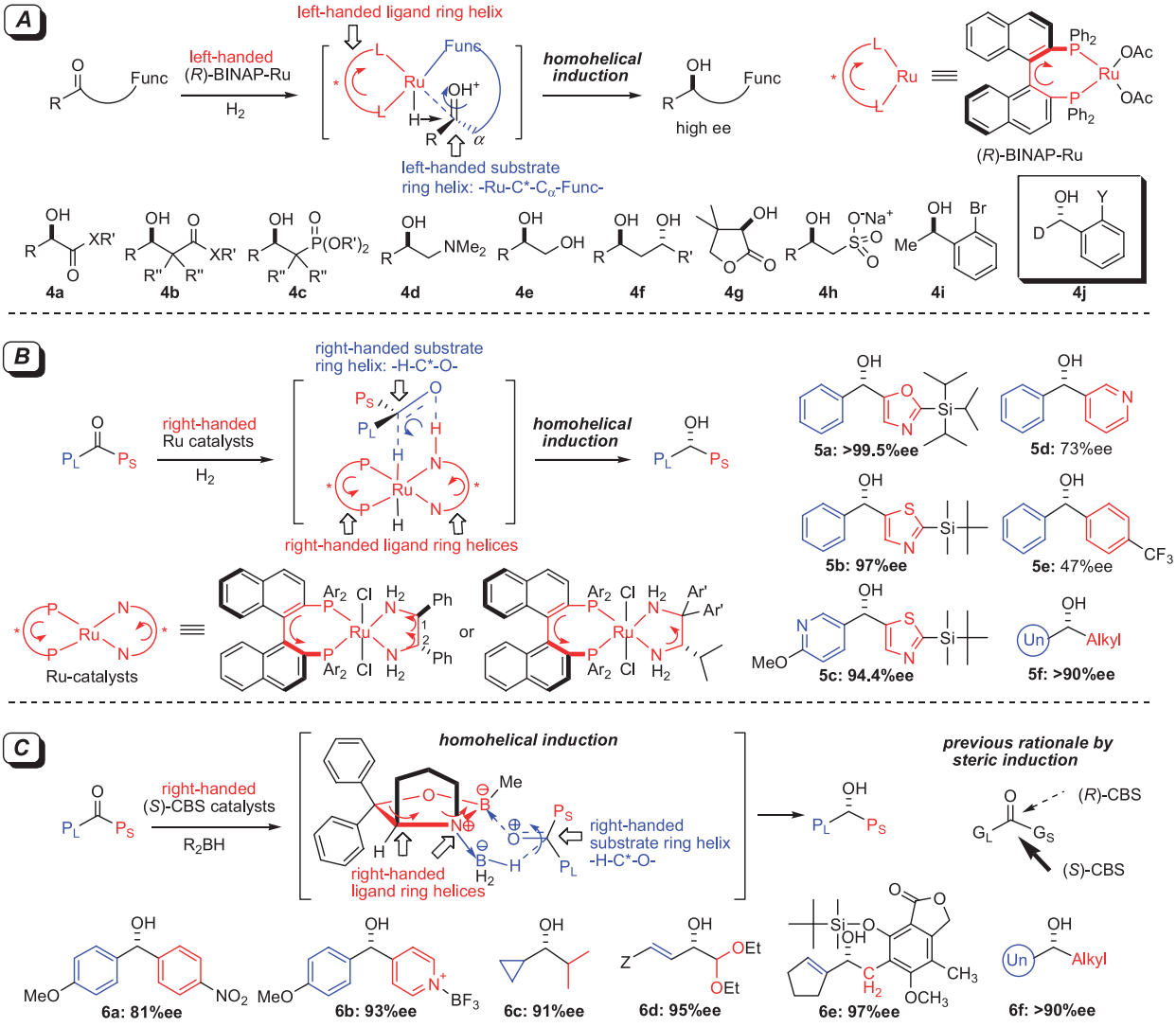
In chemical reactions, geometrical helices relate to asymmetries in the shapes of asymmetric reactants, while physical helices characterize fine electronic tunings, but not steric size. Steric effects in asymmetric interactions have been analyzed frequently. The question considered here is whether electronic effects also play a role. Since, there are only two chiralities, right- and left-handed helicity, the diastereomeric interactions between two chiral molecules are either homohelical (when the interacting helices have the same handedness) or heterohelical (when they do not). The interesting question is whether one is energetically more favorable and, if so, which. In a separate paper,[14a] we have shown, by employing the classical electron-on-a-helix theoretical model of Tinoco and Woody,[14b] that a homohelical electronic interaction is always lower in energy than its diastereomeric heterohelical electronic interaction and their energetic difference, which in an asymmetric reaction corresponds to the difference between the free energy changes that determines the magnitude of enantioselectivity, is sufficient to bring about high enantiomeric excess (ee). Indeed, the remarkable observation is that, in experiment after experiment, homohelical interactions always seem to be favored. A chiral host recognizes a guest of the same helical handedness, and the electronic handedness of a chiral catalyst seems to govern the favored direction for its complexation to a pro-chiral substrate that allows it to preserve its helicity in the enantioselection-determining step[15] and, therefore, the stereochemistry of the product it gives. This principle of conservation of helical asymmetry makes stereochemical predictions possible. In asymmetric induction, a reversal of catalyst handedness, which, as shown below, does not necessarily correlate to a reversal of catalyst chirality (configuration and conformation), often results in the reversal of product stereochemistry.

An example is enantioselective allylation catalyzed by chiral Pd-complexes **2a** and **2b**.[16] While the scaffolds in **2a** and **2b** have the same sense of chirality, inverting the orientation of the amide function reverses the sense of the product's chirality (Scheme 2). This can readily be understood on the basis of an analysis of the handedness of the catalyst ring helices which are crucial in executing chiral induction (specifically herein these helices are –N–C^1*–C^2*– at the C^1* center and –C^1*–C^2*–N– at the C^2* center in **2a**, –C(O)–C^1*–C^2*– at the C^1* center and –C^1*–C^2*–C(O)– at the C^2* center in **2b**, respectively. Only these helices need to be considered because they fall into the corresponding catalyst ring structure, therefore, determine the catalyst's handedness). The polarizability sequence around chiral centers flips from N<C* in **2a** to C=O>C* in **2b**, so **2a** is right-handed and **2b** is left-handed. Consequently, they induce opposite chiralities in the products. Particularly interesting are the highly enantioselective hydrogenations of dehydroamino acids catalyzed by the chiral rhodium complexes because, as **3a** and **3b** in Scheme 2 shows, the principle of homohelical interactions again accounts for the directions of enantioselection while steric theories, most notably the so-called quadrant rule, appear to fail.[17] The bulkier phosphorus-substituents in both catalysts occupy the top-left and bottom-right quadrants. However, curiously, **3a** gives (+)-amino acids and **3b** the (−)-enantiomers, both in high ee.[18] These seemingly puzzling results would be expected if helical electronic effects prevail. Since in both catalysts two of the substituents at each phosphorus atom, the CH_2 and Rh, are the same (Rh>CH_2 in polarizability), the different results could be attributed to the opposite handedness of the catalyst ring helices in **3a** and **3b**, that is, –CH_2–P^1*–Rh– at the P^1* center and –CH_2–P^2*–Rh– at the P^2* center. It is the larger of the two diaryl substituents and the smaller of the two dialkyl substituents that has the larger local polarizability. It merits a note that the catalyst handedness-favored product enantiomer correlations reached here are generally applicable to other highly enantioselective catalysts examined in the same reactions.

2.1. Homohelical induction in asymmetric catalysis

Although the principles of this helix theory are applicable to any asymmetric process, in the following discussions we choose to focus on asymmetric hydrogenations for the following considerations: (1) these fields are most fruitfully developed and the several reactions of known mechanisms, established by pioneering studies,[2a] provide a solid platform on which the independent helix analysis, thus the predictive power of the theory, can be tested against numerous experiments; (2) a reaction mechanism itself does not reveal its potential stereochemical bias towards a pro-chiral substrate, so previous stereochemical rationales have largely been applying the steric hindrance into the corresponding enantioselection-determining steps in those known mechanisms and deducing the sense of asymmetric induction by the more sterically favored pathways. Spectacular exceptions to each of these steric rationales exist and it is curious to see whether this electronic theory, specifically helical electronic effects and conservation of helicity, could yield more general catalyst-product stereochemical correlations; (3) these fields encompass both metal-based catalysis and organo-catalysis thus are of exemplary generalities for the theory to illustrate its principles and utilities.

Scheme 3 shows how a molecule is being hydrogenated, the respective mechanism has been established. Case A illustrates ruthenium-catalyzed hydrogenations of functionalized ketones. Func-C_α–(C=O)–R where 'Func' is a functional group, should coordinate to a (*R*)-BINAP-ruthenium catalyst.[19] The left-handed helicity of the (*R*)-BINAP ligand induces a left-handed helicity in the substrate ring Ru–C*–C_α-Func. The essential points are that the ruthenium atom, whose polarizability is much larger than that of any organic C_α fragment, is bonded to the carbonyl carbon and the polarizabilities of the R groups, which could be alkyls or aryls, should all be larger than that of the hard acid OH^+. The enantiomeric excesses achieved in these hydrogenations are all high, and the directions of enantioselection are all in accord with this model. Notably, the direction of



Scheme 3. Homohelical induction in (A) Ru-catalyzed hydrogenations of functionalized ketones; (B) Ru-catalyzed hydrogenations of simple ketones; and (C) Itsuno-Corey reductions using an (*S*)- oxazaborolidine catalyst. The catalysts' helicities are as indicated and the hydrogenations all proceed with the stereochemistries according to the homohelical induction principle. Observed ee is listed under the structure. The ketone substituents of larger polarizability are shown on the left (in blue) and those of smaller polarizability are shown on the right (in red). Notice that hydrogen attaches to the same face of each ketone, even when the larger group is on the right (examples **5a–c**, **5e**, and **6c–e**). Substrates whose substituents do not differ appreciably in polarizability are reduced with low ees (examples **5d**, **5e**). Func=functional group; R=alkyls or aryls. X=O, NH, NR and S; Y=OMe, Br. Z=$CH(CH_3)OSi^tBu(Ph)_2$. Ar=3,5-$(CH_3)_2C_6H_3$, Ar′=*p*-$OCH_3C_6H_4$. Un=unsaturated group. G_L=substituent of larger size; G_S=substituent of smaller size.

enantioselection is reversed in the hydrogenations of *o*-methoxy- and *o*-bromo-benzaldehydes to give **4j**, which is in accord with the theory because deuterium, unlike other R groups, is less polarizable than OH^+.[20]

Case B is ruthenium-catalyzed hydrogenations of unfunctionalized ketones. In the case of simple unfunctionalized ketones, asymmetric hydrogenations are catalyzed by diphosphine-diamine-Ru-compounds, but the mechanisms followed are very different.[21] They involve the pericyclic transfer of hydrogens from ligand nitrogen to substrate oxygen and from ruthenium to carbon. Accordingly, the very large difference between the polarizabilities of Ru and C_α, which dominate the chiralities in the case of functionalized carbonyl hydrogenations, in this case cannot make the chiralities insensitive to the nature of ketone substitutents. Because the polarizability difference between H and O in a partially broken C=O bond is relatively small, it is the polarizability distinction between the two carbonyl substitutents P_L and P_S that determines the twisting of the substrate ring helix –H–C*–O–. Since in both catalysts in Scheme 3, the diphosphine ring and diamine ring both have right-handed helicities, that is, helix -P–C=C–C=C–P- from the atropisomeric skew and helices –N–C^1*–C^2– at the C^1* center and –C^1–C^2*–N– at the C^2* center (both analyzed by two local polarizability sequences: Ph>H; and C*>N. Note also that it is exemplified here that a complete knowledge on the local polarizability ranking of all the four groups is not needed because, as previously emphasized in helicity analyses of **1**–**3**, usually only one helix at a chiral center, that is, the helix that develops along the catalyst/ligand ring structure, is critical for chiral interaction thus is under concern), the homohelical induction principle requires the hydride to attack preferentially as shown, because only with this enantiofacial selection can the substrate ring helix –H–C*–O– also

develop right-handed helicity in the transition state (polarizability sequences: O > H; and $P_L > P_S$). Note that it is not the sizes of the substituents that are important, but their local polarizabilities, which accords with experience, for only aromatic and unsaturated ketones have thus far been found to give high enantioselectivities. Herein, for **5a–d** substituents local polarizabilities are known to follow benzene > pyridine > thiazole > oxazole,[22] and for **5e** benzene is more polarizable than another benzene that is electron-withdrawn by a *para*-CF_3 group. Interestingly, it can also be seen that the higher the local polarizability distinction, the higher the ee. It should be pointed out that application of conventional steric considerations to **5d** is rather hopeless because the substituents are nearly equal in sizes, and to **5a–c** and **5e** yields wrong enantiomers because in each of them the group on the right is larger than that on the left.[19,23]

Case C shows the expected outcomes of oxazaborolidine-BH_3 catalyzed ketone reductions using a so-called Corey–Bakshi–Shibata ('CBS') catalyst.[24] The (*S*)-configured catalyst has right-handed helicity.[10] For **6a–b**, whose substituents are isosteric, it is unclear how steric effects could lead to the large enantiomeric excesses observed. For **6c–e**, whose left-side substituents are less bulkier than the right-side ones, they again seem to give the wrong predictions. However, in each of these cases the homohelical induction principle does lead to the result observed. Particularly important substrates for asymmetric hydrogenations are those represented in **5f** and **6f**. It is well appreciated that the unsaturated group could be generally varied among aromatics, hetero-aromatics, ferrocenes, olefins or acetylenes, despite considerable changes on sizes, without sacrificing the enantioselections, which have been, however, customarily attributed to steric effects.[19,24] It is now clear that these groups share a highly polarizable π-electron component and it is the comparably high π-versus-σ alkyl local electronic polarizability distinctions that ensure their successes. It should be emphasized that molecules employed in the above cases are just illustrative, and as summarized in the Supplementary data, this polarizability rule not only equally effectively applies to all other substrates and other enantioselective catalysts, but also to other asymmetric reactions as well, such as transfer hydrogenations, hydroborations and Heck reactions etc., and perhaps most significantly, it accommodates results that steric theories cannot.[10,25] The above discussions illustrate some utilities of the principle of the conservation of helicity in rationalizing and predicting stereochemical outcomes for asymmetric reactions whose mechanisms in their analogous achiral processes are known. Alternatively, the principle may be also useful for clarifying reactions of unknown mechanisms under the notion that the combination of independent helicity analysis and a reasonable mechanistic proposal should lead to stereochemical results that are in accord with experimental observations.

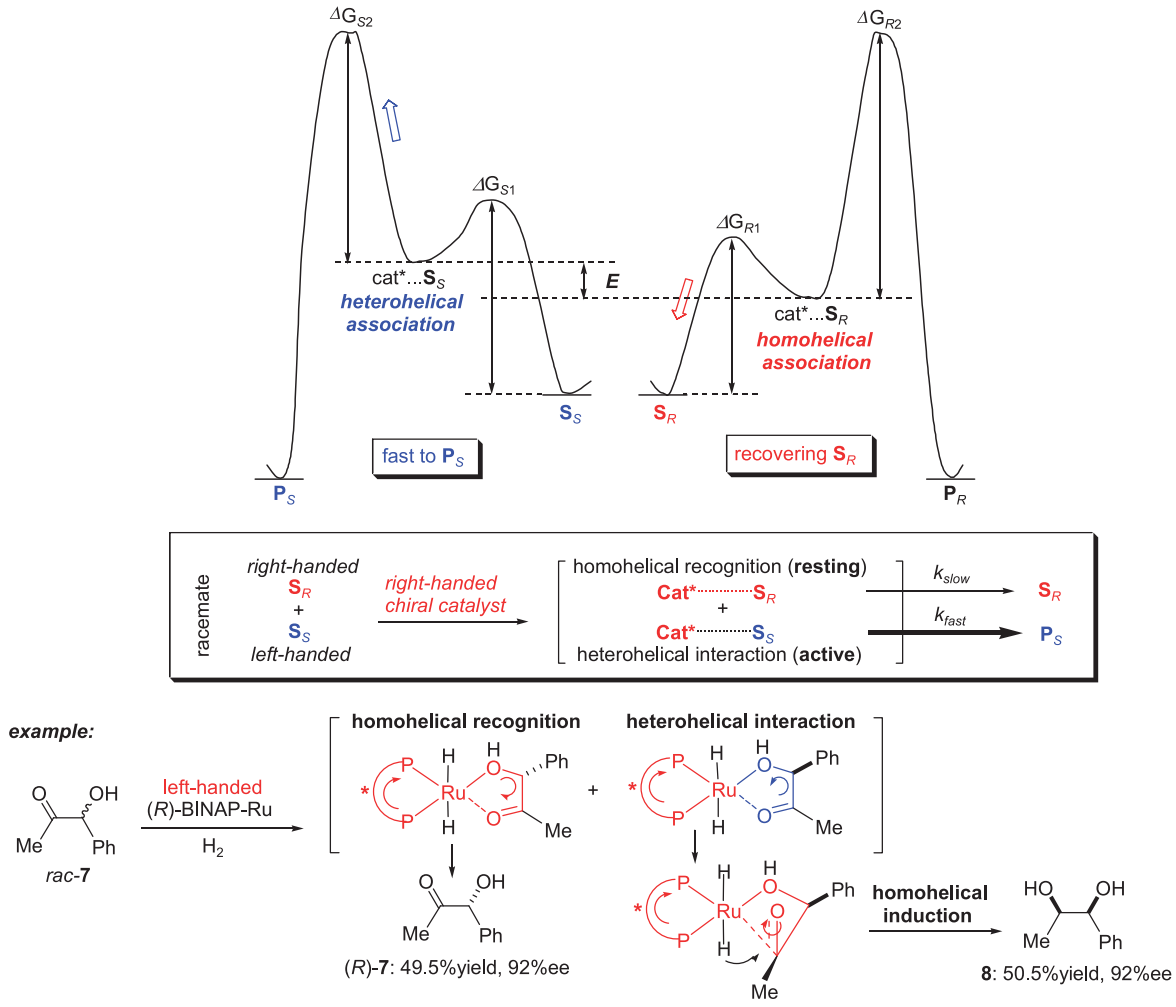
2.2. Homohelical recognition control in kinetic resolution

Kinetic resolutions originate from enantiomers in an asymmetric environment reacting at different rates.[26] They are often achieved by treating racemates with chiral catalysts, which, ideally, leads to the derived product and the recovery of the more slowly reacting enantiomer, both in high yield and enantiomeric excess. Conceptually the realization of a kinetic resolution process is attributed to a chiral catalyst's ability to discriminate the enantiomers, that is, chiral recognition occurs only between one enantiomer and the catalyst.[27] There are two basic stereochemical questions associated with such a process. One, how does a chiral catalyst enantioselectively recognize that enantiomer? Two, does that recognition render a resultant substrate-catalyst combination more reactive, or less?

We have proposed above that chiral molecular recognition electronically follows a homohelical interaction mechanism, in which the chiral host can enantioselectively recognize the guest enantiomer that possesses the same helical handedness in their enantio-discriminating complexations. Applying this homohelical recognition principle to a kinetic resolution system seems to be informative in answering both questions posed above: the catalyst can selectively recognize one enantiomer of the racemate by electronically favorable homohelical interaction and that electronic preference makes the corresponding combination lower in energy and thus less reactive.

The idea is illustrated in Scheme 4. Considered is the kinetic resolution of a racemic substrate **S** by the action of a right-handed catalyst (cat*). The reaction in this simplified picture has two steps: the association of catalyst with substrate, in which both a homohelical pair cat*-$\mathbf{S}_R$ and a heterohelical pair cat*-$\mathbf{S}_S$ are formed; and the subsequent derivatization reaction that is often rate-determining. If, as shown previously, homohelical electronic interactions are favored, intermediate cat*-$\mathbf{S}_R$ is lower in energy than cat*-$\mathbf{S}_S$. This may raise the barrier ΔG_{R2} above that of ΔG_{S2}. In consequence, cat*-$\mathbf{S}_R$ releases $\mathbf{S}_R$, and the cat*-$\mathbf{S}_S$ defines a kinetically active reaction channel that delivers the derived product $\mathbf{P}_S$. At a certain conversion, both $\mathbf{S}_R$ and $\mathbf{P}_S$ would be produced in excess. This conclusion is of practical utilities because a simple examination of helical electronic interactions in the catalyst–substrate associations, whose structures are often more easily inferable than those of the intermediates in the derivatization steps, could suggest useful clues to the reaction stereochemical outcomes.[28]

Kinetic resolution of *rac*-**7** by stereoselective hydrogenation catalyzed by a (*R*)-BINAP-Ru catalyst exemplifies this homohelical recognition control principle (Scheme 4).[29] The catalyst features a left-handed ligand ring helix to which *rac*-**7** complexes as a functionalized ketone. The substrate ring helix –Ru–O–C*–C═O– is left-handed in (*R*)-**7** and right-handed in (*S*)-**7** owing to polarizability sequences C═O > O, and Ph > H. Therefore, (*R*)-BINAP-Ru/(*R*)-**7** is homohelical and (*R*)-BINAP-Ru/(*S*)-**7** is heterohelical. The former, because it is lower in energy, leads to (*R*)-**7** being recovered in a 49.5% yield and 92% ee. The latter leads to hydrogenation and, as already discussed in case A of Scheme 3, the establishment of stereochemistry at the newly formed chirality is controlled by homohelical induction, which yields **8** in a 50.5% yield and 92% ee. This example not only shows that the full stereochemical course



Scheme 4. A simple homohelical recognition control profile for the stereochemical course of a kinetic resolution. When a chiral catalyst interacts with a racemate, the homohelical recognition pair leads to the substrate enantiomer being recovered and the heterohelical interaction pair is reacting. The bottom shows the homohelical recognition control in kinetic resolution of *rac*-**7** by (*R*)-BINAP-Ru-catalyzed stereoselective hydrogenation.

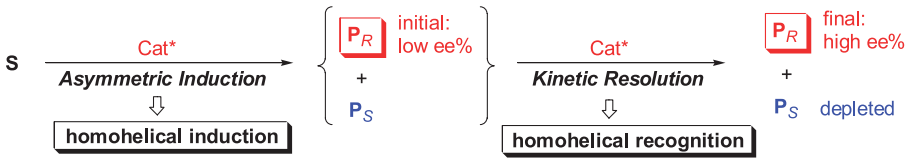
in an efficient kinetic resolution process can be rationally deduced on the basis of homohelical recognition/induction analysis, but it also suggests that the tendency to gain homohelical interaction in an initially unfavorable heterohelical catalyst–substrate association may serve as the driving force for kinetic activity. Thus, homohelical interactions are generally favorable in chiral systems. Systems that enjoy these interactions are less reactive than those that do not.

This electronic theory accounts for the observed results for a wide variety of efficient kinetic resolution systems. It is very predictive. It also accommodates results that conventional steric reasoning cannot. Details are assembled in the supplementary data.[10] Among the systems analyzed are: stereoselective ketone hydrogenations, transfer hydrogenations, ring closing metatheses, sulfides/sulfoxides oxidations, lactones ring openings, kinetic resolution of alkyne-containing substrates, epoxides ring openings (hydrolytic kinetic resolutions), kinetic resolutions of allylic alcohols by dioxirane-catalyzed oxidation, asymmetric epoxidations-based kinetic resolution of secondary allylic, furyl, pyrryl, thienyl and amino alcohols, asymmetric dihydroxylations-based kinetic resolutions, asymmetric alcoholyses of anhydrides, asymmetric ring opening of anhydrides with chiral Lewis acids, Pd-catalyzed aerobic oxidative kinetic resolution of alcohols, kinetic acylations of alcohols by chirally modified DMAPs, and several other processes related to the above systems. Aided by this theory, we also suggest answers to some important questions, such as why dihydroxylations lead to poor kinetic resolutions even though they lead to excellent asymmetric inductions.

Two consequences of homohelical control as the governing electronic factor in efficient kinetic resolutions relate to the stereochemical link between asymmetric induction and kinetic resolution.

1. Since both asymmetric induction and kinetic resolution are both favored by homohelical interactions, enantioselective syntheses should be facilitated by one-pot processes in which the same catalyst or two different catalysts of the same helicity bring about both reactions. This is illustrated in Scheme 5.

Not only does asymmetric catalysis tend to generate an excess of product enantiomer $\mathbf{P}_R$ from pro-chiral substrate **S**, but the subsequent kinetic resolution step tends to



Scheme 5. A 'push–pull' mechanism for product enantio-enrichment in a one-pot asymmetric catalysis-kinetic resolution reaction.

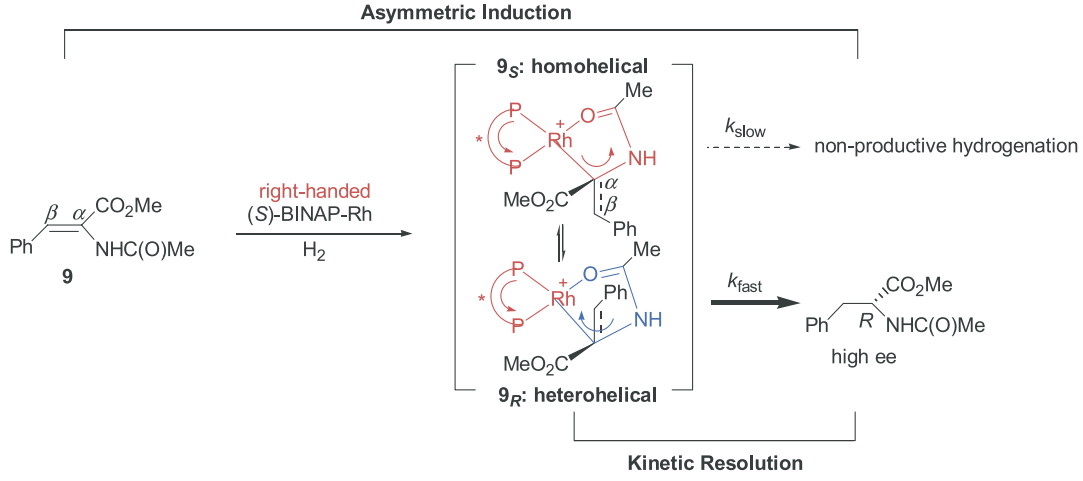
enhance the selectivity by depleting the oppositely handed and more reactive enantiomer $\mathbf{P}_S$ (the latter is more reactive because it forms the heterohelical complex with the catalyst). In other words, while homohelical electronic interaction generates homohelicity in the former, it preserves it in the latter! This suggests that appropriate combinations of asymmetric catalysis and kinetic resolution in a single flask, even with catalysts of mediocre enantio-differentiation ability, should allow reactions that initially give products of low ee to give them, ultimately, in high ee. There should be a 'push–pull' mechanism for enantio-enrichment. Systems employing this strategy, although rare presently, have already proven successful.[10,30]

2. Are asymmetric induction and kinetic resolution stereochemically identical? The fundamental basis for both is clearly homohelical electronic interaction. Consider, for example, asymmetric hydrogenation of enamides **9** catalyzed by chiral diphosphine/Rh complexes. It is known that in this reaction, the minor, not the predominant catalyst–substrate complex, leads to the observed product enantiomer.[31] When the catalyst is, for example, right-handed (*S*)-BINAP-Rh, helical electronic interaction analysis shows that the predominant complex $\mathbf{9}_S$ is homohelical and the minor one $\mathbf{9}_R$, is heterohelical (Scheme 6). Substrate ring helicity is assigned primarily based on the helix –O═C–NH–C_α–Rh– on the C_α center (polarizabilitites: Rh > N, and ester C═O > β-2° CH_2). It has been shown that C_α lies closest to the Rh coordination plane and enantioselectivities in enamide hydrogenations are governed by the nature of the C_α-substituents.[32]

This suggests that there is no clear conceptual boundary between asymmetric induction and kinetic resolution. They share the same homohelical identity in realizing stereochemical control. When viewed as the transformation of an achiral alkene substrate to a chiral amino acid product, the reaction is formally an asymmetric induction. However, when viewed as the transformation of the catalyst–substrate complexes $\mathbf{9}_S$ and $\mathbf{9}_R$ (in which the substrate becomes chiral) to products, it is essentially a kinetic resolution! The key point is that the catalyst-substrate complexes have strong tendency to achieve homohelical electronic interactions that lower the system energy (as compared to the corresponding heterohelical interaction). If the homohelical character acquired in this early-stage complexation is not sufficiently high and more energy lowering can be gained in a late-stage intermediate along the reaction coordinate, as in the vast majority of cases of asymmetric synthesis, the reaction will proceed through this homohelical pathway to deliver the favored product enantiomer. However, if an inversed situation is encountered, such as that found in this type of hydrogenation, the initial homohelical complexation characterizes a resting state which is reluctant to undergo further reaction, and consequently the dominant process is kinetic resolution. This homohelical interaction paradox on asymmetric induction-versus-kinetic resolution essentially exists in all chirality producing processes, and an overwhelming predominance of either one can lead to high levels of enantioselection.

3. Conclusion

In summary, the assumption that there is an electronic interaction between chiral molecules, which we call homohelical interaction or the conservation of helical asymmetry, leads to correct analyses of the outcomes of many asymmetric transformations, even in cases that seem not to be predicted correctly on the basis of prevailing theories, which consider largely steric effects. The applications discussed suggest that helical electronic effects



Scheme 6. The operation of kinetic resolution in asymmetric enamide hydrogenation.

may generally exert greater control than steric effects in enantioselection. In the next paper in this issue, it is further shown that high ees in an asymmetric reaction can be achieved when the characteristics of the interacting helices, such as those of a catalyst and the substrate complexed to it, are matched.[33] Consideration of such interactions could help guide the design of effective chiral catalysts and lead to new theories for electronic control in asymmetric induction. Using this principle, we suggest that homohelical recognition control is the governing electronic factor in kinetic resolutions. The described 'push–pull' mechanism for enantio-enrichment might at a very general level account for the homochirality observed in Nature. The theory is novel, simple, and general, and it possesses predictive power. We believe that generalizing molecular chirality on the basis of inherent helicity and unifying asymmetric induction and kinetic resolution in a single framework of homohelical electronic interaction should facilitate the rational discovery of new efficient asymmetric reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.05.058

General helix structure analyses for molecules of axial-, planar-, and other types of chiralities; detailed helicity assignments for chiral catalysts mentioned in the text; more illustrative examples of homohelical induction analysis in various asymmetric catalytic processes; and homohelical recognition control analyses for all kinetic resolution systems mentioned in the text.

References and notes

1. *Chirality in Natural and Applied Science*; Lough, W. J., Wainer, I. W., Eds.; CRC: New York, 2002.
2. (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999. (b) Ahuja, S. Chiral Separations by Chromatography; Oxford University Press: New York, 2000.
3. For a highlight on part of this work, see: (a) Rouhi, A. M. *Chem. Eng. News* **2003**, *81*, 34. September 29. For a brief overview, see: (b) Wang, D. Z. *Mendeleev Commun.* **2004**, *14*, 244.
4. Caldwell, D. J.; Eyring, H. *The Theory of Optical Activity*; Wiley: New York, 1971.
5. (a) Brewster, J. H. *Top. Steroechem.* **1967**, *2*, 1. (b) Brewster, J. H. *Top. Curr. Chem.* **1974**, *47*, 29.
6. Yin, Y. *HuaXueTongBao* **1993**, *10*, 1.
7. When right-handed helicity dominates, the molecule is dextrorotatory at long wavelengths, and left-handed helicity leads to levorotation. As concluded by Brewster in Ref. 5a, 'as a general rule, that a system in which electrons are constrained to right-handed helical paths will give a positive Cotton effect and dextro-rotation at long wavelength, enters, explicitly or implicitly, into all of the major theoretical models of optical activity'. Such a polarizability-bond structure connection thus provides a new way to assign absolute stereochemistry on the basis of optical rotation. See Ref. 10.
8. (a) Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5475. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 1084.
9. Polarizability characterizes the sensitivity of a group's electron density to distort in an electric field. It increases with higher electron density, lower nuclear attraction, larger electron shells, larger volume and smaller HOMO-LUMO energy gap. The exact value of a group's polarizability often depends on its chemical environment. A large set of bond/group polarizabilities has been compiled. Miller, K. J. *J. Am. Chem. Soc.* **1990**, *112*, 8533.
10. Supporting material accompanies this article on Tetrahedron online.
11. Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5483.
12. For discussions on the distinct difference between geometrical and physical features of chirality, see: Gilat, G. In *Concepts in Chemistry: a Contemporary Challenge*; Rouvray, D. H., Ed.; Research Studies: Taunton, 1996; Chapter 10, pp 325–354.
13. Physical helix analysis for naturally occurring L-amino acids of a general structure H_2N–C*(R)(H)–CO_2H yields a significant insight, that is, no matter what the R group is, the H_2N–C*–CO_2H fragment is always twisted into a right-handed micro-helix in all L-amino acids owing to the simple polarizability sequences: $CO_2H > NH_2$; and any R > H. Nature varies R but not H! In other words, the L-amino acids, previously conventionally called as left-handed, are virtually right-handed biological motifs in their absolute meanings. This right-handed homohelicity in all L-amino acids could be an essential structural foundation for both the formation/replication of homochiral peptides and the stability of their right-handed three dimension macro-helical structures.
14. (a) Wang, D. Z. *Chirality* **2005**, *17*, S177. (b) Tinoco, I., Jr.; Woody, R. W. *J. Chem. Phys.* **1964**, *40*, 160.
15. Note that in some reactions the enantioselection-determining step may not include the transition state thus is not necessarily also the rate-determining step.
16. Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386.
17. Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.
18. (a) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weikauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946. (b) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635.
19. Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.
20. Ohta, T.; Tsutsumi, T.; Takaya, H. *J. Organomet. Chem.* **1994**, *484*, 191.

21. Sandoval, C. A.; Ohkuma, T.; Muniz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490.
22. (a) Archibong, E. F.; Thakkar, A. *J. Mol. Phys.* **1994**, *81*, 557. (b) Kassimi, N. E.; Lin, Z. *J. Phys. Chem. A* **1998**, *102*, 9906. (c) Jug, K.; Chiodo, S.; Calaminici, P.; Avramopoulos, A.; Papadopoulos, M. G. *J. Phys. Chem. A* **2003**, *107*, 4172. (d) Bulgarevich, S. B.; Yusman, T. A.; Osipov, O. A. *J. Gener. Chem.* **1984**, *54*, 1427. (e) Kassimi, N. E.; Doerksen, R. J.; Thakkar, A. J. *J. Phys. Chem.* **1996**, *100*, 8752.
23. Chen, C.-Y.; Reamer, R. A.; Chilenski, J. R.; McWilliams, J. C. *Org. Lett.* **2003**, *12*, 2003. Predictions on the stereochemical outcomes of these substrates were in fact among those made earlier on the American Chemical Society's 38th National Organic Symposium, Bloomington, Indiana, June 8–12, 2003.
24. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
25. The analyses presented so far should not yield an expression that the roles of metal are unimportant for enantioselectivity. Although the general homohelical-versus-heterohelical energetic preference does not depend on the presence of a metal, a metal could, in addition to catalyzing a reaction, affects the reaction's stereochemical outcome in several ways: (1) upon complexation to a chiral ligand, for example, a phosphine, a metal could significantly change the phosphorus local polarizability through d–π bonding thus may inverse the sense of the helicity of the resulted catalyst; (2) a metal could change its modes of enantio-induction and recognition towards the same substrate, depending on specific chemical environments. Fox example, in the hydrogenation of a simple ketone R_1–C(O)–R_2, the same metal catalyst may lead to different ees of opposite senses if it binds to the pro-chiral carbonyl in a direct η^2-fashion under one situation and in a pericyclic fashion, as shown in the transition state of B of Scheme 3 in the text, under another situation. The conservation of helicity would lead to opposite carbonyl enantiofacial recognitions because in the former the involved polarizability relationship is M > O and in the latter H < O. It may be further noted that this issue is also related to interesting metal-switched sense of asymmetric induction observed in some systems; (3) most generally and importantly, a metal helps couple a catalyst helix and its substrate helix together to allow them to interact, and its nature can significantly influence the efficiency of the corresponding catalyst-substrate helical character matching, an issue that is crucial for determining the magnitude of enantioselectivity and is examined in details in the next paper (see Ref. 33). This last consideration (3) applies to other means as well that may couple the interacting helices together, such as coordination, hydrogen-bonding, π–π stacking, electrostatics, etc. The analyses presented should not be taken to dismiss the roles of steric and other effects in stereochemical control either. As stated at the beginning, this is an alternative, helical electronic effects-based stereochemical rational for highly enantioselective chiral interactions. The fact that in several broadly successful enantioselective reactions these rationales are shown to be more general and predictive than those formulated previously on the basis of considerations on steric and other effects suggests that the roles of helical electronic effects are usually predominant. For further discussion on the relationships between helical electronic effects and steric and other effects in stereochemical controls in the general context of asymmetric catalysis, see Ref. 14a.
26. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1998**, *18*, 249.
27. Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407.
28. That the stereochemical outcomes here could be correlated to the helical electronic interactions between a catalyst and its substrate in their initial association step, without necessarily engaging in those interactions in the transition states of the derivatization step, is somewhat unusual and may be a characteristic of efficient kinetic resolution systems, in which the reaction profiles depend critically on the chiral discrimination of enantiomers by the chiral catalyst. Disruption of an electronically favorable homohelical catalyst–substrate association in the derivatization step should result in an energy penalty that may contribute to a higher transition state barrier.
29. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 2.
30. Selected examples for tandem asymmetric induction-kinetic resolution using a single catalyst: (a) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. (b) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529. For tandem asymmetric induction-kinetic resolution using two different catalysts of the same helicity: (c) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1997**, *8*, 3927.
31. Halpern, J. *Pure. Appl. Chem.* **1983**, *99*, 32. It may be noted that the Halpern mechanism does not violate the general reactivity–stability correlations along the whole reaction coordinate: the kinetically more productive reaction cycle features a transition state that is lower in energy than that of its competing cycle. See also Ref. 32.
32. Landis, C. R.; Feldgus, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2863. The C_α-substituent here –CO_2Me can be replaced by other groups such as –CO_2H, –C(O)NH_2, –CN, –C(O)Ph, –Ph, –P(O)$(OR)_2$ etc. without affecting the sense of asymmetric hydrogenation. Previously it was thought that these groups share some electron-withdrawing abilities (Koenig, K. E. In *Asymmetric Synthesis*, *Vol. 5*, 1985). But it seems to be more appropriate to attribute the similar stereochemical profiles to their comparable polarizabilities which are all higher than β-2° ***C***H_2, thus the corresponding enamides all define the substrate ring helicities of the same handedness upon complexation to the Rh centers. Conceivably, if -CO_2Me is replaced with a group that is less polarizable than β-2° ***C***H_2, the enantiofacial selection should be inversed. This is indeed the case for an enamide with a 3°-carbon C_α substituent, such as ***C***Me_3 or 1-adamantyl. For experimental demonstration of this polarizability argument, see: (a) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084. (b) Gridnev, I. D.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 10486. (c) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 5268.
33. Wang, D. Z. *Tetrahedron* **2005**, *61*, the following paper in this issue see doi:10.1016/j.tet.2005.05.059.

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Catalyst–substrate helical character matching determines enantiomeric excess

David Zhigang Wang*

Department of Chemistry, Columbia University, 3000 Broadway, MC 3151, New York, NY 10027, USA

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Abstract—In the framework of a helix theory recently developed for molecular chiralities and chiral interactions, it is further proposed that for an asymmetric reaction to be highly enantioselective, the helical characters, that is, the local energies of electrons on the helices, of the catalyst and the substrate complexed with it in the corresponding enantioselection-determining step must be matched. These helical characters can be analyzed on the basis of molecular polarizability and structure properties under a given reaction mechanism. This proposal highlights the importance of polarizability matching in three-dimension chiral space and in essence is a chiral version of the classical hard and soft acid–base theory. It also from an electronic effect angle sheds light on the nature of the conventional lock-and-key origin of high enantioselection and carries the message that, to design a good catalyst (the key), rather than focusing on the rigidity, bulkiness or C_2-symmetry of the catalyst, one should focus more on the helical character of the substrate (the lock) with which the catalyst will interact. It is generally easier to discover a highly enantioselective catalyst for a substrate of a large helical character than for a substrate of a small helical character. The proposal is supported by theoretical modeling as well as numerous experiments and is used to understanding various aspects of current asymmetric catalysis.

1. Introduction

In the preceding paper in this issue we described that an electronic effect, that is, homohelical interaction, controls the stereochemical courses of chiral recognition and induction processes.[1] Although the principle of the conservation of helical asymmetry allows for prediction on the sense of chiral induction in a catalytic asymmetric reaction, it does not yet address another important question, that is, along that sense, under what condition(s) can the magnitude of enantiomeric excess (ee) be ca. 100%; or for a given substrate, how chiral should a catalyst be to maximize asymmetric induction?

Using the well-established electron-on-a-helix theoretical model of Tinoco and Woody, we have shown that a homohelical electronic interaction is always lower in energy than its diastereomeric heterohelical interaction, and their energetic difference, that is, the difference between the free energy changes for homohelical and heterohelical interactions in an enantioselection-determining step, $\Delta\Delta G^{\neq} = E_{\text{homo}} - E_{\text{hetero}}$, is sufficient to bring about high ee and is maximized when the local energies of electrons on the interacting helices are the same.[2] Because this energy is collectively determined by a molecular helix's parameters, which include radius, pitch, length, and mass of the electrons on the helix, the above conclusion equivalently shows that for a reaction to be highly enantioselective, these characteristics of the interacting helices must be similar. In short, they must be helically matched.

Since the origins of helical electronic structures in a chiral molecule are closely associated with its polarizability properties, as shown in the preceding paper, the conclusion highlights the importance of polarizability matching in a three-dimension chiral space and is essentially a chiral version of the classical hard and soft acid–base theory.[3] It also incorporates itself into a larger theoretical framework concerning the general correlations between molecules' polarizabilities (softness, or its inverse, hardness) and their stabilities and reactivities.[2] Moreover, it in essence electronically reproduces the conventional lock-and-key wisdom on the origin of high ee, and carries the following important message: to design a good catalyst (the key), rather than focusing on the rigidity, bulkiness or C_2-symmetry of the catalyst,[4] one should focus more on the polarizability properties, thus the helical character, of the substrate (the lock) with which the catalyst will interact. For a given asymmetric reaction, it suggests a useful way to rank

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* Tel.: +1 212 854 4964; fax: +1 212 932 1289;
e-mail: zw61@columbia.edu

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a variety of chiral catalysts on the basis of their helical characters and then to investigate their matching with the helical character of the complexed substrate thus the ee resulted. Details of the theoretical treatment may be found in that paper,[2] we herein just quote two rules directly derived from it that are necessary for the ranking purposes in the following analysis. They are: a molecular helix's helical character (local electronic energy) increases as its length, which usually correlates to its ring size, decreases (Rule I); and, at a fixed helix length, increases as its radius, which correlates to the relevant groups' polarizability distinctions that result bonds' helical deformations, decreases (Rule II). These ranking rules are readily applicable to real molecules and will be closely followed throughout this paper. It should be noted that in the context of this helix theory, the terms, that is, the helical character and the local energy of electrons of a helix, are equivalent, but the former is more descriptive to helix parameters and molecular structures thus will be preferentially used. Although the method is qualitative at the present stage, it allows for, as shown in the following discussion, estimations of relative ee a catalyst or a substrate may achieve in a reaction without necessarily involving any numeric calculation, which is of considerable practical advantages to practicing chemists.

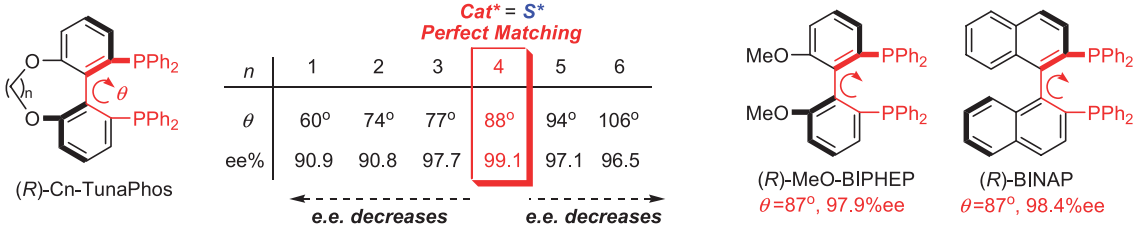
2. Results and discussion

The catalyst–substrate helical character matching readily yields a catalyst structure–enantioselection correlation that a catalyst possessing a helical character (Cat*) that is either higher or lower than the substrate helical character (S*) should lead to energetic mismatching thus reduced $\Delta\Delta G^{\neq}$ thus diminished ee.[5] Indeed, numerous experiments in literature independently carried out by various groups are in accord with this conclusion. To illustrate this point, we choose to focus on asymmetric hydrogenation since this is undoubtedly the most developed field in asymmetric catalysis and the availability of several series of structurally closely resemble chiral catalysts examined under identical or comparable reaction conditions enables facile comparisons on helical characters and enantioselections.

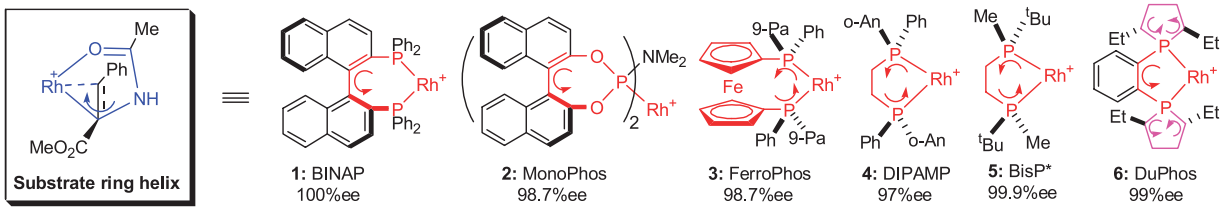
At the outset, a straightforward demonstration of the dependence of ee on the catalyst–substrate helical character matching comes from the well-designed Cn-TunePhos in Ru-catalyzed asymmetric hydrogenation of β-ketoesters, for example, methyl acetoacetate.[6] Its biphenyl backbone helix character could be delicately modulated by systematically changing the linker length ($n=1$–6) thus changing the biphenyl bite angle θ from 60 to 106°, which in turn varies both the pitch and the radius of the ligand ring helix (shown in red, Scheme 1).

It has been previously shown that (*R*)-MeO-BIPHEP and (*R*)-BINAP, both having a bite angle of 87°, were excellent ligands for enantioselective reduction of methyl acetoacetate (97.9 and 98.4% ee, respectively). In other words, the catalyst ring helix characters of BIPHEP–Ru and BINAP–Ru should be close to that of methyl acetoacetate complexed with these Ru-catalysts. To best mimic that character, it is immediately expectable that a Cn-TunePhos with a bite angle close to 87° (herein 88° when $n=4$) would be most successful in the same reaction.[7] Furthermore, other TunePhos with a helix character that is either lower or higher than that of C_4-TunePhos would be less effective in asymmetric induction. Indeed, these predictions are in accord with the experiments: as θ increases, ee increases first, reaches a maximum when $n=4$, and falls off as θ increases further. Plots of ee-versus-θ for hydrogenations of several other β-ketoesters visualize similar profiles (Scheme 1).[6,8]

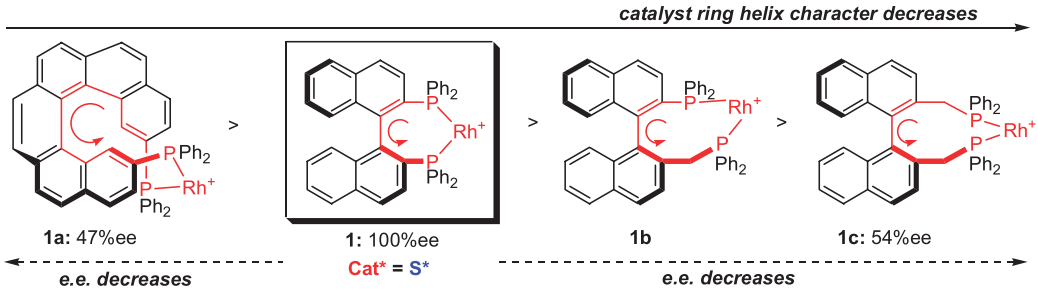
Summarized on the right part of Scheme 2 are some landmark chiral phosphorus–Rh catalysts, which differ considerably in sterics, in asymmetric hydrogenation of (*Z*)-methyl acetamidocinnamate. The extremely high ees achieved indicate a nearly perfect catalyst–substrate helical character matching, therefore catalyst ring helical characters of **1**–**6** (in red) should be all equal to that of the substrate



Scheme 1. Critical dependence of ee on the catalyst–substrate helical character matching in Ru-Cn-TunePhos-catalyzed asymmetric hydrogenation of methyl acetoacetate.



Scheme 2. Perfect catalyst–substrate helical character matching leads to extremely high ees in Rh-catalyzed asymmetric hydrogenation of (*Z*)-PhCH=C(CO_2Me)NHAc. The catalysts are all shown in enantiomers featuring right-handed ring helices (in red) thus all give (*R*)-phenyl alanine methyl ester.[1] 9-Pa, *o*-phenanthryl; *o*-An, 2-anisyl.

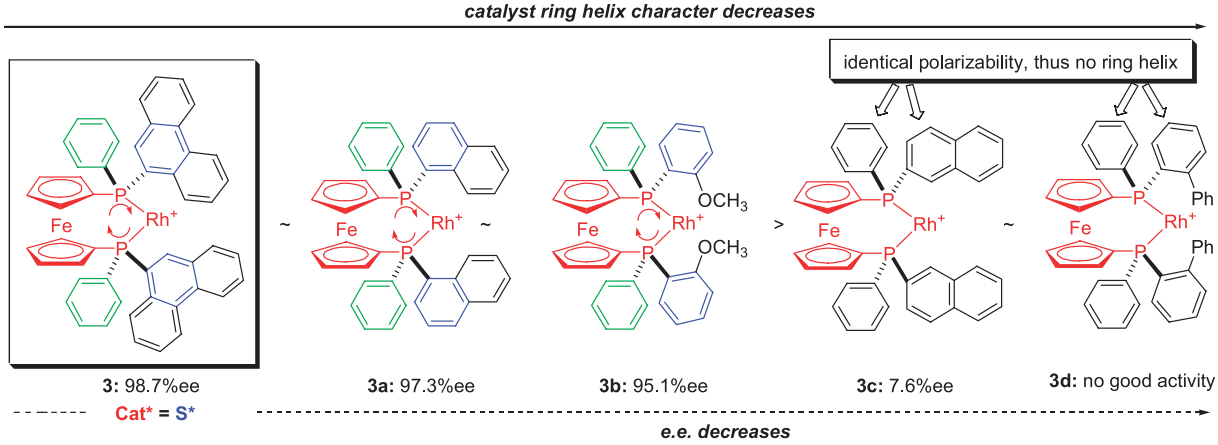


Scheme 3.

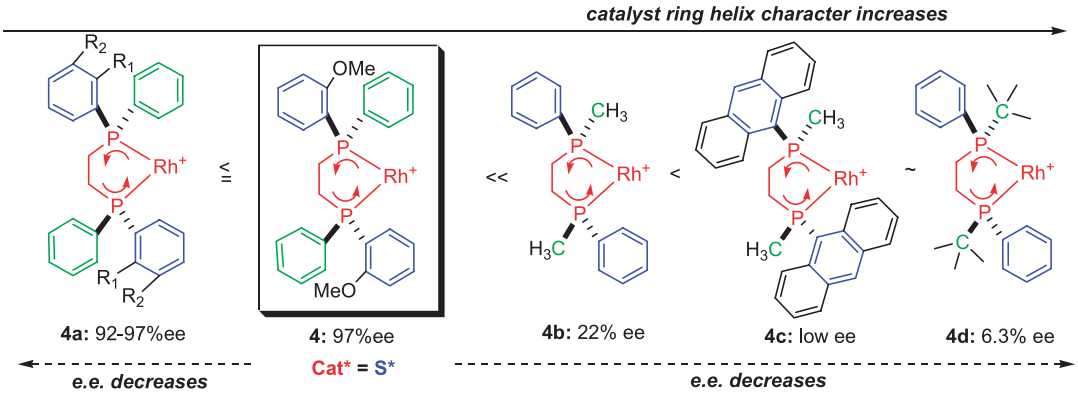
ring helix (in blue, on the left part), which is significant due to large polarizability distinctions between transition metal Rh and *N*H, and between C=O and 2°–CH_2.[1]

At first sight, structurally diverse **1**–**6** do not seem to be equivalent in helical character, however, doubt could be quickly removed when group polarizabilities around stereogenic P centers are examined, which suggests that, although the helix parameters of each of these catalyst ring helices differ, these different parameters compensate, rendering their helical characters similar to each other.[9] The significant helix character of **1** is obvious from its large atropisomeric skew of the rigid binaphthyl rings. In **5**, polarizability difference between local CH_3 carbon and tertiary CMe_3 carbon is relatively small (1° C>3° C),[1] but Rh is much more polarizable than CH_2 in the ethane bridge. This leads to a consequence that even a small CH_3-versus-CMe_3 local polarizability difference is capable of generating a large helix twist in the two P* catalyst ring helices, that is, –CH_2–P*–Rh–, in the –Rh–P*–CH_2–CH_2–P*– ring through the remarkable Rh-versus-CH_2 'polarizability amplifier'. Besides, the catalyst ring helix in **5** is five-membered, rather than seven-membered in **1** which corresponds to a larger therefore helix character-lowering helix length; and the two P*-helices in **5** lie at closest vicinities to the Rh catalytic center to execute homohelical interaction, rather than that in **1** the binaphthyl backbone helix and Rh is spaced by two achiral P atoms. These situations may indeed make the helix character in point-chiral **5** comparable to that in axial-chiral **1**. Similar considerations equally apply to **3** and **4**. In both of them the catalyst ring helices are primarily generated by polarizability differences of the local Csp^2 carbons, that is, the carbons directly attached with the P atoms (in the following related discussion in Schemes 4–7, however, the whole local aromatic rings, rather than these local carbons, are highlighted in colors for the sake of clarity. The blue-versus-green aromatic rings there would thus indicate the high-versus-low polarizabilities on the local carbons). For **6**, the ring helix –P–C*–CH_2– at each chiral carbon center and Rh are spaced by an electron-rich P atom, helix character lowering induced by which is thus compensated by synergistic helices from four stereogenic carbons (shown in purple, polarizabilities: CH_2Me>H, and electron-rich P>CH_2). A unique feature of **6** is its 'tandem homohelical induction' mode in asymmetric catalysis, that is, the original helices in the phospholane rings (in purple) first transmit their twists into –Rh–P–phenyl–P– ring which in turn interacts with the substrate ring helix. Compound **2** merits special attention in that, the atropisomeric binaphthyl helix, although significant in helix character, interacts with the substrate ring helix through a linear P–Rh bond, but not through an usual metal atom joint or a ring junction whose cyclic features have been repeatedly demonstrated to be more effective for asymmetric induction.[1] At a general perspective, such relatively inefficient catalyst–substrate stereochemical transmission through a single bond spacer may account for much failure met with monodentate ligands in asymmetric catalysis.[10] As compared to its close bidentate analog **1**, for **2** to be comparably helical thus highly enantioselective, there must be more than one MonoPhos ligands associated with Rh in the actual catalyst. In fact, there could be two.[11]

Catalysts **1**–**6** and their many analogs provide an excellent platform on which the critical dependence of ee on the



Scheme 4.



Scheme 5.

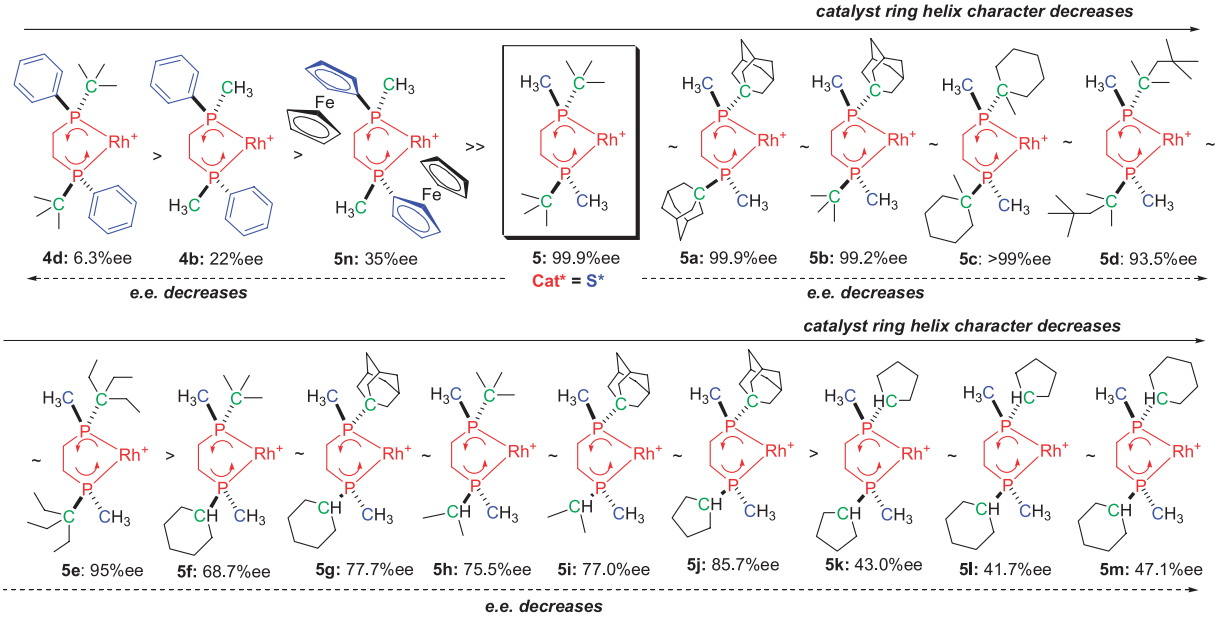
degree of catalyst–substrate helix character matching can be examined. As shown below, catalysts possessing a helix character that is either higher or lower than the perfect value suggested by **1**–**6** universally lead to lower ees.

As shown in Scheme 3, catalyst ring helix character of **1** can be increased by replacing binaphthyl backbone with a highly twisted and polarizable π-helicene skeleton, or decreased by extending the ligand ring size, which increases the ring helix length (Rule I), with one or two CH_2 spacers. These produce analogs **1a**, **1b** and **1c**, respectively. Both **1a** and **1c** are found to be far less enantioselective catalysts.[12]

In Scheme 4, electron density at α-position of the naphthalene is more polarizable than that at its β-position which is as polarizable as a carbon center of the benzene.[13] This makes the local *C*sp^2 carbon of the α-attached phenyl ring (in blue) of 9-phenanthryl in **3** or 1-naphthyl in **3a** is more polarizable than that of the phenyl ring itself (in green). Electron donating OMe-enhanced phenyl ring in **3b** is also more polarizable than the phenyl ring in their corresponding local *C*sp^2 carbons. These three catalysts mimic each other well in the catalyst ring helix characters and consequently afford comparable ees (Rule II). In contrast, **3c** has an β-attached 2-naphthyl, and *ortho*-phenyl of 2-biphenylyl in **3d** is atropisomeric to the phenyl ring to which it attaches thus poses little electronic influence on it. Therefore, P-substituents in **3c** and **3d**, although differ in sizes, do not differ in local polarizabilities thus do not define any appreciable helices in the corresponding catalyst ring structures. They lead to racemic products.[9]

In Scheme 5, **4** is slightly higher than **4a** (R_1 = Me, Et; R_2 = H) in helical character because *ortho*-OMe is more electron-donating than *ortho*-R_1, but it is much lower than **4b–d** because the aryl-versus-alkyl substituents polarizability distinctions are high (Rule II).[1] Accordingly, **4a** induces a lower ee and **4b–d** are essentially non-stereoselective catalysts.[14] It may be noted that the coordinative ability of the methoxy group of **4** has been recognized to be unimportant for asymmetric induction.[14a]

BisP*–Rh **5** and **5a–n** represent perhaps a class of catalysts most delicately examined to date on ligand structure–ee correlations in asymmetric enamides hydrogenations (Scheme 6).[15] Rule II allows for facile helical character



Scheme 6.

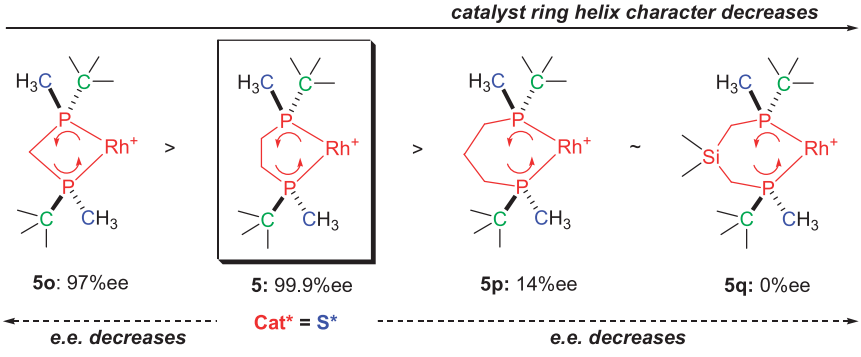
ranking of them. Replacing 3° CMe_3 carbon with another equally polarizable tertiary carbon, as in **5a–e**, does not change the resultant catalyst ring helical characters hence the ees. Systematically replacing one or both of the two 3° carbons with more polarizable 2° carbons, as in **5f–j** and **5k–m**, respectively, leads to catalysts of descending helical characters thus declining ees. They are all much lower in helical character than **4d**, **4b** or **5n** which has a large Ph-versus-3° CMe_3 (or 1° CH_3) or a ferrocene Cp ring-versus-1° CH_3 P-substituents local polarizability difference, respectively; therefore they are all far less enantioselective catalysts. Moreover, regardless of variations in P-substituents' sizes, catalysts of comparable helical characters give comparable ees whose values correlate to their deviations from **5**, which further highlights the critical helical electronic control in asymmetric induction.[1,16,17]

By extending the ethane linker of **5** into a propane, or shortening it into a methylene, **5p–q** of lower helix characters or **5o** of a higher helix character can be made, respectively, (Rule I). They all lead to diminished ees (Scheme 7).[15]

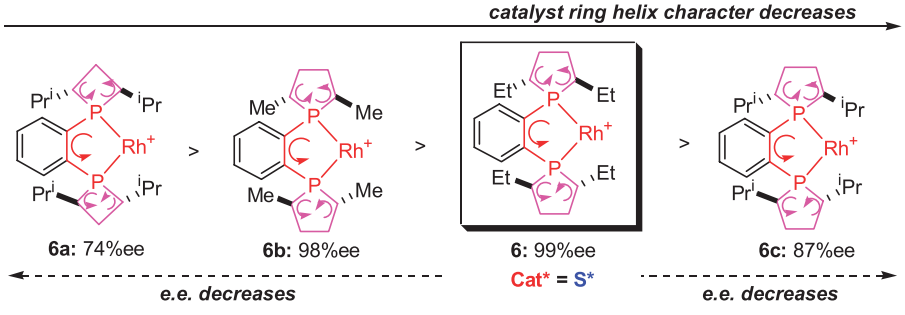
The helical character of **6** can be modulated by replacing CH_2 carbons in -Et with slightly more polarizable 1° CH_3 carbons or less polarizable 2° $CHMe_2$ carbons, the resultant higher helical character **6b** and lower helical character **6c** (Rule II) both yield lower ees (Scheme 8).[18] However, ee changes here are less pronounced than those found in BisP*–Rh catalysts in Scheme 6 because helices variations at the remote C* centers are not sensitively sensed in catalysis. Compound **6a**, which has a smaller phospholane ring thus a smaller helix length, should possess a helix character that is higher than **6** and **6b–c** (Rule I). It indeed results in a much lower ee.

Although our analyses so far are focused on hydrogenations, there seems to be no reason to suppose that such critical dependence of ee on catalyst–substrate helix character matching is a privileged issue associated only with this type of asymmetric induction. Unfortunately, the lack of a variety of structurally comparable catalysts in many other asymmetric catalytic reactions hampers similar helix character-ee correlations. Nevertheless, scattered examples abound in literature. For example, in asymmetric epoxidations, chiral metal–Salen complexes have been established to be efficient catalysts,[19a] implying good matching between their helix characters and those of the olefins in enantioselection-determining steps. Replacing the weakly helical chiral *trans*-1,2-diamino-cyclohexane in the Salen ligands with a large skewed [1,1′-binaphthalene]-2,2′-diamine apparently would significantly increase the helix characters of the resultant catalysts that should then be much higher than those of olefin substrates, therefore high ees can not be anticipated. By contrast, using a ring-extended, thus less helical, analog [1,1′-binaphthalene]-2,2′-diethanamine has achieved good ees in epoxidation.[19b]

Since the invention of BINAP ligand, there have been, and still are, many intensive efforts of incorporating it and its various atropisomeric analogs into other asymmetric reactions with hopes of effecting high ees. It is clear now that, the helix characters of BINAP type ligands, although often match with those of enamides in hydrogenations, may not resemble those of other substrates in other processes. Therefore, their successes in hydrogenations may not be transferable. For a given reaction, without detailed information of the reaction mechanism and of the substrate helix character in that particular mechanistic framework, it is rather difficult, if not impossible, to predict beforehand whether such efforts are worthy of pursuing. At this point, it



Scheme 7.



Scheme 8.

may be also interesting to note that previous studies on electronic effects in asymmetric induction, primarily by means of electron-withdrawing or donating modulations on the corresponding catalyst or/and substrate structures, may be correlated to modulations on their electronic polarizabilities thus on their helical characters.[20]

Clearly, the above results strongly support the notion that for a high ee to be realized, helical characters of the catalyst and of the substrate complexed with it must be matched. This principle might help account for several interesting observations in asymmetric synthesis, such as why autocatalysis[21] tends to be highly enantioselective and why absolute asymmetric syntheses,[22] despite years of efforts, unexceptionally met with failures. In the former a perfect catalyst–substrate helical character matching can be automatically satisfied because the catalyst and the product share the same structure;[23] and in the latter the chiral light is not even in the same structural domain as organic molecules, therefore there is barely any degree of matching between them. In general, it is easier, either by design or by serendipity, to discover a highly enantioselective catalyst for a substrate of a large helical character than for a substrate of a small helical character. Autocatalysis and absolute asymmetric syntheses represent two extreme situations in the global catalyst–substrate helical character matching-enantioselection correlation profiles for various asymmetric syntheses, and chances of success are evidently not evenly distributed between them. While asymmetric catalysis with substrates that are capable of defining relatively high helical characters in their corresponding enantioselection-determining steps has enjoyed enormous progresses in the past three decades, such as hydrogenations of enamides and functionalized ketones, hydrogenations and alkylations of simple aromatic or hetero-aromatic substituted C=X (X=C, O, N) bonds, and epoxidations, dihydroxylations and hydrogenations of *trans*-olefins, realizing highly enantioselective transformations for their counterpart substrates of low helical characters, such as unfunctionalized and/or purely alkyl substituted C=X bonds, particularly those of a *cis*-geometry, remains formidably challenging.[1,2]

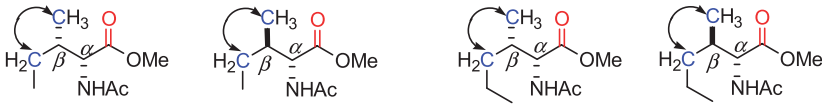
For a given asymmetric reaction, the catalyst–substrate helix character matching yields two practically useful implications. One, for a catalyst inducing a moderate ee, making a few analogs of it with finely tuned helical characters and examining their performances should help point out the promising direction for further endeavors, that is, whether a catalyst of a higher or lower helix character should be tried next;[24] two, for a catalyst inducing high ee, its helical character may serve as a 'reference' that guides further catalyst designs, that is, a new catalyst that mimics such a reference helix character should be also efficient. Studies fulfilling this strategy have indeed had many proven successes.[4] For examples, mimicking the BINAP moiety of the Noyori transfer hydrogenation catalysts with a comparably helical spiro-Phos ligand leads to new catalysts that also achieved very high ees;[25] mimicking the BisP* ligands helix characters leads to the invention of new and robust TangPhos catalyst in enamides hydrogenations.[26] In fact, successes in the field of asymmetric hydrogenations owe much to the inspirational atropisomeric skew design criterion suggested by the BINAP type ligands.

The discussion developed so far has been largely confined to helical character matching issues between various catalysts and a fixed substrate. However, application of the principle in the opposite direction, that is, the helix character matching between various substrates and a fixed catalyst, is also profitable. Mimicking the helix character of a substrate that achieves high ee under the action of a certain catalyst in a reaction may lead to expanded scope of substrates that attain high ees with the same catalyst. This is often very desirable and, in fact, widely practiced in asymmetric catalysis.[4]

Still focusing on enamides hydrogenation, the directly relevant issues are so-called catalyst structural modularity and substrate *Z*/*E* geometry tolerance. Some eminent diphosphine–Rh catalysts, notably DuPhos, BPE and BICP, had been demonstrated to tolerate olefin *Z*/*E* geometry in highly enantioselective hydrogenations, which was previously attributed to their structural modularity or tunability. On the basis of the catalyst–substrate helix character matching principle, we, however, reasoned that these successes perhaps have more to do with the *Z*/*E* substrates' helix character resemblance than with the catalysts' modularity. As shown previously,[1] the enamide C_α substituent, often a very polarizable π-group, is the major contributor to the substrate ring twist and the C_β center tends to be placed outside the Rh's square planar coordination plane. In hydrogenation of some β, β′-disubstituted enamides, when the C_α substituents (in red) are very polarizable and C_β substituents (in blue) are simple alkyls that display little local carbon polarizability difference, as in **7a–d** in Scheme 9, the C_α substituents overwhelmingly dominate the substrate ring twists thus both *Z*/*E* isomers have essentially the same helix character upon their complexations to the Rh centers. Therefore, they are hydrogenated not only in the same sense but also in virtually identical ees.[27]

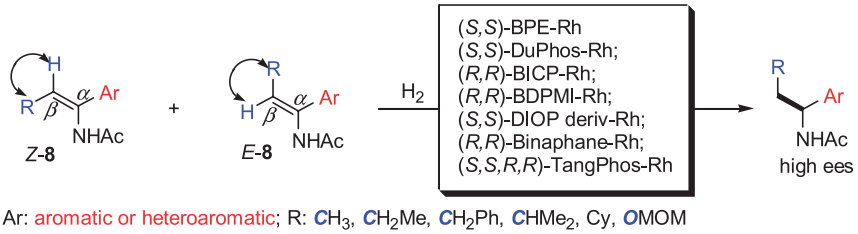
When C_α substituent in **8** is an aromatic ring that is even more polarizable than the ester carbonyl in **7** thus increasingly dominates the substrate ring helical characters, an even greater and broader level of *Z*/*E* tolerance is observed in various catalyst systems (Scheme 10).[28]

However, when β-substituents polarizability differences get relatively larger, as phenyl-versus-alkyls in **9a–d**, and C=C-versus-alkyls in **9e–f**, *Z*/*E* isomers shall develop



7a: 98.2%ee **7b:** 98.3%ee **7c:** 98.0%ee **7d:** 96.6%ee

Scheme 9.



Scheme 10.

different helix characters, thus variations of ee in hydrogenation of *Z*- and *E*-isomers appear (Scheme 11).[27]

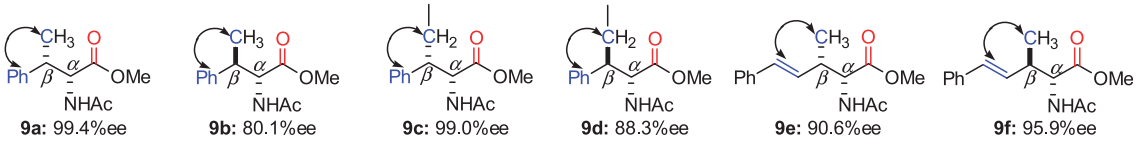
When β-substituents polarizability differences get very large, as phenyl-versus-H in **10**, the helices at C_β centers may also contribute appreciably to substrate ring twists and *Z*/*E* isomers can have significantly different helix characters. In these cases, hydrogenations of *Z*- and *E*-isomers may not only proceed with sharply different ees, but even in opposite senses (Scheme 12).[29]

Dramatic responding of ees on *Z*/*E* geometry could also be anticipated in some other enamides in which the reversed substrate structure and polarizability characters are met, that is, small C_α substituent polarizability coupled with large C_β substituents polarizability differences. In these cases, *Z*- and *E*-isomers differ much in substrate helix characters, and consequently can not be hydrogenated in comparable ees by the same catalyst, as exemplified in Scheme 13 with Duphos–Rh catalyzed hydrogenations. Similar *Z*/*E* effects on ee, albeit less pronounced, were also observed with the BICP–Rh catalyst.[30]

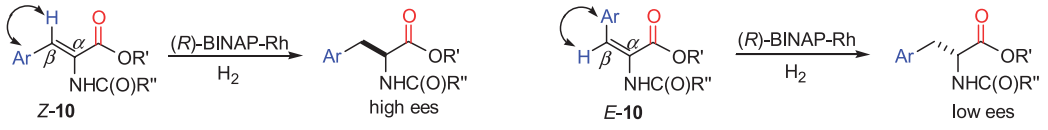
The above analyses illustrate that a simple examination of substrate substituents' polarizabilities and their distribution characters can significantly help estimate the potential of *Z*/*E* geometry tolerance in asymmetric hydrogenations. In terms of substrate helical character, this *Z*/*E* issue in asymmetric induction is not special and has no difference from the widely-seen small ee variations associated often with an aromatic-to-hetero-aromatic switch yet large ee variations associated with an aromatic-to-alkyl switch in substrate structures in many types of asymmetric catalysis.[1,2,4] The essential underlying principle is that the degree of catalyst–substrate helix character matching determines the magnitude of ee.

3. Conclusion

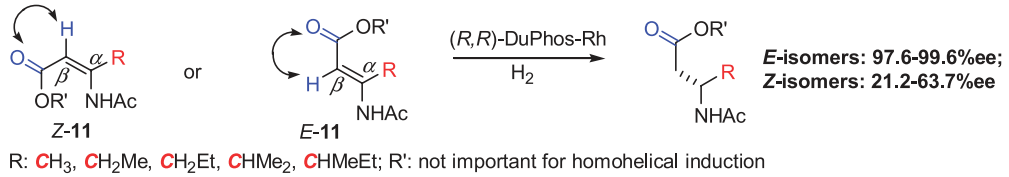
In summary, as a continuation of our efforts to understand chiral interactions from an electronic effect perspective, we proposed here that for an asymmetric reaction to be highly enantioselective, the corresponding helix characters of the catalyst (the key) and of the substrate complexed with it (the lock) in the enantioselection-determining step must be matched. This conclusion is new and useful. Although the focus of the present two papers[1] on this helix theory is placed on examinations of the conservation of helicity and helical character matching principles in asymmetric syntheses, their validities evidently do not depend on any individual reaction's own characteristics and they may be generally applicable to other types of chiral interactions as well. We believe that considering such local helical electronic effects and developing computational strategies that can quantitatively address them would help gain insights into efficient asymmetric induction that are beyond conventional geometry- or size-based scenarios, and are



Scheme 11.



Scheme 12.



Scheme 13.

meaningful for catalyst rational design. This goal seems to be achievable in light of the considerable maturity in current methods for polarizability calculations.[31] Work towards this goal is now underway.

Acknowledgements

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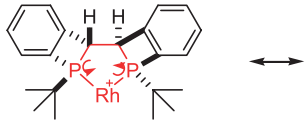
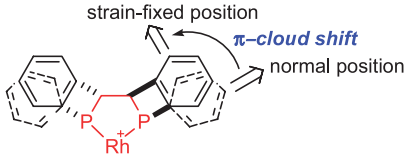
References and notes

1. Wang, D. Z. *Tetrahedron*, **2005**, *61*, the preceding article in this issue: see doi: 10.1016/j.tet.2005.05.058.
2. (a) Wang, D. Z. *Chirality* **2005**, *17*, S177. The paper also examines the relationships between helical electronic effects and steric and other effects in stereochemical controls in the general context of asymmetric catalysis. (b) Tinoco, I., Jr.; Woody, R. W. *J. Chem. Phys.* **1964**, *40*, 160.
3. For classical treatments, see: (a) Pearson, R. G. *J. Chem. Ed.* **1968**, *45*, 581. (b) Pearson, R. G. *J. Chem. Ed.* **1968**, *45*, 643. (c) Pearson, R. G. *J. Chem. Ed.* **1987**, *64*, 561.
4. (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (c) Noyori, R. Asymmetric Catalysis in Organic Synthesis; Wiley: New York, 1994.
5. An alternative statement of this principle would be that in a reaction a catalyst that effects a high ee towards a substrate would effect lower ees towards other substrates that have either higher or lower helical characters. Illustrations are given in the text. This principle helps guide the selection of more promising substrates for a catalyst. It is important to note that similarities in substrate helix characters often do not translate into similarities in their structural or steric characters. In asymmetric catalysis this gives a catalyst both specificity (highest ee towards one substrate) and versatility (comparable ees towards many other, helically resemble substrates). See Refs. 1,2,4 for many examples.
6. Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223.
7. Strictly speaking, the actual bite angles of their Ru complexs, but not the free ligands, should be used for helix character comparisons. But it is reasonable to assume that these analogous ligands undergo very similar bite angle changes upon their complexations to the Ru centers.
8. Remarkably, other investigations, although employing different methodologies, uniformly reveal the existence of an optimum point in the catalyst property-ee correlations, see: (a) Harada, T.; Takeuchi, M.; Hatsuda, M.; Ueda, S.; Oku, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2479. (b) Gao, D.; Schefzich, S.; Lipkowitz, K. B. *J. Am. Chem. Soc.* **1999**, *121*, 9481.
9. For **1**: Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7930. ; the ee is for acetamidocinnamic acid. **2**: van den Berg, M.; Minnaard, A. J.; Schudde, E.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539. **3**: Nettekoven, U.; Kamer, P. C. J.; van Leeuven, P. W. N. W.; Widhalm, M.; Spek, A. L.; Lutz, M. *J. Org. Chem.* **1999**, *64*, 3996. **4**: Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Backman, G. L.; Weikauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946. **5**: Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635. **6**: Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518.
10. Asymmetric catalysis by monodentate ligands: Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, *48*, 315. In general, these reactions are relatively difficult to achieve high ees due to inefficient catalyst–substrate homohelical interactions. In the absence of appreciable helical electronic control, steric and other effects may therefore play decisive roles in realizing high enantioselections. For further discussion, see Ref. 2a.
11. (a) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willians, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308. (b) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348 and note 11 therein. Although bidentate catalysts are conventionally regarded to be more efficient than monodentate catalysts in asymmetric induction, the helix theory suggests what is important may be the efficiency of the corresponding catalyst–substrate stereochemical communication thus their helical character matching.
12. For **1a**: Reetz, M. T.; Beuttenmuller, E. W.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 3211. ; ee of **1a**: private communication with Professor M. T. Reetz. **1b**: Takaya, H.; Ota, T.; Inagaki, K. Eur. Pat. Appl. (EP 96-301720 19960313), 1996. **1c**: Tamao, K.; Yamomoto, H.; Matsumoto, H.; Miyake, N.; Hayashi, T.; Kumada, M. *Tetrahedron. Lett.* **1977**, *16*, 1389.
13. Millefiori, S.; Alparone, A. *J. Mol. Struct. (Theochem)* **1998**, *422*, 179.
14. For **4a**: (a) Wada, Y.; Imamoto, T.; Tsuruta, H.; Yamaguchi, K.; Gridnev, I. D. *Adv. Synth. Catal.* **2004**, *346*, 777. (b) Imamoto, T.; Tsuruta, H.; Wada, Y.; Masuda, H.; Yamaguchi, H. *Tetrahedron. Lett.* **1995**, *36*, 8271. Experiments here also showed the ees induced by **4a** to be $>99\%$ when R_1 and R_2 are both electron-releasing alkyls or when R_1 is a more bulky alkyl. These situations bring minor modifications to ees. **4b**: Horner, L.; Simons, G. Z. *Naturforsch.* **1984**, *39b*, 512. ; the substrate is *N*-benzoyl-α-aminocinnamic acid. **4c**: Maienza, F.; Spindler, F.; Thommen, M.; Pugin, B.; Mezzetti, A. *Chimia* **2001**, *55*, 694. Maienza, F.; Spindler, F.; Thommen, M.; Pugin, B.; Malan, C.; Mezzetti, A. *J. Org. Chem.* **2002**, *67*, 5239.
15. (a) Ref. 9 for **5**.(b) Ohashi, A.; Imamoto, T. *Org. Lett.* **2001**, *3*, 373. (c) Ohashi, A.; Kikuchi, S.; Yasutake, M.; Imamoto, T. *Eur. J. Org. Chem.* **2002**, 2535. (d) Imamoto, T. *Pure Appl. Chem.* **2001**, *73*, 373. (e) Sugiya, M.; Nohia, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 705. (f) Crepy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79. (g) Oohara, N.; Katagiri, K.; Imamoto, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2171. (h) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988.
16. In this light the high ee induced by catalyst **5n** of a P-stereogenic ligand having both an aromatic and an aliphatic substituents, but in a highly strained electronic environment, should not be

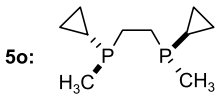
surprising. Its catalyst ring –Rh–P*–C*–C*–P*– (in red) features right-handed helices arising largely from the two P* centers (namely the helix –C*–P*–Rh– at each P* center; local polarizability sequences: Rh > *C**H; and Ph > 3° (*C*Me$_3$) therefore it induces (*R*)-phenyl alanine in excess. The 4-membered ring forces its phenyl ring π-electron cloud to move from the normal position to a strain-fixed position, weakening spatially its polarizability interactions with the Rh center that are directly responsible for formation of the ring helices; In addition, the rotations around the P–Csp^2 bonds are now restricted, rendering such phenyl–Rh interactions to be further weakened by the enhanced π-polarizability anisotropy. These effects lead to a net consequence that the effective polarizability of phenyl ring is substantially reduced thus the catalyst ring helical character of **5n** is much lower than those of other catalysts of similar aromatic-versus-alkyl P-substituents but in an unstrained electronic environment, such as **4b–d**, and may be close to that of the perfect catalyst **5**. This, in conjunction with steric effects posed by its rigid structure, might have made it a highly enantioselective catalyst. See: Imamoto, T.; Crépy, K. V. L.; Katagiri, K. *Tetrahedron: Asymmetry* **2004**, *15*, 2213.

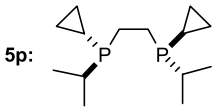


5n: right-handed, 96%ee (*R*)

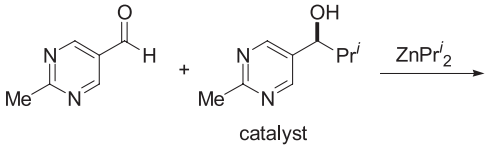


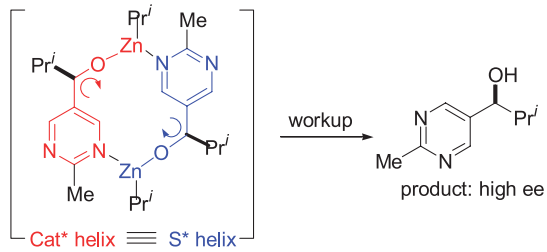
17. At this point qualitative predictions on some unknown P-stereogenic diphosphine ligands may be made. Enantiopure ligands **5o** and **5p** depicted below, when complexed to an Rh presursor, are expected to develop right-handed helicities (–CH$_2$–P*–Rh–) of considerable helical characters in their –Rh–P*–CH$_2$–CH$_2$–P*– catalyst rings (due to local polarizabilities: Rh > *C*H$_2$; and cyclopropyl *C*H > *C*H$_3$, *C*HMe$_2$) therefore to induce good-to-high ees of (*R*)-products in the hydrogenation of (*Z*)-methyl acetamidocinnamate and other α-(acylamino) acrylic derivatives. These predictions may be interesting in that the conventional steric theories, such as the quadrant rule, would predict opposite senses of asymmetric induction between them with a reasonable size sequence of isopropyl > cyclopropyl > methyl and low ees since steric distinctions in them much resemble those in mediocre catalysts **5k–m** and are significantly less than those in highly enantioselective catalysts **5** and **5a–e**. They invite experimental investigations.





18. (a) Marinetti, A.; Jus, S.; Genêt, J.-P. *Tetrahedron Lett.* **1999**, *40*, 8365.(b) See Ref. 9 for **6**. By contrast, 1,1′-bis(phosphetano)ferrocenes are highly enantioselective catalysts because P–ferrocene–P backbone in them is longer than P–phenyl–P in the Duphos–Rh catalysts. The concurrent presences of helix character-increasing 4-membered phospholane rings and a helix character-decreasing longer backbone may thus make their catalyst ring helical characters still comparable to those of the Duphos–Rh catalysts. See: Marinetti, A.; Labrue, F.; Genêt, J.-P. *Synlett* **1999**, *12*, 1975.
19. (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.(b) p 656 of Ref. 4a.
20. For representative works, see: (a) Rajanbabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101. (b) Jacobsen, E. N.; Zhang, W.; Guler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703.
21. Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471.
22. Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3418.
23. In this regard it should be emphasized here that asymmetric autocatalysis (and other self-replications) do not simply mean that the catalyst and the product share the same structure, but mean that their structural moieties actually involved in catalyst–substrate helical character matching should be the same. The Soai autocatalytic systems are outstanding examples, see: Soai, K.; Sato, I. *Chirality* **2002**, *14*, 548. In the proposed transition state model by Blackmond and Brown et al., as shown below, the catalyst ring helix is identical to the substrate ring helix in all aspects thus a perfect helix character matching between them is achieved, see: Blackmond, D. G.; McMillian, C. R.; Ramdeehul, S.; Schorm, A.; Brown, J. M. *J. Am. Chem. Soc.* **2001**, *103*, 10103. This, in conjunction with the operation of non-linear effect in these systems, not only furnishes product in extremely high ees, but also makes chirality amplifications extremely efficient. See: Singleton, D. A.; Vo, L. K. *J. Am. Chem. Soc.* **2002**, *124*, 10010. For non-linear effect in asymmetric catalysis, see: Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2923.





24. For examples, hydrogenation of (*Z*)-PhCH=C(CO$_2$Me)NHAc with Me–BPE–Rh yields a 85% ee, with Et–BPE–Rh yields a 93% ee. These results imply that, under comparable steric conditions, slightly decreasing the catalyst ring helix characters in this particular reaction would be electronically beneficial for higher ee, thus further optimizations may focus on R–BPE–Rh catalysts with R of a less polarizable local carbon, such as that of a 2°-alkyls, but not with R of a more polarizable local carbon, such as that of a cyclopropyl or aromatic rings. Indeed, ^{i}Pr–BPE–Rh induces a 93% ee, see Ref. 9 for **6**. Variations on these ees may be arguably attributed to steric influences, but this seems to be disfavored by the facts that increasing substituent size from Me to Et and to ^{i}Pr leads

to increases of ee in BPE–Rh systems, but decreases of ee in structurally resemble DuPhos–Rh systems under otherwise identical conditions. Moreover, there were attempts to incorporate additional chiral centers in Me–BPE–Rh's ethane linker in the pursuit of higher ees. Since the above results suggest that the helix character of Me–BPE–Rh is actually higher than that of the complexed substrate, higher ee would be anticipated when the introduced ring helices brought about by the new chiral centers are opposite, but not same, in handedness to the original BPE phospholane ring helices. Indeed, the former case leads to a 98% ee while the latter leads to an even lower 77% ee. See: Fernandez, E.; Gillon, A.; Heslop, K.; Horwood, E.; Hyett, D. J.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 1663. In line with the above considerations, two other BPE–Rh-like catalysts in which the phospholane rings are replaced with largely skewed BINOL units, or with 4-membered rings, should both be significantly higher in helical character than the complexed substrate, therefore high ees cannot be anticipated. Indeed, a 19% ee was found with the former catalyst and a 15% ee with the latter. See: Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961. andMarinetti, A.; Labrue, F.; Pons, B.; Jus, S.; Ricard, L.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 2583.

25. Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404. Because helical character of the 1,1′-spirobiindane backbone resembles that of the 1,1′-binaphthalene, it is not surprising that these spiro-ligands are also very effective for asymmetric enamides hydrogenations and conjugative additions in which the binaphthalene-derivatized catalysts were successful. See (a) Ref. 11b. (b) Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Chem. Commun.* **2002**, *5*, 280. (c) Zhou, H.; Wang, W.-H.; Fu, Y.; Xie, J.-H.; Shi, W.-J.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2003**, *68*, 1582.
26. Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612.
27. Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. The effect of *Z*/*E* double bond isomerization, which occurs in some systems but is not general, is ignored in our discussion. For a system involving *E*/*Z* isomerization, see Ref. 9 for **1**; for a system without *E*/*Z* isomerization, see: Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.
28. (a) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 9590. (b) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679. (c) Lee, S.; Zhang, Y.; Song, C.; Lee, J.; Choi, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 847.(d) Ref. 27. (e) Zhu, G.; Casalnuovo, A. L.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 8100. (f) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142. (g) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084. (h) Yan, Y. Y.; Rajanbabu, T. V. *Org. Lett.* **2000**, *2*, 4137. Another important class of substrates are itaconates which are helically closely resemble to enamides in hydrogenation transition states. For remarkable *Z*/*E* tolerances observed in various itaconates, see: (i) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1931. In fact, from a very general perspective the similar stereochemical profiles for various classes of structurally diverse substrates could be understood on the basis of their comparable substrates ring helix characters which could be quickly examined by their substituents' polarizabilities, their distribution patterns around pro-chiral centers and the substrate-metal coordination modes. See: (j) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.
29. (a) Ref. 9 for **1**.(b) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1247. The low ees of *E*-isomers suggest helix character-mismatched catalyst–substrate interactions.
30. Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907.
31. For some recent reviews, see: (a) Hasanein, A. A. *Adv. Chem. Phys.* **1993**, *85*, 415. (b) Maroulis, G. *Rev. Mod. Quantum Chem.* **2002**, *1*, 320. (c) Munn, R. W.; Papadopoulos, M. G.; Reis, H. *Pol. J. Chem.* **2002**, *76*, 155.

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Galanthamine analogs: 6*H*-benzofuro[3a,3,2,-*e*,*f*][1]benzazepine and 6*H*-benzofuro[3a,3,2-*e*,*f*][3]benzazepine

Anita H. Lewin,* Jerzy Szewczyk, Joseph W. Wilson and F. Ivy Carroll

Organic and Medicinal Chemistry, Research Triangle Institute, PO Box 12194, Research Triangle Park, North Carolina 27709-2194, USA

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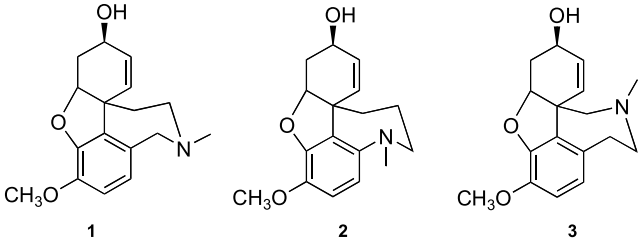
Abstract—The known cholinesterase inhibitory capability of the *Amarylidaceae* alkaloid galanthamine prompted preparation of analogs in which the position of the nitrogen within the azepine ring is altered. The analogs 6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepine and 6*H*-benzofuro[3a,3,2-*e*,*f*][3]benzazepine were prepared in 19 and 2.5%, respectively, following Kametani and Shimizu approaches, respectively. The aniline derivative 6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepine failed to undergo most of the reactions typical for galanthamine. Thus, it neither oxidized to the analogous narwedine, nor epimerized to the analogous epigalanthamine, nor reduced to the lycoramine analog, under the conditions used for galanthamine.

1. Introduction

The *Amarylidaceae* alkaloid galanthamine (**1**), available in the form of its hydrobromide salt as the drug Nivalin, has been identified as a cholinesterase inhibitor. It is widely used in Europe, especially in neuromuscular diseases such as myasthenia gravis,[4] as well as in antagonism of skeletal neuromuscular blockade (e.g., by curare),[2] drug-induced respiratory depression (e.g., by narcotics)[3] and central anticholinergic effect induced by scopolamine.[15] The positive results obtained by the use of Nivalin to treat patients suffering from Alzheimer's dementia[5] have prompted the suggestion that galanthamine (**1**) and/or its congeners may be active in the treatment of this disorder. As part of a program directed towards the preparation of analogs of **1** the synthesis of compounds in which the position of the azepine nitrogen is altered was targeted. Thus, the syntheses of the [1]benzazepine analog **2** and of the [3]benzazepine analog **3** were undertaken. The recent publication[9] of the synthesis of **3** prompts us to report our results for **2** and **3**.



2. Results

Our preparation of the [1]benzazepine **2** followed the classic Kametani synthesis of galanthamine,[6] utilizing the oxidative cyclization of the bromo-protected bisphenol **13** (Scheme 1). The acid chloride **8** and the aniline **12**, both required for preparation of the precursor to **13**, were prepared as follows. Starting from commercially available *p*-hydroxyphenylpropionic acid (**4**) the benzyl protected analog (**7**) was prepared by esterification of **4** with methanolic hydrochloric acid to give the methyl ester **5** (in 95% yield) followed by benzylation to give **6** (in 92% yield) and saponification (90% yield). Treatment of **7** with thionyl chloride afforded the required acid chloride **8** in quantitative yield. Synthesis of the aniline **12** was accomplished by formylation of commercially available 3-hydroxy-4-methoxyaniline (**9**) with ethyl formate (85% yield) to give the formanilide **10** and O-protection by benzylation with benzyl bromide to afford **11** in 85% yield. Bromination of **11** with *N*-bromoacetamide in chloroform

Keywords: Galanthamine; 6*H*-Benzofuro[3a,3,2-*e*,*f*][1]benzazepine; 6*H*-Benzofuro[3a,3,2-*e*,*f*][3]; Kametani synthesis; Shimizu synthesis.
* Corresponding author. Tel.: +1 919 541 6691; fax: +1 919 541 8868; e-mail: ahl@rti.org

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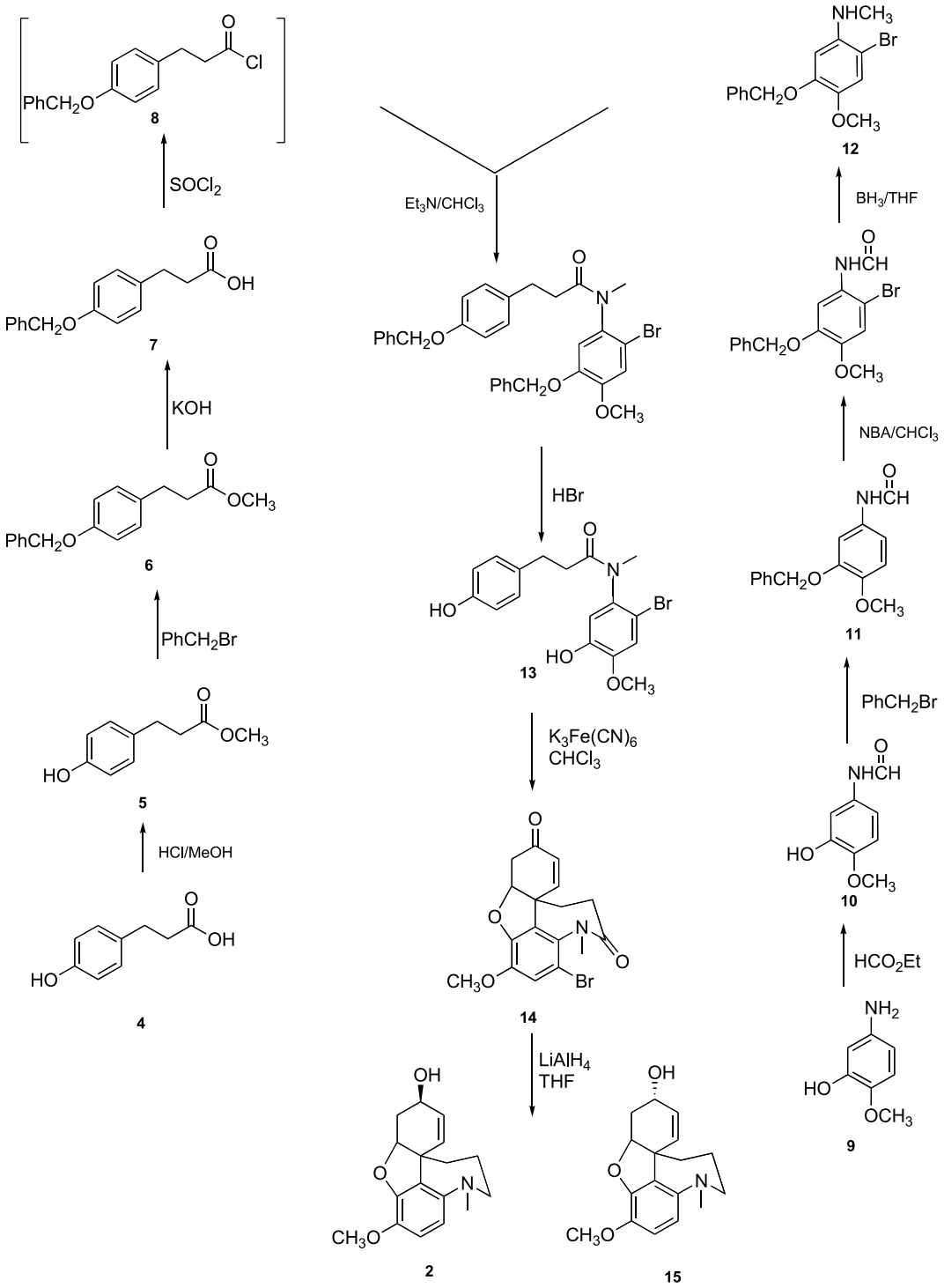
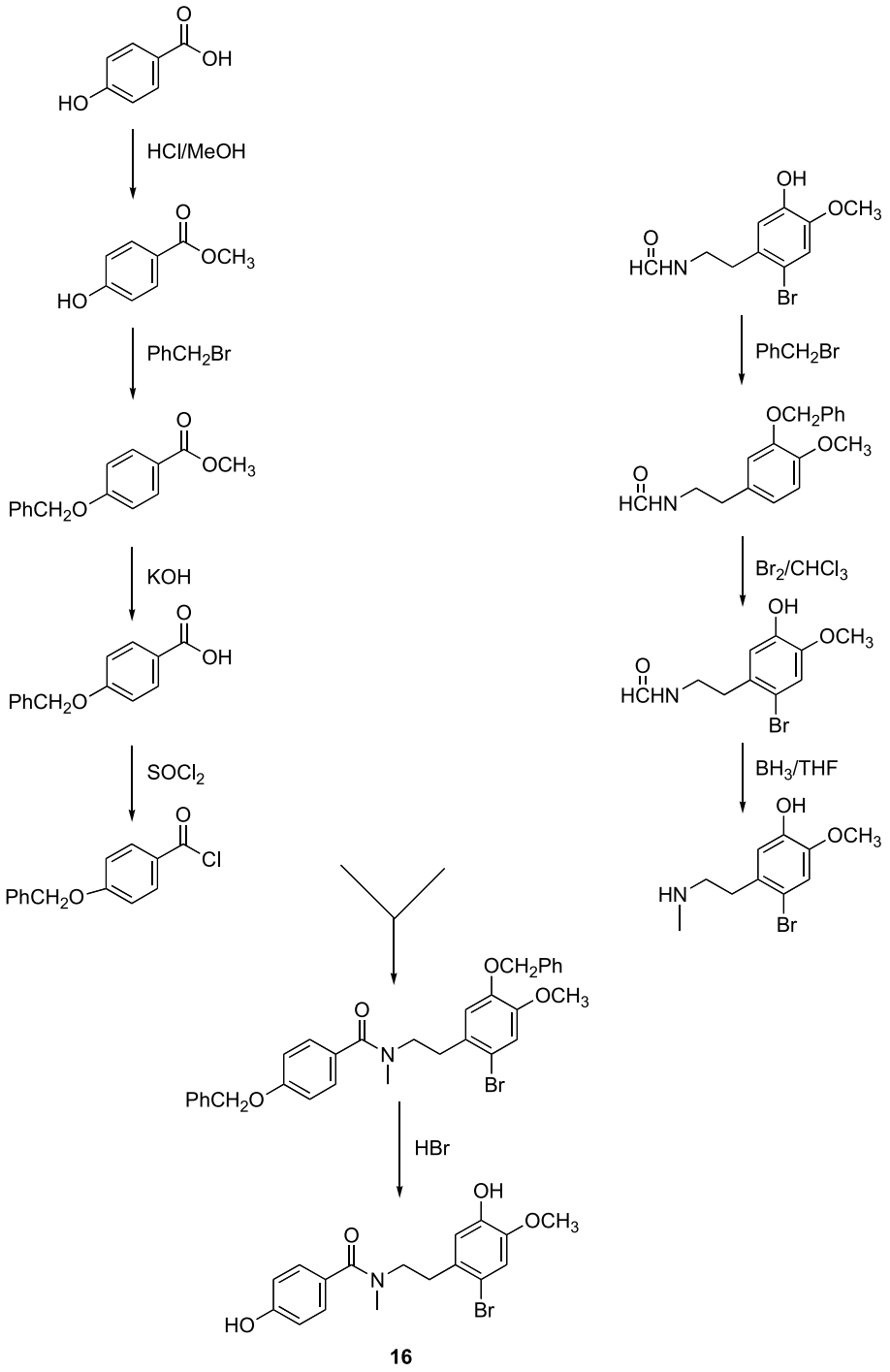


Scheme 1.

and reduction with diborane provided the required *N*-methyl-5-benzyloxy-2-bromo-4-methoxyaniline (**12**). Coupling of the acid chloride **8** with the aniline **12**, followed by debenzylation with hydrobromic acid, gave the bisphenol **13** required for cyclization in 81% yield. Oxidative cyclization by potassium ferricyanide gave the narwedine-type bromoamide **14** in 50% yield. Reduction of **14** with lithium aluminum hydride effected both reduction of the keto and amide groups to give the galanthamine analog **2** in 59% yield; it was accompanied by the epimeric alcohol **15** (7% yield). The overall yield from commercially available starting materials was 18.9%.

Attempts to prepare the [3]benzazepine **3** following an analogous route (Scheme 2) or following our improved protocol for the preparation of galanthamine[12] (Scheme 3) were unsuccessful. Thus, treatment of either bisphenol **16** or bisphenol **17** with potassium ferricyanide led to rapid consumption of the starting material and formation of multiple products; none was formed in quantities justifying

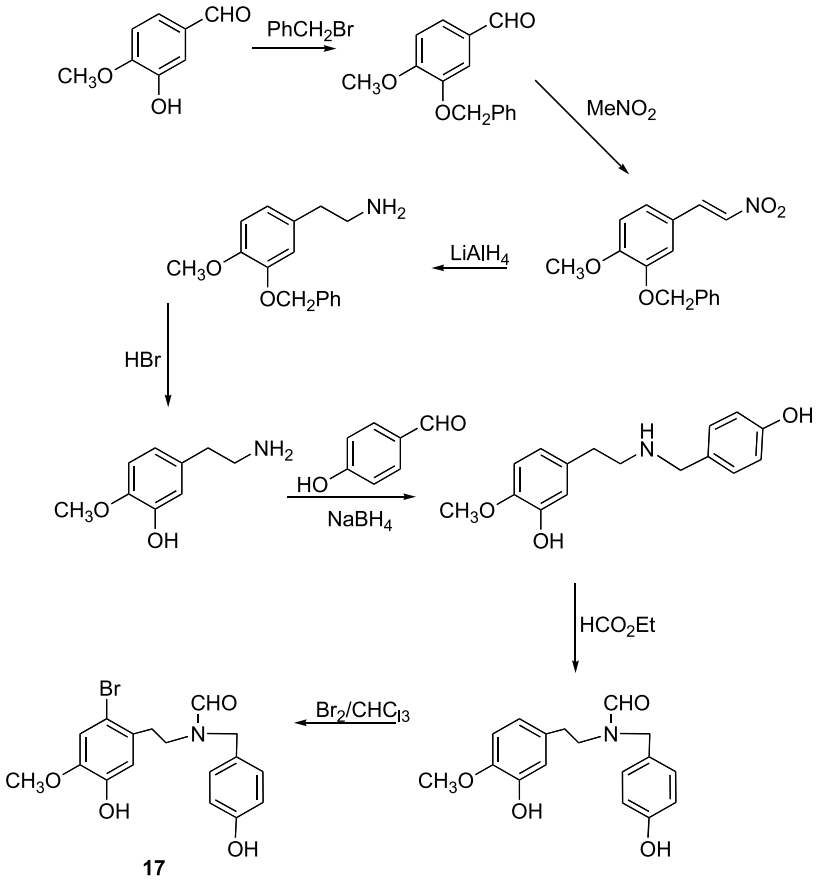


Scheme 2.

isolation and identification. Use of the dibrominated bisphenol intermediate in our modified[13] Shimizu synthesis[10] (Scheme 4) afforded the product **3** in 11% yield. The oxidative cyclization precursor **25** was obtained by formylation (46% yield) of the product obtained from reductive amination of 3-bromo-4-hydroxybenzaldehyde (**24**)[7] (prepared in 83% yield by bromination of commercially available 4-hydroxybenzaldehyde **23**) with 2-bromo-5-hydroxy-4-methoxyphenethylamine (**22**). The latter[1] was prepared by bromination of commercially available 3-hydroxy-4-methoxyphenylacetic acid (**18**) to afford the known[11] 2-bromo-5-hydroxy-4-methoxphenylacetic acid **19** (96% yield), followed by esterification and in situ conversion to the amide **21** (82% yield) and borane reduction (93% yield). The overall yield of **3** from commercially available starting materials was only 2.5%.

3. Discussion

We had previously determined that the yield in the oxidative cyclization step in the synthesis of galanthamine could be substantially improved by enhancing both the chloroform solubility and the steric hindrance to chelation of the



Scheme 3.

oxidative cyclization substrate.[13] A further example of the important role of molecular distribution properties is provided by comparison of our results to those of Poschalko et al.[9] Thus, while we were unable to isolate any meaningful amounts of cyclized product by attempted oxidation of the precursor **17** in chloroform, the cyclization product was obtained in 19–25% yield when the reaction was carried out in toluene.[9] Moreover, whereas the galanthamine precursor, 1,7-dibromo-*N*-formyl-*N*-nornarwedine had been obtained in 38–43% yield from the dibromo bisphenol,[13] the analogous 10-aza-compound **26**, the precursor of the [3]benzazepine analog **3**, was obtained in only 11%. Thus, although the oxidative cyclization process has been successfully applied to the synthesis of carbocyclic galanthamine analogs,[14] the results of our preparation of **2** and **3** confirm that this cyclization is highly sensitive to molecular features.

Altering the position of the nitrogen atom has striking effects on reactivity. Specifically, attempts to oxidize **2** to the narwedine analog **29** using manganese dioxide produced only minute amounts of **29** (Scheme 5), although treatment of galanthamine (**1**) afforded narwedine in 87% yield under the same conditions (unpublished results). Similarly, attempted epimerization of **2** to **30** (Scheme 5), under conditions that had been used successfully to convert galanthamine (**1**) to epigalanthamine failed; ^{1}H NMR (data not shown) suggested that the reaction product was the diene **31** (Scheme 5). The instability of this material precluded characterization. Preparation of the lycoramine analog **32** could not be carried out under the conditions used to convert galanthamine (**1**) to lycoramine due to the insolubility of **2** in ethanol. Attempted hydrogenation of the hydrochloride salt of **2** in ethanol produced 6-desoxylycoramine (**33**), presumably by catalytic hydrogenation of the diene **31** formed by the reaction of **2** with hydrochloric acid (Scheme 5). The lycoramine analog **32** was successfully prepared by hydrogenation of **2** in tetrahydrofuran; **33** was a byproduct (Scheme 6).

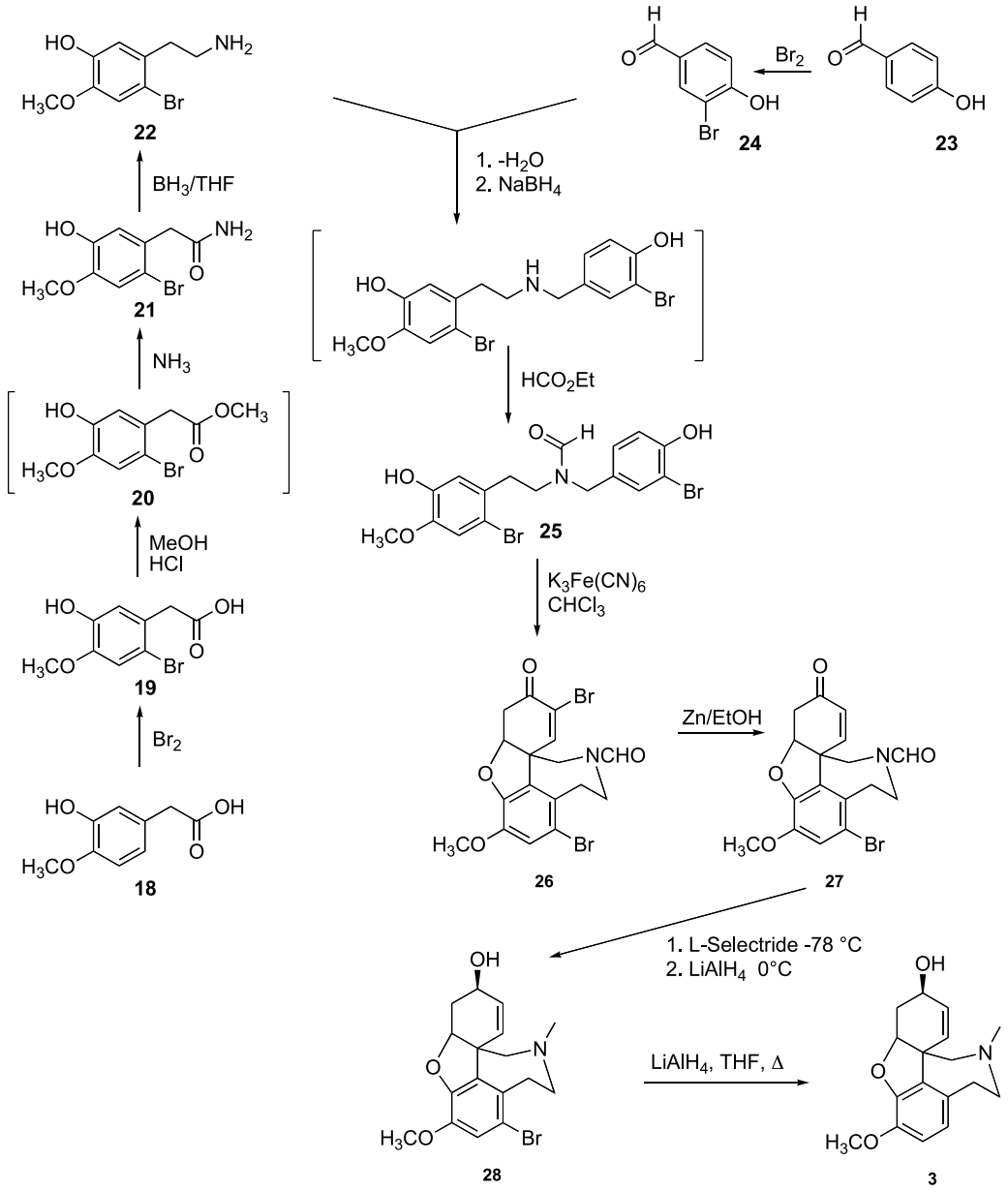
4. Conclusion

Oxidative cyclization has been utilized to prepare the [1]- and [3]benzazepine analogs of galanthamine, **2** and **3**, respectively. Despite the general structural similarity of **2**, **3**, and galanthamine (**1**), these compounds differ greatly in the reaction yields associated with the oxidative cyclization reaction as well as in their chemical reactivity.

5. Experimental

5.1. General

Melting points were determined on a Koffler hot stage. Proton magnetic resonance spectra were obtained on either a Bruker WM250 or a Varian EM390 spectrometer. Chemical shifts are relative to internal tetramethylsilane. Mass Spectra were recorded on an Applied Biosystems, Sciex



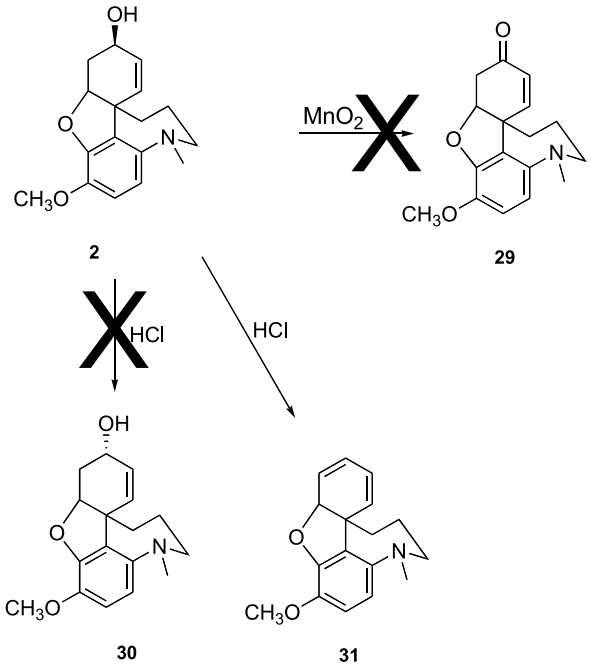
Scheme 4.

API single quadrupole mass spectrometer using atmospheric pressure chemical ionization.

5.1.1. 3-(4-Hydroxyphenyl)propionic acid methyl ester (5). After 3 h at ambient temperature a solution of 3-(4-hydroxyphenyl)propionic acid (**4**) (50 g, 0.3 mol) in 5% methanolic HCl (500 mL) was evaporated, and the residue was dissolved in EtOAc (300 mL). The solution was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and evaporated, giving a yellow oil (51.3 g, 95% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.55, 2.74 (AA′BB′, $J_{AB}=J_{AB'}=4$ Hz, CH_2CH_2), 3.60 (s, 3, $COOCH_3$), 6.67, 7.00 (AA′BB′, $J_{AB}=7.2$ Hz, $J_{AB'}=2.8$, 4 Hz, ArH), 9.18 (s, 1, OH). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67. Found: C, 66.55; H, 6.75.

5.1.2. 3-(4-Benzyloxyphenyl)propionic acid methyl ester (6). To a solution of 3-(4-hydroxyphenyl)propionic acid methyl ester (**5**) (36 g, 0.2 mol) in DMF (distilled, 275 mL) was added K_2CO_3 (165 g) followed by benzyl chloride (26 mL). After stirring for 18 h at 120 °C, this mixture was poured into ice-water (1500 mL) and concentrated HCl was added to pH 1. The solid product was removed by filtration and dried under vacuum to give 49.7 g (92% yield) of white crystals: ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.56–2.83 (AA′BB′, $J_{AB}=7.5$ Hz, $J_{AB'}=7.5$, 4 Hz, CH_2CH_2), 3.62 (s, 3, $COOCH_3$), 4.98 (s, 2, OCH_2), 6.86, 7.07 (AA′BB′, $J_{AB}=8.5$ Hz, $J_{AB'}=2.5$, 4 Hz, ArH), 7.2–7.43 (m, 5, Ph). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.56; H, 6.67. Found: C, 75.50; H, 6.74.

5.1.3. 3-(4-Benzyloxyphenyl)propionic acid (7). To a suspension of 3-(4-benzyloxyphenyl)propionic acid methyl ester (**6**) (54 g, 0.2 mol) in MeOH (500 mL) was added 0.4 N KOH (1 L), and the mixture was stirred at 60 °C until TLC showed the saponification to be complete. The volatile



Scheme 5.

solvent (MeOH) was evaporated, the pH brought to 1 with concentrated HCl, and the solution extracted with EtOAc (2×400 mL). The combined extract was dried over $MgSO_4$ and evaporated. The residue was triturated with hexane to give 46 g (90% yield) of white crystals, mp 122–123 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.60, 2.86 (AA′BB′, $J_{AB}=J_{AB'}=7.5$, 4 Hz, CH_2CH_2), 4.99 (s, 2, OCH_2), 6.86, 6.90 (AA′BB′, $J_{AB}=8.5$ Hz, $J_{AB'}=2.5$, 4 Hz, ArH), 7.2–7.4 (m, 5, Ph), 11.4 (br s, 1, COOH). Anal. Calcd for $C_{16}H_{16}O_3$: C, 75.00; H, 6.25. Found: C, 75.04; H, 6.30.

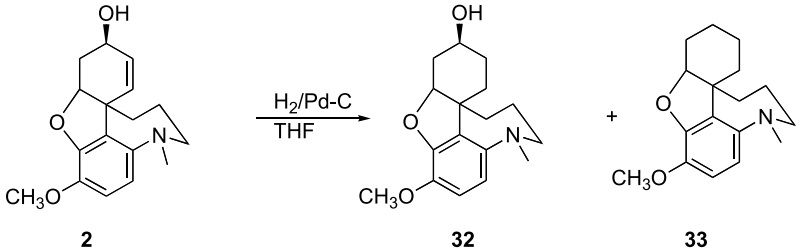
5.1.4. 3-Hydroxy-4-methoxyformanilide (10). To a suspension of 3-hydroxy-4-methoxyaniline (**9**) (20.85 g, 0.15 mol) in HCOOEt (500 mL) was added HCOOH (3 drops). The reaction mixture was refluxed for 48 h at which time TLC indicated all the starting material had been consumed. The solvent was evaporated, and the residue was dissolved in warm Me_2CO and passed through a 5×5.5 cm charcoal column (Norit). Evaporation of the solvent yielded 21.3 g of gray crystals (85%): ^{1}H NMR (250 MHz, $CDCl_3$/DMSO-d_6) exhibits the presence of two amide rotamers δ (ppm): 3.75 (s, 3, OCH_3), 6.61, 7.00 (2dd, $J=8.5$, 2.5, 1 Hz, H-6), 6.70, 7.25 (2d, $J=2.5$, 1 Hz, H-2), 6.85 (d, $J=8.5$, 1 Hz, H-5), 8.22, 8.62 (2d, $J=2$, 10, 1 Hz, CHO), 9.13 (br s, 1, OH), 9.89, 9.98 (2s, 1, NH). Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.39; N, 8.38. Found: C, 57.57; H, 5.44; N, 8.36.

5.1.5. 3-Benzloxy-4-methoxyformanilide (11). To a mixture of 3-hydroxy-4-methoxyformanilide (**10**) (16.7 g, 0.1 mmol) and K_2CO_3 (75 g) in DMF (100 mL) was added benzyl chloride (12 mL, 0.107 mol), and the mixture was stirred for 8 h at 120 °C. After cooling to room temperature, the reaction mixture was poured into ice-water, the pH was adjusted to 1 with concentrated HCl and the resultant solid was collected by filtration. After drying the brown powder weighed 21 g (82% yield): ^{1}H NMR (250 MHz, $CDCl_3$) exhibits the presence of two amide rotamers δ (ppm): 3.81, 3.84 (2s, 3, OCH_3), 5.06, 5.10 (2s, 2, OCH_2), 6.50–6.70 (m, 3, ArH), 7.20–7.38 (m, 5, Ph), 7.40, 8.17 (br s, d, $J=0.5$, 1 Hz, NH), 8.35, 8.43 (2d, $J=10$, 2, 1 Hz, CHO). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.04: H, 5.84; N, 5.45. Found: C, 70.12; H, 5.88; N, 5.40.

5.1.6. *N*-Methyl-2-bromo-5-benzyloxy-4-methoxyaniline (12). To a solution of 3-benzyloxy-4-methoxyformanilide (**11**) (25.7 g, 0.1 mol) in dry THF (600 mL) at 0 °C was added *N*-bromoacetamide (15.2 g, 0.11 mol) in several portions. After stirring overnight, the solvent was evaporated, and the residue was dissolved in $CHCl_3$ (500 mL). This solution was washed twice with H_2O (100 mL), dried over $MgSO_4$, and evaporated. Chromatography on SiO_2 (2% MeOH in $CHCl_3$) afforded 29 g (86%) of the intermediate bromo formamide as an off-white powder: ^{1}H NMR (90 MHz, $CDCl_3$) δ (ppm): 3.80 (s, 3, OCH_3), 5.08 (s, 2, OCH_2), 6.95 (s, 1, H-3), 7.20–7.45 (m, 6, Ph and NH), 8.07 (s, 1, H-6), 8.35 (d, $J=2$, 1 Hz CHO).

A solution of the above product (16.8 g, 0.05 mol) in THF (100 mL) was cooled to 0 °C, and 1 M $BH_3\cdot$THF (100 mL, 0.1 mol) was added. After refluxing for 30 min, the reaction mixture was cooled to 0 °C, and the excess BH_3 was decomposed by the addition of H_2O followed by 10% NaOH. Stirring was continued for 30 min, EtOAC (200 mL) was added, and the layers were separated. The organic layer was evaporated, and the aqueous layer was washed with EtOAc (200 mL). The combined organic phase was dried and evaporated to give **12** as an off-white semisolid, after drying under high vacuum (14.6 g, 91% yield): ^{1}H NMR (90 MHz, $CDCl_3$) δ (ppm): 2.65 (s, 3, NCH_3), 3.68 (s, 3, OCH_3), 3.65–3.95 (br s, 1, NH), 5.03 (s, 2, OCH_2), 6.20 (s, 1, H-6), 6.97 (br s, 1H-3), 7.12–1.40 (m, 5, Ph). Anal. Calcd for $C_{15}H_{16}BrNO_2$: C, 55.92; H, 5.01; N, 4.35. Found: C, 55.94; H, 5.02; N, 4.27.

5.1.7. *N*-Methyl-3-(4-hydroxphenyl)propion-(2-bromo-5-hydroxy-4-methoxy)anilide (13). A solution of 3-(4-benzyloxyphenyl)propionic acid (**7**) (25.6 g, 0.1 mol) in $SOCl_2$ (75 mL) was refluxed for 2 h. The excess $SOCl_2$ was removed at reduced pressure; the residue was dissolved in



Scheme 6.

$CHCl_3$ (pentene stabilized) and the solvent evaporated. After drying under high vacuum for 2 h, 27.5 g (100% yield) of the product **8** was obtained. A portion (14 g, 0.051 mol) was dissolved in $CHCl_3$ (150 mL) (pentene stabilized) and the solution was added to a solution of *N*-methyl-2-bromo-5-benzyloxy-4-methoxyaniline (**12**) (16.1 g, 0.05 mol) in $CHCl_3$ (pentene stabilized, 200 mL), followed by Et_3N (56 g) in $CHCl_3$ (50 mL). After stirring for 1 h, TLC showed the starting material to be consumed. The reaction mixture was then washed with 1% HCl, followed by H_2O, dried and evaporated to give a brown oil (23.8 g, 85% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.05–2.30 (AA′, 2, CH_2CO), 2.65–2.87 (BB′, 2, CH_2CH_2CO), 3.10 (s, 3, NCH_3), 3.80 (s, 3, OCH_3), 4.95 and 5.00 (2s, 4, CH_2O), 6.55 (s, 1H-3), 6.80–7.10 (AA′BB′, 4, ArH), 7.25 (s, H-6), 7.20–2.50 (m, 10, Ph).

To a solution of this oil (14 g, 0.025 mol) in EtOH (75 mL) was added 48% HBr (150 mL) and the mixture was stirred for 2 h at 60 °C. The reaction mixture was treated with charcoal and allowed to come to room temperature. The residue obtained after filtration through a pad of Celite and evaporation of the solvent was dissolved in EtOAc (200 mL), and the solution was washed with H_2O, dried over $MgSO_4$ and evaporated. The product (7.7 g, 81% yield) was obtained as an off-white semicrystalline solid after purification by column chromatography using SiO_2 and 2% MeOH in $CHCl_3$ on the eluent: ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.27, 2.83 (AA′BB′, $J_{AB}=8.5$, 4 Hz, CH_2CH_2), 3.13 (s, 3, NCH_3), 3.89 (s, 3, OCH_3), 5.60–6.50 (br s, 2, OH), 6.28 (s, 1H-3), 6.70, 6.88 (AA′BB′, $J_{AB}=9$ Hz, $J_{AB'}=2$, 4 Hz, ArH), 7.03 (s, 1, H-6). Anal. Calcd for $C_{17}H_{18}BrNO_4$: C, 53.68; H, 4.74; N, 3.68. Found: C, 53.78; H, 4.82; N, 3.62.

5.1.8. (4aα)-4a,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-12-methyl-11-oxobenzofuro[3a,3,2-*e*,*f*][1]benzazepin-6-one (14). To a well-stirred mixture of $CHCl_3$ (3000 mL), aqueous 5% $NaHCO_3$ (500 mL) and $K_3Fe(CN)_6$ (57 g, 0.173 mol) at 60 °C was added *N*-[3-(4-hydroxyphenyl)propionyl]-*N*-methyl-2-bromo-5-hydroxy-4-methoxyaniline (**13**) (11 g, 0.029 mol) in one portion. After stirring at 60 °C for 1.5 h the layers were separated, the $CHCl_3$ evaporated and the residue filtered through a 5 cm column of SiO_2 in EtOH stabilized $CHCl_3$. Evaporation of the solvent afforded 5.5 g (50%) of the product **14** (TLC pure) as a pink foam: ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.03–3.15 (m, 6H, CH_2CH_2 and $CH_2C{=}O$), 3.36 (s, 3, NCH_3), 3.88 (s, 3, OCH_3) 4.84 (m, 1, H-4), 6.00 (d, $J=9$, 1 Hz, H-8), 6.36 (dd, $J=9$, 2, 1 Hz, H-7), 7.08 (s, 1, H-2). Anal. Calcd for $C_{17}H_{16}BrNO_4$: C, 53.97; H, 4.23; N, 3.70. Found: C, 54.03; H, 4.30; N, 3.62.

5.1.9. (4aα,6β)-4a,5,9,10,11,12-Hexahydro-3-methoxy-12-methyl-6*H*-benzofuro-[3a,3,2-*e*,*f*][1]benzazepin-6-ol (2) and (4aα,6α)-4a,5,9,10,11,12-hexahydro-3-methoxy-12-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepin-6-ol (15). A solution of (4α)-4a,5,9,19,11,12-hexahydro-1-bromo-3-methoxy-12-methyl-11-oxobenzofuro[3a,3,2-*e*,*f*]-[1]benzazepin-6-one (**14**) (3.8 g, 0.01 mol) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (5 g, 0.47 mol) in THF (100 mL). The reaction mixture was refluxed for 36 h and stirred at room temperature for an additional 48 h. The excess $LiAlH_4$ was decomposed by the sequential addition of H_2O and 15% NaOH. The solids were removed by filtration and washed with EtOAc (200 mL). The combined organic phase was dried with $MgSO_4$ and evaporated. The product mixture was separated by column chromatography eluting with 0.4% EtOH in $CHCl_3$ affording 1.7 g (59%) of the 4α,6β isomer **2** and 0.2 g (7%) of the 4α,6α isomer **15**: ^{1}H NMR for **2** (250 MHz, $CDCl_3$) δ (ppm): 1.41, 1.71 (AB, 2, H-9), 1.88, 2.15 (AB, 2, H-10), 2.04, 2.68 (AB, $J=15.6$, 2 Hz, H-5), 2.35 (d, $J=11.4$, 1 Hz, OH), 2.78, 3.30 (AB, 2, H-11), 2.86 (s, 3, NCH_3), 3.80 (s, 3, OCH_3), 4.11 (m, $J=11.4$, 1 Hz, H-6), 4.58 (m, 1, H-4), 5.90 (dd, $J=10.3$, 4.8, 0.9, 1 Hz, H-7), 6.00 (dd, $J=10.3$, 0.9, 1 Hz, H-8), 6.28 (d, $J=8.75$, 1 Hz, H-1), 6.69 (d, $J=8.75$, 1 Hz, H-2): ^{1}H NMR for **15** (250 MHz, $CDCl_3$) δ (ppm): 1.49, 1.87 (AB, 2, H-9), 1.72, 2.75 (AB, 2, H-5), 1.82, 2.07 (AB, 2, H-10), 2.11 (br s, 1, OH), 2.75, 3.24 (AB, 2, H-11), 2.81 (s, 3, NCH_3), 3.78 (s, 3, OCH_3), 4.55 (m, 1, H-4), 4.59 (m, 1, H-6), 5.68 (d, $J=10.3$, 1 Hz, H-7), 6.01 (d, $J=10.3$, 1 Hz, H-8), 6.22 (d, $J=8.7$, 1 Hz, H-1), 6.64 (d, $J=8.7$, 1 Hz, H-2).

5.1.10. (4aα,6β)-4a,5,9,10,11,12-Hexahydro-3-methoxy-12-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepin-6-ol (2) hydrochloride. The free base **2** (1.7 g, 0.006 mol) was dissolved in EtOH, and ethanolic HCl was added. The solvent was evaporated, and the product was recrystallized from EtOH/Et_2O to give 1.7 g (89%) of the hydrochloride salt, mp 181.5–182.0 °C. Anal. Calcd for $C_{11}H_{22}C1NO_3 \cdot 1/4H_2O$: C, 62.20; H, 6.87; N, 4.27. Found: C, 62.23; H, 6.93; N, 4.26.

5.1.11. 2-Bromo-5-hydroxy-4-methoxyphenylacetic acid (19).[11] To a solution of 3-hydroxy-4-methoxyphenylacetic acid (**18**) (70 g, 0.386 mol) in HOAc (1000 mL) was added a solution of Br_2 (67.74 g, 0.424 mol) in HOAc (100 mL) at room temperature. The mixture was stirred overnight and the solvent evaporated. The residue was dissolved in toluene and the solvent evaporated. The residue was treated with toluene (800 mL), the mixture heated for 15 min, cooled to room temperature and the product filtered, to afford 97 g (96%) of semicrystalline solid: ^{1}H NMR (90 MHz, DMSO-d_6) δ (ppm): 3.48 (s, 2, CH_2), 3.69 (s, 3, OCH_3), 6.70 (s, 1, Ar), 6.97 (s, 1, Ar). *m*/*z* Calcd for $C_9H_9BrO_4$: 259.9685 and 261.9664. Found: 259.9691 and 261.9674.

5.1.12. 2-Bromo-5-hydroxy-4-methoxyphenylacetamide (21). Dry HCl was passed through a solution of 2-bromo-5-hydroxy-4-methoxphenylacetice acid (**19**) (97 g, 0.371 mol) in MeOH (1000 mL) at 0 °C for 30 min. The mixture was left overnight, then the solvent was evaporated, and the residue (**20**) was dissolved in EtOAc. The solution was washed twice with water, aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and the solvent was evaporated. The ester was dissolved in MeOH (800 mL) and NH_3 was bubbled through for 8 h at 0 °C. The reaction mixture was left in the dark for 10 days. The volatiles were removed under reduced pressure and the residue was suspended in MeOH (150 mL) and filtered, affording 79 g (82%) of amide **21**, mp 185–187: ^{1}H NMR (90 MHz, DMSO-d_6) δ (ppm): 3.25 (s, 2, CH_2); 3.75 (s, 3, OCH_3); 6.50–7.40 (m, 4, NH_2, Ar); 8.82 (s, 1, OH). *m*/*z* Calcd for $C_9H_{10}BrNO_2$: 258.9844 and 260.9824. Found: 258.9840 and 260.9827.

5.1.13. 2-Bromo-5-hydroxy-4-methoxyphenethylamine (22).[1] To the amide **21** (64 g, 0.246 mol) in a 2 L round-bottom flask was added slowly 1 N BH_3/THF (800 mL, 0.266 mol). The reaction mixture was refluxed for 5 h, cooled to 0 °C and concentrated methanolic HCl was added (500 mL). After stirring overnight, the solvent was evaporated, the residue redissolved in MeOH and the solvent evaporated again. This operation was repeated three times. The residue was dissolved in MeOH (500 mL) and the pH was brought to 8 by addition of MeONa in MeOH. The precipitated salt was removed by filtration and the solvent was evaporated at reduced pressure to afford 56 g (93%) of **22** as a light brown wax: ^{1}H NMR (90 MHz, DMSO-d_6) δ (ppm): 2.84 (s, 4, CH_2CH_2); 3.72 (s, 3, OCH_3); 6.78 (s, 1, Ar); 7.02 (s, 1, Ar).

5.1.14. 3-Bromo-4-hydroxybenzaldehyde (24). To a solution of 4-hydroxybenzaldehyde (**23**) (50 g, 0.409 mol) in a mixture of $CHCl_3$ (500 mL) and MeOH (50 mL) was added a solution of Br_2 (71 g, 23 mL, 0.45 mol) in $CHCl_3$ (100 mL) dropwise at room temperature. The mixture was stirred for 2 h and washed with water to neutral pH. The organic phase was dried with $MgSO_4$ and the solvent was evaporated. Recrystallization from $CHCl_3$ afforded 68.4 g (83%) of **24**, mp 118–120 °C (lit.[8] 124 °C).

5.1.15. *N*-(2-Bromo-5-hydroxy-4-methoxyphenethyl)-*N*-(3-bromo-4-hydroxybenzyl)formamide (25). A mixture of the aldehyde **24** (45.7 g, 0.227 mol) and the crude amine **22** (56 g, 0.227 mol) in anhydrous MeOH (1600 mL) and molecular sieves 4 Å (230 g) was stirred overnight at room temperature. After the sieves were removed by filtration and the mixture diluted to 3200 mL with MeOH, $NaBH_4$ (19 g, 0.5 mol) was added in six equal portions at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was treated with 15% HCl/MeOH to pH 1, and the mixture was left overnight at room temperature. The solvent was then removed under reduced pressure, the residue redissolved in MeOH, and the NaCl removed by filtration. This procedure was repeated three times. The residue was then dissolved in MeOH (700 mL) and methanolic MeONa was added until the pH was 8. The precipitated NaCl was filtered off, and the solvent was evaporated. The residue was suspended in HCOOEt (1000 mL) with NEt_3 (10 mL), and the mixture was refluxed until TLC ($CHCl_3$/MeOH/NH_4OH aqueous, 90:10:1) showed complete consumption of starting material (3 days). The solvent was removed under reduced pressure. The crude material was purified on a SiO_2 (1000 g) column (2% MeOH in $CHCl_3$) providing 48 g (46%) of the formamide **25** as a semicrystalline light yellow solid: ^{1}H NMR (90 MHz, DMSO-d_6) shows two rotamers δ (ppm): 2.50–2.95 (m, 2, $ArCH_2$); 3.22–3.55 (m, 2, $ArCH_2CH_2N$); 3.82 (s, 3, OCH_3); 4.18 and 4.45 (two-s, 2, $ArCH_2N$); 6.55–7.33 (m, 5, Ar); 8.00 and 8.28 (two-s, 1, CHO). *m/z* Calcd for $C_{17}H_{17}Br_2NO_4$: 456.9524, 458.9504, and 460.9486. Found: 456.9523, 458.9519, and 460.9482.

5.1.16. (*rac*)-(4aα)-4a,5,9,10,11,12-Hexahydro-1,7-dibromo-3-methoxy-10-formyl-6*H*-benzofuran[3a,3,2-*e*,*f*][3]benzazepin-6-one (26). To a well stirred biphase of $CHCl_3$ (3500 mL) and a solution of $K_3Fe(CN)_6$ (27.3 g, 0.083 mol) and $NaHCO_3$ (14 g, 0.17 mol) in H_2O (27.5 mL) at 60 °C in a 5 L Morton flask under N_2 was added formamide **25** (10 g, 0.022 mol) in one portion. After stirring at 60 °C for 2 h, the reaction mixture was cooled and the $CHCl_3$ layer was separated. The aqueous layer was washed with $CHCl_3$ (1000 mL). The combined organic phase was evaporated and the product was separated on 100 g of SiO_2 using 1% MeOH in $CHCl_3$ as eluant. After solvent removal under reduced pressure, 1.1 g (11% yield) of HPLC-pure product was obtained as a yellow foam: ^{1}H NMR (90 MHz, $CDCl_3$) showed two rotamers δ (ppm): 2.62–3.56 (m, 6, 3×CH_2); 3.75 (s, 3, OCH_3); 3.80–4.12 (m, 1, H-12a); 4.58–4.82 (m, 1, H-4a); 4.45 and 4.48 (two-d, J= 17, 1 Hz, H-12b); 6.75–6.90 (m, 1, H-8); 6.95 (s, 1, H-2); 8.01 and 8.05 (two-s, 1, CHO). MS (APCI-ESI) calcd for $C_{17}H_{15}Br_2NO_4$: 455/457/459. M^+-1. Found: 456/458/460; M^--1. Found: 454/456/458. High resolution mass spectra could not be obtained for this material.

5.1.17. (*rac*)-(4aα)-4a,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-10-formyl-6*H*-benzofuro[3a,3,2-*e*,*f*][3]benzazepin-6-one (27). To a solution of dibromoenone **26** (0.89 g, 0.002 mol) in EtOH (50 mL) was added 2.6 g of activated zinc powder. The mixture was refluxed until HPLC (2% MeOH in $CHCl_3$) showed completion of the reaction (overnight). The solution was filtered hot and the zinc was washed thoroughly with hot EtOH. The alcohol was evaporated and the residue was separated on a SiO_2 column (1% MeOH in $CHCl_3$) providing 0.65 g (88%) of the product **27** as a white foam: ^{1}H NMR (90 MHz, $CDCl_3$) showed two rotamers δ (ppm): 2.55–3.08 (m, 5); 3.10–3.98 (m, 2); 3.70 (s, 3, OCH_3); 4.45–4.84 (m, 2, H-4a, H-9); 5.92 and 6.02 (two-d, J=10, 1 Hz, H-7); 6.46 and 6.50 (two-d-d, J=10, 1.8, 1 Hz, H-8); 6.90 (s, 1, Ar); 8.00 and 8.18 (two-s, 1, CHO). *m/z* Calcd for $C_{17}H_{16}BrNO_4$: 377.0263 and 379.0242. Found: 377.0263 and 379.0226.

5.1.18. (*rac*)-(4aα,6β)-4a,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-10-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][3]-benzazepin-6-ol (28). A solution of (*rac*)-(4aα)-4a,5,9,10,11,12-hexahydro-1-bromo-3-methoxy-10-formyl-6*H*-benzofuro[3a,3,2-*e*,*f*][3]benzazepin-6-one (**27**) (3.67 g, 0.0097 mol) in dry THF (150 mL) at −78 °C was stirred under dry argon for 20 min, and 1 M L-Selectride (19.5 mL, 0.0195 mol) was added dropwise. After stirring at −78 °C for 2 h, the mixture was allowed to warm up to 0 °C, and 1 M $LiAlH_4$/THF (19.5 mL, 0.0195 mol) was added dropwise. Stirring was continued overnight. Excess reducing agent was decomposed by sequential addition of H_2O (2.65 mL) and 10% NaOH (8 mL). The inorganic salts were removed by filtration, and the solution was dried with $MgSO_4$. Column chromatography on SiO_2 (2% MeOH in $CHCl_3$) provided 2.55 g (72%) of **28** as a white foam: ^{1}H NMR (90 MHz, $CDCl_3$) δ (ppm): 1.62–1.90 (m, 2), 2.01–2.25 (m, 3), 2.30 (s, 3, NCH_3), 2.35–2.75 (m, 2), 2.80–3.22 (m, 2), 3.70 (s, 3, OCH_3), 3.99–4.11 (m, 1, H-6), 4.51 (m, 1, H-4), 5.86–6.02 (m, 2, H-7, H-8), 6.79 (s, 1, H-2). *m/z* Calcd for $C_{17}H_{20}BrNO_3$: 365.0627 and 367.0606. Found: 365.0630 and 367.0619.

5.1.19. (*rac*)-(4aα,6β)4a,5,9,10,11,12-Hexahydro-3-methoxy-10-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][3]-benzazepin-6-ol (3). A solution of (*rac*)-(4aα,6β)-4a,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-10-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][3]benzazepin-6-ol **28** (2.55 g, 0.007 mol)

in dry THF (150 mL) was added to a suspension of 4 g (0.073 mol) of $LiAlH_4$ (4 g, 0.073 mol) at 0 °C, and the mixture was refluxed for 72 h. After cooling to 0 °C, the excess $LiAlH_4$ was decomposed by sequential addition of H_2O (4 mL) and 10% NaOH (12 mL). The inorganic salts were removed by filtration, the filtrate dried over $MgSO_4$, and the solvent evaporated. Column chromatography on SiO_2 (3% MeOH in $CHCl_3$) provided 1.98 g of **3**. The amine was converted to a *p*-toluenesulfonic acid salt, which was collected by filtration and recrystallized from EtOH/ether providing 2.8 g (96%) of **3**·TsOH, mp 206 °C (dec); IR (KBr): 3300, 3010, 1510, 1450, 1235, 1145, 1050, 790, 690 cm^{-1}: ^1H NMR (250 MHz, DMSO-d_6) δ (ppm): 2.04–2.29 (m, 1), 2.29 (s, 3, NCH_3), 2.80–2.97 (m, 3), 3.21–3.71 (m, 5), 3.73 (s, 3, OCH_3), 4.07–4.15 (m, 1, H-6), 4.52–4.58 (m, 1, H-4), 5.87–5.98 (m, 2, H-7, H-8), 6.67 (d, J=8.2, 1 Hz, H-2), 6.90 (d, J=8.2, 1 Hz, H-1), 7.12 (d, J=8.0, 2 Hz, H-3, H-5), 7.48 (d, J=8.0, 2 Hz, H-2, H-6), 9.66 (br s, 1, N=H). Anal. Calcd for $C_{24}H_{29}NO_6S$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.85; H, 6.39, N, 3.03.

5.1.20. (4aα)-4a,5,7,8,9,10,11,12-Octahydro-3-methoxy-12-methyl-6*H*-benzofuro-[3a,3,2-*e*,*f*][1]benzazepine (33) hydrochloride. To a solution of (4aα,6)-4a,5,9,10,11,12-hexahydro-3-methoxy-12-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepin-6-ol (**2**) (1.1 g, 3.5 mmol) in 1% ethanolic HCl (50 mL) was added Pd/C (200 mg) and the mixture was hydrogenated for 2 h at 40 psi. The catalyst was removed by filtration, and the product was crystallized from EtOH/Et_2O to afford 1.1 g (92%) of the hydrochloride salt of the product, mp 205–220° (dec): ^1H NMR (250 MHz, D_2O) δ (ppm): 1.17–1.82 (m, 7), 2.00–2.62 (m, 5), 3.23 (s, 3, NCH_3), 3.53 (t, 1, H-11a), 3.69–3.89 (m, 1, H-11e), 3.89 (s, 3, OCH_3), 4.22 (br s, 1, H-4), 4.82 (s, 4, NH+HOD), 7.01 (AB, 2, ArH). Anal. Calcd for $C_{17}H_{23}NO_2 \cdot HCl$: C, 65.91; H, 7.75; N, 4.52; Cl, 11.47. Found: C, 65.70; H, 7.86; N, 4.48; Cl, 11.48.

5.1.21. (4aα,6β)-4a,5,7,8,9,10,11,12-Octahydro-3-methoxy-6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepin-6-ol (32) hydrochloride. To a solution of (4aα,6β)-4a,5,9,10,11,12-hexahydro-3-methoxy-12-methyl-6*H*-benzofuran[3a,3,2-*e*,*f*][1]benzazepin-6-ol (**2**) (2.87 g, 0.01 mol) in THF (150 mL) was added 10% Pd/C (400 mg), and the mixture was shaken under 40 psi of H_2 for 7 h. The catalyst was removed by filtration, the solvent evaporated, and the residue purified by chromatography using 0.2–0.5% EtOH in $CHCl_3$ to afford 1.39 (46%) of **32**. The desoxy compound **33** was isolated in 26% as a byproduct. Treatment of **32** with 1% HCl in EtOH gave the hydrochloride salt. Crystallization from EtOH/Et_2O gave 1.2 g (81%) of the pure salt, mp 235 °C (dec): ^1H NMR (250 MHz, D_2O) δ (ppm): 1.60–2.63 (m), 3.27 (2, 3, NCH_3), 3.55 (t, 1, H-11a), 3.74–3.82 (m, 1, H-11e), 3.89 (s, 3, OCH_3), 4.17 (br s, 1, H-4), 4.33 (br s, 1, H-6), 4.80 (s, 1.5, NH–HOD), 7.01 (AB, 2, ArH). Anal. Calcd for $C_{17}H_{24}ClNO_3$: C, 62.67; H, 7.37; N, 4.50; Cl, 10.91. Found: C, 62.76; H, 7.46; N, 4.27; Cl, 10.85.

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References and notes

1. Battersby, A. R.; Southgate, R.; Staunton, J.; Hirst, M. *J. Med. Chem. Soc. (C)* **1966**, 1052–1057.
2. Cozanitis, D. A. *Acta Anaesthesiol. Belg.* **1977**, *28*, 53–60.
3. Cozanitis, D. A.; Toivakka, E. *Anaesthesia* **1974**, *29*, 581–584.
4. Giuliani, G. *Minerva Med.* **1964**, *55*, 238–241.
5. Heinrich, M.; Lee Teoh, H. *J. Ethnopharmacol.* **2004**, *92*, 147–162.
6. Kametani, T.; Yamaki, K.; Yagi, H.; Fukumoto, K. *J. Chem. Soc. (C)* **1969**, 2602.
7. Paal, C. *Chem. Ber.* **1895**, *28*, 2410.
8. Paal, C. *Berichte de Deutsche Chemische Gesellschaft* **1895**, 2407–2414.
9. Poschalko, A.; Welzig, S.; Treu, M.; Nerdinger, S.; Mereiter, K.; Jordis, U. *Tetrahedron* **2002**, *58*, 1513–1518.
10. Shimizu, K.; Tomoika, K.; Yamada, S.-I.; Koga, K. *Chem. Pharm. Bull.* **1978**, *26*, 3765.
11. Szantzy, C.; Dornyie, G.; Blasko, G.; Barczai-Beke, M.; Pechy, P. *Arch. Pharm. (Weinheim)* **1981**, *314*, 983–991.
12. Szewczyk, J.; Lewin, A. H.; Carroll, F. I. *J. Heterocycl. Chem.* **1988**, *25*, 1809–1811.
13. Szewczyk, J.; Wilson, J. W.; Lewin, A. H.; Carroll, F. I. *J. Heterocycl. Chem.* **1995**, *32*, 195.
14. Treu, M.; Jordis, U. *Molecules* **2002**, *7*, 374–381.
15. Winslow, J. T.; Camacho, F. *Psychopharmacology (Berl)* **1995**, *121*, 164–172.

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Carbamoylimidazolium and thiocarbamoylimidazolium salts: novel reagents for the synthesis of ureas, thioureas, carbamates, thiocarbamates and amides

Justyna A. Grzyb,[a] Ming Shen,[a] Chiaki Yoshina-Ishii,[a] W. Chi,[b] R. Stanley Brown[b] and Robert A. Batey[a,*]

[a]*Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ont., Canada M5S 3H6*
[b]*Department of Chemistry, Queen's University, Kingston, Ont., Canada K7L 3N6*

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Dedicated to the memory of Dr. Bruce Graham, former Director of Research and Development, Crompton Chemical, Guelph, Ontario.

Abstract—Carbamoylimidazolium salts act as efficient *N*,*N*-disubstituted carbamoylating reagents. These salts are readily prepared by the sequential treatment of secondary amines with *N*,*N*′-carbonyldiimidazole (CDI) and iodomethane. The carbamoylimidazolium salts are more efficient carbamoyl transfer reagents than the intermediate carbamoylimidazoles, as a result of the 'imidazolium' effect. Kinetic studies on the base promoted hydrolysis of both carbamoylimidazoles and carbamoylimidazolium salts reveal over a hundred-fold rate acceleration. The salts react with amines, thiols, phenols/alcohols, and carboxylic acids in high yields, without the need for subsequent chromatographic purification of the products, producing ureas, thiocarbamates, carbamates, and amides, respectively. Analogous thiocarbamoylimidazolium salts were also synthesized from secondary amines and *N*,*N*′-thiocarbonyldiimidazole (TCDI), followed by methylation with iodomethane.

1. Introduction

The reaction of nucleophiles with acyl transfer reagents, such as acid chlorides, is one of the most important classes of functionalization reaction used in organic synthesis. Such reactions are also important for the generation of combinatorial libraries,[1] both using solid-phase organic synthesis (SPOS)[2] and parallel solution-phase techniques.[3] The corresponding transfer of an electrophilic carbamoyl group ($R^1R^2NC{=}O$) to nucleophiles is used in the formation of ureas, carbamates and thiocarbamates. A variety of reagents are useful synthetic equivalents to carbamoyl cations (Fig. 1). Isocyanates **1** are used as monosubstituted carbamoyl transfer reagents ($R^1NHC{=}O$), and act as synthetic equivalents to monosubstituted carbamoyl cations. Carbamoyl chlorides **2** are the most commonly used synthetic equivalents to disubstituted carbamoyl cations. Unfortunately, there are significant drawbacks associated with the use of carbamoyl chlorides. They have limited commercial availability and their synthesis requires the use of toxic phosgene. In addition, they are highly reactive, prone to hydrolysis, and their relative instability does not render them suitable for long-term storage and archiving. These considerations are particularly important where 'off the shelf' reagents or a series of combinatorial 'building blocks' are required.

As a solution to these problems, we envisaged the use of carbamoylimidazolium salts **3** as *N*,*N*′-disubstituted carbamoyl cation equivalents (Fig. 1).[4] The corresponding carbamoylimidazoles **4**, are much less reactive towards nucleophilic attack and have to be activated as carbamoylimidazolium salts. Such activation of carbonylimidazole as carbonylimidazolium salts has been demonstrated previously in a number of systems.[5,6–9] Acylimidazolium salts were shown, initially by Jencks, to be more reactive than acylimidazoles in their reactions with nucleophiles.[6]

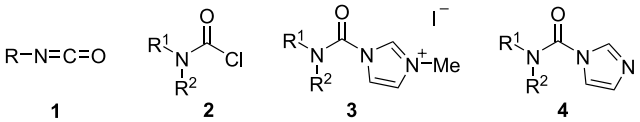

Figure 1. *N*-monosubstituted and *N*,*N*′-disubstituted carbamoyl cation equivalents.

Keywords: Carbamoylimidazolium salts; Thiocarbamoylimidazolium salts; Ureas; Thioureas; Carbamates; Thiocarbamates; Amides.
* Corresponding author. Tel./fax: +1 416 978 5059; e-mail: rbatey@chem.utoronto.ca

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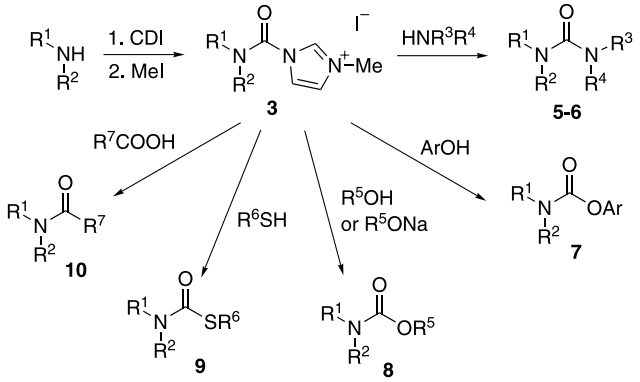
Similarly, alkoxycarbonylimidazolium salts are also activated towards nucleophilic attack by amines.[7] Rapoport has applied this strategy in the selective protection of the amino functionality in nucleosides, as amides, carbamates, and thiocarbamates.[8] Dicationic 1,1′-carbonylbis(3-methylimidazolium) ions have been used for alkoxycarbonylations of amino acids for peptide and ester bond forming reactions.[9]

We now outline a full study on the use of carbamoylimidazolium salts **3** as *N*,*N*′-disubstituted carbamoyl transfer reagents, as well as the use of the corresponding sulfur analogs. Specifically, we show their application to the synthesis of ureas, thioureas, carbamates, thiocarbamates, and amides using solution-phase methods (Scheme 1).[4] There has also been a recent application of these reagents in polymer-supported chemistry.[10]

2. Results and discussion

Carbamoylimidazolium salts **3** are readily prepared from *N*,*N*′-carbonyldiimidazole (CDI) via a two-step procedure. CDI, used as the phosgene equivalent in this synthesis, is a commercially available and easily handled crystalline solid.[5] Stable and isolable carbamoylimidazoles **4** were obtained in high yields by refluxing the secondary amines with CDI in THF for 16 h (Table 1, **4a**–**4e**). The reaction of L-proline benzylester hydrochloride, morpholine, *O*,*N*-dimethylhydroxylamine and 1,4-dioxa-8-aza-spiro[4.5]-decane with CDI under refluxing conditions afforded undesirable byproducts. However, when these reactions were stirred at rt in dichloromethane, the desired carbamoylimidazoles were cleanly formed in high yields (Table 1, **4f**–**4i**). After simple aqueous work-up, the carbamoylimidazoles **4** were reacted with MeI in acetonitrile at rt for 24 h. The carbamoylimidazolium salts **3** were obtained after evaporation of the solvent and volatile reagents.

A wide variety of carbamoylimidazolium salts **3** have been prepared for which the analogous carbamoyl chlorides are not commercially available. Since our goal was the development of carbamoyl transfer reagents suitable for a range of synthetic applications, including combinatorial library synthesis, the long-term thermal, hydrolytic and air stability of the salts is an important practical consideration.



Scheme 1.

The stability of different salts in solution and in the solid-state by using ^{1}H NMR analysis was observed. The carbamoylimidazolium salts **3a**, **3c** and **3h** derived from tetrahydroquinoline, *N*-methylaniline and *O*,*N*-dimethylhydroxylamine, respectively, were chosen as test compounds for stability studies. The stability of the compounds in the solid state was evaluated using freshly prepared salts, stored at rt without exclusion of air and moisture. The same compounds were also evaluated as stock solutions in $CDCl_3$ stored at rt. Salt **3a** is a very stable, non-hygroscopic, crystalline solid, which can be stored for extended periods of time without discoloration. There are only trace amounts of decomposition products appearing after 3 months of storage either in $CDCl_3$ solution or in solid state. Salt **3c** is a very hygroscopic yellow foam. However, NMR studies showed that the salt remained at the same purity level even after 3 months. A $CDCl_3$ solution of **3c** showed only trace amount of decomposition product after 3 months of storage. Salt **3h**, a white crystalline solid, was the least stable compound, with significant color change occurring after several days of storage in the solid state. However, decomposition can be avoided by storing the solid in a freezer at −20 °C. Decomposition was also observed in the $CDCl_3$ solution of salt **3h** after 24 h showing 12% contamination with the decomposition product. After 48 h, the decomposition caused significant color change and some precipitation.

X-ray crystallographic and IR data, clearly show the structural effects of the well-known imidazolium effect. X-ray crystallographic analysis of the salt **3b** shows a relatively short C(5)–N(3) bond (1.327(6) Å) and a longer C(5)–N(1) bond (1.466(6) Å) (Fig. 2).[11] This reflects the greater double bond character of the C(5)–N(3) bond. The C(5)–N(1) bond is longer and weaker because the lone-pair of electrons on the imidazolium nitrogen does not have a significant resonance effect with the carbonyl group, since it is part of the aromatic π-system of the imidazolium ring. These C–N bond distances compare to values of approximately 1.371–1.379 Å for simple tetrasubstituted ureas, and 1.325–1.346 Å for amides. The degree of pyramidalization of N(3) is intermediate between that of idealized sp^3 and sp^2 hybridization geometries (such as in aliphatic amines and amides, respectively). The infra-red C=O stretch absorption frequencies of the carbamoylimidazolium salts **3** usually lie in the range of 1710–1730 cm^{-1}, whereas those of the carbamoylimidazoles **4** occur some 30 cm^{-1} lower, in the range of 1680–1700 cm^{-1}, indicative of a

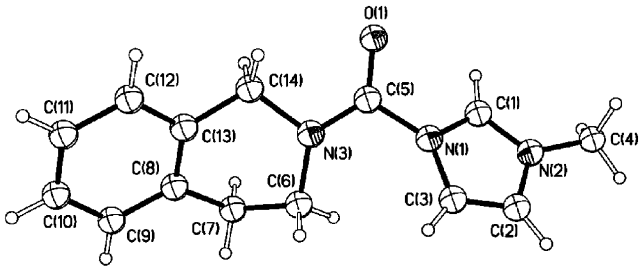
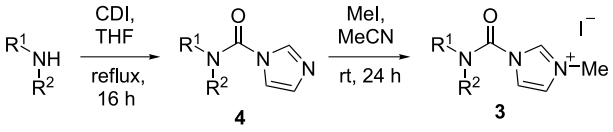
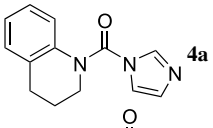
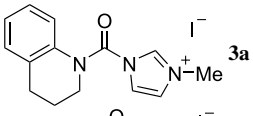
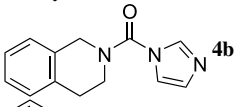
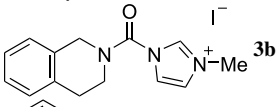
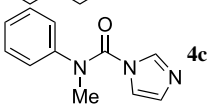
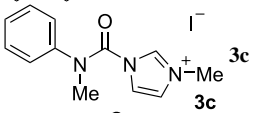
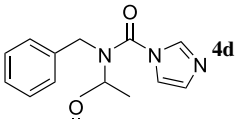
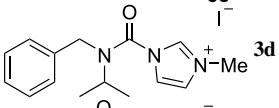
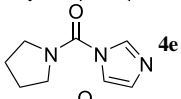
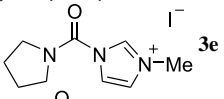
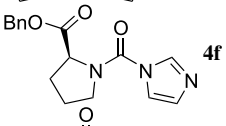
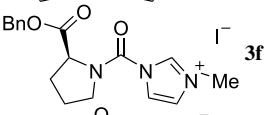
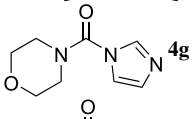
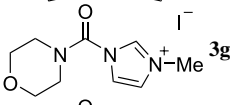
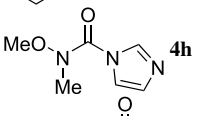
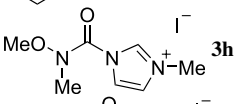
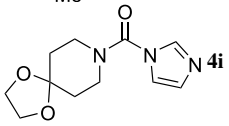
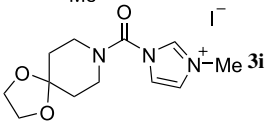


Figure 2. Solid-state structure of the carbamoylimidazolium cation of salt **3b** as determined by X-ray crystallographic analysis.[11] Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

Table 1. Carbamoylimidazole **4**[a] and carbamoylimidazolium salt **3**[b] formation



Carbamoylimidazole	Yield (%)[c]	Carbamoylimidazole	Yield (%)[c]
 **4a**	88	 **3a**	Quant.
 **4b**	88	 **3b**	Quant.
 **4c**	87	 **3c**	Quant.
 **4d**	92	 **3d**	Quant.
 **4e**	87	 **3e**	Quant.
 **4f**	96[d]	 **3f**	98
 **4g**	90[d]	 **3g**	82
 **4h**	96[d]	 **3h**	93
 **4i**	95[d]	 **3i**	96

[a] Secondary amine (1.0 equiv) and CDI (1.1 equiv) in THF were refluxed for 16 h.
[b] Carbamoylimidazole and MeI (4.0 equiv) in acetonitrile were stirred for 24 h.
[c] Isolated yields without flash chromatography.
[d] Secondary amine (1.0 equiv), CDI (1.1 equiv) (triethylamine (1 equiv) in case of HCl salt was added) in CH_2Cl_2 were stirred at rt for 24 h.

stronger C═O bond in the **3** compared to **4**. The stronger C═O bond in the salts presumably offsets a correspondingly weaker C(═O)–N(imidazole) bond.

2.1. Reactivity studies of carbamoylimidazolium salts 3: base promoted hydrolysis

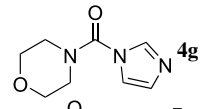
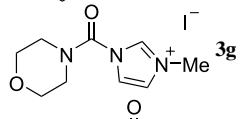
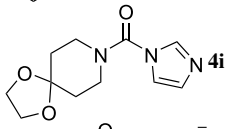
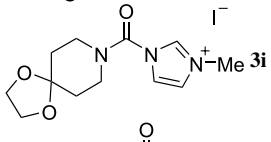
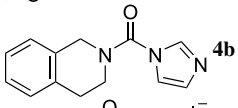
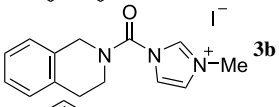
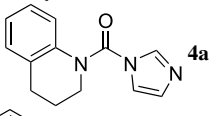
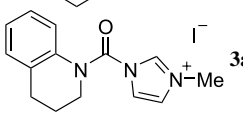
A hydrolysis study of the carbamoylimidazolium salts **3** and carbamoylimidazoles **4** was undertaken both to give a guide to their hydrolytic stability, but more importantly to provide kinetic data for their reactivity with the simple nucleophile hydroxide. Thus, second order rate constants for the hydroxide promoted hydrolysis of carbamoylimidazoles and carbamoylimidazolium salts were measured at 25 °C using UV/visible spectroscopic measurements, by observing the rate of change in absorbance at 230 nm (Table 2, Entries 1 and 2), 225 nm (Table 2, Entries 3 and 5), 235 nm (Table 2, Entries 4 and 6), 270 nm (Table 2, Entry 7) and 265 nm (Table 2, Entry 8).

The results show that hydroxide promoted hydrolysis of carbamoylimidazolium salts **3** occurs over 100-fold more rapidly than the corresponding carbamoylimidazoles. These results compare with a second order rate constant of $1.5\times 10^5\ M^{-1}\ s^{-1}$ measured for the hydroxide promoted hydrolysis of $CH_3CO–ImMe^+$ (acetylimidazolium ion), measured at $\mu=0.2$ (NaCl).[6]

2.2. H/D exchange studies of carbamoylimidazolium salts 3

The imidazolium salts **3** are very weak acids, as indicated by H/D exchange at the C-2 position of the imidazolium ring (Fig. 3). For example, compound **3i** undergoes deuterium exchange in CD_3OD, with complete exchange occurring after approximately 24 h, as measured by ^1H NMR. The addition of tertiary amine bases, such as triethylamine, to a solution of the salts **3** in CD_3OD accelerates the H/D exchange process, with full deuterium exchange occurring

Table 2. Second order rate constants for the aqueous hydroxide promoted hydrolysis of carbamoylimidazoles **4** and carbamoylimidazolium salts **3** at $T=25\,^{\circ}C$, $\mu=0.1$ (KCl)

Entry	Compounds	k_2 ($M^{-1}\,s^{-1}$)
1	 **4g**	0.34±0.14
2	 **3g**	96±13
3	 **4i**	0.11±0.04
4	 **3i**	38.0±7.9
5	 **4b**	0.094±0.037
6	 **3b**	31.1±5.3
7	 **4a**	0.038±0.008
8	 **3a**	16.0±0.9

within 1 h. The use of a triethylamine/CD_3OD combination results in the formation of the corresponding carbamates after approximately 20 h, through nucleophilic attack of CD_3OD vide infra. The H/D exchange process presumably occurs through the intermediacy of an imidazol-2-ylidene carbene (Fig. 3). The weak acidity of the salts **3** has been exploited by our laboratories for the formation of *N*-carbamoyl substituted heterocyclic carbene Pd(II) complexes.[12] Also, Hlasta has reported the nucleophilic addition reaction of these carbenes to aldehydes, via in situ generated carbamoylimidazolium salts.[13]

2.3. Synthesis of tri- and tetrasubstituted ureas 5 and 6

The initial synthetic targets that we envisaged for the reactions of the salts **3** were for the generation of ureas. There are numerous methods for the synthesis of mono-, di- and trisubstituted ureas, the most significant of which involves treatment of amines with isocyanates.[14] However, there are only a few methods for the formation of unsymmetrical tetrasubstituted ureas.[15] The most well established method involves treatment of a carbamoyl chloride with a secondary amine.[16] Katritzky has demonstrated the use of 1,1′-carbonylbisbenzotriazole[5] as a phosgene equivalent for the synthesis of unsymmetrical tetrasubstituted ureas under refluxing conditions.[17]

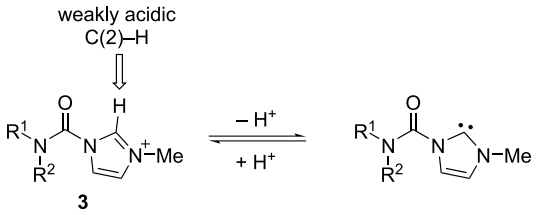


Figure 3. H/D exchange of carbamoylimidazolium salts **3** at the C-2 position via imidazol-2-ylidene carbenes.

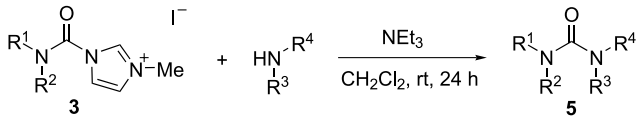
Reaction of carbamoylimidazolium salts **3** with secondary amines is an experimentally straightforward and general protocol for the synthesis of unsymmetrical tetrasubstituted ureas. Addition of secondary amines to a solution of carbamoylimidazolium salts in dichloromethane in the presence of triethylamine, afforded tetrasubstituted ureas in high yields (Table 3). A range of different secondary amines were successfully reacted forming the ureas **5a–h** in excellent yields. Similarly, the addition of primary amines to the salts **3** afforded the corresponding trisubstituted ureas **5i–l**. In most cases, the detectable byproducts, *N*-methylimidazole and triethylamine hydrochloric acid, can be removed by washing the organic phase with dilute acid. This greatly facilitates the purification protocol, and we have previously demonstrated that this method is amenable for the semi-automated solution-phase parallel synthesis of ureas.[4c] X-ray crystallographic analysis of the tetrasubstituted urea **5b** shows C(6)–N(8) and C(6)–N(1) bond distances of 1.381(3) Å and 1.354(3) Å, respectively, (Fig. 4). The preferential conjugation of N(8) with the aromatic system of the tetrahydroquinoline ring results in smaller resonance effect between the carbonyl group and N(8), which is reflected by the longer C(6)–N(8) bond distance.

Unfortunately, the experimental procedure developed for aliphatic amines is not suitable for the reaction of more weakly nucleophlic amines, such as anilines. However, reaction as the anilide anions, which are much more reactive nucleophliles, provides a convenient synthetic protocol for the formation of the corresponding ureas. Thus, pretreatment of the anilines with a strong base such as *n*-BuLi (or KHMDS), followed by addition of the salts **3** generates the corresponding ureas **6** (Table 4).

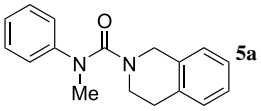
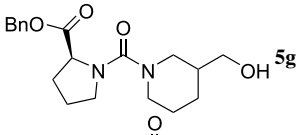
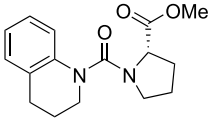
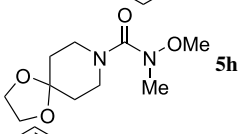
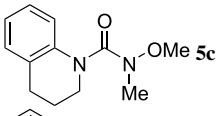
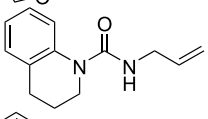
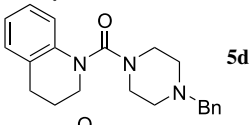
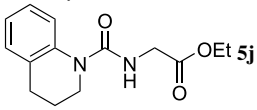
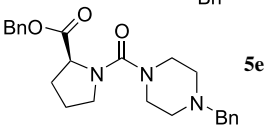
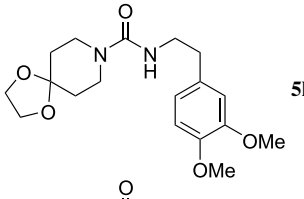
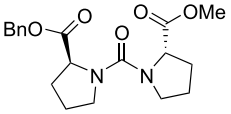
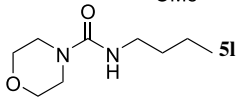
2.4. Synthesis of carbamates 7 and 8

Organic carbamates represent an important class of compounds in pharmacology, agriculture[18] and in synthetic chemistry as protecting groups for amines.[19] The standard method for their formation involves transfer of an electrophilic alkoxy carbonyl group to a nucleophilic amine. In certain cases, the alternate process of reacting a nucleophilic alcohol with an electrophilic carbamoylation reagent may be desirable. Examples of this latter process include the use of phosgene derivatives such as isocyanates or carbamoyl chlorides,[20] which upon attack by alcohols generates *N*-mono- and *N*-disubstituted carbamates, respectively. Several alternative methods that avoid the use of toxic materials have also been developed.[21] We envisaged that the salts **3**, while relatively unreactive with alcohols, would react with nucleophlic alkoxides to produce the corresponding carbamates **7/8**. In the case of phenols, tertiary amines

Table 3. Synthesis of ureas **5**[a] from carbamoylimidazolium salts **3** and amines



3 **5**

Urea	Yield (%)[b]	Urea	Yield (%)[b]
 **5a**	96	 **5g**	82
 **5b**	89	 **5h**	74
 **5c**	77	 **5i**	84
 **5d**	96	 **5j**	89
 **5e**	81	 **5k**	Quant.
 **5f**	78	 **5l**	70

[a] Imidazolium salt **3** (1.0 equiv), amine (or HCl salts) (1.0 equiv) and triethylamine (1.0 equiv, or 2.0 equiv for HCl salts) in CH_2Cl_2 were stirred at rt for 24 h.
[b] Isolated yields.

are suitable bases for the in situ generation of the reactive phenoxides. Thus, heating the substrates overnight at reflux in acetonitrile, in the presence of one molar equivalent of triethylamine, gave the corresponding carbamates **7** in excellent yields (Table 5). Again, the byproducts are easily removed by washing the organic phase with dilute acid. Using this method carbamates **7** were obtained with sufficiently high purity such that chromatographic purification was not required.

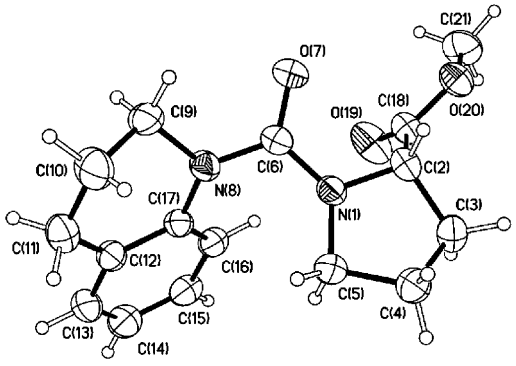
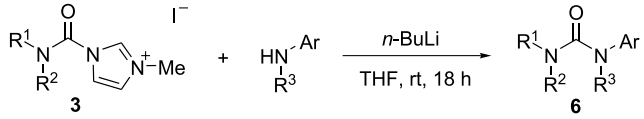


Figure 4. Solid-state structure of the tetrasubstituted urea **5b** as determined by X-ray crystallographic analysis. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

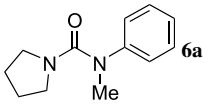
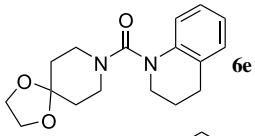
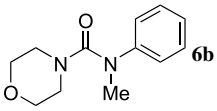
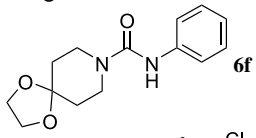
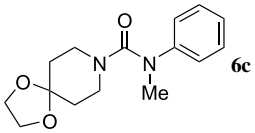
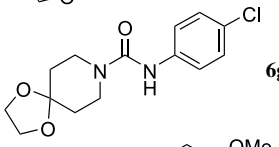
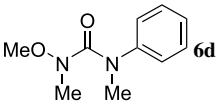
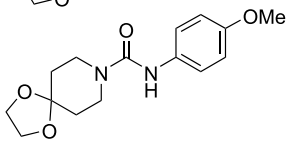
Aliphatic alcohols react slowly with carbamoylimidazolium salts even under reflux conditions in the presence of triethylamine. The lower acidity of aliphatic alcohols presumably prevents the formation of the alkoxide anion under these conditions, which would serve as the reactive nucleophile. Less acidic alcohols will react with carbamoylimidazolium salts, when first converted into more nucleophilic sodium alkoxides. Thus, formation of the alkoxides by the treatment of a mixture of the alcohol and the carbamoylimidazolium salt **3** in THF/DMF with NaH led to the formation of the desired carbamates **8** after stirring at rt for 24 h. Formation of Cbz and Alloc carbamates from amines is thus possible via the corresponding carbamoylimidazolium salts, therefore, providing another strategy for the formation of these synthetically important carbamate protecting groups.

The use of alcohols as solvents in the presence of triethylamine at rt also results in carbamate formation, as exemplified by the addition of 2,2,2-trifluoroethanol with **3i** in the presence of triethylamine at rt, to give carbamate **8b** (Table 5), as well as by the addition of CD_3OD to **3i**, vide supra. Under these conditions it is likely that base assisted

Table 4. Aryl substituted ureas **6**[a] synthesized from carbamoylimidazolium salts **3** and anilines



3 **6**

Amide	Yield (%)[b]	Amide	Yield (%)[b]
 **6a**	90	 **6e**	97
 **6b**	96	 **6f**	76
 **6c**	97	 **6g**	70
 **6d**	87	 **6h**	65

[a] Amine (1.0 equiv) and *n*-BuLi (1.5 equiv) in THF were stirred at rt for 1 h. Imidazolium salt **3** (1.2 equiv) was then added and the reaction stirred for 18 h.
[b] Isolated yields.

attack of the alcohols to **3** occurs, rather than by direct attack of alkoxides.

2.5. Synthesis of thiocarbamates 9

Thiocarbamates are generally prepared from carbamoyl chlorides and thiols,[22] chlorothiolformates and amines[23] or via the thione–carbamate rearrangement.[24] Unfortunately, the necessary intermediates are typically prepared from phosgene or thiophosgene. Now the thiocarbamates **9** can be easily synthesized in a similar manner to the carbamate analogs described above (Table 6). Addition of one equivalent of either alkylthiols or thiophenols to carbamoylimidazolium salts **3** at rt in chloroform or dichloromethane, in the presence of triethylamine, provided the desired thiocarbamates **9** in excellent yield and purity. The successful reaction of an *N*-protected cysteine (Table 6, **9e**) suggests that this reaction may be useful for the functionalization of thiol residues in peptide chemistry.

2.6. Synthesis of tertiary amides 10

The amide functional group is one of the most important functionalities in organic chemistry, due to its presence in natural products, pharmaceutical and other biologically active compounds. The most common method of synthesizing amides involves reaction of an amine with an activated derivative of a carboxylic acid, such as an acid chloride. In many cases the use of acid chlorides is not favourable, since they can be difficult to work, are not easily stored, and lead to undesirable side reactions. Thus, the more general method of combining an amine and a carboxylic acid in the presence of various coupling reagents, has grown in importance, particularly for small-scale synthesis.[25] Although these coupling reagents usually give good results, they are often expensive, some are toxic, while others are not very soluble in organic solvents, and the amide products require chromatographic purification from the coupling reagent byproducts.

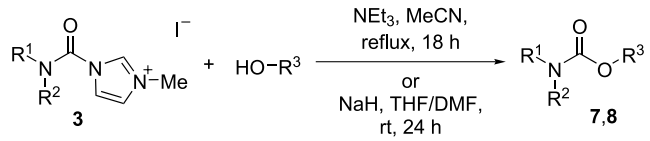
The carbamoylimidazolium salts **3** react with carboxylic acids in the presence of triethylamine, in acetonitrile at rt, to form tertiary amides **10** in excellent yields (Table 7). The desired products are of sufficient purity after aqueous work-up that chromatographic purification is not required. For example, this approach provides a very convenient approach for the synthesis of Weinreb amides **10h–l** from the corresponding imidazolium salt **3h**.[4d]

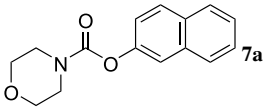
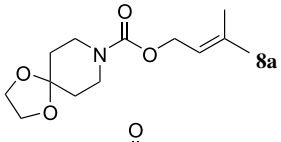
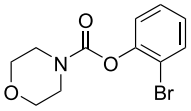
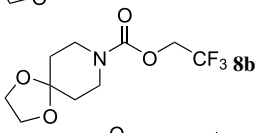
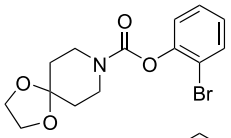
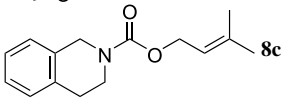
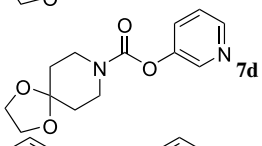
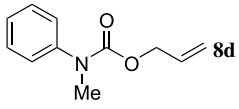
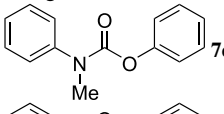
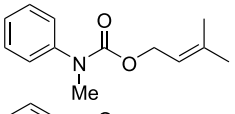
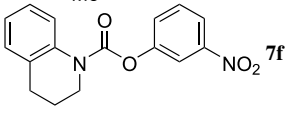
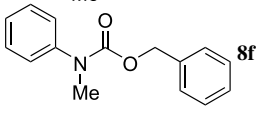
These reactions are noteworthy, in that the carbamoylimidazolium salts **3** act as coupling reagents, leading to the formation of an activated acyl transfer agent, while simultaneously generating a nucleophilic secondary amine, which then react together to form the tertiary amides **10**. In essence, the salts **3** serve as preactivated amine reagents that are capable of reacting directly with carboxylic acids, without the requirement for the introduction of additional coupling reagents. This is an unusual approach, the best analogy for which, is the reaction of carboxylic acids with isocyanates at 60 °C, to give secondary amides. The isocyanates similarly act as coupling reagent and amine source.[26]

2.7. Synthesis of thiocarbamoylimidazolium salts 12

The success of carbamoylimidazolium salts **3** as *N*,*N*-disubstituted carbamoyl transfer reagents, encouraged us to

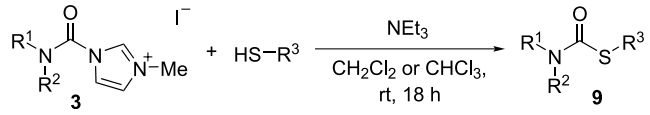
Table 5. Carbamate **7**[a] and **8**[b] synthesized from carbamoylimidazolium salts **3** and phenols or alcohols

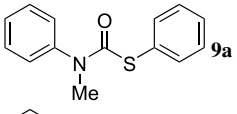
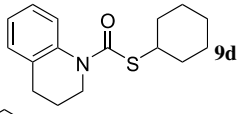
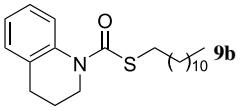
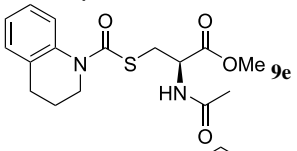
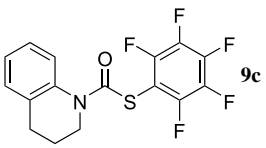
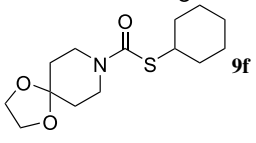


Carbamate	Yield (%)[c]	Carbamate	Yield (%)[c]
 **7a**	93	 **8a**	57
 **7b**	71	 **8b**	95[d]
 **7c**	94	 **8c**	83
 **7d**	88	 **8d**	78
 **7e**	86	 **8e**	63
 **7f**	94	 **8f**	83

[a] Imidazolium salt **3** (1.0 equiv), phenol (1.0 equiv) and triethylamine (1.0 equiv) in acetonitrile were refluxed for 18 h.
[b] Imidazolium salt **3** (1.0 equiv), alcohol (1.0 equiv) and NaH (1.0 equiv) in THF/DMF (1:1) were stirred at rt for 24 h.
[c] Isolated yields.
[d] Imidazolium salt **3** (1.0 equiv) and triethylamine (1.0 equiv) in CF_3CH_2OH were stirred at rt for 18 h.

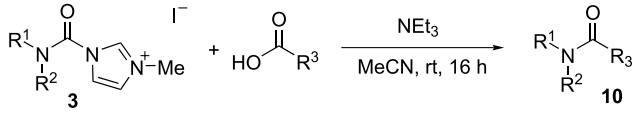
Table 6. Thiocarbamates **9**[a] synthesized from carbamoylimidazolium salts **3** and thiols



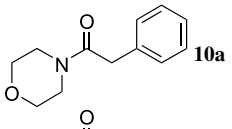
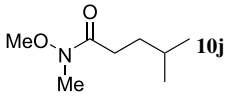
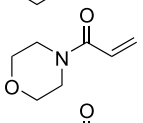
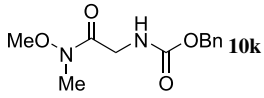
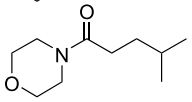
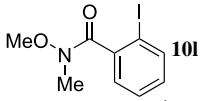
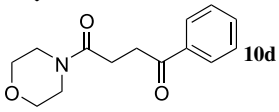
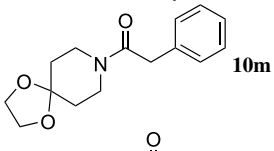
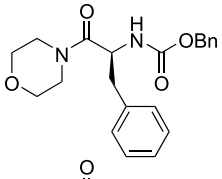
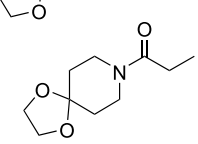
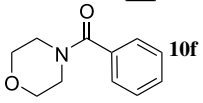
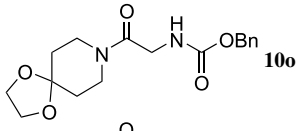
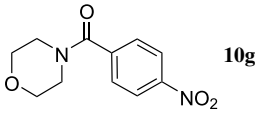
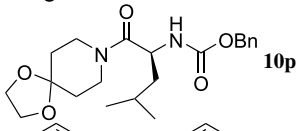
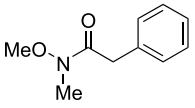
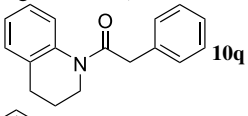
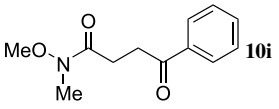
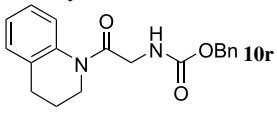
Thiocarbamate	Yield (%)[b]	Thiocarbamate	Yield (%)[b]
 **9a**	86	 **9d**	91
 **9b**	84	 **9e**	71
 **9c**	92	 **9f**	94

[a] Imidazolium salt **3** (1.0 equiv), thiol (1.0 equiv) and triethylamine (1.0 equiv) in CH_2Cl_2 or $CHCl_3$ were stirred at rt for 18 h.
[b] Isolated yield.

Table 7. Amides **10**[a] synthesized from carbamoylimidazolium salts **3** and carboxylic acids



3 **10**

Amide	Yield (%)[b]	Amide	Yield (%)[b]
 **10a**	92	 **10j**	92
 **10b**	75	 **10k**	93
 **10c**	97	 **10l**	86
 **10d**	94	 **10m**	92
 **10e**	96	 **10n**	99
 **10f**	95	 **10o**	87
 **10g**	75	 **10p**	62
 **10h**	94	 **10q**	80
 **10i**	95	 **10r**	82

[a] Imidazolium salt (1.0 equiv), carboxylic acid (1.0 equiv) and triethylamine (1.0 equiv) were stirred at rt for 16 h.
[b] Isolated yields.

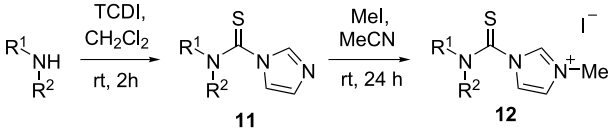
investigate the use of the analogous sulfur based thiocarbamoylimidazolium salts **12**. We anticipated that these salts would act as *N*,*N*-disubstituted thiocarbamoyl transfer reagents. The need for such reagents is particularly acute, since thiocarbamoyl chlorides are currently used for this purpose, the synthesis of which requires the use of highly toxic thiophosgene.

The thiocarbamoylimidazolium salts **12** can be readily prepared by analogous chemistry to that employed for the synthesis of **3**, using thiocarbonyldiimidazole (TCDI) as the precursor. Thus, reaction of secondary amines with TCDI proceeded in dichloromethane at rt to give thiocarbamoylimidazoles **11**, which are usually viscous yellow or brown oils. Alkylation of the unpurified thiocarbamoylimidazoles **11** with 4 equiv of MeI in acetonitrile gave the crude products **12** as brown oils. Recrystallization is required to obtain the pure products **12**. Although the compounds are not stable as oils, the recrystallized products are yellow crystals, which can be stored for extended periods of time without decomposition (Table 8).

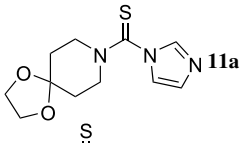
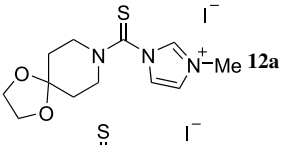
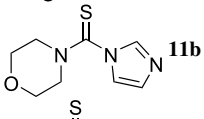
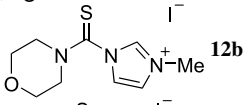
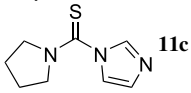
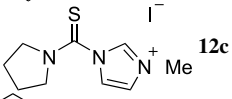
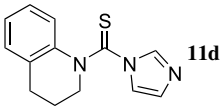
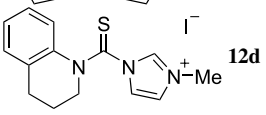
2.8. Synthesis of unsymmetrical tri- and tetrasubstituted thioureas 13

An example of the utility of thiocarbamoylimidazolium salts **12** as *N*,*N*-disubstituted thiocarbamoyl transfer reagents is exemplified by their reactivity with primary and secondary amines, to give tri- and tetrasubstituted thioureas **13**, examples of which are known to be biologically interesting. By far the most common method of preparing thioureas is the reaction of isothiocyanates with amines.[27] TCDI has also been employed in thiourea synthesis, but the addition of the second amine requires heating and the reaction most likely proceeds through

Table 8. Thiocarbamoylimidazole **11**[a] and thiocarbamoylimidazolium salt **12**[b] formation



11 **12**

Thiocarbamoylimidazole	Yield (%)[c]	Imidazolium salt	Yield (%)[c]
 **11a**	96	 **12a**	78
 **11b**	90	 **12b**	65
 **11c**	90	 **12c**	Quant.
 **11d**	Quant.	 **12d**	76

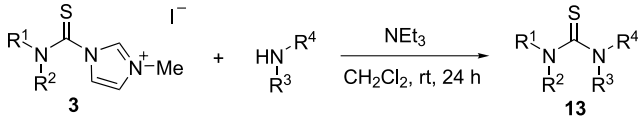
[a] Secondary amine (1.0 equiv) and TCDI (1.1 equiv) in CH_2Cl_2 were stirred at rt for 2 h.
[b] Thiocarbamoylimidazole (1.0 equiv) and MeI (4.0 equiv) in acetonitrile were stirred at rt for 24 h.
[c] Isolated yields.

an isothiocyanate.[28] Reaction of **12** with secondary amines in dichloromethane at rt results in the formation of thioureas **13** (Table 9). The salts **12** are less reactive than the salts **3**, since replacement of the oxygen by sulfur lowers their electrophilicity. This has practical implications, as demonstrated by the lower reaction yields of **13** obtained with primary amines (Table 9, compound **13f**), compared to reactions with the more nucleophilic secondary amines (Table 9, compound **13e**). Thiocarbamoylimidazolium salt **12d** was observed to show very poor reactivity with diallylamine and pyrrolidine. These results show that thiocarbamoylimidazolium salts are good thiocarbamoyl transfer reagents, offering a more practical solution than the use of thiocarbamoyl chlorides, which is particularly useful for the formation of tetrasubstituted thioureas.

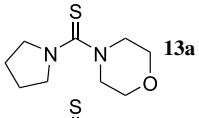
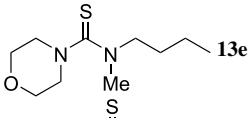
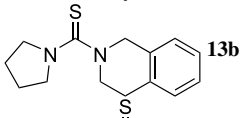
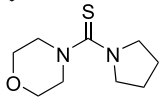
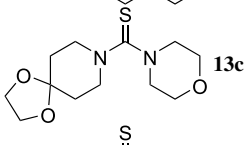
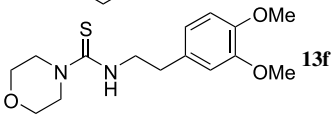
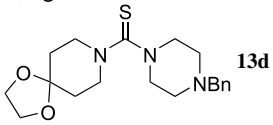
2.9. Application of carbamoylimidazolium salts 3 in target oriented synthesis

We envisaged that reaction of diethyl phosphonoacetic acid with the salts **3** would lead to the formation of diethyl phosphonoacetamides, which can then be used in

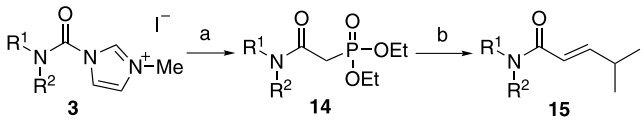
Table 9. Thioureas **13**[a] synthesized from thiocarbamoylimidazolium salts **12** and amines



3 **13**

Thiourea	Yield (%)[b]	Thiourea	Yield (%)[b]
 **13a**	Quant.	 **13e**	71
 **13b**	Quant.	 **13a**	45
 **13c**	94	 **13f**	21
 **13d**	84		

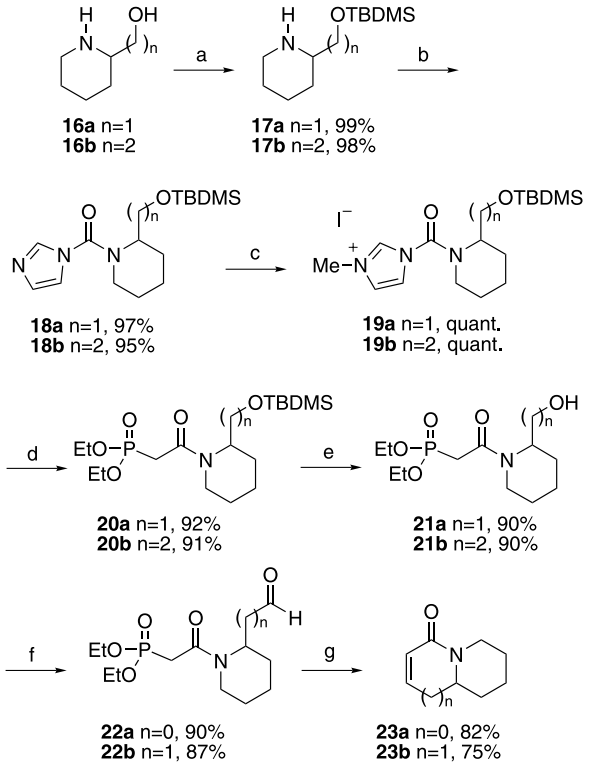
[a] Thiocarbamoylimidazolium salts **12** (1.0 equiv), secondary amines (1.2 equiv) and triethylamine (1.2 equiv) in CH_2Cl_2 were stirred at rt for 24 h.
[b] Isolated yields.



Scheme 2. (a) Diethyl phosphonoacetic acid, NEt_3, MeCN, reflux, 1 day; (b) isobutyraldehyde, LiCl, DBU, MeCN, rt, 16 h.

Wadsworth–Horner–Emmons reactions to form α,β-unsaturated amides or lactams. Reaction of the carbamoylimidazolium salts with diethyl phosphonoacetic acid in the presence of triethylamine results in the formation of diethyl phosphonoacetamides **14**, which can be used in either inter- or intramolecular Wadsworth–Horner–Emmons reactions with aldehydes and ketones (Scheme 2). For example, conversion of **3g** to the morpholine derived diethyl phosphonoacetamide **14**, followed by treatment with isobutyraldehyde yielded α,β-unsaturated amide **15** as the *E*-isomer.

A similar approach was used in a model synthesis of the fused bicyclic lactams **23a** and **23b** (Scheme 3). **23a** is an intermediate in the synthesis of indolizidines such as 2-epilentiginosine and lentiginosine,[29] while **23b** can be used in the synthesis of quinolizidine ring systems, and is an intermediate in the synthesis of leontiformine and leontiformidine.[30] The synthesis of **23a** and **23b** began with the protection of 2-piperidinemethanol or 2-piperidineethanol with TBDMSCl in 99 and 98% yield, respectively, without purification. The protected amines **17a** and **17b** were reacted with CDI in CH_2Cl_2 at rt to generate the carbamoylimidazoles in greater then 95% yield after column chromatography, which was necessary to remove some of the byproducts from the TBDMSCl protection step. **18a** and **18b** were then methylated with methyl iodide according to the standard procedure to generate the carbamoylimidazolium salts **19a** and **19b** in quantitative yields. The installation of the phosphonate moiety necessary for the Wadsworth–Horner–Emmons reaction was accomplished through the amide bond forming reaction between **19a** and **19b** and diethyl phosphonoacetic acid at 50 °C to give **20a** and **20b** in 92 and 91% yield, respectively.



Scheme 3. (a) TBDMSCl, pyr, CH_2Cl_2, rt, 4 h; (b) CDI, CH_2Cl_2, rt, 1 day; (c) MeI, MeCN, rt, 1 day; (d) Diethyl phosphonoacetic acid, NEt_3, MeCN, 50 °C, 1 day; (e) TBAF, THF, rt, 30 min; (f) *o*-$C_6H_4COOI(OAc)_2$ (i.e., Dess–Martin periodinane reagent), CH_2Cl_2, rt, overnight; (g) NaH, THF, 0 °C, 40 min.

The final fused bicycles were obtained through deprotection to the alcohols **21a** and **b** with TBAF, followed by oxidation with the Dess–Martin reagent to give aldehydes **22a** and **b**, which had to be chromatographed through a very short silica column to minimize decomposition. Oxidation using Swern conditions, TPAP/NMO, and PCC were less effective. The final cyclization was carried out with sodium hydride in THF at 0 °C to give the products **23a** and **23b** in 82 and 75% yield. Attempts to cyclize the aldehyde **22a** directly or with minimal amount of purification gave very low yields.

3. Conclusions

Carbamoylimidazolium salts behave as convenient *N*,*N*′-disubstituted carbamoyl transfer reagents, showing increased reactivity over carbamoylimidazoles as a result of the imidazolium effect. These compounds, as well as their thiocarbamoylimidazolium counterparts, are readily prepared by a simple two-step procedure from the corresponding secondary amines, and are obtained in excellent yield and purity following straightforward work-up procedures. The salts serve as useful 'building blocks' which can be utilized to generate a variety of functional groups, such as ureas, thioureas, carbamates, thiocarbamates, and amides, under mild reaction conditions. We are currently applying this methodology to the formation of combinatorial libraries.

4. Experimental

4.1. General

THF was distilled from sodium metal/benzophenone ketyl under nitrogen. CH_2Cl_2 and CH_3CN were distilled from CaH_2 under nitrogen. All other commercial reagents were used as received (Aldrich, Fischer Scientific Ltd or BDH). All glassware was flame-dried and allowed to cool under a stream of dry nitrogen. Melting points are uncorrected. ^1H and ^{13}C NMR were recorded at 400 and 100 MHz, respectively, on a Varian Unity 400 spectrometer and Gemini 200 MHz spectrometer. Proton chemical shifts were internally referenced to the residual proton resonance in $CDCl_3$ (δ 7.26) or CD_3OD (δ 3.31) or DMSO-d_6 (δ 2.50). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.20) or CD_3OD (δ 49.00) or DMSO-d_6 (δ 39.50). Phosphorus chemical shifts were referenced to 85% phosphoric acid (external). FT-IR spectra were recorded on a Perkin-Elmer Spectrum 1000, with samples loaded as neat films on NaCl plates or as KBr

discs. Low-resolution mass spectra were recorded on a Bell and Howell 21-490 spectrometer, and high resolution spectra were recorded on an AEI MS3074 spectrometer. Specific optical rotation was determined on a Perkin-Elmer 243B Polarimeter under the conditions indicated using the sodium D line (589 nm). Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel plates, (Silicycle, Inc.), visualized with a UV254 lamp (Spectroline, Longlife Filter) and stained with 20% phosphomolybdic acid in ethanol or ninhydrin. Spectral data are provided for all new compounds and for compounds which lack full characterization in the literature.

4.2. General procedure for the preparation of carbamoylimidazoles 4a–4e

To a suspension of *N*,*N*′-carbonyldiimidazole (CDI, 60.0 mmol) in THF (100 mL) was added the amine (55.0 mmol). The mixture was refluxed for 16 h. Removal of solvent under vacuum gave a viscous oil, which was dissolved in CH_2Cl_2 (100 mL) and washed with water (2× 100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield the carbamoylimidazole **4a–e**.

4.2.1. 1-(1*H*-Imidazol-1-ylcarbonyl)-1,2,3,4-tetrahydroquinoline (3,4-dihydro-2*H*-quinolin-1-yl)-imidazol-1-ylmethanone (4a).[4a,c] Yellow solid; mp=71–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, d, J=1.0 Hz), 7.18 (1H, m), 7.06 (1H, m), 6.98 (1H, m), 6.92 (1H, m), 6.89 (1H, m), 6.64 (1H, m), 3.86 (2H, t, J=6.5 Hz), 2.82 (2H, t, J=6.5 Hz), 2.07 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 137.8, 137.5, 131.9, 129.6, 129.1, 127.1, 125.9, 123.2, 118.3, 45.9, 26.7, 24.1; IR (KBr pellet) 3122, 2958, 1691, 1578, 1492, 1396, 1215, 1100, 916 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 227 (46), 160 (94), 142 (13), 132 (100), 117 (11), 77 (17); HRMS (EI) *m*/*z* calcd (M^+) 227.1059, found 227.1051.

4.2.2. 2-(1*H*-Imidazol-1-ylcarbonyl)-1,2,3,4-tetrahydroisoquinoline (4b).[4c] Yellow solid; mp=82–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, s), 7.26–7.08 (6H, m), 4.75 (2H, s), 3.82 (2H, t, J=6.0 Hz), 3.04 (2H, t, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 136.6, 133.4, 131.5, 129.5, 128.6, 127.0, 126.5, 126.0, 117.6, 48.1, 44.2, 28.3; IR (KBr pellet) 3098, 2898, 1681, 1428, 1240, 1162, 1104, 1077, 1052, 933 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 227 (69), 160 (100), 142 (49), 130 (10), 117 (36), 103 (14), 91 (12); HRMS (EI) *m*/*z* calcd (M^+) 227.1061, found 227.1059.

4.2.3. *N*-Methyl-*N*-phenyl-1*H*-imidazole-1-carboxamide (4c).[4c,31] Yellow solid; mp=62–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, s), 7.38–7.29 (3H, m), 7.11–7.07 (2H, m), 6.81–6.76 (2H, m), 3.45 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 142.0, 136.8, 129.3, 127.9, 127.1, 125.1, 117.7, 39.2; IR (KBr pellet) 3126, 2949, 1702, 1592, 1492, 1458, 1385, 1294, 1253, 1118, 1096, 1026, 983 cm^{-1}.

4.2.4. *N*-Benzyl-*N*-isopropyl-1*H*-imidazole-1-carboxamide (4d).[4c] Foamy yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, s), 7.38 (2H, m), 7.31 (3H, m), 7.21 (1H, s), 7.04 (1H, s), 4.58, (2H, s), 4.16 (1H, m), 1.35 (3H, s), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 137.2, 136.9, 129.8, 129.1, 127.8, 126.8, 117.8, 51.7, 48.6, 20.6; IR (neat) 2975, 1690, 1414, 1217, 1069, 1020, 965, 754 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 243 (1), 176 (25), 92 (10), 91 (100), 85 (14), 83 (23), 68 (6), 65 (7), 51 (9); HRMS (EI) *m*/*z* Calcd (M^+) 243.1367, found 243.1372.

4.2.5. 1-(Pyrrolidin-1-ylcarbonyl)-1*H*-imidazole (4e).[32] White solid; mp 50–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, s), 7.36 (1H, br s), 7.08 (1H, br s), 3.64–3.61 (4H, m), 2.00–1.97 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 136.9, 129.6, 117.7, 48.9 (br), 25.7 (br); IR (KBr pellet) 2976, 1694, 1417, 1102, 843 cm^{-1}.

4.2.6. Benzyl 1-(1*H*-imidazol-1-ylcarbonyl)-L-prolinate (4f).[4a,c] To a solution of CDI (0.890 g, 5.50 mmol) in CH_2Cl_2 (15 mL) was added L-proline benzyl ester hydrochloride (1.21 g, 5.00 mmol) and triethylamine (0.700 mL, 5.00 mmol). The mixture was stirred for 48 h at rt, then washed with water (2×20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum to yield **4g** as colorless, viscous oil (1.44 g, 96%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.35 (6H, br s), 7.07 (1H, s), 5.20 (2H, m), 4.67 (1H, m), 3.76 (2H, m), 2.35 (1H, m), 2.06 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 149.4, 136.5, 135.1, 129.4, 128.3, 128.1, 127.8, 117.3, 66.8, 60.6, 49.5, 29.1, 24.6; IR (neat) 3583, 3469, 3122, 2980, 2957, 1746, 1682, 1417, 1171, 1100, 901 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 299 (1), 232 (12), 164 (12), 160 (6), 158 (11), 91 (100), 70 (21); HRMS (EI) *m*/*z* calcd (M^+) 299.1270, found 299.1255; $[\alpha]_D^{23}$ −61° (*c* 1.00, CH_2Cl_2).

4.3. General procedure for the preparation of carbamoylimidazoles with CH_2Cl_2 as solvent

To a cooled (cold water bath) solution of CDI (44.0 mmol) in CH_2Cl_2 (30 mL) was added the amine (40.0 mmol) dropwise. After the solids dissolved, giving a slightly yellowish clear solution, the water bath was removed, and the mixture stirred for a further 24 h. The reaction was diluted with CH_2Cl_2 (20 mL), and quenched with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (4× 50 mL), the combined organic layers dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield carbamoylimidazoles **4g–4i**.

4.3.1. 4-(1*H*-Imidazol-1-ylcarbonyl)morpholine (4g).[4c,33] White solid; mp=83–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, s), 7.17 (1H, m), 7.08 (1H, m), 3.73 (4H, m), 3.61 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 136.4, 129.4, 117.5, 65.9, 46.3.

4.3.2. *N*-Methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide (4h).[4d] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (1H, s), 7.55 (1H, m), 7.03 (1H, m), 3.66 (3H, s), 3.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 137.1, 128.6, 118.0, 60.6, 33.8; IR (neat) 3121, 2938, 1690, 1421, 1227, 1061, 965, 735 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 155 (100), 125 (34), 95 (38), 88 (55), 68 (63); HRMS (EI) *m*/*z* Calcd (M^+) 155.0695, found 155.0700.

4.3.3. 8-(1*H*-Imidazol-1-ylcarbonyl)-1,4-dioxa-8-azaspiro[4.5]decane (4i).[4c] White solid; mp=121–123 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, s), 7.16 (1H, m), 7.06 (1H, m), 3.96 (4H, s), 3.65 (4H, m), 1.75 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 136.7, 129.5, 117.8, 106.1, 64.4, 44.5, 34.9; IR (KBr pellet) 3112, 2869, 2855, 1700, 1464, 1427, 1361, 1243, 1098, 1026, 913 cm^{-1}; MS (EI) *m/z* (relative intensity) 237 (22), 170 (100), 142 (82), 99 (37), 98 (27), 70 (19); HRMS (EI) *m/z* Calcd (M^+) 237.1113, found 237.1111.

4.4. General procedure for the preparation of carbamoylimidazolium salts 3

To a solution of carbamoylimidazole **4** (8.00 mmol) in acetonitrile (15 mL) was added methyl iodide (32.0 mmol). The mixture was stirred at rt for 24 h. The solvent was removed under vacuum to yield the carbamoylimidazolium salt **3a–i**.

4.4.1. 1-(3,4-Dihydroquinolin-1(2*H*)-ylcarbonyl)-3-methyl-1*H*-imidazol-3-ium iodide (3a).[4a,c] Yellow solid; mp 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (1H, s), 7.61 (1H, s), 7.25–7.22 (2H, m), 7.15 (1H, m), 7.08 (1H, m), 6.95 (1H, d, J=8.0 Hz), 4.12 (3H, s), 3.93 (2H, t, J=6.5 Hz), 2.93 (2H, t, J=6.5 Hz), 2.11 (2H, m); ^{13}C NMR (50 MHz, DMSO-d_6) δ 146.4, 138.3, 135.9, 132.2, 129.0, 126.3, 125.9, 123.3, 123.2, 121.2, 46.7, 36.4, 25.7, 22.9; IR (KBr pellet) 3438, 3074, 2937, 1722, 1583, 1535, 1493, 1459, 1356, 1014, 749 cm^{-1}; MS (FAB) *m/z* (relative intensity) 242 (100), 160 (40), 154 (83), 138 (29), 137 (52), 136 (61), 132 (14), 120 (12), 107 (23), 91 (12); HRMS (FAB) *m/z* Calcd (M^+-127) 242.1293, found 242.1296.

4.4.2. 1-(3,4-Dihydroisoquinolin-2(1*H*)-ylcarbonyl)-3-methyl-1*H*-imidazol-3-ium iodide (3b).[4c] Yellow solid; mp=166–168 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (1H, br s), 8.09 (1H, br s), 7.89 (1H, br s), 7.22 (4H, br s), 4.75 (2H, br s), 3.94 (3H, m), 3.72 (2H, br s), 2.96 (2H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.8, 137.3, 133.9, 131.5, 128.1, 126.7, 126.4, 126.1, 123.5, 120.8, 47.5 (br), 44.2, 36.5, 27.6; IR (KBr pellet) 3144, 3078, 2968, 1711, 1408, 1354, 1150, 1132, 978 cm^{-1}; MS (FAB) *m/z* (relative intensity) 242 (100), 190 (3), 144 (5), 117 (5), 160 (39); HRMS (FAB) *m/z* calcd (M^+-127) 242.1293, found 242.1284.

4.4.3. 3-Methyl-1-{[methyl(phenyl)amino]carbonyl}-1*H*-imidazol-3-ium iodide (3c).[4a,c] Yellow solid, mp 95–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (1H, s), 7.55 (1H, br s), 7.37–7.31 (5H, m), 7.01 (1H, br s), 4.02 (3H, s), 3.45 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 139.7, 137.2, 129.8, 128.3, 125.7, 122.8, 120.2, 40.3, 37.1; IR (KBr pellet) 3457, 3076, 1732, 1594, 1494, 1372, 1271, 1152, 983, 920 cm^{-1}; MS (FAB) *m/z* (rel. intensity) 217 (20), 216 (100), 154 (14), 136 (11), 107 (6), 93 (7); HRMS (FAB) *m/z* calcd (M^+-127) 216.1137, found 216.1130.

4.4.4. 1-{[Benzyl(isopropyl)amino]carbonyl}-3-methyl-1*H*-imidazol-3-ium iodide (3d).[4c] Yellow foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (1H, m), 7.31–7.07 (7H, m), 4.88 (2H, s), 4.44 (1H, m), 4.14 (3H, s), 1.45 (3H, s), 1.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 136.8, 136.0, 129.3, 128.2, 126.8, 123.7, 120.4, 52.7, 49.2, 37.9, 20.6; IR (neat) 3063, 1723, 1536, 1414, 1342, 1171, 1138, 748, 617 cm^{-1}; MS (FAB) *m/z* (relative intensity) 259 (9), 258 (50), 180 (5), 176 (21), 173 (17), 132 (6), 92 (9), 91 (100), 83 (14); HRMS (FAB) *m/z* Calcd (M^+-127) 258.1621, found 258.1620.

4.4.5. 3-Methyl-1-(pyrrolidin-1-ylcarbonyl)-1*H*-imidazol-3-ium iodide (3e). White solid; mp=102–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (1H, s), 7.83 (1H, m), 7.55 (1H, m), 4.31 (3H, s), 2.07 (4H, br m), 2.05 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 136.8, 123.8, 121.2, 51.0 (br), 49.6 (br), 38.3, 26.6 (br), 34.4 (br); IR (KBr pellet) 3446, 3078, 1716, 1404, 1257, 1136, 827; MS (FAB) *m/z* (relative intensity) 180 (100), 98 (81), 83 (15); HRMS (FAB) *m/z* Calcd (M^+-127) 180.1137, found 180.1139.

4.4.6. Benzyl 1-[(3-methyl-1*H*-imidazol-3-ium-1-yl)carbonyl]-L-prolinate iodide (3f).[4a,c] Foamy yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.30 (1H, s), 7.78–7.32 (7H, m), 5.18 (2H, br s), 4.70 (1H, br s), 4.24 (3H, br s), 4.12–3.93 (2H, m), 2.49 (1H, br s), 2.12 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.8, 145.1, 136.2, 134.7, 128.3, 128.1, 127.7, 123.9, 120.4, 68.0, 61.5, 51.4, 37.7, 29.9, 25.4; IR (neat) 3448, 3069, 1728, 1584, 1537, 1407, 1175, 1094 cm^{-1}; MS (FAB) (rel. intensity) 314 (100), 173 (66), 154 (11), 136 (10), 107 (6), 91 (69); HRMS (FAB) *m/z* calcd (M^+-127) 314.1505, found 134.1499; $[\alpha]_D^{23}$ −44° (*c* 1.01, CH_2Cl_2).

4.4.7. 3-Methyl-1-(morpholin-4-ylcarbonyl)-1*H*-imidazol-3-ium iodide (3g).[4c] White solid; mp=165–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.04 (s, 1H), 7.87 (s, 1H), 3.91 (s, 3H), 3.66 (s, 4H), 3.52 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.5, 137.4, 123.5, 120.9, 65.3, 46.2, 36.5; IR (KBr pellet) 3115, 2862, 1718, 1437, 1244, 1145, 1117, 996; MS (FAB) *m/z* (relative intensity) 196 (100), 185 (14), 175 (5), 115 (10), 114 (50), 111 (5); HRMS (FAB) *m/z* calcd (M^+-127) 196.1086, found 196.1103.

4.4.8. 1-{[Methoxy(methyl)amino]carbonyl}-3-methyl-1*H*-imidazol-3-ium iodide (3h).[4d] White solid; mp=115–117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (1H, s), 7.88 (1H, m), 7.77 (1H, m), 4.30 (3H, s), 3.94 (3H, s), 3.43 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) 144.6, 138.1, 123.9, 121.4, 63.6, 38.6, 35.1; IR (KBr pellet) 3063, 1714, 1459, 1385, 1160, 1085, 954, 739, 725 cm^{-1}; MS (ESI) *m/z* (rel. intensity) 170 (100), 139 (10); HRMS (ESI) *m/z* calcd (M^+-127) 170.0924, found 170.0916.

4.4.9. 1-(1,4-Dioxa-8-azaspiro[4.5]dec-8-ylcarbonyl)-3-methyl-1*H*-imidazol-3-ium iodide (3i).[4c] White solid; mp 169–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.03 (m, 1H), 7.87 (m, 1H), 3.91 (m, 7H), 3.54 (s, 4H), 1.76 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.5, 137.4, 123.5, 120.9, 105.6, 63.9, 44.4 (br), 36.5, 33.8; IR (KBr pellet) 3078, 2886, 1735, 1573, 1534, 1419, 1369, 1218, 1138, 1092, 1027 cm^{-1}; MS (FAB) *m/z* (relative intensity) 252 (100), 185 (63), 170 (83), 142 (75), 126 (10); HRMS (FAB) *m/z* Calcd (M^+-127) 252.1348, found 252.1355.

4.5. Kinetics of hydroxide promoted hydrolysis of 3 and 4

Stock solutions of **3** and **4** (0.02 M in MeCN) were prepared, then sealed with rubber septa and placed in a freezer. Buffer

solutions were made using HCl (pH 2.0–3.11), EPPS (pH 7.9–8.7), CHES (pH 9.2–9.8), CAPS (pH 10.29–11.10) and NaOH (pH 11.98). Concentrations of 0.010, 0.020, and 0.030 M were used for CAPS, CHES and EPPS, and in all cases the ionic strength of the solutions was held at 0.10 by the addition of KCl.

The second order rate constants for the hydroxide promoted hydrolysis of carbamoylimidazoles and carbamoylimidazolium salts were measured at 25 °C by observing the rate of change in absorbance at 230 nm (Table 2, Entries 1 and 2), 225 nm (Table 2, Entries 3 and 5), 235 nm (Table 2, Entries 4 and 6), 270 nm (Table 2, Entry 7) and 265 nm (Table 2, Entry 8), using an OLIS modified Cary-17 UV/visible spectrophotometer. Reactions were initiated by injecting 10 μL of the substrate solution into 2.5 mL of the buffer solution, which had been thermally equilibrated in the instrument cell holder for 10 min. Absorbance versus time profiles were fit by NLLSQ methods using Prism software to give pseudo-first order rate constants. Second order rate constants were determined by dividing the pseudo-first order rate constant by the concentration of hydroxide and are given in Table 2.

4.6. General procedure for the preparation of tri- or tetrasubstituted ureas 5

To a solution of carbamoylimidazolium salt **3** (1.00 mmol) in CH_2Cl_2 (10 mL) was added the primary or secondary amine (1.00 mmol) and triethylamine (1.00 mmol). The mixture was stirred at rt for 24 h, then washed with 1.0 N HCl (2×5 mL) and brine (5 mL), the organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to yield urea **5a–l**.

4.6.1. *N*-Methyl-*N*-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (5a).[4a] Clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–6.91 (9H, m), 4.41 (2H, s), 3.57 (2H, t, J=6.0 Hz), 3.51 (3H, s), 2.71 (2H, t, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 146.6, 134.5, 133.5, 129.3, 128.4, 126.1, 126.0, 125.8, 124.4, 123.8, 47.6, 43.5, 39.5, 28.2; IR (neat) 2928, 1594, 1493, 1440, 1403, 1259, 1113, 928 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 266 (95), 235 (11), 208 (62), 189 (13), 160 (100), 142 (69), 132 (56), 117 (55), 107 (73), 91 (23); HRMS (EI) *m*/*z* calcd (M^+) 266.1419, found 26.1426.

4.6.2. Methyl 1-(3,4-dihydroquinolin-1(2*H*)-ylcarbonyl)-L-prolinate (5b).[4a,c] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, m), 7.10 (2H, m), 6.90 (1H, m), 4.56 (1H, t, J=7.5 Hz), 3.81–3.69 (4H, m), 3.42–3.36 (1H, m), 3.12–3.02 (2H, m), 2.75–2.62 (2H, m), 2.24 (1H, m), 2.00 (1H, m), 1.88–1.74 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 158.3, 140.1, 129.2, 128.3, 126.4, 122.1, 120.8, 59.8, 51.9, 48.9, 44.8, 29.5, 26.8, 25.1, 23.8; IR (neat) 2951, 2880, 1745, 1640, 1579, 1495, 1403, 1174, 1026 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 288 (49), 229 (23), 160 (37), 128 (100); HRMS (EI) *m*/*z* calcd (M^+) 288.1474, found 288.1474; $[\alpha]_D^{23}$ +125.2° (*c* 1.02, CH_2Cl_2).

4.6.3. *N*-Methoxy-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (5c). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.23 (1H, m), 7.09–7.05 (2H, m), 6.94–6.90 (1H, m), 3.66 (2H, t, J=6.0 Hz), 3.47 (3H, s), 3.01 (3H, s), 2.73 (2H, t, J=6.5 Hz), 1.96–1.90 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 139.6, 128.9, 128.5, 125.8, 122.9, 121.9, 59.5, 45.6, 35.8, 26.6, 23.6; IR (neat) 2932, 1663, 1493, 1374, 965 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 220 (42), 160 (91), 142 (16), 132 (100), 117 (19), 77 (19); HRMS (EI) *m*/*z* calcd (M^+) 220.1212, found 220.1220.

4.6.4. 1-[(4-Benzylpiperazin-1-yl)carbonyl]-1,2,3,4-tetrahydroquinoline (5d).[4a,c] White solid; mp 171–173 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55–6.90 (9H, m), 4.02 (2H, br s), 3.67–3.57 (6H, m), 2.88–2.70 (6H, m), 2.01–1.88 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.1, 139.6, 130.7, 129.6, 129.2, 128.9, 128.7, 128.3, 126.4, 122.7, 119.9, 60.7, 50.9, 45.2, 42.9, 26.5, 23.3; IR (KBr pellet) 2940, 1640, 1578, 1492, 1300, 1260, 1202, 1176 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 335 (15), 203 (26), 160 (22), 146 (24), 132 (37), 91 (100); HRMS (EI) *m*/*z* calcd (M^+) 335.1998, found 335.1990.

4.6.5. Benzyl 1-[(4-benzylpiperazin-1-yl)carbonyl]-L-prolinate (5e).[4a] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66–7.29 (10H, m), 5.30–5.02 (2H, m), 4.69–4.57 (1H, m), 4.11–3.68 (6H, m), 3.46–3.21 (4H, m), 2.95–2.30 (3H, m) 2.00–1.78 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4, 160.8, 135.5, 131.3, 130.0, 129.1, 128.5, 128.3, 128.2, 127.9, 66.6, 61.0, 59.8, 50.4, 49.6, 42.5, 29.2, 25.5; IR (neat) 2950, 2451, 1741, 1634, 1418, 1276, 1174, 1081, 1031, 957, 922, 734, 700, 644 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 407 (25), 275 (15), 203 (16), 159 (26), 146 (35), 134 (34), 132 (39), 120 (12), 108 (16), 91 (100); HRMS (EI) *m*/*z* calcd (M^+) 407.2209, found 407.2199; $[\alpha]_D^{23}$ −24.0° (*c* 1.01, CH_2Cl_2).

4.6.6. Benzyl 1-{[(2*S*)-2-(methoxycarbonyl)pyrrolidin-1-yl]carbonyl}-L-prolinate (5f). Yellow oil; ^{1}H NMR (200 MHz, MeOH-d_4) δ 7.34–7.23 (5H, m), 5.21–5.04 (2H, m), 4.83–4.37 (3H, m), 3.69 (3H, m), 3.58–3.53 (3H, m), 2.29–2.18 (2H, m), 1.98–1.71 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3, 172.6, 158.4, 136.2, 128.5, 127.7, 126.5, 65.6, 63.0, 60.1, 60.0, 51.6, 48.2, 28.9, 28.9, 24.9; IR (neat) 2953, 2880, 1740, 1616, 1438, 1343, 1279, 1173, 1096, 1042, 1004, 914, 752, 699 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 360 (5), 301 (20), 225 (77), 160 (30), 156 (35), 142 (15), 128 (100), 108 (41), 91 (76); HRMS (EI) *m*/*z* calcd (M^+) 360.1685, found 360.1682; $[\alpha]_D^{23}$ −25.8° (*c* 1.00, MeOH).

4.6.7. Benzyl 1-{[3-(hydroxymethyl)piperidin-1-yl]carbonyl}-L-prolinate (5g). Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) (rotamers) δ 7.35–7.28 (5H, m), 5.24–5.06 (2H, m), 4.71–4.59 (2H, m), 3.61–3.05 (8H, m), 2.30 (1H, m), 2.08–1.25 (8H, m); ^{13}C NMR (50 MHz, DMSO-d_6) (rotamers) δ 172.5, 172.5, 161.2, 142.4, 136.1, 128.3, 127.9, 127.5, 126.5, 126.3, 65.4, 63.6, 63.6, 62.8, 59.9, 59.8, 49.5, 49.2, 49.2, 49.1, 46.5, 46.2, 38.5, 38.2, 29.0, 27.0, 24.9, 24.8, 24.4, 24.1; IR (neat) 3406, 2931, 2820, 1735, 1615, 1435, 1353, 1303, 1169, 1082, 1028, 748, 699 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 347 (6), 212 (88), 204 (7), 142 (100), 114 (33), 98 (17), 91 (57), 81 (18), 70 (92); HRMS (EI) *m*/*z* Calcd (M^+) 346.1893, found 346.1904.

4.6.8. *N*-Methoxy-*N*-methyl-1,4-dioxa-8-azaspiro[4.5] decane-8-carboxamide (5h). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (4H, s), 3.47 (3H, s), 3.43 (4H, t, J=6.0 Hz), 2.84 (3H, s), 1.60 (4H, t, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 106.9, 64.2, 58.5, 43.4, 36.3, 34.9; IR (neat) 2959, 1648, 1473, 1437, 1260, 1099 cm^{-1}; MS (EI) *m/z* (rel. intensity) 230 (9), 170 (100), 142 (98), 99 (29); HRMS (EI) *m/z* calcd (M^+) 230.1267, found 230.1255.

4.6.9. *N*-Allyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (5i).[4a,4c,34] White solid; mp=55–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.12 (4H, m), 5.84 (1H, m), 5.18 (2H, m), 3.92 (2H, d, J=5.0 Hz), 3.81 (2H, t, J=6.0 Hz), 2.73 (2H, t, J=6.5 Hz), 2.01–1.88 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 139.4, 135.4, 132.5, 129.7, 126.7, 124.4, 123.4, 115.9, 43.6, 43.5, 27.2, 24.0; IR (neat) 3325, 2947, 1654, 1512, 1321, 1202, 912 cm^{-1}.

4.6.10. Ethyl *N*-(3,4-dihydroquinolin-1(2*H*)-ylcarbonyl) glycinate (5j). White solid; mp=49–50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, m), 7.26–7.14 (2H, m), 7.06 (1H, m), 5.67 (1H, br m), 4.20 (2H, q, J=7.0 Hz), 4.05 (2H, d, J=5.5 Hz), 3.78 (2H, t, J=6.0 Hz), 2.77 (2H, t, J=6.5 Hz), 1.94 (2H, m), 1.29 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 156.5, 139.1, 132.6, 129.7, 126.9, 124.7, 123.4, 61.5, 43.7, 42.9, 27.2, 24.1, 14.4; IR (KBr pellet) 3385, 2983, 1751, 1643, 1507, 1395, 1195, 1034 cm^{-1}; MS (EI) *m/z* (relative intensity) 262 (84), 217 (8), 189 (10), 160 (18), 133 (100), 118 (17), 103 (5); HRMS (EI) *m/z* calcd (M^+) 262.1317, found 262.1328.

4.6.11. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxamide (5k).[4c,35] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, m), 6.63 (2H, m), 4.76 (1H, t, J=5.5 Hz), 3.86 (4H, s), 3.76 (6H, s), 3.33 (6H, m), 2.67 (2H, t, J=7.0 Hz), 1.55 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 148.4, 147.0, 131.6, 120.3, 111.6, 110.9, 106.6, 63.9, 55.4, 55.3, 42.0, 41.6, 35.6, 34.3; IR (neat) 3334, 2960, 1614, 1515, 1232, 1142, 1030 cm^{-1}.

4.7. General procedure for the preparation of tri- or tetrasubstituted ureas 6

To a solution of amine (1.00 mmol) in THF (6 mL) was added *n*-BuLi (1.50 mmol), and the reaction was stirred for 1 h. Then the carbamoylimidazolium salt **3** (1.20 mmol) was added. The mixture was stirred at rt for 18 h, then diluted with CH_2Cl_2 (20 mL) and washed with 0.2 N HCl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with 0.2 N HCl (2×20 mL) and brine (15 mL), the organic layer dried ($MgSO_4$), filtered and concentrated in vacuo. The products were obtained following column chromatography.

4.7.1. *N*-Methyl-*N*-phenylpyrrolidine-1-carboxamide (6a). Peach solid; mp=64–66 °C; R_f=0.5 (100% EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.26 (2H, m), 7.10–7.07 (3H, m), 3.21 (3H, s), 3.04 (4H, t, J=6.5 Hz), 1.69–1.64 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 146.4, 129.3, 125.0, 124.6, 48.1, 39.9, 25.7; IR (KBr pellet) 2972, 2875, 1638, 1594, 1499, 1431, 1383, 1248, 1106, 764, 703 cm^{-1}; MS (EI) *m/z* (rel. intensity) 204 (100), 173 (17), 106 (27), 98 (86), 55 (54); HRMS (EI) *m/z* Calcd (M^+) 204.1263, found 204.1258.

4.7.2. *N*-Methyl-*N*-phenyl-1,4-dioxa-8-azaspiro[4.5] decane-8-carboxamide (6c). Yellow oil; R_f=0.55 (1:9 Hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.25 (2H, m), 7.07–7.04 (3H, m), 3.85 (4H, s), 3.25 (4H, t, J=6.0 Hz), 3.17 (3H, s), 1.45 (4H, t, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 147.2, 129.7, 124.7, 123.9, 107.3, 64.5, 43.9, 39.8, 34.7; IR (KBr pellet) 2960, 2880, 1648, 1595, 1496, 1432, 1254, 1109, 1033, 945, 761 cm^{-1}; MS (EI) *m/z* (rel. intensity) 276 (73), 170 (65), 142 (100), 106 (32), 77 (37); HRMS (EI) *m/z* calcd (M^+) 276.1474, found 276.1471.

4.7.3. *N*-Methoxy-*N*,*N*′-dimethyl-*N*′-phenylurea (6d). Yellow oil; R_f=0.5 (6:4 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.28 (2H, m), 7.16–7.12 (3H, m), 3.19 (3H, s), 2.90 (3H, s), 2.82 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 145.8, 129.0, 126.0, 126.0, 58.0, 40.3, 34.0; IR (KBr pellet) 2934, 1669, 1596, 1497, 1465, 1371, 1122, 1054, 764, 697 cm^{-1}; MS (EI) *m/z* (relative intensity) 194 (25), 163 (27), 134 (100), 106 (59), 77 (31); HRMS (EI) *m/z* calcd (M^+) 194.1058, found 194.1058.

4.7.4. 1-(1,4-Dioxa-8-azaspiro[4.5]dec-8-ylcarbonyl)-1,2,3,4-tetrahydroquinoline (6e). Yellow oil; R_f=0.45 (1:9 Hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.92 (3H, m), 6.80 (1H, t, J=7.0 Hz), 3.84 (4H, s), 3.50 (2H, t, J=6.0 Hz), 3.31 (4H, t, J=6.0 Hz), 2.67 (2H, t, J=6.5 Hz), 1.90–1.83 (2H, m), 1.58 (4H, t, J=5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 140.8, 129.0, 127.4, 126.3, 121.8, 119.5, 106.9, 64.2, 45.5, 43.7, 34.7, 26.9, 23.4; IR (KBr pellet) 2955, 2880, 1649, 1493, 1417, 1246, 1096, 946, 754 cm^{-1}; MS (EI) *m/z* (rel. intensity) 302 (95), 170 (81), 142 (100), 132 (42), 98 (26); HRMS (EI) *m/z* calcd (M^+) 302.1630, found 302.1632.

4.7.5. *N*-Phenyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxamide (6f). White solid; mp=138–139 °C; R_f=0.3 (4:6 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.18 (4H, m), 7.00–6.92 (2H, m), 3.94 (4H, s), 3.53 (4H, t, J=5.5 Hz), 1.67 (4H, t, J=5.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 139.2, 128.6, 122.8, 120.2, 106.9, 64.5, 42.6, 35.1; IR (KBr pellet) 3319, 2958, 1638, 1535, 1445, 1240, 1111, 945, 753 cm^{-1}; MS (EI) *m/z* (rel. intensity) 262 (77), 217 (15), 170 (54), 142 (100), 119 (16); HRMS (EI) *m/z* calcd (M^+) 262.1317, found 262.1314.

4.7.6. *N*-(4-Chlorophenyl)-1,4-dioxa-8-azaspiro[4.5] decane-8-carboxamide (6g). Peach solid; mp=199–201 °C; R_f=0.35 (4:6 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.19 (4H, m), 6.56 (1H, s), 3.98 (4H, s), 3.56 (4H, t, J=6.0 Hz), 1.74 (4H, t, J=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 137.7, 128.8, 128.0, 121.2, 106.9, 64.7, 42.9, 35.2; IR (KBr pellet) 3341, 1639, 1534, 1494, 1240, 1116, 1089, 946 cm^{-1}; MS (EI) *m/z* (relative intensity) 296 (59), 251 (9), 170 (73), 153 (23), 142 (100), 98 (28); HRMS (EI) *m/z* calcd (M^+) 296.0928, found 296.0921.

4.7.7. *N*-(4-Methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5] decane-8-carboxamide (6h). Beige solid; mp=154–156 °C;

R_f=0.2 (1:1 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (2H, d, J=9.0 Hz), 6.75 (2H, d, J=9.0 Hz), 6.72 (1H, s), 3.93 (4H, s), 3.72 (3H, s), 3.45 (4H, t, J=5.5 Hz), 1.65 (4H, t, J=5.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 155.3, 132.1, 122.6, 113.9, 107.0, 64.5, 55.6, 42.6, 35.1; IR (KBr pellet) 3318, 2958, 1634, 1513, 1421, 1235, 1109, 1034, 946, 822 cm^{-1}; MS (EI) *m/z* (rel. intensity) 292 (100), 247 (13), 170 (33), 149 (68), 142 (98), 98 (30); HRMS (EI) *m/z* calcd (M^+) 292.1423, found 292.1422.

4.8. General procedure for the preparation of carbamate 7 from phenols

To a solution of carbamoylimidazolium salt **3** (1.00 mmol) in acetonitrile (6 mL) was added the phenol (1.00 mmol) and triethylamine (1.00 mmol). The reaction was refluxed overnight. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (15 mL) and 0.1 M HCl (15 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to yield carbamate **7a–f**.

4.8.1. 2-Naphthyl morpholine-4-carboxylate (7a).[4b] Clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.78 (3H, m), 7.58 (1H, m), 7.49–7.42 (2H, m), 7.29–7.26 (1H, m), 3.77–3.74 (4H, m), 3.71 (2H, br s), 3.59 (2H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 148.6, 133.5, 131.0, 129.0, 127.5, 127.3, 126.2, 125.3, 121.2, 118.2, 66.3, 66.2, 44.6, 43.9; IR (KBr pellet) 2956, 2853, 1722, 1418, 1230, 1161, 1115, 1063 cm^{-1}; MS (EI) *m/z* (relative intensity) 257 (71), 144 (11), 127 (14), 114 (100), 70 (51); HRMS (EI) *m/z* Calcd (M^+) 257.1052, found 257.1045.

4.8.2. 2-Bromophenyl morpholine-4-carboxylate (7b).[4b] ^{1}H White solid, mp 62–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.05 (4H, m), 3.74 (6H, m), 3.56 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 148.4, 133.0, 128.3, 126.9, 124.0, 116.3, 66.5, 45.0, 44.2; IR (KBr pellet) 2917, 1715, 1214, 763 cm^{-1}; MS (EI) *m/z* (relative intensity) 206 (89), 156 (8), 114 (100), 70 (59); HRMS (EI) *m/z* calcd (M^+) 286.0079, found 286.0083.

4.8.3. 2-Bromophenyl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (7c).[4b] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (1H, m), 7.29–7.02 (3H, m), 3.94 (4H, s), 3.78–3.63 (4H, m), 1.79–1.74 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 148.4, 132.8, 128.2, 126.6, 124.0, 116.3, 106.5, 64.2, 42.7, 42.4, 35.0, 34.5; IR (neat) 2960, 1732, 1423, 1214, 1104, 945, 750 cm^{-1}; MS (EI) (rel. intensity) 341 (5), 262 (15), 170 (77), 142 (100), 99 (38); HRMS (EI) *m/z* calcd (M^+) 341.0263, found 341.0270.

4.8.4. Pyridin-3-yl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (7d).[4b] White solid; mp=102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36–8.33 (2H, m), 7.47–7.44 (1H, m), 7.27–7.23 (1H, m), 3.87 (4H, s), 3.83–3.52 (4H, m), 1.87–1.28 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 147.6, 145.8, 143.2, 128.9, 123.3, 106.1, 64.1, 42.3, 42.1, 34.6, 34.2; IR (KBr pellet) 2892, 1723, 1219, 1108, 958 cm^{-1}; MS (EI) *m/z* (rel. intensity) 264 (3), 170 (100), 142 (76), 99 (25), 70 (14); HRMS (EI) *m/z* calcd (M^+) 264.1110, found 264.1110.

4.8.5. Phenyl methyl(phenyl)carbamate (7e).[4b,36] White solid; mp=56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.20 (10H, m), 3.48 (3H. s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 151.5, 143.1, 129.4, 129.2, 126.7, 126.0, 125.5, 121.8, 38.3; IR (KBr pellet) 1735, 1600, 1560, 1260, 1239, 1233 cm^{-1}.

4.8.6. 3-Nitrophenyl 3,4-dihydroquinoline-1(2*H*)-carboxylate (7f).[4b] Yellow solid; mp=78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.04 (2H, m), 7.74 (1H, br s), 7.55–7.51 (2H, m), 7.24–7.06 (3H, m), 3.93 (2H, m), 2.85 (2H, t, J=6.5 Hz), 2.05 (2H, t, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.3, 148.5, 137.1, 130.5, 129.7, 128.6, 128.1, 126.0, 124.4, 123.7, 120.2, 117.3, 45.3, 27.0, 23.3; IR (KBr pellet) 2949, 1725, 1493, 1349, 1117, 991 cm^{-1}; MS (EI) *m/z* (rel. intensity) 298 (41), 160 (100), 142 (13), 132 (78), 117 (10), 77 (10); HRMS (EI) *m/z* calcd (M^+) 298.0954, found 298.0944.

4.9. General procedure for the preparation of carbamate 8 from alcohols

To a solution of carbamoylimidazolium salt **3** (2.00 mmol) and alcohol (2.00 mmol) in THF/DMF (2:1, 12 mL) was added portionwise NaH (2.20 mmol, 80% in mineral oil). The solution was stirred at rt for 1 day. H_2O (10 mL) and Et_2O (20 mL) were added, and the organic layer was washed with H_2O (2×10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The oil was purified by flash column chromatography (CH_2Cl_2) to yield carbamate **8e–f**.

4.9.1. 3-Methylbut-2-en-1-yl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (8a).[4b] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.30–5.27 (1H, m), 4.52 (2H, d, J=7.0 Hz), 3.90 (4H, s), 3.49–3.47 (4H, m), 1.69 (3H, s), 1.64 (3H, s), 1.61–1.58 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.3, 137.9, 119.4, 106.9, 64.3, 62.2, 41.8, 34.7, 25.6, 17.9; IR (neat) 2961, 2879, 1694, 1428, 1231, 1112 cm^{-1}; MS (EI) *m/z* (rel. intensity) 255 (37), 196 (16), 186 (3), 170 (19), 142 (27), 99 (41); HRMS (EI) *m/z* calcd (M^+) 255.1471, found 255.1468.

4.9.2. 2,2,2-Trifluoroethyl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (8b).[4b] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.42 (2H, q, J=8.5 Hz), 3.91 (4H, s), 3.53–3.52 (4H, m), 1.64–1.63 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.1, 123.1 (q, J=277.5 Hz), 106.5, 64.3, 61.3 (q, J=54.0 Hz), 42.4, 42.1, 34.8, 34.5; IR (neat) 2966, 1714, 1474, 1232, 1166, 962 cm^{-1}; MS (EI) *m/z* (rel. intensity) 269 (74), 210 (19), 186 (100), 170 (23), 99 (65); HRMS (EI) *m/z* calcd (M^+) 269.0875, found 269.0873.

4.9.3. 3-Methylbut-2-en-1-yl 3,4-dihydroisoquinoline-2(1*H*)-carboxylate (8c).[4b] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24–7.14 (4H, m), 5.40–5.33 (1H, m), 4.63–4.60 (4H, m), 3.71–3.65 (2H, m), 2.86–2.80 (2H, m), 1.75 (3H, s), 1.71 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.6, 137.8, 134.4, 133.2, 128.5, 126.2, 126.1, 125.9, 119.4, 62.2, 45.5, 41.3, 28.7, 25.6, 17.8; IR (neat) 2930,

1703, 1428, 1227, 1118, 984 cm^{-1}; MS (EI) *m/z* (relative intensity) 245 (5), 176 (47), 132 (36), 104 (19), 69 (100); HRMS (EI) *m/z* Calcd (M^+) 245.1416, found 245.1415.

4.9.4. 3-Methylbut-2-en-1-yl methyl(phenyl)carbamate (8e).[4b] Clear oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.25 (5H, m), 5.33 (1H, m), 4.61 (2H, d, $J=7.0$ Hz), 3.30 (3H, s), 1.73 (3H, s), 1.68 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.6, 143.3, 137.8, 128.6, 125.6, 125.4, 119.3, 62.4, 37.4, 25.5, 17.8; IR (neat) 2934, 1707, 1598, 1498, 1386, 1353, 1298, 1277, 1153 cm^{-1}; MS (EI) *m/z* (rel. intensity) 219 (3), 175 (3) 160 (9), 151 (24) 107 (59), 69 (100); HRMS (EI) *m/z* calcd (M^+) 219.1259, found 219.1251.

4.9.5. Benzyl methyl(phenyl)carbamate (8f).[4b,37] Yellow oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.20 (10H, m), 5.20 (2H, s), 3.35 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 143.5 (d), 136.8, 129.0, 128.6, 128.0, 127.8, 126.3, 125.9, 67.4, 37.9; IR (neat) 2950, 1705, 1596, 1496, 1387, 1348, 1152 cm^{-1}.

4.10. General procedure for the preparation of thiocarbamate 9

To a suspension of carbamoylimidazolium salt **3** (1.00 mmol) in CH_2Cl_2 (6 mL) was added the thiol (1.00 mmol) and triethylamine (1.00 mmol). After stirring at rt overnight, the reaction was diluted with CH_2Cl_2 (5 mL) and 0.1 M HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were washed with H_2O (10 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by flash column chromatography (98:2 Hexane: ethyl acetate) to yield the thiocarbamate **9a–f**.

4.10.1. *S*-Phenyl methyl(phenyl)thiocarbamate (9a).[4b,38] White solid; mp = 66–67 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.40 (10H, m), 3.37 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.4, 141.8, 135.4 (d), 129.5 (d), 129.4, 129.0 (d), 128.8 (d), 128.6 (d), 128.2 (d), 38.5; IR (neat) 2950, 1666, 1592, 1484, 1443, 1341, 1272, 1106 cm^{-1}.

4.10.2. *S*-Dodecyl 3,4-dihydroquinoline-1(2*H*)-carbothioate (9b).[4b] Clear oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72–7.70 (1H, m), 7.17–7.06 (3H, m), 3.78 (2H, t, $J=6.0$ Hz), 2.90 (2H, t, $J=7.0$ Hz), 2.75 (2H, t, $J=6.5$ Hz), 2.00–1.94 (2H, m), 1.63–1.58 (2H, m), 1.39–1.24 (18H, m), 0.86 (3H, t, $J=7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.6, 138.1, 131.3, 125.8, 125.8, 124.9, 124.7, 45.0, 31.8, 30.8, 29.9, 29.5, 29.5, 29.4, 29.4, 29.2, 29.1, 28.9, 26.8, 23.6, 22.6, 14.0; IR (neat) 2852, 1661, 1489, 1295, 1194, 1090, 937 cm^{-1}; MS (EI) *m/z* (relative intensity) 361 (79), 193 (12), 160 (100), 132 (50), 118 (6); HRMS (EI) *m/z* Calcd (M^+) 361.2439, found 361.1444.

4.10.3. *S*-(Pentafluorophenyl) 3,4-dihydroquinoline-1(2*H*)-carbothioate (9c).[4b] White solid; mp = 78–79 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (1H, m), 7.23–7.18 (3H, m), 3.85 (2H, t, $J=6.5$ Hz), 2.81 (2H, t, $J=6.5$ Hz), 2.11–1.98 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 150.3 (m), 145.3 (m), 140.2 (m), 137.2, 135.1 (m), 132.5, 128.9, 126.3, 124.5, 45.9, 26.6, 23.6 (1 missing signal); ^{19}F NMR (376 MHz, $CDCl_3$) δ −131 (2F, m), −150 (1F, m), −161 (2F, m); IR (KBr pellet) 1664, 1517, 1470, 1295, 1094, 976 cm^{-1}; MS (EI) *m/z* (relative intensity) 359 (17), 199 (24), 160 (100), 132 (78), 118 (19); HRMS (EI) *m/z* calcd (M^+) 359.0403, found 359.0419.

4.10.4. *S*-Cyclohexyl 3,4-dihydroquinoline-1(2*H*)-carbothioate (9d).[4b] Clear oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (1H, d, $J=8.0$ Hz), 7.20–7.02 (3H, m), 3.76 (2H, tr, $J=6.0$ Hz), 3.49 (1H, m), 2.75 (2H, tr, $J=6.5$ Hz), 2.07–1.15 (12H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.3, 138.1, 131.3, 128.6, 125.8, 124.9, 124.8, 45.0, 44.2, 33.5, 26.9, 26.2, 25.6, 23.6; IR (neat) 2930, 1646, 1580, 1488, 1446, 1362, 1295, 1197, 1162, 1089 cm^{-1}; MS (EI) *m/z* (rel. intensity) 275 (89), 193 (25), 172 (47), 160 (69), 133 (100), 83 (37); HRMS (EI) *m/z* calcd (M^+) 275.1344, found 275.1335.

4.10.5. Methyl *N*-acetyl-*S*-(3,4-dihydroquinolin-1(2*H*)-ylcarbonyl)-L-cysteinate (9e).[4b] Yellow foam; ^1H NMR (200 MHz, $CDCl_3$) δ 7.61–7.59 (1H, m), 7.15–7.06 (3H, m), 6.73 (1H, d, $J=5.5$ Hz), 4.73–4.69 (1H, m), 3.78–3.69 (5H, m), 3.33 (2H, d, $J=6.0$ Hz), 2.72 (2H, t, $J=6.5$ Hz), 1.97–1.91 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 169.9, 167.8, 137.4, 131.7, 128.6, 125.9, 125.5, 124.5, 52.9, 52.4, 45.4, 32.0, 26.6, 23.5, 22.9; IR (neat) 3290, 2950, 1760, 1682, 1647, 1372, 1296, 1090 cm^{-1}; MS (EI) *m/z* (rel. intensity) 336 (44), 277 (19), 193 (6), 160 (100), 144 (13), 132 (93); HRMS (EI) *m/z* calcd (M^+) 336.1144, found 336.1140.

4.10.6. *S*-Cyclohexyl 1,4-dioxa-8-azaspiro[4.5]decane-8-carbothioate (9f).[4b] White solid; mp = 56–57 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 3.87 (4H, s), 3.51–3.34 (5H, m), 1.91–1.88 (2H, m), 1.63–1.37 (7H, m), 1.34–1.16 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.7, 106.8, 64.3, 44.7, 43.6, 41.4, 34.7, 33.5, 25.9, 25.4; IR (KBr pellet) 2931, 1644, 1447, 1263, 1033, 914 cm^{-1}; MS (EI) *m/z* (rel. intensity) 285 (18), 252 (20), 204 (66), 170 (100), 142 (80), 99 (32); HRMS (EI) *m/z* calcd (M^+) 285.1399, found 285.1408.

4.11. General procedure for the preparation of amides 10 from carboxylic acids

To a suspension of **3** (1.00 mmol) in acetonitrile (6 mL) were added the carboxylic acid (1.00 mmol) and triethylamine (1.00 mmol). The reaction was stirred at rt overnight. The solvent was removed in vacuo and the residue dissolved in CH_2Cl_2 (15 mL) and 0.2 N HCl (15 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with 0.2 N HCl (15 mL), 0.5 M K_2CO_3 (25 mL), and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the amide **10a–l**.

4.11.1. 4-(4-Methylpentanoyl)morpholine (10c).[4d,39] Yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60–3.37 (8H, m), 2.25–2.20 (2H, m), 1.55–1.39 (3H, m), 0.83 (6H, d, $J=6.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 67.1, 66.8, 46.2, 42.0, 34.2, 31.3, 28.0, 22.5; IR (neat) 2956, 1651, 1429, 1273, 1116, 1030, 851 cm^{-1}; MS (EI) *m/z* (rel. intensity) 170 (10), 142 (15), 129 (100), 114 (30), 86 (41),

57 (63); HRMS (EI) *m/z* calcd (MH+) 186.1494, found 186.1495.

4.11.2. Benzyl [(1*S*)-1-benzyl-2-morpholin-4-yl-2-oxoethyl]carbamate (10e).[4d,40] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.17 (10H, m), 6.17 (1H, d, J=8.5 Hz), 5.12–5.01 (2H, m), 4.89–4.81 (1H, m), 3.66–3.22 (6H, m), 3.07–2.82 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 156.0, 136.6, 136.5, 129.8, 128.8, 128.7, 128.3, 128.2, 127.4, 67.0, 66.6, 66.2, 51.6, 46.2, 42.5, 40.4; IR (neat) 3289, 1716, 1636, 1528, 1455, 1231, 1114, 751 cm^{-1}; MS (EI) *m/z* (rel. intensity) 368 (3), 254 (60), 217 (53), 210 (62), 91 (100); HRMS (EI) *m/z* calcd (M^+) 368.1736, found 368.1726.

4.11.3. *N*-Methoxy-*N*-methyl-4-oxo-4-phenylbutanamide (10i).[4d,41] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, J=7.0 Hz), 7.49–7.36 (3H, m), 3.70 (3H, s), 3.27 (2H, t, J=6.5 Hz), 3.14 (3H, s), 2.84 (2H, t, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 173.4, 137.0, 133.2, 128.7, 128.2, 61.4, 33.2, 32.4, 26.3.

4.11.4. *N*-{2-[Methoxy(methyl)amino]-2-oxoethyl}-4-methylpentanamide (10j).[4d] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (3H, s), 3.11 (3H, s), 2.35 (2H, t, J=7.5 Hz), 1.60–1.40 (3H, m), 0.85 (6H, d, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 61.4, 33.7, 32.4, 30.1, 28.0, 22.5; IR (neat) 2957, 1669, 1467, 1345, 1177, 1001 cm^{-1}; MS (EI) *m/z* (rel. intensity) 144 (12), 103 (48), 99 (79), 81 (100), 61 (99); HRMS (EI) *m/z* calcd (M^+) 159.1259, found 159.1253.

4.11.5. 2-Iodo-*N*-methoxy-*N*-methylbenzamide (10l).[4d,42] White solid; mp=55–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.83–7.80 (1H, m), 7.38–7.34 (1H, m), 7.26–7.24 (1H, m), 7.09–7.05 (1H, m), 3.51 (3H, br s), 3.31 (3H, br s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 141.7, 139.1, 130.4, 127.8, 127.4, 92.5, 61.2, 32.7 (1 missing signal); MS (EI) *m/z* (rel. intensity) 291 (18), 231 (100), 203 (31), 104 (8), 76 (26); HRMS (EI) *m/z* Calcd (M^+) 290.9756, found 290.9760.

4.11.6. 8-(Phenylacetyl)-1,4-dioxa-8-azaspiro[4.5]decane (10m).[4d] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.16 (5H, m), 3.85 (4H, d, J=2.0 Hz), 3.68 (2H, s), 3.65 (2H, t, J=6.0 Hz), 3.43 (2H, t, J=6.0 Hz), 1.58 (2H, t, J=6.0 Hz), 1.37 (2H, t, J=5.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 135.3, 128.9, 128.7, 127.0, 107.0, 64.6, 44.4, 41.3, 40.1, 35.4, 34.8; IR (neat) 2962, 2878, 1630, 1440, 1360, 1250, 1097, 1029 cm^{-1}; MS (EI) *m/z* (rel. intensity) 261 (73), 170 (100), 142 (80), 118 (37), 91 (77); HRMS (EI) *m/z* calcd (M^+) 261.1365, found 261.1368.

4.11.7. 8-Propionyl-1,4-dioxa-8-azaspiro[4.5]decane (10n).[4d] White solid; mp 59–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (4H, s), 3.58 (2H, t, J=6.0 Hz), 3.41 (2H, t, J=6.0 Hz), 2.25 (2H, m), 1.56 (4H, m), 1.03 (3H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 107.0, 64.6, 43.5, 39.8, 35.7, 34.9, 26.6, 9.7; IR (KBr pellet) 2961, 2873, 1648, 1419, 1226, 1075, 928, 816 cm^{-1}; MS (EI) *m/z* (rel. intensity) 199 (72), 142 (35), 99 (100), 86 (35), 57 (53); HRMS (EI) calcd (M^+) 199.1208, found 199.1214.

4.11.8. Benzyl [2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-oxoethyl]carbamate (10o).[4d] White solid; mp=84–86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.24 (5H, m), 5.90 (1H, s), 5.06 (2H, s), 3.97 (2H, d, J=4.0 Hz), 3.90 (4H, s), 3.64 (2H, t, J=5.5 Hz), 3.37 (2H, t, J=5.5 Hz), 1.65–1.60 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 156.0, 136.3, 128.3, 127.8, 127.8, 106.4, 66.6, 64.3, 42.4, 42.2, 40.0, 35.0, 34.4; IR (KBr pellet) 3306, 2962, 2878, 1717, 1635, 1520, 1443, 1218, 1058, 734 cm^{-1}; MS (EI) *m/z* (rel. intensity) 334 (24), 243 (27), 170 (41), 142 (84), 108 (38), 99 (100); HRMS (EI) *m/z* calcd (M^+) 334.1529, found 334.1529.

4.11.9. Benzyl [(1*S*)-1-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylcarbonyl)-3-methylbutyl]carbamate (10p). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (5H, m), 5.74 (1H, d, J=9.0 Hz), 5.06 (2H, s), 4.80–4.72 (1H, m), 3.95 (4H, s), 3.76–3.53 (4H, m), 1.76–1.65 (5H, m), 1.51–1.38 (2H, m), 0.99 (3H, d, J=6.5 Hz), 0.91 (3H, d, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 156.0, 136.3, 128.3, 127.9, 127.9, 106.7, 66.9, 64.6, 64.6, 49.2, 43.6, 43.1, 40.5, 35.7, 34.9, 24.9, 23.6, 22.2; IR (thin film) 3293, 2958, 1715, 1640, 1531, 1454, 1231, 1100, 1044, 945 cm^{-1}; MS (EI) *m/z* (rel. intensity) 390 (2), 334 (3), 220 (24), 176 (45), 142 (28), 91 (100); HRMS (EI) *m/z* calcd (M^+) 390.2155, found 390.2168.

4.11.10. 1-(Phenylacetyl)-1,2,3,4-tetrahydroquinoline (10q).[43] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.12 (9H, m), 3.87 (2H, s), 3.80 (2H, t, J=6.5 Hz), 2.60 (2H, br s), 1.89 (2H, t, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 139.3, 135.5, 128.9, 128.6, 128.5, 126.8, 126.2, 125.7, 124.9, 43.2, 41.4, 26.6, 24.1 (1 carbon missing); IR (thin film) 3029, 2946, 1652, 1580, 1492, 1383, 1165, 1074, 760, 719 cm^{-1}; MS (EI) *m/z* (rel. intensity) 251 (95), 160 (26), 133 (100), 117 (18), 91 (60); HRMS (EI) *m/z* calcd (M^+) 251.1310, found 251.1310.

4.11.11. Benzyl [2-(3,4-dihydroquinolin-1(2*H*)-yl)-2-oxoethyl]carbamate (10r). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.13 (9H, m), 5.78 (1H, s), 5.10 (2H, s), 4.15 (2H, d, J=4.5 Hz), 3.76 (2H, br s), 2.72 (2H, br m), 2.00–1.92 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.4, 137.8, 136.6, 129.0, 128.6, 128.2, 128.2, 126.6, 126.1, 124.3, 67.0, 44.0, 43.6, 26.8, 23.7 (1 carbon missing); IR (thin film) 3326, 2947, 1722, 1660, 1492, 1404, 1237, 1048, 759 cm^{-1}; MS (EI) *m/z* (rel. intensity) 324 (42), 216 (18), 160 (27), 133 (100), 91 (60); HRMS (EI) *m/z* calcd (M^+) 324.1474, found 324.1479.

4.12. General procedure for the preparation of thiocarbamoylimidazoles

To a suspension of *N*,*N*′-thiocarbonyldiimidazole (5.50 mmol) in CH_2Cl_2 (5 mL) was added amine (5.00 mmol). The mixture was stirred at rt for 2 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and washed with water (3×20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to yield the product thiocarbamoylimidazole **11a–d**.

4.12.1. 8-(1*H*-Imidazol-1-ylcarbonothioyl)-1,4-dioxa-8-azaspiro[4.5]decane (11a). Beige solid; mp=89–92 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81–7.80 (1H, m), 7.14–7.13

(1H, m), 7.02 (1H, m), 3.95–3.94 (8H, m), 1.80 (4H, br s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.2, 137.0, 129.4, 119.0, 105.6, 64.3, 49.4, 34.6; IR (KBr pellet) 3114, 1507, 1362, 1238, 1079, 935 cm^{-1}; MS (EI) *m/z* (rel. intensity) 253 (97), 186 (100), 158 (91), 142 (27), 99 (66); HRMS (EI) *m/z* calcd (M^+) 253.0885, found 253.0876.

4.12.2. 4-(1*H*-Imidazol-1-ylcarbonothioyl)morpholine (11b). White solid; mp = 84–90 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (1H, s), 7.10–7.09 (1H, m), 6.98–6.97 (1H, m), 3.82–3.67 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.4, 137.1, 129.8, 118.9, 66.0, 51.7; IR (KBr pellet) 2975, 1487, 1436, 1362, 1304, 1239, 1115, 1029, 962 cm^{-1}; MS (EI) *m/z* (rel. intensity) 197 (80), 130 (100), 111 (7), 86 (89); HRMS (EI) *m/z* calcd (M^+) 197.0623, found 197.0625.

4.12.3. 1-(Pyrrolidin-1-ylcarbonothioyl)-1*H*-imidazole (11c). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.96 (1H, m), 7.33–7.32 (1H, m), 7.07–7.06 (1H, m), 3.91 (2H, br m), 3.65 (2H, br m), 2.05 (4H, br m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 137.0, 129.6, 118.9, 54.9, 53.7, 26.7, 24.6; IR (neat) 3114, 2975, 1694, 1495, 1358, 1281, 1043, 954, 825, 746 cm^{-1}; MS (EI) *m/z* (rel. intensity) 181 (81), 114 (100), 84 (12), 72 (59), 55 (33); HRMS (EI) *m/z* calcd (M^+) 181.0674, found 181.0677.

4.12.4. 1-(1*H*-Imidazol-1-ylcarbonothioyl)-1,2,3,4-tetrahydroquinoline (11d). Beige solid; mp = 75–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, s), 7.74 (1H, s), 7.26–7.23 (2H, m), 7.12 (3H, br m), 4.96 (2H, s), 4.03 (2H, m), 3.08 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 139.1, 137.3, 132.6, 129.2, 128.4, 127.0, 126.4, 122.3, 119.3, 52.2, 26.4, 24.2; IR (KBr pellet) 3118, 1652, 1471, 1233, 1062, 928 cm^{-1}; MS (EI) *m/z* (rel. intensity) 143 (100), 215 (17), 176 (55), 142 (33), 117 (48); HRMS (EI) *m/z* calcd (M^+) 243.0830, found 243.0831.

4.13. General procedure for the preparation of thiocarbamoylimidazolium salts 12

To a solution of thiocarbamoylimidazole (8.00 mmol) in acetonitrile (15 mL) was added methyl iodide (32.0 mmol). The mixture was stirred at rt for 24 h. The solvent was removed under vacuum to yield the thiocarbamoyl imidazolium salt **12a–d** as a yellow viscous oil. Recrystalization in methanol/ethyl acetate gave yellow crystals.

4.13.1. 1-(1,4-Dioxa-8-azaspiro[4.5]dec-8-ylcarbonothioyl)-3-methyl-1*H*-imidazol-3-ium iodide (12a). Yellow solid; mp = 192–196 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.62 (1H, s), 8.09–80.8 (1H, m), 7.86–7.84 (1H, m), 4.17 (2H, br s), 3.93 (4H, s), 3.90 (3H, s), 3.63 (2H, br s), 1.89–1.80 (4H, br m); ^{13}C NMR (50 MHz, DMSO-d_6) δ 172.0, 137.2, 123.7, 121.2, 105.2, 64.0, 50.0, 36.4, 34.0 (br); IR (KBr pellet) 2962, 1639, 1457, 1236, 1097, 906 cm^{-1}; MS (FAB) *m/z* (rel. intensity) 268 (59), 227 (6), 186 (100), 158 (31), 142 (13); HRMS (EI) *m/z* calcd ($M^+ - 127$) 268.1120, found 268.1136.

4.13.2. 3-Methyl-1-(morpholin-4-ylcarbonothioyl)-1*H*-imidazol-3-ium iodide (12b). Yellow solid; mp = 205–210 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.65 (1H, s), 8.10–8.09 (1H, m), 7.88–7.87 (1H, m), 4.13–3.99 (2H, br s), 3.91 (3H, s), 3.87–3.67 (6H, br m); ^{13}C NMR (50 MHz, DMSO-d_6) δ 171.9, 137.5, 123.8, 121.2, 65.4 (br), 52.0, 36.6; IR (KBr pellet) 3065, 1507, 1437, 1242, 1052, 963 cm^{-1}; MS (FAB) *m/z* (rel. intensity) 121 (51), 185 (100), 175 (12), 130 (45).

4.13.3. 3-Methyl-1-(pyrrolidin-1-ylcarbonothioyl)-1*H*-imidazol-3-ium iodide (12c). Yellow solid; mp = 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (1H, br m), 7.91 (1H, br m), 7.60 (1H, br m), 4.25 (3H, s), 4.07 (2H, br m), 3.89–3.86 (2H, m), 2.18–2.11 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 168.6, 136.1, 123.7, 121.9, 56.2, 55.4, 38.2, 26.8, 24.7; IR (KBr pellet) 3064, 1579, 1516, 1447, 1331, 1193, 956, 855 cm^{-1}; MS (FAB) *m/z* (rel. intensity) 196 (92), 114 (100); HRMS (FAB) *m/z* calcd ($M^+ - 127$) 196.0908, found 196.0908.

4.13.4. 1-(3,4-Dihydroquinolin-1(2*H*)-ylcarbonothioyl)-3-methyl-1*H*-imidazol-3-ium iodide (12d). Yellow solid; mp = 199–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (1H, s), 7.65 (1H, s), 7.59 (1H, s), 7.36 (1H, d, J = 9.0 Hz), 7.23 (1H, m), 7.06 (1H, m), 6.91 (1H, d, J = 8.0 Hz), 4.20 (2H, t, J = 6.5 Hz), 3.86 (3H, s), 2.88 (2H, t, J = 6.0 Hz), 2.09–2.06 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 171.6, 138.4, 137.6, 134.6, 128.8, 127.6, 127.0, 123.4, 123.1, 121.6, 53.6, 36.5, 25.8, 23.7; MS (FAB) *m/z* (rel. intensity) 258 (45), 236 (20), 176 (100), 160 (29), 146 (35).

4.14. General procedure for the synthesis of thioureas 13

To a solution of thiocarbamoylimidazolium salt **12** (0.50 mmol) in CH_2Cl_2 (1.0 mL) was added a primary or secondary amine (0.600 mmol) and triethylamine (0.60 mmol). The reaction was stirred at rt for 2 h, and diluted with CH_2Cl_2 (10 mL). The mixture was washed with 1N HCl solution (2×5 mL) and brine. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford thiourea **13a–e**.

4.14.1. 4-(Pyrrolidin-1-ylcarbonothioyl)morpholine (13a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (4H, t, J = 4.5 Hz), 3.67–3.63 (4H, m), 3.46 (4H, t, J = 4.5 Hz), 1.94–1.91 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 66.8, 53.2, 51.4, 25.6; IR (neat) 2965, 2854, 1434, 1346, 1269, 1215, 1115, 1030, 872 cm^{-1}; MS (EI) *m/z* (rel. intensity) 200 (100), 167 (37), 143 (30), 130 (11), 114 (61), 96 (10), 86 (53), 70 (45); HRMS (EI) *m/z* calcd (M^+) 200.0983, found 200.0992.

4.14.2. 2-(Pyrrolidin-1-ylcarbonothioyl)-1,2,3,4-tetrahydroisoquinoline (13b). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.10 (4H, m), 4.65 (2H, s), 3.73–3.66 (6H, m), 3.00 (2H, t, J = 6.0 Hz), 1.94–1.91 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 134.6, 133.7, 128.6, 126.6, 126.4, 126.3, 53.2, 53.0, 49.0, 29.0, 25.6; IR (neat) 2967, 1667, 1435, 1207, 1107, 920, 751 cm^{-1}; MS (EI) *m/z* (rel. intensity) 246 (73), 161 (22), 147 (20), 132 (100), 117 (41), 103 (17), 90 (18), 83 (17), 70 (42); HRMS (EI) *m/z* calcd (M^+) 246.1192, found 246.1191.

4.14.3. 8-(Morpholin-4-ylcarbonothioyl)-1,4-dioxa-8-azaspiro[4.5]decane (13c). White solid; mp = 94–96 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (4H, s), 3.61–3.55 (8H, m), 3.45–3.43 (4H, m), 1.67–1.64 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 106.6, 66.1, 64.2, 51.8, 49.0, 34.5; IR (neat) 2849, 1644, 1427, 1232, 1094, 854, 754 cm^{-1}; MS (EI) *m/z* (rel. intensity) 272 (100), 239 (29), 215 (17), 186 (34), 154 (22), 142 (19), 127 (11), 99 (22), 86 (56), 72 (11); HRMS (EI) *m/z* calcd (M^+) 272.1204, found 272.1195.

4.14.4. 8-[(4-Benzylpiperazin-1-yl)carbonothioyl]-1,4-dioxa-8-azaspiro[4.5]decane (13d). White foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (5H, m), 3.94 (4H, s), 3.65–3.58 (8H, m), 3.53 (2H, s), 2.52–2.50 (4H, m), 1.75–1.73 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 136.9, 129.1, 128.2, 127.3, 106.8, 64.3, 62.6, 52.4, 51.2, 49.2, 34.7; IR (neat) 2955, 1883, 1475, 1422, 1357, 1236, 1138, 1086, 1034 cm^{-1}; MS (EI) *m/z* (rel. intensity) 361 (42), 328 (20), 238 (33), 229 (76), 215 (36), 186 (56), 159 (58), 146 (42), 99 (28), 91 (100); HRMS (EI) *m/z* calcd (M^+) 361.1830, found 361.1824.

4.14.5. *N*-Butyl-*N*-methylmorpholine-4-carbothioamide (13e). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72–3.66 (4H, m), 3.56 (2H, t, J=7.5 Hz), 3.38–3.35 (4H, m), 3.03 (3H, s), 1.60–1.53 (2H, m), 1.24 (2H, sextet, J=7.5 Hz), 0.87 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 66.4, 54.6, 51.9, 40.4, 29.1, 19.8, 13.7; IR (neat) 2928, 1495, 1455, 1392, 1248, 1116, 1029, 875 cm^{-1}; MS (EI) *m/z* (rel. intensity) 216 (67), 183 (23), 159 (18), 130 (48), 98 (37), 86 (100), 74 (35), 57 (29); HRMS (EI) *m/z* calcd (M^+) 216.1301, found 216.1296.

4.14.6. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]morpholine-4-carbothioamide (13f). Yellow solid, mp 79–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78–6.76 (1H, m), 6.70–6.68 (2H, m), 5.52 (1H, br m), 3.88 (2H, td, J=7.0 Hz, J=5.5 Hz), 3.83 (3H, s), 3.82 (3H, s), 3.65 (8H, br s), 2.85 (2H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 149.0, 147.7, 131.1, 120.5, 111.7, 111.2, 66.0, 55.8, 55.8, 47.2, 46.8, 34.5; IR (KBr pellet) 3373, 2932, 1515, 1261, 1235, 1141, 1025 cm^{-1}; MS (EI) *m/z* (rel. intensity) 310 (10), 223 (27), 164 (99), 151 (100), 107 (8), 87 (6), 72 (7); HRMS (EI) *m/z* calcd (M^+) 310.1362, found 310.1351.

4.14.7. Diethyl (2-morpholin-4-yl-2-oxoethyl)phosphonate (14).[44] To a suspension of **3f** (4.00 mmol) in dry MeCN (24.0 mL) were added diethyl phosphonoacetic acid (4.00 mmol) and triethylamine (4.00 mmol). The reaction mixture was refluxed for 24 h. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 and washed with 0.2 N HCl. The aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic layers were washed with 0.2 N HCl, 0.5 M K_2CO_3, and brine, dried ($MgSO_4$), and concentrated in vacuo. Product **14** was obtained without further purification as a yellow oil (76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11–4.07 (4H, m), 3.66–3.49 (8H, m), 2.98 (2H, d, J=22.0 Hz), 1.26 (6H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (d, J=6.0 Hz), 66.9, 66.8, 62.8 (d, J=7.0 Hz), 47.5, 42.5, 33.4 (d, J=132.0 Hz), 16.5 (d, J=7.0 Hz); ^{31}P (121 MHz, $CDCl_3$) δ 22.11; IR (thin film) 2981, 2859, 1644, 1442, 1258, 1115, 1032, 970, 788 cm^{-1}; MS (EI) *m/z* (relative intensity) 235 (64), 179 (92), 125 (66), 86 (89), 57 (100); HRMS (EI) *m/z* Calcd (MH^+) 266.1157, found 266.1155.

4.14.8. 4-[(2*E*)-4-Methylpent-2-enoyl]morpholine (15). To a suspension of LiCl (1.24 mmol) in acetonitrile (15 mL) was added **14** (1.24 mmol) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.04 mmol) and isobutyrylaldehyde (1.04 mmol). The reaction was stirred at rt for 16 h. The solvent was then removed in vacuo and the crude product dissolved in CH_2Cl_2 and washed with 0.1 N HCl, brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by column chromatography (100% EtOAc) to give a yellow oil (85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (1H, dd, J=15.0 Hz, J=7.0 Hz), 6.05 (1H, dd, J=15.0 Hz, J=1.5 Hz), 3.57–3.47 (8H, br m), 2.39–2.32 (1H, m), 0.96 (6H, d, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 153.2, 116.5, 66.8, 46.1, 42.3, 31.2, 21.6; IR (thin film) 2961, 2857, 1658, 1620, 1432, 1270, 1229, 1116, 975, 846 cm^{-1}; MS (EI) *m/z* (rel. intensity) 183 (25), 168 (18), 140 (68), 97 (100), 86 (30); HRMS (EI) *m/z* calcd (M^+) 183.1259, found 183.1264.

4.15. General procedure for TBDMS protection of alcohol 16

To a solution of 2-piperidinemethanol (17.3 mmol) in CH_2Cl_2 (35 mL) was added imidazole (34.7 mmol). After stirring for 5 min., *t*-butyldimethylsilyl chloride (19.1 mmol) was added and the reaction mixture was stirred at rt for 4.5 h. The reaction mixture was diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (×4). The combined organic layers were washed once with H_2O, dried ($MgSO_4$), filtered and concentrated in vacuo to give **17**.

4.15.1. 2-(*tert*-Butyldimethylsilanyloxymethyl)piperidine (17a).[4d] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51–3.47 (1H, m), 3.38–3.34 (1H, m), 3.06–3.02 (1H, m), 2.62–2.52 (2H, m), 1.76–1.72 (1H, m), 1.57–1.24 (4H, m), 1.09–0.90 (1H, m), 0.85 (9H, s), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.1, 58.4, 46.8, 28.6, 26.6, 26.1, 24.6, 18.4, −5.2; IR (thin film) 3343, 2931, 1472, 1463, 1330, 1089, 930, 837, 777 cm^{-1}; MS (EI) *m/z* (rel. intensity) 230 (3), 214 (7), 172 (27), 84 (100), 73 (8); HRMS (EI) *m/z* calcd (MH^+) 230.1940, found 230.1947.

4.16. General procedure for formation of carbamoylimidazole 18

To a solution of **17** (13.9 mmol) in CH_2Cl_2 (28 mL) was added CDI (15.2 mmol). The reaction mixture was stirred at rt for 1 day, diluted with H_2O and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic layers were washed with H_2O (×2), dried ($MgSO_4$), filtered and concentrated in vacuo. The product was obtained following column chromatography.

4.16.1. [2-(*tert*-Butyldimethylsilanyloxymethyl)piperidin-1-yl]imidazol-1-yl-methanone (18a).[4d] Pale yellow oil; R_f=0.5 (3:7 Hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (1H, s), 7.25 (1H, s), 7.02 (1H, m), 5.26 (1H, br s), 3.94 (1H, t, J=10.0 Hz), 3.58–3.55 (1H, m), 3.07–3.02 (1H, m), 1.74–1.55 (6H, m), 0.84 (9H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 137.2, 129.4, 118.3, 61.0, 55.7, 41.8, 26.0, 25.8, 25.5, 19.7, 18.4, −5.3; IR (thin film) 3120, 2931, 1694, 1422, 1385, 1249,

1103, 1003, 839, 779 cm^{-1}; MS (EI) *m/z* (relative intensity) 323 (1), 308 (6), 266 (100), 256 (27), 178 (58), 73 (44); HRMS (EI) *m/z* Calcd (M^+) 323.2029, found 323.2035.

4.16.2. {2-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]piperidin-1-yl}imidazol-1-yl-methanone (18b).[4d] Pale yellow oil; R_f=0.55 (3:7 Hexane/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (1H, s), 7.22 (1H, s), 7.06 (1H, s), 4.44 (1H, br s), 3.90–3.87 (1H, m), 3.67–3.62 (2H, m), 3.13 (1H, t, J= 12.5 Hz), 2.04–1.98 (1H, m), 1.87–1.83 (1H, m), 1.75–1.67 (5H, m), 1.57–1.54 (1H, m), 0.86 (9H, s), −0.01 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 137.1, 129.6, 118.1, 60.3, 51.5, 42.4, 33.2, 28.7, 26.1, 26.0, 19.1, 18.5, −5.1, −5.2; IR (thin film) 3117, 2856, 1682, 1472, 1246, 1201, 1099, 989, 828, 775 cm^{-1}; MS (EI) *m/z* (rel. intensity) 322 (5), 280 (100), 270 (22), 198 (11), 184 (20), 73 (27); HRMS (EI) *m/z* calcd ($M-H^+$) 336.2107, found 336.2115.

4.17. General procedure for formation of carbamoylimidazolium salts 19

To a solution of **18** (27.7 mmol) in MeCN (55 mL) was added MeI (110.8 mmol) and the reaction mixture was stirred at rt for 1 day. The solvent was evaporated in vacuo to give the product.

4.17.1. 3-[2-(*tert*-Butyldimethylsilanyloxymethyl)piperidine-1-carbonyl]-1-methyl-3*H*-imidazol-1-ium iodide (19a).[4d] Foamy yellow solid; very hygroscopic; ^1H NMR (400 MHz, $CDCl_3$) δ 9.97 (1H, s), 7.69 (1H, s), 7.67 (1H, s), 4.39–4.37 (1H, m), 4.24 (3H, s), 4.07–4.02 (1H, m), 3.95 (1H, t, J=10.5 Hz), 3.63–3.59 (1H, m), 3.12–3.05 (1H, m), 2.20–2.10 (1H, m), 1.70–1.46 (5H, m), 0.84 (9H, s), 0.058 (3H, s), 0.054 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 136.3, 123.8, 120.7, 60.2, 55.8 (br), 41.7 (br), 37.6, 25.4, 25.0, 24.2, 18.6, 17.8, −5.8, −5.9; IR (thin film) 3076, 2951, 1723, 1537, 1418, 1252, 1150, 1100, 1004, 839, cm^{-1}; MS (ESI) *m/z* (rel. intensity) 338 (9), 270 (7), 256 (100), 197 (31); HRMS (ESI) *m/z* calcd (M^+-127) 338.2258, found 338.2265.

4.17.2. 3-{2-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]piperidine-1-carbonyl}-1-methyl-3*H*-imidazol-1-ium iodide (19b).[4d] Foamy light yellow solid; very hygroscopic; ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (1H, s), 7.72 (1H, s), 7.66 (1H, s), 4.62 (1H, br s), 4.25 (3H, s), 3.85 (1H, br s), 3.67–3.64 (2H, m), 3.34 (1H, br s), 2.07–1.61 (8H, m), 0.82 (9H, s), −0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 137.1, 124.2, 121.1, 60.2, 52.6 (br), 44.0 (br), 38.2, 32.8, 28.5 (br), 26.0, 25.8, 18.5, 18.3, −5.2; IR (thin film) 2930, 2857, 1720, 1639, 1420, 1255, 1098, 836, 776 cm^{-1}; MS (ESI) *m/z* (rel. intensity) 352 (11), 271 (27), 270 (100); HRMS (ESI) *m/z* calcd (M^+-127) 352.2414, found 352.2427.

4.18. General procedure for formation of amide 20

To a solution of **19** (6.29 mmol) in MeCN (38 mL) were added diethylphosphonoacetic acid (6.92 mmol) and Et_3N (6.92 mmol). The reaction mixture was stirred at 50 °C for 1 day. The solvent was removed in vacuo and the crude product was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (×4). The combined organic layers were washed with H_2O, 0.5 M K_2CO_3, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The product was obtained following column chromatography.

4.18.1. Diethyl {2-[2-(*tert*-Butyldimethylsilanyloxymethyl)piperidin-1-yl]-2-oxoethyl}phosphonate (20a).[4d] Yellow oil; R_f=0.2 (100% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) (rotamers) δ 4.55–4.50 (1H, m), 4.25–4.07 (4H, m), 3.88–3.81 (1H, m), 3.56–3.46 (2H, m), 3.08–2.79 (2H, m), 2.59–2.51 (1H, m), 1.78–1.35 (6H, m), 1.33–1.28 (6H, m), 0.85 (2.67H, s), 0.83 (6.33H, s), 0.02 (4.2H, s), −0.01 (1.8H, s); ^{13}C NMR (100 MHz, $CDCl_3$) (rotamers) δ 164.7 (d, J=5.5 Hz), 163.7 (d, J=5.0 Hz), 62.6 (d, J=6.0 Hz), 62.5 (d, J=6.0 Hz), 62.4 (d, J=7.0 Hz), 62.0 (d, J= 6.0 Hz), 61.4, 60.7, 44.0, 37.0, 33.8 (d, J=133.0 Hz), 33.8 (d, J=133.0 Hz), 25.8, 25.8, 25.8, 25.6, 25.2, 24.3, 19.8, 19.0, 18.1, 16.3 (d, J=6.0 Hz), 16.3 (d, J=6.0 Hz), −5.5, −5.6; ^{31}P NMR (121 MHz, $CDCl_3$) (rotamers) δ 23.68, 22.78; IR (thin film) 2932, 2858, 1638, 1443, 1254, 1102, 1027, 969, 838, 779 cm^{-1}; MS (EI) *m/z* (rel. intensity) 409 (5), 350 (46), 322 (19), 262 (100), 172 (38), 84 (90); HRMS (EI) *m/z* calcd (MH^+) 408.2335, found 408.2332.

4.18.2. Diethyl (2-{2-[2-(*tert*-butyldimethylsilanyloxy)ethyl]piperidin-1-yl}-2-oxoethyl)phosphonate (20b).[4d] Yellow oil; R_f=0.5 (95:5 EtOAc/MeOH); ^1H NMR (300 MHz, $CDCl_3$) (rotamers) δ 4.79 (0.3H, br s), 4.54–4.48 (0.7H, br m), 4.33–4.27 (0.7H, br m), 4.18–4.04 (3.3H, m), 3.62–3.42 (3H, m), 3.05–2.79 (2H, m), 2.54–2.44 (1H, m), 1.86–1.81 (2H, m), 1.73–1.50 (6.3H, m), 1.36–1.24 (5.7H, m), 0.86 (6.3H, s), 0.84 (2.7H, s), 0.02 (1.8H, s), 0.00 (4.2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 163.8 (d, J=5.0 Hz), 162.9 (d, J=5.0 Hz), 62.7 (d, J=6.0 Hz), 62.6, 62.5 (d, J=6.5 Hz), 62.0 (d, J=6.5 Hz), 61.1, 59.1, 50.4, 46.5, 43.0, 37.1, 34.0 (d, J=132.0 Hz), 33.6 (d, J= 133.5 Hz), 33.3, 33.2, 29.5, 28.8, 26.4, 26.2, 25.8, 19.5, 19.2, 18.5, 16.7 (d, J=6.0 Hz), 16.7 (d, J=6.5 Hz), −5.9, −5.0; ^{31}P NMR (121 MHz, $CDCl_3$) (rotamers) δ 23.55, 22.84; IR (thin film) 2931, 2858, 1640, 1444, 1255, 1095, 1024, 967, 835, 777 cm^{-1}; MS (EI) *m/z* (rel. intensity) 422 (8), 365 (81), 336 (100), 308 (27), 243 (39); HRMS (EI) *m/z* calcd (MH^+) 422.2492, found 422.2480.

4.19. General procedure for TBDMS deprotection to alcohol 21

To a solution of **20** (14.7 mmol) in THF (70 mL) was added tetrabutylammonium fluoride (17.7 mmol). The reaction mixture was stirred at rt for 30 min, quenched with H_2O and extracted with CH_2Cl_2 (×4), dried ($MgSO_4$), filtered and concentrated in vacuo. The product was obtained following column chromatography.

4.19.1. Diethyl {2-[2-(hydroxymethyl)piperidin-1-yl]-2-oxoethyl}phosphonate (21a).[4d] Yellow oil; yield: 94%; R_f=0.3 (9:1 EtOAc/MeOH); ^1H NMR (400 MHz, $CDCl_3$) (rotamers) δ 4.51 (1H, br s), 4.23 (1H, br d, J=13.5 Hz), 3.91–3.84 (4H, m), 3.65 (1H, br t, J=10.5 Hz), 3.52–3.14 (2.6H, m), 2.96–2.68 (1.7H, m), 2.43 (0.7H, br t, J= 12.5 Hz), 1.56–1.22 (6H, m), 1.19–1.02 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) (rotamers) δ 164.8 (d, J=5.5 Hz), 164.1 (d, J=5.5 Hz), 62.9 (d, J=6.0 Hz), 62.8 (d, J=6.5 Hz),

62.5 (d, J=6.5 Hz), 62.5 (d, J=6.0 Hz), 60.8, 60.5, 55.9, 50.9, 43.4, 37.2, 33.8 (d, J=132.0 Hz), 33.6 (d, J=132.0 Hz), 26.1, 25.7, 25.3, 24.9, 19.6, 19.3, 16.4, 16.3; ^{31}P NMR (121 MHz, $CDCl_3$) (rotamers) δ 23.72, 23.00; IR (thin film) 3412, 2939, 2869, 1624, 1446, 1245, 1025, 972, 787 cm^{-1}; MS (EI) m/z (rel. intensity) 294 (8), 263 (72), 262 (100), 248 (16), 84 (92); HRMS (EI) m/z calcd (MH^+) 294.1470, found 294.1461.

4.19.2. Diethyl {2-[2-(2-hydroxyethyl)piperidin-1-yl]-2-oxoethyl}phosphonate (21b).[4d] Yellow oil; R_f=0.3 (9:1 EtOAc/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 4.89–4.86 (0.7H, m), 4.56–4.52 (0.3H, br m), 4.37–4.4.36 (0.3H, br m), 4.22–4.11 (3.7H, m), 3.82–3.70 (1.7H, m), 3.65–3.58 (1.3H, m), 3.43–3.01 (3.7H, m), 2.63–2.56 (0.3H, br m), 2.09–1.94 (1.3H, m), 1.78–1.46 (7H, m), 1.40–1.30 (5.7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 165.4 (d, J=6.0 Hz), 63.1 (d, J=6.5 Hz), 62.8 (d, J=3.5 Hz), 62.7 (d, J=3.5 Hz), 62.4 (d, J=6.0 Hz), 58.2, 58.0, 50.6, 45.6, 43.2, 37.2, 33.7 (d, J=132.0 Hz), 32.9 (d, J=134.0 Hz), 32.6, 32.4, 29.2, 29.0, 25.9, 25.6, 19.3, 16.4 (d, J=6.5 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) (rotamers) δ 23.83, 22.31; IR (thin film) 3441, 2942, 1626, 1448, 1247, 1025, 975, 788 cm^{-1}; MS (EI) m/z (rel. intensity) 308 (14), 307 (10), 262 (78), 179 (20), 128 (100), 84 (65); HRMS (EI) m/z calcd (MH^+) 308.1623, found 308.1638.

4.20. General procedure for oxidation of alcohol to the aldehyde 22

To a solution of **21** (3.75 mmol) in CH_2Cl_2 (37 mL) was added 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (Dess–Martin reagent, 4.50 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was filtered through Celite, and the filtrate diluted with 0.5 M K_2CO_3 and extracted with CH_2Cl_2 (×4). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The product was obtained after column chromatography.

4.20.1. Diethyl [2-(2-formylpiperidin-1-yl)-2-oxoethyl] phosphonate (22a).[4d] Yellow oil; R_f=0.14 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 9.66 (0.2H, s), 9.51 (0.8H, s), 5.18 (0.7H, br d, J=5.5 Hz), 4.73–4.61 (0.3H, br m), 4.24–4.08 (4H, m), 3.93–3.89 (1H, br m), 3.23–2.94 (3H, m), 2.64–2.57 (0.2H, m), 2.42–2.25 (0.8H, br m), 1.83–1.47 (4H, m), 1.39–1.25 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) (rotamers) δ 200.9, 200.0, 165.2, 165.1, 63.6, 62.8 (d, J=6.5 Hz), 62.7 (d, J=6.5 Hz), 59.3, 45.8, 40.5, 33.9 (d, J=131.0 Hz), 33.5 (d, J=133.0 Hz), 25.2, 24.7, 24.6, 23.4, 20.9, 20.8, 16.4 (d, J=6.5 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 20.65; IR (thin film) 2940, 2866, 1731, 1639, 1444, 1249, 1025, 972, 833, 787 cm^{-1}; MS (EI) m/z (rel. intensity) 292 (5), 262 (49), 179 (9), 151 (8), 123 (12), 84 (100); HRMS (EI) m/z calcd (M^+) 291.1236, found 291.1230.

4.20.2. Diethyl {2-oxo-2-[2-(2-oxoethyl)piperidin-1-yl] ethyl}phosphonate (22b).[4d] Yellow oil; R_f=0.15 (100% EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 9.63 (0.3H, s), 9.54 (0.7H, s), 5.22–5.16 (0.6H, m), 4.61–4.55 (0.2H, br m), 4.44–4.38 (0.2H, br m), 4.06–3.96 (4H, m), 3.69–3.64 (0.7H, br m), 3.37–3.25 (0.3H, m), 3.06–2.85 (3H, m), 2.67–2.39 (2H, m), 1.75–1.34 (7H, m), 1.18 (6H, t, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 200.3, 199.5, 163.8 (d, J=5.5 Hz), 163.2 (d, J=5.5 Hz), 62.5 (d, J=6.5 Hz), 62.3 (d, J=6.5 Hz), 48.4, 44.5, 44.2, 43.8, 42.8, 37.2, 33.5 (d, J=132.5 Hz), 33.3 (d, J=132.5 Hz), 29.3, 28.2, 25.5, 25.2, 18.9, 18.5, 16.2 (d, J=6.5 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) (rotamers) δ 21.63, 20.92; IR (thin film) 2939, 2867, 1721, 1631, 1250, 1024, 970 cm^{-1}; MS (EI) m/z (rel. intensity) 305 (9), 179 (17), 150 (28), 126 (100), 98 (74), 84 (80); HRMS (EI) m/z calcd (M^+) 305.1392, found 305.1396.

4.21. General procedure for the Wadsworth–Horner–Emmons reaction

To a solution of **22** (0.515 mmol) in THF (10 mL) at 0 °C was added NaH (0.515 mmol) and the reaction mixture was stirred at 0 °C for 40 min. The crude reaction mixture was diluted with CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (×5). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The product was obtained following column chromatography.

4.21.1. 6,7,8,8a-Tetrahydroindolizin-3(5*H*)-one (23a).[4d,29] Yellow oil; R_f=0.3 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00–6.96 (1H, m), 6.13–6.01 (1H, m), 4.27–4.23 (1H, m), 3.86–3.82 (1H, m), 2.84–2.77 (1H, m), 2.10–2.06 (1H, m), 1.92–1.87 (1H, m), 1.74–1.70 (1H, m), 1.54–1.43 (1H, m), 1.36–1.20 (1H, m), 1.05–0.94 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 147.1, 127.5, 61.5, 39.4, 30.8, 25.4, 23.6.

4.21.2. 1,6,7,8,9,9a-Hexahydro-4*H*-quinolizin-4-one (23b).[4d,30] Yellow oil; R_f=0.48 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46–6.42 (1H, m), 5.88–5.85 (1H, m), 4.50–4.46 (1H, m), 3.45–3.38 (1H, m), 2.55–2.45 (2H, m), 2.22–2.13 (1H, m), 1.83–1.78 (1H, m), 1.74–1.70 (2H, m), 1.52–1.35 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 138.2, 124.7, 54.9, 43.1, 33.5, 31.2, 24.9, 24.1; IR (thin film) 2934, 2856, 1667, 1613, 1429, 1321, 1272, 1154, 826, 814 cm^{-1}; MS (EI) m/z (rel. intensity) 151 (67), 136 (9), 122 (30), 84 (100), 68 (27); HRMS (EI) m/z calcd (M^+) 151.0997, found 151.0994.

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References and notes

1. For recent reviews on combinatorial chemistry, see: (a) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477–517. (b) Dolle, R. E. *J. Comb. Chem.* **2000**, *2*, 383–433.
2. For recent reviews on solid-phase organic synthesis, see: (a) Krchnák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61–91. (b) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549–1581. (c) Brown, A. R.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Synlett* **1998**, 817–827. (d) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527–4554. (e) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449–472.
3. For recent reviews on solution-phase organic synthesis, see: (a) An, H.; Cook, P. D. *Chem. Rev.* **2000**, *100*, 3311–3340. (b) Merritt, A. T. *Comb. Chem. High Throughput Screen.* **1998**, *1*, 57–72.
4. (a) Batey, R. A.; Santhakumar, V.; Yoshina-Ishii, C.; Taylor, S. D. *Tetrahedron Lett.* **1998**, *39*, 6267–6270. (b) Batey, R. A.; Yoshina-Ishii, C.; Taylor, S. D.; Santhakumar, V. *Tetrahedron Lett.* **1999**, *40*, 2669–2672. (c) Batey, R. A.; Shen, M.; Santhakumar, V.; Yoshina-Ishii, C. *Comb. Chem. High Throughput Screen.* **2002**, *5*, 219–232. (d) Grzyb, J. A.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7485–7488.
5. Staab, K. M.; Bauer, H.; Schneider, K. M. *Azolides in organic synthesis and biochemistry*; Wiley-VCH: Weinheim, 1998.
6. Oakenfull, D. G.; Salvesen, K.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 188–194 and references cited.
7. Guibé-Jampel, E.; Bram, G.; Wakselman, M.; Vilkas, M. *Synth. Commun.* **1973**, *3*, 111–114.
8. Watkins, B. E.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 4471–4477.
9. (a) Guibé-Jampel, E.; Bram, G.; Wakselman, M.; Vilkas, M. *Bull. Soc. Chim. Fr.* **1973**, 1021–1027. (b) Saha, A. K.; Schultz, P.; Rapoport, H. *J. Am. Chem. Soc.* **1989**, *111*, 4856–4859. (c) Kamijo, T.; Yamamoto, R.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1982**, *30*, 4242–4244.
10. Zheng, C.; Combs, A. P. *J. Comb. Chem.* **2002**, *4*, 38–43.
11. Batey, R. A.; Yoshina-Ishii, C.; Lough, A. J. *Acta Crystallogr. Sect. C* **1999**, *55*, 615–618.
12. Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411–1414.
13. (a) Hlasta, D. J. *Org. Lett.* **2001**, *3*, 157–159. (b) Deng, Y.; Hlasta, D. J. *Tetrahedron Lett.* **2002**, *43*, 189–192.
14. Ozaki, S. *Chem. Rev.* **1972**, *72*, 457–496.
15. Peterson, U. In *Houben-Weyl, Methoden der Organische Chemie*, *Vol. 4*; Thieme: Stuttgart, 1983; pp 335–367.
16. See for example: Settepani, J. A.; Pettit, G. R. *J. Org. Chem.* **1970**, *35*, 843–844.
17. Katritzky, A. R.; Pleynet, D. P. M.; Yang, B. *J. Org. Chem.* **1997**, *62*, 4155–4158.
18. (a) Adams, P.; Baron, F. A. *Chem. Rev.* **1965**, *65*, 567–602. (b) Mateen, A.; Chapalamadugu, S.; Kaskar, B.; Bhatti, A. R.; Chaudhry, G. R. *Biol. Degrad. Biorem. Toxicol. Chem.* **1994**, 198–233.
19. Greene, T. W.; Wuts, P. G. M. *Protective groups in organic synthesis*, 2nd ed.; Wiley: New York, 1991; pp 315–348.
20. For example see: (a) Babad, H.; Zeiler, A. C. *Chem. Rev.* **1973**, *73*, 75–91. (b) Toda, N.; Tago, K.; Marumoto, S.; Takami, K.; Ori, M.; Yamada, N.; Koyama, K.; Naruto, S.; Abe, K.; Yamazaki, R.; Hara, T.; Aoyagi, A.; Abe, Y.; Kaneko, T.; Kogen, H. *Bioorg. Med. Chem.* **2003**, *11*, 1935–1955. (c) Kamila, S.; Mukherjee, C.; Mondal, S. S.; De, A. *Tetrahedron* **2003**, *59*, 1339–1348. (d) Mongin, F.; Trécourt, F.; Gervais, B.; Mongin, O.; Quéguiner, G. *J. Org. Chem.* **2002**, *67*, 3272–3276. (e) Tarzia, G.; Duranti, A.; Tontini, A.; Piersanti, G.; Mor, M.; Rivara, S.; Plazzi, P. V.; Park, C.; Kathuria, S.; Piomelli, D. *J. Med. Chem.* **2003**, *46*, 2352–2360.
21. For example see: (a) Salvatore, R. N.; Shin, S. I.; Nagle, A. S.; Jung, K. W. *J. Org. Chem.* **2001**, *66*, 1035–1037. (b) Inesi, A.; Mucciante, V.; Rossi, L. *J. Org. Chem.* **1998**, *63*, 1337–1338. (c) Mulla, S. A. R.; Gupte, S. P.; Chaudhari, R. V. *J. Mol. Catal.* **1991**, *67*, L7–L10. (d) Ohta, A.; Inagawa, Y.; Mitsugi, C. *J. Heterocycl. Chem.* **1985**, *22*, 1643–1646. (e) Raucher, S.; Jones, D. S. *Synth. Commun.* **1985**, *15*, 1025–1031.
22. (a) Wuest, H. M.; Sakal, E. H. *J. Am. Chem. Soc.* **1951**, *73*, 1210–1216. (b) Weijlard, J.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 1497–1500. (c) Johnson, D. E.; DeLane, J. C.; Wisted, E. E. *J. Org. Chem.* **1987**, *52*, 3688–3690. (d) Marr, F.; Hoppe, D. *Org. Lett.* **2002**, *4*, 4217–4220.
23. (a) Overberger, C. G.; Ringsdorf, H.; Weinshenker, N. *J. Org. Chem.* **1962**, *27*, 4331–4337. (b) Marchand-Brynaert, J.; Laub, R.; De Meester, F.; Frêre, J.-M. *Eur. J. Med. Chem.* **1988**, *23*, 561–571.
24. (a) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980–3984. (b) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 410–413. (c) Nishide, K.; Miyamoto, T.; Kumar, K.; Ohsugi, S.-I.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 8569–8573.
25. For examples of some coupling methods see: (a) Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067–1068. (b) Padwa, A.; Reger, T. S. *Can. J. Chem.* **2000**, *78*, 749–756. (c) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163–1166. (d) Frérot, E.; Coste, J.; Pantaloni, A.; Dufour, M.-N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259–270. (e) Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205–208. (f) Cabré, J.; Palomo, A. L. *Synthesis* **1984**, 413–417. (g) Masaguer, C. F.; Raviña, E.; Fontenla, J. A.; Brea, J.; Tristán, H.; Loza, M. I. *Eur. J. Med. Chem.* **2000**, *35*, 83–95.
26. Blagbrough, I. S.; Mackenzie, N. E.; Ortiz, C.; Scott, A. I. *Tetrahedron Lett.* **1986**, *27*, 1251–1254.
27. (a) Katritzky, A. R.; Cai, X.; Rogovoy, B. V. *J. Comb. Chem.* **2003**, *5*, 392–399. (b) Brewer, M. D.; Dorgan, R. J. J.; Manger, B. R.; Mamalis, P.; Webster, R. A. B. *J. Med. Chem.* **1987**, *30*, 1848–1853. (c) Yoon, J. W.; Choi, H.-Y.; Lee, H. J.; Ryu, C. H.; Park, H.-G.; Suh, Y.-G.; Oh, U.; Jeong, Y. S.; Choi, J. K.; Park, Y.-H.; Kim, H.-D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1549–1552.
28. Goud, P. M.; Venkatachalam, T. K.; Uckun, F. M. *Synth. Commun.* **2003**, *33*, 1185–1193.
29. (a) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438–5443. (b) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056–9062.
30. Takatsu, N.; Ohmiya, S.; Otomasu, H. *Chem. Pharm. Bull.* **1987**, *35*, 891–894.
31. Staab, H. A.; Benz, W. *Angew. Chem., Int. Ed. Engl.* **1961**, *73*, 66.
32. Groutas, W. C.; Abrams, W. R.; Theodorakis, M. C.; Kasper, A. M.; Rude, S. A.; Badger, R. C.; Ocain, T. D.; Miller, K. E.; Moi, M. K.; Brubaker, M. J.; Davis, K. S.; Zandler, M. E. *J. Med. Chem.* **1985**, *28*, 204–209.
33. Iguchi, S.; Iwamura, H.; Nishizaki, M.; Hayashi, A.; Senokuchi, K.; Kobayashi, K.; Sakaki, K.; Hachiya, K.; Ichioka, Y.; Kawamura, M. *Chem. Pharm. Bull.* **1992**, *40*, 1462–1469.
34. Mazza, M.; Montanari, L.; Pavanetto, F. *Farmaco Ed. Sci.* **1977**, *32*, 270–277.

35. Arya, V. P.; David, J.; Grewal, R. S. *Indian J. Chem. Sect. B* **1977**, 635–640.
36. Tokitoh, N.; Okazaki, R. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3291–3297.
37. (a) Löcsei, V.; Facsko, O.; Chirilâ, T. *J. Prakt. Chem.* **1983**, *325*, 49–54. (b) Ben-Ishai, D.; Berger, A. *J. Org. Chem.* **1952**, *17*, 1564–1570.
38. Chen, C.-C.; Chen, S.-T.; Chuang, T.-H.; Fang, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2217–2221.
39. Ito, K.; Iida, T.; Fujita, T.; Tsuji, S. *Synthesis* **1981**, 287.
40. Douat, C.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **2000**, *41*, 37–40.
41. Raghuram, T.; Vijaysaradhi, S.; Singh, I.; Singh, J. *Synth. Commun.* **1999**, *29*, 3215–3219.
42. Brunette, S. R.; Lipton, M. A. *J. Org. Chem.* **2000**, *65*, 5114–5119.
43. Turbanti, L.; Cerbai, G.; Bramanti, G.; Bianchini, P.; Tellini, N. *Chim. Ther.* **1967**, *2*, 354–365.
44. Janecki, T.; Bodalski, R.; Wieczorek, M.; Bujacz, G. *Tetrahedron* **1995**, *51*, 1721–1740.

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The effects of cationic and zwitterionic micelles on the keto–enol interconversion of 2-phenylacetylfuran and 2-phenylacetylthiophene

Paolo De Maria, Antonella Fontana,* Carla Gasbarri and Gabriella Siani

Dipartimento di Scienze del Farmaco, Università 'G. d'Annunzio', Via dei Vestini, 66013 Chieti, Italy

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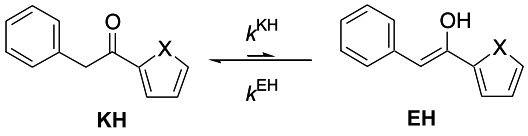
Abstract—The presence of micelles from cationic and zwitterionic surfactants increases the apparent acidity of either the keto and the enol forms of 2-phenylacetylfuran (**2PAF**) and 2-phenylacetylthiophene (**2PAT**). This effect can be attributed to the affinity of the surfactant micelles for the enolate of the two substrates. Although the equilibrium constants for keto–enol tautomerism of **2PAF** and **2PAT**, K_T=[enol]/[ketone]=$pK_a^{KH}-pK_a^{EH}$, do not change much, the presence of micelles provides an efficient method for producing appreciable quantities of the enolates under mild experimental conditions and in aqueous solutions. The obtained rate-profiles for the ketonisation reactions and the consistency of the kinetic rate constants over a wide range of 'pH' in several overlapping buffers indicate that the pH of the aqueous pseudophase (but not that at the micellar surface) can be controlled by buffers. Moreover, the increase of the acidity and the decrease of the 'water' rate of ketonisation of the enols of **2PAF** and **2PAT** upon addition of surfactants allow the uncovery of a metal ion catalysed pathway that cannot be observed in absence of surfactants.

1. Introduction

Enols and enolates play an important role as reactive intermediates in many organic reactions and the study of the kinetics and equilibria of the keto–enol interconversion has been at the center of physical organic chemistry for many years.[1] Rapid advances in the chemistry of enols have been made possible by the development of methods for generating these short-lived substances in solution under conditions where they can be observed directly and their reactions can be monitored accurately.[2] Thus, in the past 20 years, kinetic and equilibrium constants have been obtained[3] for the keto–enol tautomerism of a wide range of carbonyl compounds in water, methods of choice being the quenching of a solution of the corresponding enolate anion[4] or direct enol generation by flash photolysis.[5]

In previous papers the equilibrium constants for the keto–enol tautomerism, K_T=[enol]/[ketone]=k_{KH}/k_{EH}, of 2-phenylacetylfuran,[6] **2PAF**, and 2-phenylacetylthiophene,[7] **2PAT**, (see Scheme 1) were determined in aqueous solutions at 25 °C by combining rate constants for enolisation of the ketone (k^{KH}) and ketonisation of the enol, k^{EH} (or the enolate, k^{E}). The pK_a^{KH} values for ionisation of the keto forms were directly measured spectrophotometrically under the same conditions and pK_a^{EH} values of the enol forms were obtained from $pK_a^{KH}-pK_T$.



Scheme 1.

The previous measurements also shows[7] that the rate of ketonisation of the enolate of **2PAT** in NaOH solution is strongly depressed and that the pK_a^{KH} of the keto tautomer decreases by about 2.2 pK_a units on passing from water to an aqueous micellar solution of cetyltrimethylammonium bromide (CTAB). This effect on pK_a^{KH} and the stabilisation of the enolates of other hydrophobic ketones (structurally related to **2PAT**) by cationic and zwitterionic micelles has been recently exploited[8] for synthetic purposes in C–C and C–O bond formation reactions in aqueous solution.

In this paper we have extended kinetic determinations[7] in order to obtain the complete rate-profiles of the ketonisation reaction of the enol of **2PAT** in micellar solutions of CTAB

Keywords: Keto–enol tautomerism; Rate-profile; Micellar catalysis; 2-Phenylacetylfuran; 2-Phenylacetylthiophene.
* Corresponding author. Tel.: +39 0871 3555263; fax: +39 0871 3555204; e-mail: fontana@unich.it

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as well as of the zwitterionic surfactant 3-(*N*,*N*-dimethyl-*N*-myristylammonium)propanesulfonate, SB3-14. Similar measurements have also been performed on **2PAF** in aqueous micellar solutions of CTAB.

Catalysis by metal ions could not be previously observed for the keto–enol interconversion of **2PAF** in aqueous solution for reasons discussed elsewhere.[6] Yet in this paper we show that the presence of micelles allows the uncovery of significant contributions from metal ion catalysis (by Cu^{2+} and Ni^{2+}) in the ketonisation reaction of the enol of **2PAT**.

2. Results

2.1. Ketonisation reaction in dilute hydrochloric acid

Rate constants for H_3O^+ catalysis in aqueous solutions are available for both **2PAF**[6] and **2PAT**.[7] Rate constants for **2PAF** in the presence of 3×10^{-3} mol dm^{-3} CTAB were measured with HCl concentrations in the range 0.1–0.5 mol dm^{-3}. Rate constants for **2PAT** in the presence of 1×10^{-2} mol dm^{-3} CTAB or SB3-14 were similarly measured with HCl concentrations in the range 0.1–1.2 mol dm^{-3} and 0.3×10^{-1}–1.0 mol dm^{-3} with CTAB and SB3-14, respectively.

For both substrates the observed rate law was given by Eq. 1 with k_e being the experimental pseudo-first order rate constant and k_H being the second-order rate constant for hydronium ion catalysis.

$$k_e = k_0 + k_H[H_3O^+] \quad (1)$$

Hydronium ion catalysis for **2PAT** could be detected only at HCl concentrations >0.6 mol dm^{-3} and >0.1 mol dm^{-3} in micellar solutions of CTAB and SB3-14, respectively. The results obtained are collected in Tables 1–3.

2.2. Ketonisation reactions in buffer solutions

Rate constants for **2PAF** were measured in cyanoacetate, chloroacetate, glycolate, acetate, propionate and borate buffers in the presence of [CTAB]$=0.003$ mol dm^{-3}. Rate constants for **2PAT** were similarly measured in cyanoacetate, acetate, citrate, butyrate, cacodylate and phosphate buffers in the presence of [CTAB]$=0.01$ mol dm^{-3} and in cyanoacetate, glycolate, cacodylate, phosphate and borate buffers in the presence of [SB3-14]$=0.01$ mol dm^{-3}. The measurements in buffers were made for different sets of solutions, each set at constant buffer ratio, $r=$[B]/[BH], and constant ionic strength (1.0 mol dm^{-3}), changing the buffer concentrations. In buffer solutions, with pH equal or lower than the pK_a^{EH} of the substrates, the observed pseudo-first order rate constant, k_e, increased linearly with increasing buffer concentrations according to Eq. 2.

$$k_e = k_0 + k_{cat}[\text{buffer}] \quad (2)$$

However, k_e was independent of buffer concentration at higher pH values, due to the fact that the reactant is the enolate, whose ketonisation reaction is not catalysed by anionic bases. Rate constant values are reported in Tables 4 and 5. Separation of k_{cat}[1,9,10] into its possible general acid and general base components was not attempted.

With relatively strong bases such as phosphate and borate k_{cat} values are much lower than those expected from a

Table 1. Experimental pseudo-first order rate constants (k_e/s^{-1}) for the H_3O^+-catalysed ketonisation reaction of **2PAF** in the presence of 3×10^{-3} mol dm^{-3} CTAB at 25 °C and ionic strength 1.0 mol dm^{-3} (NaCl)

[HCl]/mol dm^{-3}	k_e/s^{-1}
0.1	0.0156
0.2	0.0278
0.3	0.0496
0.5	0.0811

Table 2. Experimental pseudo-first order rate constants (k_e/s^{-1}) for the H_3O^+-catalysed ketonisation reaction of **2PAT** in the presence of 1×10^{-2} mol dm^{-3} CTAB and SB3-14 at 25 °C and ionic strength 1.0 mol dm^{-3} (NaCl)

CTAB		SB3-14	
[HCl]/mol dm^{-3}	k_e/s^{-1}	[HCl]/mol dm^{-3}	k_e/s^{-1}
0.1	0.113[a]	0.03	0.0707
0.3	0.115	0.06	0.0743
0.5	0.116	0.1	0.0761
0.6	0.116	0.2	0.0828
0.8	0.136	0.3	0.103
0.9	0.148	0.5	0.124
1.0	0.159	0.6	0.135
1.1	0.176	0.8	0.147
1.2	0.199	0.9	0.178
		1.0	0.193

[a] Value excluded from the rate-profile of Figure 2.

Table 3. Hydronium ion-catalysed rate constants (k_H/dm^3 mol^{-1} s^{-1}) for **2PAF** and **2PAT** in aqueous solution in the absence and in the presence of surfactants

	2PAF	**2PAT**
H_2O	4.1[a]	8.69[b]
CTAB	0.168±0.013	0.155±0.014
SB3-14		0.121±0.006

[a] Value reported in Ref. 6.
[b] Value reported in Ref. 7.

Table 4. Buffer ratios r, calculated pH, k_0 and k_{cat} (Eq. 2) for the ketonisation of the enol of **2PAF** in the presence of 3×10^{-3} mol dm^{-3} CTAB at 25 °C and ionic strength 1.0 mol dm^{-3} (NaCl)

Base	r	pH	k_0[a]/s^{-1}	k_{cat}/dm^{3}mol^{-1}s^{-1}
$CNCH_2COO^-$	0.5	1.96	0.007	0.931
	1	2.27	0.006	0.906
$ClCH_2COO^-$	1	2.67	0.010	3.03
$HOCH_2COO^-$	1	3.63	0.037	1.11
	3	4.10	0.078	0.996
	5	4.32	0.084	0.891
CH_3COO^-	1	4.56	0.128	8.66
	5	5.25	0.440	12.7
CH_3CH_2-COO^-	5	5.37	0.471	22.0
	8	5.57	0.753	19.6
$B(OH)_4^-$	5	9.73	1.28	40.8

[a] Values used to draw the rate-profile of Figure 1.

Table 5. Buffer ratios r, calculated pH, k_0/s^{-1} and $k_{cat}/dm^3mol^{-1}s^{-1}$ (Eq. 2) for the ketonisation of the enol of **2PAT**, at 25 °C and ionic strength 1.0 mol dm^{-3} (NaCl) in the presence of 1×10^{-2} mol dm^{-3} CTAB and SB3-14

Base	r	pH	CTAB		SB3-14		Base	r	pH	CTAB		SB3-14	
			k_0[a]	k_{cat}	k_0[a]	k_{cat}				k_0[a]	k_{cat}	k_0[a]	k_{cat}
$CNCH_2COO^-$	0.5	1.96	0.075	1.75	0.053	0.774	$CH_3(CH_2)_2COO^-$	2	4.89	1.11	17.9		
	1	2.27	0.064	1.68	0.052	0.758		5	5.28	1.28			
	5	2.97	0.064	1.83	0.074	0.560	$(CH_3)_2AsO^{2-}$	0.5	5.76			2.66	8.06
$HOCH_2COO^-$	0.3	3.10			0.067	1.25		1	6.07	2.08		2.83	
	1	3.63			0.075	1.20		5	6.76	2.35			
	5	4.32			0.282	1.83	HPO_4^{2-}	0.5	6.69			2.26	58.8
CH_3COO^-	0.5	4.25	0.977	40.9				1	6.99	1.61	13.4		
	1	4.56	0.782	56.6				3	7.47			2.92	
	8	5.46	1.82					5	7.69			2.71	
	10	5.56	1.91					8	7.90			2.48	
Citrate	0.1	3.56	0.126	1.83			$B(OH)_4^-$	0.5	8.73			2.56	
	0.5	4.26	0.458	3.89				5	9.73			2.38	
	1	4.56	0.381	7.65									

[a] Values used to draw the rate-profile of Figure 2.

Brönsted relation established with the above mentioned buffer bases of lower pK_a. The apparent k_{cat} observed for phosphate and borate could be due to either an effective general base catalysis on the ketonisation of a small quantity of undissociate enol present in the solutions or, less likely, to general acid catalysis on the ketonisation of the enolate.

The zero buffer concentration intercepts, k_0, were then used together with the rate constants, k_e, measured in HCl and NaOH solutions (see Section 2.3 below) to construct the rate-profiles shown in Figures 1 and 2. For sake of comparison the known profiles of **2PAF**[6] and **2PAT**[7] in the absence of surfactant have also been reported in Figures 1 and 2, respectively.

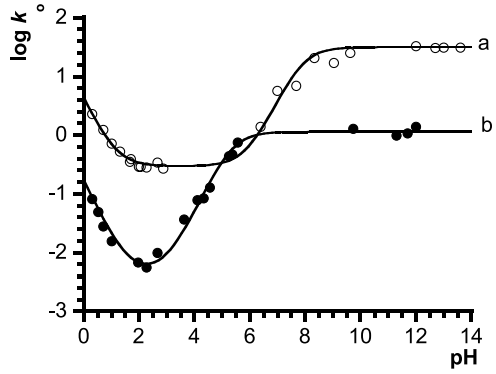


Figure 1. Rate-profiles for the ketonisation reaction of the enol of **2PAF** in aqueous solution[6] (open circles, ○: curve a) and in the presence of 3×10^{-3} mol dm^{-3} CTAB (full circles, ●: curve b). For the significance of log k_0 see Section 2.5 below. pH Values have been calculated by correcting pH-meter readings for the ionic strength of 1.0 mol dm^{-3}.

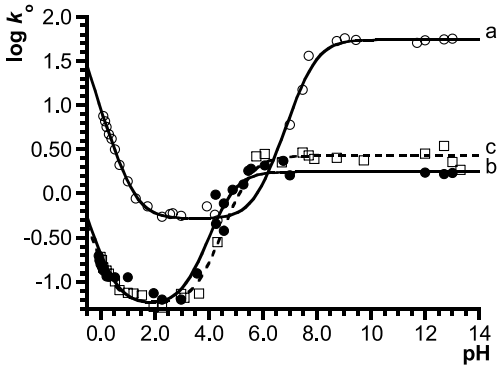


Figure 2. Rate-profiles for the ketonisation reaction of the enol of **2PAT** in aqueous solution[7] (open circles, ○: curve a), in the presence of 1×10^{-2} mol dm^{-3} CTAB (full circles, ●: curve b) and of 1×10^{-2} mol dm^{-3} SB3-14 (open squares, □: curve c). For the significance of log k_0 see Section 2.5 below. pH Values have been calculated by correcting pH-meter readings for the ionic strength of 1.0 mol dm^{-3}.

2.3. Ketonisation reaction in dilute sodium hydroxide

The following rate constants were measured with **2PAF** concentration ca. 2.5×10^{-4} mol dm^{-3} and different [NaOH] (reported in brackets) in the presence of 3×10^{-3} mol dm^{-3} surfactant:

CTAB : $k_e/s^{-1} = 0.99\ (0.002);\ 1.08\ (0.005);\ 1.38\ (0.01)$

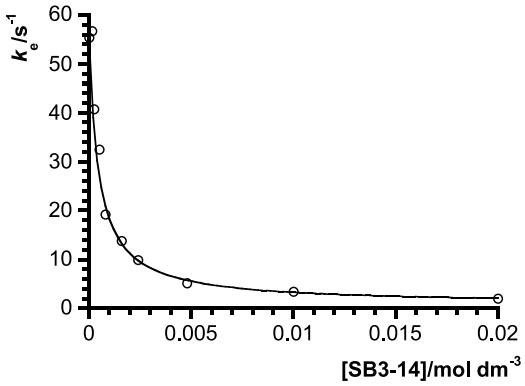


Figure 3. Effect of the addition of SB3-14 on the rate of ketonisation of the enolate of **2PAT** (2.5×10^{-4} mol dm^{-3}) in aqueous 0.05 mol dm^{-3} NaOH, ionic strength 1.0 mol dm^{-3} (NaCl) at 25.0±0.1 °C. The curve is the best fit of the non-linear regression of Eq. 9. The reported cmc value for SB3-14[11] in water is 2.8×10^{-4} mol dm^{-3}.

The corresponding results with **2PAT** concentration ca. 2.5×10^{-4} mol dm^{-3} in the presence of 1×10^{-2} mol dm^{-3} surfactant were:

CTAB : $k_e/s^{-1} = 1.73\ (0.01);\ 1.67\ (0.05);\ 1.72\ (0.1)$

SB3 − 14 :

$k_e/s^{-1} = 2.85\ (0.01);\ 3.46\ (0.05);\ 2.29\ (0.1);\ 1.86\ (0.2).$

The ketonisation rate appears to be independent of hydroxide concentration. This is because the enol–enolate ion equilibrium is shifted by the surfactant over to the side of enolate, giving rise to the final 'uncatalysed' portion of the rate-profiles[6,7] (see also the Section 3).

The above rate constants, k_e, for both enolates are strongly depressed by increasing amounts of surfactant, until a constant value is reached above the cmc of the surfactant, as can be seen for **2PAT** in Figure 3 (for a detailed discussion of this point with reference to CTAB as the surfactant see Ref. 7).

2.4. Ketonisation reaction of the enol of 2PAT in the presence of metal ions

The effect of Cu^{2+} and Ni^{2+} on the rates of ketonisation of the enol of **2PAT** was studied in unbuffered solutions in the presence of 0.01 mol dm^{-3} surfactant. Substrate concentration was ca. 2.5×10^{-4} mol dm^{-3} and ionic strength was kept constant at 1.0 mol dm^{-3} (NaCl). With CTAB, rates were measured at a number of metal ion concentrations in the range $5.0\times10^{-4}\leq Cu^{2+}\leq3.0\times10^{-3}$ mol dm^{-3} and $2.5\times10^{-3}\leq Ni^{2+}\leq1.5\times10^{-2}$ mol dm^{-3}. With SB3-14, rates were measured in the concentration range $7.5\times10^{-5}\leq Cu^{2+}\leq7.5\times10^{-4}$ mol dm^{-3} and $2.5\times10^{-5}\leq Ni^{2+}\leq5.0\times10^{-4}$ mol dm^{-3}. The measured pH of the solutions was ~5 in all cases and no dependence of the rate constants on the pH was observed. Rate constants, k_e, showed a linear increase with increasing metal ion concentration according to the rate law given by Eq. 3:

$$k_e = k_0 + k_M[M^{2+}] \quad (3)$$

where $[M^{2+}]$ represents the molar concentration of either Cu^{2+} or Ni^{2+}. There is no evidence of 'levelling off' at higher concentrations of the metal ions. The results obtained are reported in Table 6.

2.5. Rate-profiles in micellar solutions

The profiles for the ketonisation reactions of the enols of **2PAF** and **2PAT** in aqueous solutions[12] (curves a) are shown in Figures 1 and 2, respectively as plots of reported[6,7] values of log k_0 and of log k_e (in aqueous HCl and NaOH solutions) against pH. Analogous profiles are shown for **2PAF** in Figure 1 in the presence of 3×10^{-3} mol dm^{-3} CTAB (curve b) and **2PAT** in Figure 2 in the presence of 1×10^{-2} mol dm^{-3} CTAB (curve b) and SB3-14 (curve c). Log k_0 values are from Tables 4 and 5 and log k_e values are from Tables 1 and 2. The rate-profiles for **2PAF**[6] and **2PAT**[7] in water have been discussed in detail previously. Each of the present profiles in micellar solutions analogously shows a minimum and a plateau at high pH where the reaction is pH-independent, as well as two regions for H^+ and OH^- catalyses. The minimum can be attributed to the uncatalysed reaction, where the enol initially ionises to the enolate anion and H_3O^+ which then recombine to form the ketone and H_2O.[13] On the other hand, in the plateau at higher pH, the reactant is the enolate anion which is protonated by H_2O to form the ketone. The region for OH^- catalysis represents the change in reactant from the enol at lower pH to the enolate anion at high pH. The points of inflections at higher pHs of the curves b and c of Figures 1 and 2 correspond to the pK_a^{EH} values of the enols of **2PAF** and **2PAT** in the presence of CTAB (curves b) and of SB3-14 (curve c). The accurate pK_a^{EH} values and rate constants for the uncatalysed ketonisation of the enol, k_{un}^{EH}, in the presence of surfactant may be obtained from a best fit of experimental rate constants to Eq. 4

$$k_e = k_{un}^{EH} + k_H[H^+] + \{(k_{un}^{E}K_a^{EH}/K_W)\ [OH^-]\}/\{1 + (K_a^{EH}/[H^+])\} \quad (4)$$

in which $k_H = 0.168$ dm^3 mol^{-1}s^{-1} and the rate constant for the uncatalysed ketonisation of the enolate, k_{un}^{E}, is 1.15 s^{-1}

Table 6. Metal ion catalysed ketonisation reaction of the enol of **2PAT** in the presence of surfactants at 25 °C and ionic strength 1.0 mol dm^{-3} (NaCl)

	CTAB		SB3-14	
	k_0/s^{-1}	k_M/dm^{3}mol^{-1}s^{-1}	k_0/s^{-1}	k_M/dm^{3}mol^{-1}s^{-1}
Cu^{2+}	2.2(±0.4)	1320(±220)	7.0(±0.2)	3440(±380)
Ni^{2+}	1.5(±0.1)	142(±9)	2.8(±0.1)	2500(±290)

Table 7. Tautomeric and acidity constants of **2PAF** and **2PAT** in aqueous solution in the presence and in absence of surfactants

	CTAB		SB3-14		H_2O	
	2PAF	**2PAT**	**2PAF**	**2PAT**	**2PAF**[6]	**2PAT**[7]
pK_T	6.60	7.38		7.82	5.88	6.45
pK_a^{KH}	12.0	12.4[7]	13.0	13.4	14.4	14.6
pK_a^{EH}	5.36	4.97		5.61	8.50	8.15
ΔpK_a^{KH}	2.4	2.2	1.4	1.2	—	—
ΔpK_a^{EH}	3.1	3.2		2.5	—	—

Reductions of pK_a^{KH} and pK_a^{EH} values (ΔpK_a^{KH} and ΔpK_a^{EH}) of **2PAF** and **2PAT** upon passing from water to surfactant solutions.

in the presence of CTAB for **2PAF**; and $k_H = 0.155\ dm^3\ mol^{-1}s^{-1}$ and $k_{un}^E = 1.71\ s^{-1}$ in the presence of CTAB and $k_H = 0.121\ dm^3\ mol^{-1}s^{-1}$ and $k_{un}^E = 2.62\ s^{-1}$ in the presence of SB3-14 for **2PAT**, respectively. The values of k_{un}^E for the enolate ions are the average of the experimental rate constants at pH values of the plateau. The following pK_a^{EH} and k_{un}^{EH} values can be obtained from Eq. 4 in the presence of the specified surfactant:

$$\mathbf{2PAF}(\mathrm{CTAB}):\ pK_a^{EH} = 5.36(\pm 0.05),$$

$$k_{un}^{EH} = 0.005(\pm 0.001)\ s^{-1}\ (r = 0.994);$$

$$\mathbf{2PAT}(\mathrm{CTAB}):\ pK_a^{EH} = 4.97(\pm 0.08),$$

$$k_{un}^{EH} = 0.062(\pm 0.004)\ s^{-1}\ (r = 0.982);$$

$$\mathbf{2PAT}(\mathrm{SB3-14}):\ pK_a^{EH} = 5.61(\pm 0.10),$$

$$k_{un}^{EH} = 0.065(\pm 0.005)\ s^{-1}\ (r = 0.993).$$

2.6. Calculation of the tautomeric constant, K_T, in the presence of surfactants

The equilibrium constant for keto–enol tautomerism, $K_T = [\mathrm{enol}]/[\mathrm{ketone}]$ can be calculated[6] by combining ionisation constants for the enol and the keto forms: $pK_T = pK_a^{KH} - pK_a^{EH}$. The obtained values and the corresponding values in the absence of surfactant are reported in Table 7.

3. Discussion

From the practical point of view the most important effect brought about by surfactant micelles is the increase in the acidity of the keto forms (about 2 pK_a units), particularly in the case of the cationic (CTAB) surfactant (Table 7). The origin of this increased acidity is partly electrostatic and (particularly for zwitterionic micelles) partly due to hydrophobic bonding between the enolate and the micellar aggregate, as discussed elsewhere.[14]

Before attempting a comparison of the rate profiles in water and in micellar solutions (Figs. 1 and 2), it should be considered that the pH of the aqueous pseudophase, but not that at the micellar surface, can be controlled by buffers, although it may be necessary to allow for exchange of buffer anions between water and micelles. Since the rate-profiles refer to reactions through solvent-related species, the acid will be the hydronium ion and the base will be the hydroxide ion. Catalysis of the ketonisation reaction may thus involve H_3O^+, water molecules and OH^- which are adjacent to the substrate at the micellar surface but in the diffuse layer.[15] As a matter of fact the positively charged hydronium ion does not interact with cationic surfactants for electrostatic reasons and the hydroxide ion, that does not bind strongly to cationic micelles[16] and competes ineffectively with other anions for the Stern layer, will preferentially populate the diffuse Gouy–Chapman layer. If this is the case, buffers can be an effective tool to control the concentration of the catalytic species. Moreover, the success in constructing rate-profiles for both substrates in the presence of micelles (Figs. 1 and 2) can be taken as an indication of the fact that the pH of the aqueous pseudophase can be controlled independently of the particular type of buffer base and its possible exchange with the micellar surface. This is in agreement with the evidence[15] that cationic micellar head groups interact best with soft hydrophobic bases, relatively large bromide or arenesulfonate anions, or anionic transition states such as those for nucleophilic aromatic substitution reactions. On the other hand they interact less readily with hard bases of high charge density such as OH^-, or the anionic transition states for deacylation reactions.

The rate-profiles for the ketonisation of the enol of **2PAF** (Fig. 1) in water (curve a) and in CTAB solution (curve b) show limbs of slope -1 for hydronium-ion catalysis and limbs of slope $+1$ for hydroxide-ion catalysis (or the kinetically equivalent uncatalysed process of increasing amounts of the more reactive enolate). The V-shaped profile of curve b with no discernible horizontal portion for the 'uncatalyzed' reaction is understandable in terms of an overwhelming 'basic' limb probably due to the higher acidity of the enol of **2PAF** in the presence of micelles. Consequently, in the presence of CTAB, there is a higher concentration of enolate at lower pHs.

The lower ketonisation rate constants of the enol and the enolate of **2PAF** and **2PAT** (Figs. 1 and 2) in the presence of surfactant is generally ascribable to the reduction of water availability in the proximity of the micellar surface where the substrate resides. The rate-profile of **2PAT** (Fig. 2) in aqueous SB3-14 is very similar to that in the presence of CTAB suggesting the preeminent role of the hydrophobic interactions over the electrostatic interactions of the reacting substrates with the studied surfactants. Strong hydrophobic

Table 8. Binding constants (K_S/mol^{-1}dm^3) of the enolate and the keto forms of **2PAF** and **2PAT** with the surfactants

	2PAF		**2PAT**	
	Enolate	Ketone	Enolate	Ketone
K_{CTAB}	5040(±1040)	145(±42)	13000[a]	173[a]
K_{SB3-14}	724(±94)	80(±11)	1460(±190)	269(±123)

[a] Values reported in Ref. 7.

interactions have also been evidenced by Iglesias in a study of the keto–enol equilibrium of β-dicarbonyl compounds in the presence of surfactants.[17] Zwitterionic surfactants are known[8,18,19] to strongly interact with polarisable hydrophobic substrates and/or hydrophobic anions. A direct comparison of the binding constants of the enolate and the enol with the surfactants would be very informative but the low extinction coefficients in the UV–vis spectrum of the enol did not allow the measurement of the binding constant for the enol of **2PAT**. The major differences in the results obtained in surfactant solutions for **2PAF** (Fig. 1) and **2PAT** (Fig. 2) are the V-shaped profile and the appearance of acid-catalysis at higher pH for the former and the plateaux at pHs 1–4 for the latter substrate. These facts are understandable in view of the higher acidity of **2PAT** than that of **2PAF** (in CTAB solutions the pK_a^{EH} values are 4.97 and 5.36, respectively).

Several conclusions may be drawn looking at the pK values reported in Table 7. The increase in the apparent acidity of the enol and the ketone of **2PAF** and **2PAT** on passing from water to surfactant solutions is a major effect produced by the addition of surfactants (see Table 7). The increase in acidity is probably due to a strong stabilization by both non-specific electrostatic and specific hydrophobic interactions of the enolates by the surfactant micelles. This stabilisation is also apparent from: (a) the large difference in the binding constants of the enolate and the ketone with the surfactants (see Table 8) and (b) the bathochromic shift in the UV–vis spectrum of the enolates of **2PAF** and **2PAT** upon transfer from water to CTAB ($\Delta\lambda_{max}=11$ and 36 nm for **2PAF** and **2PAT**, respectively) or to SB3-14 micelles ($\Delta\lambda_{max}=13$ and 28 nm for **2PAF** and **2PAT**, respectively).

On the other hand, a smaller effect than that on pK_a is observed on pK_T for both **2PAF** and **2PAT** on passing from the aqueous to the surfactant solution. This is expected as 'the presence of micelles shifts the keto–enol equilibrium toward the enol form, which is trapped by the micelles, but the presence of micelles does not alter the equilibrium in the bulk water phase'.[20] The increase of pK_T (about 1 pK units) for both surfactants can probably be accounted for by the somewhat higher affinity of the micelles for the less polar enol tautomer with respect to the more polar keto tautomer.

Finally, the addition of surfactants allowed the detection of a metal ion catalysis for **2PAT** which for **2PAF** was offset by 'water catalysis' in aqueous solution.[6] Actually metal ion catalysis could be due to the fact that the substrate, at experimental pHs, around 5 in the presence of micelles, becomes the more reactive enolate; alternatively metal ion catalysis could be caused by a proximity effect,[21] that is the bringing together of the substrate and the metal ion by the micelle.

4. Conclusions

The presence of cationic and zwitterionic micelles decreases the pK_as of **2PAF** and **2PAT** by about 2–3 pK units and this decrease can be exploited for synthetic purposes in C–C and C–O bond formation reactions.[8] On the contrary a smaller variation of pK_Ts was observed for both substrates.

It has been shown that the pHs of the investigated aqueous pseudophases can be controlled by the use of conventional aqueous buffers. Metal ion catalysis that cannot be observed in aqueous solution becomes detectable in the presence of micelles.

5. Experimental

5.1. Instruments

The kinetic experiments were carried out with a model VI Tri-Tech Dynamic Instruments stopped-flow spectrophotometer. Absorption measurements were obtained using a Jasco V-550 UV–vis spectrophotometer or a Varian Cary 1E spectrophotometer.

5.2. Materials

All inorganic salts [NaCl, KH_2PO_4, Na_2HPO_4], cetyltrimethylammonium bromide (CTAB), 3-(*N*,*N*-dimethyl-*N*-myristylammonium)propanesulfonate (SB3-14) and buffer acids [$ClCH_2COOH$, $CNCH_2COOH$, $HOCH_2COOH$, CH_3COOH, citric acid, CH_3CH_2COOH, $CH_3CH_2CH_2$-$COOH$, $(CH_3)_2AsO_2H$, H_3BO_3] were commercial samples of Analar grade (Aldrich, Merck or Carlo Erba) and were used without further purification except CTAB which was recrystallized from acetone.

2-Phenylacetylfuran (**2PAF**) and 2-phenylacetylthiophene (**2PAT**) were prepared following previously described procedures.[6,7]

5.3. Kinetic measurements

Rates of ketonisation of the enols of **2PAF** and **2PAT** (concentration ca. 2.5×10^{-4} mol dm^{-3}) in the presence of surfactant, were measured by stopped-flow spectrophotometry upon quenching a freshly prepared solution of the enolate anion in 0.5 mol dm^{-3} aqueous NaOH with 0.5 mol dm^{-3} HCl plus the desired concentration of the buffer. The surfactant was dissolved at the desired concentration in both the acidic and the basic solutions. The initial reaction that will occur on neutralisation is the protonation of the enolate, resulting in a solution containing enol far in excess of its equilibrium concentration. In the case of the OH^- catalysed reaction, NaOH was only

partially neutralized. The kinetics associated with the return to the equilibrium position was monitored at $\lambda_{max}=351$ nm in aqueous CTAB solutions for **2PAF** and at $\lambda_{max}=383$ nm in aqueous CTAB solutions and at $\lambda_{max}=375$ nm in aqueous SB3-14 for **2PAT**.

All kinetic measurements were made at 25.0 ± 0.1 °C and at an ionic strength (I) of 1.0 mol dm^{-3} by addition of NaCl.

pH Values in buffer solution were calculated at 1.0 mol dm^{-3} ionic strength using Eq. 5[22] in which I is the ionic strength, K_a is the ionisation constant and r is the ratio of base to acid concentrations of the buffer.

$$pH = pK_a + \log r + (0.512\sqrt{I})/(1+1.5\sqrt{I}) \quad (5)$$

5.4. Acid ionisation constants

The pK_a^{KH} values of **2PAF** and **2PAT** were determined spectrophotometrically in solutions of increasing concentration of sodium hydroxide at constant concentration of surfactant.

5.4.1. pK_a^{KH} in CTAB. The $pK_a^{KH}=12.35(\pm0.01)$[7] of **2PAT** in CTAB is already known. The corresponding value for **2PAF** was determined with NaOH varying in the range 0.007–0.5 mol dm^{-3} while the concentration of the substrate was kept constant at 5×10^{-5} mol dm^{-3}. The absorbance measurements were treated with Eq. 6

$$K_a^{KH} = K_W/K_b^{KH} = K_W/\{(A_{max}-A)\,[OH^-]\}/(A-A_0) \quad (6)$$

where A, A_0 (0.008) and A_{max} (1.102) are absorbances at $\lambda=352$ nm at the specified [OH$^-$], in water and at 1.5 mol dm^{-3} NaOH, respectively. A thermodynamic pK_a^{KH} value of $11.96(\pm0.02)$ was obtained by extrapolation to zero [OH$^-$] of a linear plot of pK_a^{KH} versus [OH$^-$] assuming that this dependence becomes linear[23] below ca. 2 mol dm^{-3}.

5.4.2. pK_a^{KH} in SB3-14. The concentrations of the substrate and SB3-14 were kept constant (5×10^{-5} mol dm^{-3} and 0.01 mol dm^{-3}, respectively) while the concentration of NaOH was varied in the range 0.02–0.25 mol dm^{-3} for **2PAF** and 0.01–1.00 mol dm^{-3} for **2PAT**, respectively. The absorbance measurements were treated with Eq. 6 using A_0 and A_{max} at λ_{max} 353 and 375 nm, respectively {for **2PAF**: $A_0=0.000$ and $A_{max}=0.904$ (average between values collected in 0.75 and 1.0 mol dm^{-3} NaOH solutions); for **2PAT**: $A_0=0.000$ and $A_{max}=0.739$ (average among values collected in 1.5, 2.0 and 2.2 mol dm^{-3} NaOH solutions)}. The thermodynamic acid dissociation constants—pK_a^{KH} (**2PAF**)$=13.00(\pm0.02)$ and pK_a^{KH} (**2PAT**)$=13.43(\pm0.02)$—were obtained by extrapolation to zero [OH$^-$] of the linear plots of pK_a^{KH} versus [OH$^-$].

5.5. Binding constants

Thanks to the bathocromic shift of λ_{max} of the enolate due to the association of the substrates with the surfactants (S), it was possible to measure directly the binding constants (K_S^E) of the enolate forms of **2PAF** and **2PAT** by UV–vis spectroscopy. The binding constants (K_S^{KH}) of the keto forms of **2PAF** and **2PAT** with the surfactants were similarly determined although the spectral differences between the associated and the free ketones were considerably smaller.

5.5.1. Binding constant of 2PAF with the surfactants. In the presence of surfactant, the change in absorbance of the enolate of **2PAF** at $\lambda_{max}=351$ nm was measured as a function of the concentration of the surfactant [in the range 5×10^{-5}–0.02 mol dm^{-3}] in 0.5 mol dm^{-3} NaOH assuming that both the free and the associated enolate contribute to the observed absorbance, A. Eq. 7 was derived accordingly, where [**2PAF**]$_i$ is the initial concentration of the substrate and $\varepsilon_{E\text{-}S}$ and ε_E are the molar absorptivities of the associated and free enolate, respectively.

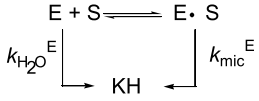
$$A = \{[\mathbf{2PAF}]_i K_S^E[S]/(1+K_S^E[S])\}\varepsilon_{E-S} + \{[\mathbf{2PAF}]_i/(1+K_S^E[S])\}\varepsilon_E \quad (7)$$

From a best fit of experimental A values to Eq. 7 K_{CTAB}^E and $K_{SB3\text{-}14}^E$ were obtained (see Table 8).

Analogously the binding constants, K_{CTAB}^{KH} and $K_{SB3\text{-}14}^{KH}$ (see Table 8) of the keto form with the surfactants were determined in aqueous solution of CTAB [in the range 1×10^{-5}–0.05 mol dm^{-3}] and of SB3-14 [in the range 1×10^{-5}–0.025 mol dm^{-3}] at $\lambda_{max}=279$ and 278 nm, respectively.

5.5.2. Binding constant of 2PAT with SB3-14. Similarly the binding constants for the enol and the keto form of **2PAT** with SB3-14 were determined. The changes in absorbance of the enol (in 0.5 mol dm^{-3} NaOH) at $\lambda_{max}=373$ nm and of the ketone at $\lambda_{max}=300$ nm were measured as a function of the concentration of the surfactant [in the range 1×10^{-4}–0.01 mol dm^{-3} and 1×10^{-4}–0.04 mol dm^{-3}, respectively]. Data are reported in Table 8.

The $K_{SB3\text{-}14}^E$ value can also be measured taking advantage of the micellar effects upon ketonisation reactions. Rates constants at different surfactant concentrations can be treated[7,15,16,24] quantitatively in terms of an equilibrium distribution of the enolate, E, between water and micelles as distinct reaction regions (Scheme 2) using Eq. 8, derived from Eq. 9, were the subscript H_2O and mic refer to aqueous and micellar pseudophases, respectively.



Scheme 2.

$$1/k_e = \{(1/k_{H_2O}^E) + (K_S^E\,[S]/k_{H_2O}^E)\}/\{1+(k_{mic}^E K_S^E[S]/k_{H_2O}^E)\} \quad (8)$$

$$k_e = \{k_{H_2O}^E + (k_{mic}^E\,K_S^E[S])\}/\{1+(K_S^E[S])\} \quad (9)$$

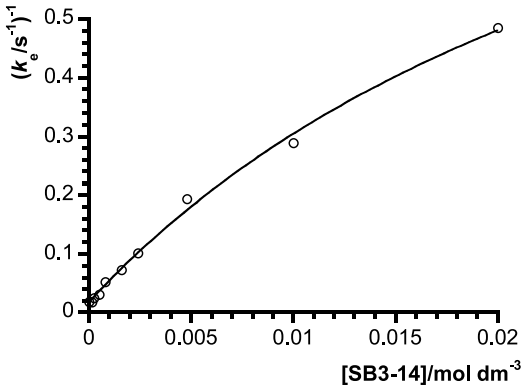


Figure 4. Plot of the experimental first order rate constants for the ketonisation of the enolate of **2PAT** in NaOH 0.05 mol dm^{-3} against the stoichiometric concentration of SB3-14, fitted to Eq. 8 (solid line).

A multiple regression analysis of Eq. 8 by using experimental k_e, $k^E_{H_2O}$ and [CTAB] values (Fig. 4) at NaOH 0.05 mol dm^{-3} affords the following results: $k^E_{mic}=0.82(\pm0.09)\ s^{-1}$, $K^E_{SB3\text{-}14}=2109(\pm120)\ mol^{-1}dm^3$, in quite good agreement with the value obtained from Eq. 7, considering that for kinetic measurements salt was added in order to keep a constant ionic strength of 1.0 mol dm^{-3} and the presence of salt can modify the micellar environment.

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References and notes

1. Bell, P. *The Proton in Chemistry*, 2nd ed.; Chapman and Hall: London, 1973.
2. Chiang, Y.; Kresge, A. J. *Science* **1991**, *253*, 395–400.
3. Toullec, J. Keto–enol equilibrium constants. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990; p 323.
4. Carey, A. R. E.; Eustace, S.; More O'Ferrall, R. A.; Murray, B. A. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2285–2296.
5. Keefe, J. R.; Kresge, A. J. Kinetics and mechanism of enolization and ketonization. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990; p 399.
6. Fontana, A.; More O'Ferrall, R. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2453–2459.
7. De Maria, P.; Fontana, A.; Cerichelli, G. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2329–2334.
8. Cerichelli, G.; Cerritelli, S.; Chiarini, M.; De Maria, P.; Fontana, A. *Chem. Eur. J.* **2002**, *8*, 5204–5210.
9. De Maria, P.; Fontana, A.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1067–1070.
10. Chiang, Y.; Kresge, A. J.; Meng, Q.; More O'Ferrall, R. A.; Zhu, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11562–11569.
11. McPherson, A. *Crystallization for Biological Macromolecules*; Cold Spring Harbor: New York, 1999.
12. For a detailed discussion of the processes occurring at the various pH regions in aqueous solutions see previous publications on **2PAF**[6], **2PAT**[7] and similar systems Chiang, Y.; Kresge, A. J.; Meng, Q.; More O'Ferrall, R. A.; Zhu, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11562–11569 and Bakulev, V. A.; Chiang, Y.; Kresge, A. J.; Meng, Q.; Morzherin, Y. Y.; Popik, V. V. *J. Am. Chem. Soc.* **2001**, *123*, 2681–2682.
13. Chiang, Y.; Kresge, A. J.; Santaballa, J. A.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 5506–5510.
14. De Maria, P.; Fontana, A.; Siani, G.; Arcadi, A.; Chiarini, M. Arkivoc. *xi* **2002**, 17–31.
15. Bunton, C. A.; Savelli, G. *Advances in Physical Organic Chemistry*; Organic reactivity in aqueous micelles and similar assemblies; 1986, 213–309.
16. Romsted, L. S. In *Surfactants in Solution*; Mittal, K. L., Lindman, B., Eds.; Micellar effects on reaction rates and equilibria; Plenum: New York, 1984; Vol. 2, pp 1015–1068.
17. Iglesias, E. *J. Chem. Soc., Perkin Trans. 2* **1997**, 431–439.
18. Di Profio, P.; Germani, R.; Savelli, G.; Cerichelli, G.; Chiarini, M.; Mancini, G.; Bunton, C. A.; Gillitt, N. D. *Langmuir* **1998**, *14*, 2662–2669.
19. Da Silva Baptista, M.; Cuccovia, I.; Chaimovich, H.; Politi, M. J. *J. Phys. Chem.* **1992**, *96*, 6442–6449.
20. Iglesias, E. *J. Phys. Chem.* **1996**, *100*, 12592–12599.
21. Bunton, C. A.; Wolfe, B. *J. Am. Chem. Soc.* **1973**, *95*, 3742–3749.
22. Albert, A.; Serjeant, E. P. *The Determination of Ionisation Constants*, 3rd ed.; Chapman and Hall: London, 1984.
23. More O'Ferrall, R. A.; Ridd, J. H. *J. Chem. Soc.* **1963**, 5030–5035.
24. Bunton, C. A.; Nome, F.; Quina, F. H.; Romsted, L. S. *Acc. Chem. Res.* **1991**, *24*, 357–364.

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An approach to the synthesis of α-(1-6)-*C*-disaccharides by tandem Tebbe methylenation and Claisen rearrangement

David J. Chambers,[a] Graham R. Evans[b] and Antony J. Fairbanks[a,*]

[a]*Chemistry Research Laboratory, Oxford University, Mansfield Road, Oxford OX1 3TA, UK*
[b]*Celltech R & D, Granta Park, Great Abington, Cambridge CB1 6GS, UK*

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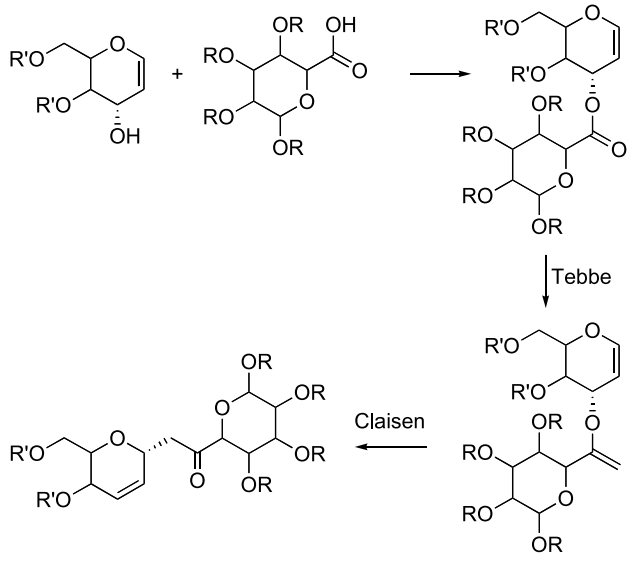
Abstract—Uronic acids, most efficiently synthesised from the corresponding alcohols by two step Dess-Martin and sodium chlorite mediated oxidation, may be used as coupling partners for esterification with an *allo* glycal as substrates for the tandem Tebbe/Claisen approach to the synthesis of 1-6 linked *C*-disaccharides. Whilst esters of glucuronic and mannuronic acids successfully undergo Tebbe methylenation, esters derived from galacturonic acids are unreactive under these conditions. Thermal Claisen rearrangement of vinyl ethers produced by methylenation yields α-*C*-disaccharides with complete control of anomeric stereochemistry.

1. Introduction

It is now well established that oligosaccharides play a huge number of crucially important roles in an enormously wide variety of fundamentally important biological systems.[1] It has also been long-proposed that carbohydrate mimetics[2] may be expected to display interesting biological activity either as enzyme inhibitors, for example, by inhibition of glycosidases or glycosyl tranferases, or as inhibitors or mediators of carbohydrate recognition events. Although the number of currently administered glycomimetic drugs is small, such molecules are expected to provide the basis of several new therapeutic strategies against a variety of disease states and infective agents in the future.[3]

Significant interest has recently, arisen in the synthesis of *C*-disaccharides,[4] in which the interglycosidic oxygen atom of a natural *O*-linked disaccharide is replaced by a methylene unit. These materials have been proposed as non-hydrolysable disaccharide mimetics, which may display interesting biological activity,[5] and therefore, perhaps therapeutic potential.

In principle the Tebbe/Claisen approach which, as recently, reported, allows stereospecific access to a wide range of *C*-glycoside materials,[6] could be advantageously applied to the synthesis of a variety of (1-6) linked *C*-disaccharides. This tandem approach initially involves esterification of a glycal possessing a free 3-hydroxyl group with a carboxylic acid. Tebbe methylenation[7] of the resultant ester can then be followed by [3,3] sigmatropic rearrangement[8,9] yielding the *C*-glycoside product in a predictable and entirely stereoselective fashion. One particular attraction of this approach is that carbohydrate-derived carboxylic acids may be used for the esterification step. In particular, selective oxidation of the primary hydroxyl of any one of the hexoses would readily provide access to suitable coupling partners. Tebbe methylenation of the resultant esters could then be followed



Scheme 1.

* Corresponding author. Tel.: +44 1865 275 647; fax: +44 1865 275 674; e-mail: antony.fairbanks@chem.ox.ac.uk

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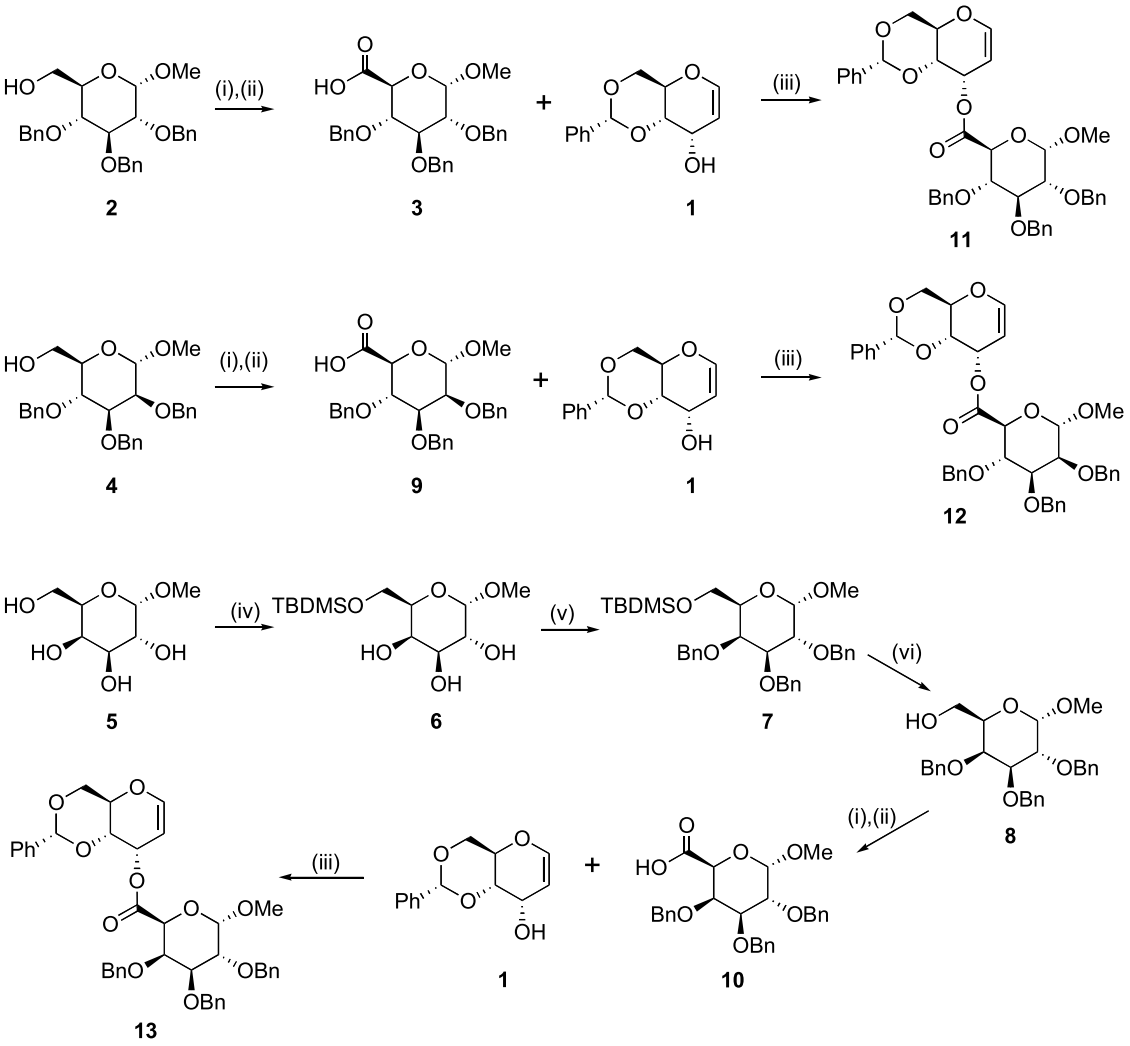
by Claisen rearrangement to yield 1-6-linked disaccharides, with complete control of anomeric stereochemistry (Scheme 1). This paper gives full details of investigations into the applicability of the tandem Tebbe/Claisen approach for the synthesis of a series of α-(1-6)-linked *C*-disaccharides.[10]

2. Results and discussion

2.1. Synthesis of uronic acid substrates and esterification

allo Glycal **1**, accessed using published synthetic routes,[11] was selected for esterification reactions, since sigmatropic rearrangement of a 3-*O* vinyl ether derived from **1** would produce a *C*-glycoside with the desired α-anomeric stereochemistry. It was envisaged that a series of uronic acids could be accessed via simple oxidation of the corresponding selectively protected alcohols in which only the primary OH-6 hydroxyl was free. The *gluco* alcohol **2** was synthesised using standard procedures[12] in order to provide a substrate for investigation of the most efficient and reliable method of achieving such an oxidation. Firstly several reagent combinations were investigated for effecting the one-pot oxidation directly to the carboxylic acid. Unfortunately the ruthenium trichloride/sodium periodate system,[13] which had proven to be an excellent method for oxidation of diacetone galactose to the corresponding galacturonic acid[6a] proved to be incompatible with the benzyl protection of the other hydroxyls of **2**. In addition, although a TEMPO[14] mediated oxidation with trichloroisocyanuric acid as co-oxidant did on one occasion provide the desired product **3** in 64% yield, the reaction proved unreliable and was unrepeatable. It was finally, concluded that in fact a two-step oxidation was the most efficient route to the desired product; sequential oxidation of alcohol **2** firstly by treatment with the Dess–Martin periodinane[15] and then immediate oxidation of the crude aldehyde product by treatment with sodium chlorite in the presence of 2-methyl-2-butene as a Cl^+ scavenger[16] yielded the desired acid **3**[17] in quantitative yield over two steps (Scheme 2).

With this optimised oxidation protocol in hand, further uronic acids were synthesised. The known *manno* alcohol **4**[18] was accessed by literature procedures. The corresponding *galacto* alcohol **8** was accessed from methyl



Scheme 2. Reagents and conditions: (i) Dess–Martin periodinane, DCM; (ii) $NaClO_2$, NaH_2PO_4, Bu^{t}OH, THF, H_2O, 2-methyl-2-butene, quantitative over two steps; (iii) DCC, DMAP, DCM; **11**, 83%; **12**, 76%; **13** 87%; (iv) TBDMSCl, imidazole, DMF, 0 °C, 92%; (v) BnBr, NaH, DMF, 84%; (vi) TsOH, MeCN, H_2O, 90%.

galactopyranoside **5** via a three-step reaction sequence. Thus, regioselective silylation of **5** with *tert*-butyldimethylsilylchloride and imidazole in DMF at 0 °C yielded the known silyl ether **6**[19] (92% yield). Benzylation of the remaining free hydroxyl groups by treatment of **6** with benzyl bromide and sodium hydride in DMF yielded completely protected galactoside **7** (84% yield). Finally, de-silylation by treatment of **7** with toluenesulfonic acid in aqueous acetonitrile[20] yielded the desired alcohol **8** (90% yield). Both *manno* and *galacto* alcohols were then oxidised smoothly to the desired carboxylic acids **9** and **10** by the two-step Dess–Martin/sodium chlorite procedure (both in quantitative yield over two steps). Finally, all three acids **3**, **9** and **10** were esterified by treatment with glycal **1** in the presence of dicyclohexylcarbodiimide (DCC) and dimethylamino pyridine (DMAP), in dichloromethane (DCM), to yield the corresponding *gluco*, *manno* and *galacto* esters **11**, **12** and **13** in 83, 76, and 87% yields, respectively, (Scheme 2).

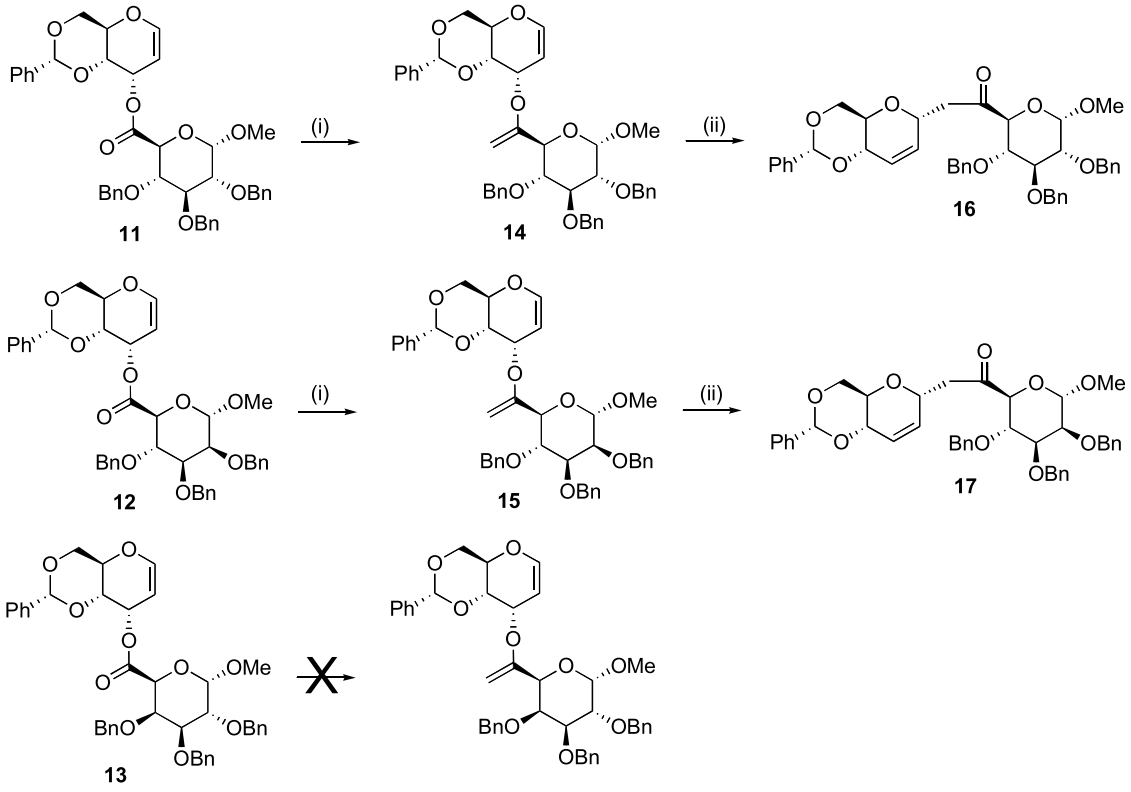
2.2. Tebbe methylenation and Claisen rearrangement

Methylenation reactions by the Tebbe reagent were attempted on the three esters **11**–**13**. Both *gluco* and *manno* esters **11** and **12** were smoothly methylenated by the Tebbe reagent to yield the desired enol ethers **14** and **15** in 82 and 76% yields, respectively, (Scheme 2). However, the corresponding *galacto* ester **13** was inert to methylenation under these conditions. Indeed despite protracted reaction times, and performing the reaction at room temperature the starting material was recovered in this case.[21]

With two substrates in hand Claisen rearrangement of both vinyl ethers **14** and **15** was undertaken. Mindful of previous studies[22] which had clearly demonstrated that in the case of α-*C*-glycosides the stereochemical purity of the product was dependent on the precise reaction conditions, thermal rearrangement of both substrates was undertaken in xylene in a sealed tube at 185 °C. Pleasingly under these conditions vinyl ethers **14** and **15** both underwent smooth stereocontrolled rearrangement to yield only the desired α-*C*-glycoside products **16** and **17** in 66 and 83% yields, respectively, (Scheme 3).

3. Conclusions

These studies demonstrate that the use of uronic acids, together with glycals in which the 3-hydroxyl group is not protected, allows access to (1-6)-linked *C*-disaccharide materials via the tandem Tebbe/Claisen approach. Uronic acid substrates for this reaction sequence were most efficiently obtained from selectively protected hexoses by a two-step oxidation process involving treatment of the alcohol firstly with the Dess–Martin periodinane and then immediate further, oxidation with sodium chlorite. The product carboxylic acids were readily esterified with the 3-hydroxyl group of the glycal. The efficiency of the Tebbe methylenation step was actually dependent on the stereochemistry of the uronic acid; whilst both *gluco* and *manno* esters readily underwent methylenation the *galacto* counterpart was resistant to reaction. Both *gluco* and *manno* vinyl ethers then underwent smooth thermal Claisen reaction to yield the desired α-*C*-disaccharide products with complete



Scheme 3. Reagents and conditions: (i) Tebbe reagent, THF, pyridine, −40 °C to rt, 16 h; **14**, 82%; **15**, 76%; (ii) 185 °C, xylene, sealed tube, 12 h; **16**, 66%; **17**, 83%.

control of stereochemistry. Further studies on the use of this tandem approach to *C*-disaccharide synthesis and in particular iteration of the process to allow access to (1-6)-linked *C*-oligosaccharides 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 (δ_H) spectra were recorded on a Bruker DPX 400 (400 MHz), or on a Bruker DQX 400 (400 MHz) spectrometer, and spectra were assigned using COSY and HMQC experiments. Carbon nuclear magnetic resonance (δ_C) spectra were recorded on a Bruker DPX 400 (100.6 MHz), or on a Bruker DQX 400 (100.6 MHz) and were assigned using HMQC experiments. Multiplicities were assigned using DEPT or APT sequences. All chemical shifts are quoted on the δ-scale in parts per million (ppm) using residual solvent as internal standard. Infrared spectra were recorded on a Perkin-Elmer 150 Fourier Transform spectrophotometer. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab20-250, Micromass Platform 1 APCI, or Trio-1 GCMS (DB-5 column) spectrometers, using desorption chemical ionization (NH_3 DCI), electron impact (EI), electron spray ionisation (ESI), chemical ionization (NH_3 CI), atmospheric pressure chemical ionization (APCI), and fast atom bombardment (FAB) techniques as stated. Optical rotations were measured 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 the Inorganic Chemistry Laboratory, Oxford. Thin layer chromatography (TLC) was carried out on Merck glass backed sheets, pre-coated coated with $60F_{254}$ silica. Plates were developed using 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and available reagents were dried and purified before use according to standard procedures; dichloromethane (DCM) was distilled from calcium hydride immediately before use. 4,6-*O*-Benzylidene-D-allal **1** was synthesised following literature procedures.[11]

4.2. General procedure A: esterification

Glycal (1.0 equiv) and carboxylic acid (1.2–1.5 equiv) were dissolved in anhydrous DCM, and *N*,*N*′-dimethyl-4-amino pyridine (0.2 equiv) and then dicyclohexylcarbodiimide (2.0 equiv) were added. The reaction mixture was stirred under an atmosphere of argon until TLC indicated the complete consumption of starting material. The reaction mixture was concentrated in vacuo, the residue taken up in ethyl acetate, and the suspension filtered through Celite®. The solution was concentrated in vacuo, and the residue purified by flash column chromatography.

4.3. General procedure B: Tebbe methylenation

The enol ether (1.0 equiv) was dissolved in a 4:1 mixture of anhydrous THF and anhydrous pyridine and the solution cooled to −40 °C under an atmosphere of argon. Tebbe reagent (0.5 M in toluene, 2.0–4.0 equiv depending on age and quality) was added drop-wise, and the reaction mixture allowed to warm to room temperature with stirring. After 16 h, when TLC indicated complete consumption of starting material, the reaction mixture was cooled to 0 °C and quenched by drop-wise addition of sodium hydroxide (0.5 M aqueous solution) until effervescence ceased. The mixture was diluted with petrol, stirred for 30 min, and sonicated for a further, 10 min. The mixture was poured onto a short column of silica and eluted (petrol and ether with 2% triethylamine), concentrated in vacuo and purified by flash column chromatography (silica; petrol and ether with 2% triethylamine).

4.3.1. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucuronic acid 3. Alcohol **2** (256 mg, 0.55 mmol) was dissolved in anhydrous DCM (15 ml) and Dess–Martin periodinane (350 mg, 0.83 mmol) was added. The mixture was stirred under an atmosphere of argon for 1 h, when TLC (petrol/ethyl acetate, 1:1) indicated consumption of starting material (R_f 0.4) and formation of a single product (R_f 0.3). The mixture was diluted with ether (12 ml) and sodium bicarbonate (12 ml) and sodium thiosulphate (2 g) was added. The mixture was stirred for 1 h, and was then diluted with ether (50 ml) and the layers separated. The aqueous phase was extracted with ether (4×25 ml) and the combined organic layers were washed with saturated aqueous sodium bicarbonate (50 ml) and water (50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give crude aldehyde as a colourless oil; δ_H (400 MHz, $CDCl_3$)[23] 3.41 (3H, s, OCH_3), 3.53 (1H, dd, $J_{1,2}=3.4$ Hz, $J_{2,3}=9.7$ Hz, H-2), 3.60 (1H, at, $J=9.6$ Hz, H-4), 4.11 (1H, at, $J=9.1$ Hz, H-3), 4.19 (1H, d, $J_{4,5}=10.6$ Hz, H-5), 4.64–4.68 (3H, m, H-1, 2×PhCH), 4.81–4.85 (2H, m, 2×PhCH), 4.89 (1H, d, $J=10.6$ Hz, PhCH), 5.03 (1H, d, $J=10.6$ Hz, PhCH), 7.28–7.38 (15H, m, 15×Ar-H), 9.67 (1H, s, H-6).

The crude aldehyde was dissolved in a mixture of *tert*-butanol (7 ml), THF (3 ml), water (3 ml) and 2-methyl-2-butene (2 ml). Sodium dihydrogenphosphate (0.4 g) and then sodium chlorite (80%, 62 mg, 0.55 mmol) were added, and the mixture stirred under an atmosphere of argon for 16 h. After this time, TLC (petrol/ethyl acetate, 1:1) indicated complete consumption of starting material (R_f 0.5) and formation of a major product (R_f 0.1). The mixture was quenched by addition of hydrochloric acid (10 ml of a 1 M aqueous solution). The organic layer was separated, and the aqueous layer extracted with ethyl acetate (4×25 ml). The combined organic layers were washed with water (50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give the *gluco* acid **3** (319 mg, quant.) as a colourless oil; $[\alpha]_D^{22}$ +28.9 (*c*, 1.2 in $CHCl_3$) [lit. $[\alpha]_D^{20}$ +3 (*c*, in $CHCl_3$)];[17] δ_H (400 MHz, $CDCl_3$) 3.40 (3H, s, OCH_3), 3.57 (1H, dd, $J_{1,2}=3.4$ Hz, $J_{2,3}=9.9$ Hz, H-2), 3.70 (1H, dd, $J_{3,4}=9.1$ Hz, $J_{4,5}=10.2$ Hz, H-4), 4.01 (1H, at, $J=9.4$ Hz, H-3), 4.22 (1H, d, H-5), 4.60–4.66, 4.79–4.83 (6H, m, 5×PhCH, H-1), 4.97 (1H, d, $J=10.7$ Hz, PhCH), 7.20–7.36 (15H, m, 15×Ar-H).

4.3.2. Methyl 6-*O*-*tert*-butyldimethylsilyl-α-D-galacto-pyranoside 6. Methyl α-D-galactopyranoside **5** (5.07 g, 26.1 mmol) was dissolved in anhydrous DMF (60 ml) and

cooled to 0 °C. Imidazole (4.44 g, 65 mmol) and then *tert*-butyldimethylsilyl chloride (4.72 g, 31 mmol) were added to the solution, and the mixture was stirred for 19 h, when TLC (ethyl acetate) indicated complete consumption of starting material (R_f 0) and formation of a single product (R_f 0.3). The mixture was concentrated in vacuo and the residue taken up in ethyl acetate (400 ml). The solution was washed with water (2×200 ml) and brine (2×200 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate) to afford silyl ether **6** (7.41 g, 92%) as an amorphous white solid; $[\alpha]_D^{21}$ +102 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$)[19] 0.09 (6H, s, 2×$SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 3.41 (3H, s, OCH_3), 3.73–3.78 (2H, m, H-3, H-5), 3.80–3.90 (3H, m, H-2, H-6, H-6′), 4.04 (1H, br d, J= 2.9 Hz, H-4), 4.80 (1H, d, $J_{1,2}$=3.8 Hz, H-1).

4.3.3. Methyl 2,3,4-tetra-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-α-D-galactopyranoside 7. Alcohol **6** (7.00 g, 23 mmol) was dissolved in anhydrous DMF (100 ml) and cooled to 0 °C. Benzyl bromide (12.2 ml, 102 mmol) and then sodium hydride (3.27 g, 82 mmol) were added and the reaction mixture stirred under an atmosphere of argon for 16 h, when TLC (petrol/ethyl acetate, 9:1) indicated consumption of starting material (R_f 0) and formation of a major product (R_f 0.3). The reaction mixture was quenched by drop-wise addition of methanol (10 ml), poured into water (500 ml) and extracted with ether (5×100 ml). The combined organic phases were washed with water (2×200 ml) and brine (2×200 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 19:1) to afford benzyl ether **7** (11.0 g, 84%) as a colourless oil; $[\alpha]_D^{21}$ +19.6 (*c*, 0.9 in $CHCl_3$); ν_{max} (thin film) no significant peak s; δ_H (400 MHz, $CDCl_3$) 0.08 (6H, s, 2×$SiCH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 3.42 (3H, s, OCH_3), 3.61–3.70 (2H, m, H-6, H-6′), 3.74–3.78 (1H, m, H-5), 3.96–4.00 (2H, m, H-3, H-4), 4.09 (1H, dd, $J_{1,2}$=3.5 Hz, $J_{2,3}$=9.8 Hz, H-2), 4.65, 5.02 (2H, 2×d, J=11.3 Hz, $PhCH_2$), 4.73 (1H, d, H-1), 4.75, 4.88 (2H, 2×d, J= 12.0 Hz, $PhCH_2$), 4.79, 4.93 (2H, 2×d, J=12.0 Hz, $PhCH_2$), 7.27–7.46 (15H, m, 15×Ar-H); δ_C (100.6 MHz, $CDCl_3$) −5.4, −5.4 (2×q, 2×$SiCH_3$), 18.2 (s, $SiC(CH_3)_3$), 25.9 (q, $SiC(CH_3)_3$), 55.2 (q, OCH_3), 62.0 (t, C-6), 71.1 (d, C-5), 73.3, 73.6, 74.8 (3×t, 3×$PhCH_2$), 75.2 (d, C-4), 76.5 (d, C-2), 79.2 (d, C-3), 98.8 (d, C-1), 127.5, 127.7, 127.9, 128.1, 128.2, 128.2, 128.3, 128.4 (8×d, 15× Ar-C), 138.6, 138.9, 138.9 (3×s, 3×Ar-C); *m/z* (ES^+) 637 ($M+NH_4^+ + CH_3CN$, 100), 601 ($M+Na^+$, 3%). (HRMS (ES^+) Calcd for $C_{34}H_{50}NO_6Si$ ($M+NH_4^+$) 596.3407. Found, 596.3408). (Found: C, 70.21; H, 8.33. $C_{34}H_{46}O_6Si$ requires C, 70.55; H, 8.01%).

4.3.4. Methyl 2,3,4-tetra-*O*-benzyl-α-D-galactopyranoside 8. Silyl ether **7** (8.57 g, 14.8 mmol) was dissolved in acetonitrile (100 ml). Water (20 ml) was added, and the pH of the solution adjusted to pH 3 by the addition of toluene sulphonic acid. The reaction mixture was stirred for 19 h, until TLC (petrol/ethyl acetate, 4:1) indicated consumption of starting material (R_f 0.7) and formation of a major product (R_f 0.1). The reaction mixture was concentrated in vacuo and the residue taken up in ethyl acetate (300 ml). The solution was washed with saturated aqueous sodium bicarbonate (2×150 ml) and brine (150 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 2:1) to afford alcohol **8** (6.20 g, 90%) as an amorphous white solid; $[\alpha]_D^{21}$ +7.01 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr disc) 3482 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.38 (3H, s, OCH_3), 3.49–3.52 (1H, m, H-6), 3.70–3.76 (2H, m, H-5, H-6′), 3.89 (1H, d, $J_{3,4}$=2.8 Hz, H-4), 3.96 (1H, dd, $J_{2,3}$=10.1 Hz, H-3), 4.07 (1H, dd, $J_{1,2}$=3.6 Hz, H-2), 4.66, 4.99 (2H, 2×d, J=11.6 Hz, $PhCH_2$), 4.72, 4.87 (2H, 2×d, J=11.9 Hz, $PhCH_2$), 4.73 (1H, d, H-1), 4.77, 4.92 (2H, 2× d, J=11.7 Hz, $PhCH_2$), 7.28–7.44 (15H, m, 15×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 55.4 (q, OCH_3), 60.4 (t, C-6), 70.2 (d, C-5), 73.6, 73.6, 74.4 (3×t, 3×$PhCH_2$), 75.0 (d, C-4), 76.5 (d, C-2), 79.1 (d, C-3), 98.8 (d, C-1), 127.6, 127.6, 127.8, 128.0, 128.1, 128.4, 128.4, 128.5, 128.6 (9×d, 15×Ar-C), 138.1, 138.4, 138.7 (3×s, 3×Ar-C); *m/z* (ES^+) 951 (2M+ Na^+, 3), 523 ($M+NH_4^+ + CH_3CN$, 100), 487 ($M+Na^+$, 5%). (HRMS (ES^+) Calcd for $C_{28}H_{32}O_6Na$ ($M+Na^+$) 487.2097. Found, 487.2087).

4.3.5. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannuronic acid 9. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **4** (435 mg, 0.81 mmol) was dissolved in anhydrous DCM (15 ml) and Dess–Martin periodinane (514 mg, 1.21 mmol) was added. The mixture was stirred under an atmosphere of argon for 3 h, when TLC (petrol/ethyl acetate, 1:1) indicated consumption of starting material (R_f 0.6) and formation of a single product (R_f 0.8). The mixture was diluted with ether (20 ml) and saturated aqueous sodium bicarbonate (20 ml) and sodium thiosulphate (2 g) were added. The mixture was stirred for 1 h, and was then diluted with ether (50 ml) and the layers separated. The aqueous phase was extracted with ether (4×25 ml) and the combined organic layers were washed with saturated aqueous sodium bicarbonate (2× 50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give crude aldehyde as a colourless oil; δ_H (400 MHz, $CDCl_3$)[24] 3.40 (3H, s, OCH_3), 3.78 (1H, at, J=2.7 Hz, H-2), 3.96 (1H, dd, $J_{2,3}$=2.8 Hz, $J_{3,4}$=8.0 Hz, H-3), 4.05–4.12 (2H, m, H-4, H-5), 4.63 (2H, s, $PhCH_2$), 4.67 (1H, d, J= 11.2 Hz, PhCH), 4.73 (2H, s, $PhCH_2$), 4.84–4.87 (2H, m, H-1, PhCH), 7.22–7.51 (15H, m, 15×Ar-H), 9.75 (1H, s, H-6). The crude residue was dissolved in a mixture of *tert*-butanol (9 ml), THF (3 ml), water (3 ml) and 2-methyl-2-butene (2 ml). Sodium dihydrogenphosphate (0.4 g) and then sodium chlorite (80%, 91 mg, 0.81 mmol) were added, and the mixture was stirred under an atmosphere of argon for 16 h. After this time, TLC (petrol/ethyl acetate, 1:1) indicated complete consumption of starting material (R_f 0.8) and formation of a major product (R_f 0.5). The mixture was quenched by addition of hydrochloric acid (30 ml of a 1 M aqueous solution). The organic layer was separated, and the aqueous layer extracted with ethyl acetate (4×25 ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate (4×30 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give the *manno* carboxylic acid **9** (488 mg, quant.) as a colourless oil; $[\alpha]_D^{23}$ +15.0 (*c*, 1.2 in $CHCl_3$); ν_{max} (thin film) 3386 (br, OH), 1725 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.46 (3H, s, OCH_3), 3.79 (1H, at, J=3.2 Hz, H-2), 3.92 (1H, dd, $J_{2,3}$= 3.1 Hz, $J_{3,4}$=7.8 Hz, H-3), 4.23 (1H, at, J=7.8 Hz, H-4), 4.32 (1H, d, J=7.7 Hz, H-5), 4.61, 4.65 (2H, 2×d, J= 11.9 Hz, $PhCH_2$), 4.70–4.82 (4H, m, 4×PhCH), 4.97 (1H,

d, $J_{1,2}$=3.1 Hz, H-1), 7.18–7.64 (15H, m, 15×Ar-H), 8.72 (1H, br s, OH); δ_C (100.6 MHz, $CDCl_3$) 55.7 (q, OCH_3), 71.4 (d, C-5), 72.4, 73.0, 74.4 (3×t, 3×$PhCH_2$), 74.5 (d, C-2), 75.6 (d, C-4), 78.5 (d, C-3), 99.6 (d, C-1), 127.7, 127.7, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5 (8×d, 15×Ar-C), 137.8, 138.0, 138.2 (3×s, 3×Ar-C), 174.0 (s, C-6); *m/z* (ES^+) 537 ($M+NH_4^+ + CH_3CN$, 100), 501 ($M+Na^+$, 20%). (HRMS (ES^+) Calcd for $C_{28}H_{34}NO_7$ ($M+NH_4^+$) 496.2335. Found, 496.2328).

4.3.6. Methyl 2,3,4-tri-*O*-benzyl-α-D-galacturonic acid 10. *Galacto* alcohol **8** (1.75 g, 3.8 mmol) was dissolved in anhydrous DCM (40 ml) and Dess–Martin periodinane (2.39 g, 5.6 mmol) was added. The mixture was stirred under an atmosphere of argon for 3 h, when TLC (petrol/ethyl acetate, 1:1) indicated consumption of starting material (R_f 0.4) and formation of a single product (R_f 0.5). The mixture was diluted with ether (75 ml) and saturated aqueous sodium bicarbonate (75 ml) and sodium thiosulphate (3 g) were added. The mixture was stirred for 1 h, and the layers separated. The aqueous phase was extracted with ether (3×25 ml) and the combined organic layers were washed with brine (3×75 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give crude aldehyde as a colourless oil; δ_H (400 MHz, $CDCl_3$) 3.42 (3H, s, OCH_3), 3.98 (1H, dd, $J_{3,4}$=2.7 Hz, $J_{4,5}$=10.0 Hz, H-4), 4.10–4.14 (2H, m, H-2, H-5), 4.32 (1H, at, J=2.2 Hz, H-3), 4.57, 4.93 (2H, 2×d, J=11.1 Hz, $PhCH_2$), 4.72, 4.88 (2H, 2×d, J=11.9 Hz, $PhCH_2$), 4.77, 4.89 (2H, 2×d, J=11.7 Hz, $PhCH_2$), 4.83 (1H, d, $J_{1,2}$=3.5 Hz, H-1), 7.24–7.43 (15H, m, 15×Ar-H), 9.54 (1H, d, $J_{5,6}$=1.5 Hz, H-6); δ_C (100.6 MHz, $CDCl_3$) 55.9 (q, OCH_3), 73.5, 73.8, 74.9 (3×t, 3×$PhCH_2$), 75.6, 76.0, 76.1 (3×d, C-2, C-3, C-5), 78.1 (d, C-4), 99.3 (d, C-1), 127.5, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5 (9×d, 15×Ar-C), 137.9, 138.3, 138.4 (3×s, 3×Ar-C), 200.5 (d, C-6). The residue was dissolved in a mixture of *tert*-butanol (32 ml), THF (14 ml), water (14 ml) and 2-methyl-2-butene (9 ml). Sodium dihydrogenphosphate (1.8 g) and then sodium chlorite (80%, 425 mg, 3.8 mmol) were added, and the mixture stirred under an atmosphere of argon for 16 h. After this time, TLC (petrol/ethyl acetate, 1:1) indicated complete consumption of starting material (R_f 0.6) and formation of a major product (R_f 0.1). The mixture was quenched by addition of hydrochloric acid (100 ml of a 1 M aqueous solution). The organic layer was separated, and the aqueous layer extracted with ethyl acetate (5×30 ml). The combined organic layers were washed with water (3×75 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give the *galacto* acid **10** (1.82 g, quant.) as a white crystalline solid, mp 126–130 °C (ether/petrol); $[\alpha]_D^{21}$ +38.2 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr disc) 3220 (br, OH), 1775 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.41 (3H, s, OCH_3), 4.01 (1H, dd, $J_{2,3}$=10.1 Hz, $J_{3,4}$=2.8 Hz, H-3), 4.08 (1H, dd, $J_{1,2}$=3.4 Hz, H-2), 4.34 (1H, at, J=2.1 Hz, H-4), 4.39 (1H, d, $J_{4,5}$=1.4 Hz, H-5), 4.62, 4.95 (2H, 2×d, J=11.0 Hz, $PhCH_2$), 4.68 (1H, d, J=12.3 Hz, PhCH), 4.77 (1H, d, J=11.5 Hz, PhCH), 4.78 (1H, d, H-1), 4.87 (2H, d, J=11.4 Hz, 2×PhCH), 7.24, 7.42 (15H, m, 15×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 56.2 (q, OCH_3), 70.4 (d, C-5), 73.4, 73.8, 75.2 (3×t, 3×$PhCH_2$), 75.5 (d, C-2), 76.4 (d, C-4), 77.9 (d, C-3), 99.4 (d, C-1), 127.5, 127.7, 127.7, 127.9, 128.1, 128.1, 128.2, 128.4, 128.5 (9×d, 15×Ar-C), 138.0, 138.2, 138.2 (3×s, 3×Ar-C), 171.2 (s, C-6); *m/z* (ES^+) 537 ($M+NH_4^+ + CH_3CN$, 100), 501 ($M+Na^+$, 5%). (HRMS (ES^+) Calcd for $C_{28}H_{34}NO_7$ ($M+NH_4^+$) 496.2335. Found, 496.2328).

4.3.7. Methyl 6-*O*-(4′,6′-*O*-benzylidene-3′-*O*-yl-D-allal)-2,3,4-tri-*O*-benzyl-α-D-glucuronic ester 11. *General procedure A*. 4,6-*O*-Benzylidene-D-allal **1**[11] (158 mg, 0.67 mmol), *gluco* acid **3** (558 mg, 1.0 mmol), *N*,*N*-dimethyl-4-amino pyridine (16 mg, 0.14 mmol), dicyclohexylcarbodiimide (278 mg, 1.4 mmol) in DCM (30 ml) gave ester **11** (388 mg, 83%) as a colourless oil; $[\alpha]_D^{21}$ +119 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film) 1746 (s, C=O), 1636 (m, C=C–O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.45 (3H, s, OCH_3), 3.60 (1H, dd, $J_{1,2}$=3.5 Hz, $J_{2,3}$=9.9 Hz, H-2 Glc), 3.80–3.87 (2H, m, H-4 Glc, H-6 All), 4.00–4.05 (2H, m, H-4 All, H-3 Glc), 4.13–4.22 (1H, m, H-5 All), 4.27 (1H, d, $J_{4,5}$=9.8 Hz, H-5 Glc), 4.41 (1H, dd, $J_{5,6'}$=5.0 Hz, $J_{6,6'}$=10.6 Hz, H-6′ All), 4.67 (1H, d, $J_{1,2}$=3.4 Hz, H-1 Glc), 4.68 (1H, d, J=12.0 Hz, PhCH), 4.72, 4.76 (2H, 2×d, J=11.0 Hz, $PhCH_2$), 4.80 (1H, d, J=10.8 Hz, PhCH), 4.83 (1H, d, J=12.1 Hz, PhCH), 4.95 (1H, d, J=11.0 Hz, PhCH), 5.03 (1H, at, J=5.9 Hz, H-2 All), 5.46 (1H, dd, $J_{2,3}$=5.8 Hz, $J_{3,4}$=3.9 Hz, H-3 All), 5.62 (1H, s, $PhCHO_2$), 6.49 (1H, d, $J_{1,2}$=6.0 Hz, H-1 All), 7.21–7.54 (20H, m, 20×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 55.5 (q, OCH_3), 63.6 (d, C-3 All), 64.9 (d, C-5 All), 68.5 (t, C-6 All), 70.5 (d, C-5 Glc), 73.6, 74.7, 75.8 (3×t, 3×$PhCH_2$), 75.8, 81.5 (2×d, C-4 All, C-3 Glc), 79.2, 79.4 (2×d, C-4 Glc, C-2 Glc), 97.8 (d, C-2 All), 98.6 (d, C-1 Glc), 101.6 (d, $PhCHO_2$), 126.2, 126.2, 127.4, 127.6, 127.6, 127.9, 128.0, 128.1, 128.2, 128.2, 128.3, 128.5, 129.1, 129.3 (14×d, 20×Ar-C), 137.0, 138.1, 138.2, 138.6 (4×s, 4×Ar-C), 147.8 (d, C-1 All), 168.9 (s, C-6 Glc); *m/z* (ES^+) 1447 ($2M+NH_4^+ + CH_3CN$, 3), 753 ($M+NH_4^+ + CH_3CN$, 100%). (HRMS (ES^+) Calcd for $C_{41}H_{46}NO_{10}$ ($M+NH_4^+$) 712.3122. Found, 712.3112).

4.3.8. Methyl 6-*O*-(4′,6′-*O*-benzylidene-3′-*O*-yl-D-allal)-2,3,4-tri-*O*-benzyl-α-D-mannuronic ester 12. *General procedure A*. 4,6-*O*-Benzylidene-D-allal **1**[11] (408 mg, 1.74 mmol), *manno* acid **9** (1.25 g, 2.6 mmol), *N*,*N*-dimethyl-4-amino pyridine (43 mg, 0.35 mmol), dicyclohexylcarbodiimide (719 mg, 3.5 mmol) in DCM (30 ml) gave recovered 4,6-*O*-benzylidene-D-allal **1** (60 mg) and ester **12** (919 mg, 76%, 89% based on recovered starting material) as a colourless oil; $[\alpha]_D^{22}$ +147 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film) 1748 (s, C=;O), 1636 (w, C=C–O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.52 (3H, s, OCH_3), 3.72 (1H, dd, $J_{1,2}$=4.9 Hz, $J_{2,3}$=3.0 Hz, H-2 Man), 3.81–3.87 (2H, m, H-3 Man, H-6 All), 4.00 (1H, dd, $J_{3,4}$=4.1 Hz, $J_{4,5}$=10.4 Hz, H-4 All), 4.20 (1H, dat, J=5.2, 10.3, 10.3 Hz, H-5 All), 4.27 (1H, at, J=6.3 Hz, H-4 Man), 4.38–4.46 (3H, m, PhCH, H-5 Man, H-6′ All), 4.52 (1H, d, J=11.7 Hz, PhCH), 4.62–4.72 (2H, m, 2×PhCH), 4.71 (1H, d, J=11.2 Hz, PhCH), 4.76 (1H, d, J=12.3 Hz, PhCH), 4.94 (1H, at, J=5.9 Hz, H-2 All), 5.06 (1H, d, H-1 Man), 5.30 (1H, dd, $J_{2,3}$=6.1 Hz, H-3 All), 5.60 (1H, s, $PhCHO_2$), 6.40 (1H, d, $J_{1,2}$=6.0 Hz, H-1 All), 7.19–7.48 (20H, m, 20×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 56.0 (q, OCH_3), 63.5 (d, C-3 All), 64.9 (d, C-5 All), 68.6 (t, C-6 All), 72.2, 72.8 (2×t, 3×$PhCH_2$), 72.5 (d, C-5 Man), 74.8 (d, C-2 Man), 75.7, 75.8 (2×d, C-4 All, C-4 Man), 76.7 (d, C-3 Man), 98.1 (d, C-2 All), 99.4 (d, C-1 Man), 101.9 (d, $PhCHO_2$), 126.3, 127.5,

127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 129.2 (9×d, 20× Ar-C), 137.0, 138.0, 138.1, 138.4 (4×s, 4×Ar-C), 147.4 (d, C-1 All), 169.1 (s, C-6 Man); *m/z* (ES^+) 712 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd for $C_{41}H_{46}NO_{10}$ ($M+NH_4^+$) 712.3122. Found, 712.3132). (Found: C, 70.51; H, 6.14. $C_{41}H_{42}O_{10}$ requires C, 70.88; H, 6.09%).

4.3.9. Methyl 6-*O*-(4′,6′-*O*-benzylidene-3′-*O*-yl-D-allal)-2,3,4-tri-*O*-benzyl-α-D-galacturonic ester 13. *General procedure A*. 4,6-*O*-Benzylidene-D-allal **1**[11] (168 mg, 0.72 mmol), *galacto* acid **10** (595 mg, 1.1 mmol), *N*,*N*-dimethyl-4-amino pyridine (18 mg, 0.14 mmol), dicyclohexylcarbodiimide (296 mg, 1.4 mmol) in DCM (30 ml) gave ester **13** (433 mg, 87%) as a white crystalline solid, mp 149–152 °C (ethyl acetate / petrol); $[\alpha]_D^{21}$ +140 (*c*, 1.2 in $CHCl_3$); ν_{max} (KBr disc) 1771 (s, C=O), 1637 (m, C=C–O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.41 (3H, s, OCH_3), 3.85 (1H, at, $J=10.5$ Hz, H-6 All), 4.00–4.04 (2H, m, H-3 Gal, H-4 All), 4.08 (1H, dd, $J_{1,2}=3.0$ Hz, $J_{2,3}=10.1$ Hz, H-2 Gal), 4.27 (1H, dat, $J=5.4$, 10.4, 10.4 Hz, H-5 All), 4.34 (1H, d, $J_{3,4}=1.4$ Hz, H-4 Gal), 4.41, 4.64 (2H, 2×d, $J=11.0$ Hz, $PhCH_2$), 4.43 (1H, s, H-5 Gal), 4.51 (1H, dd, $J_{5,6'}=5.0$ Hz, $J_{6,6'}=10.6$ Hz, H-6′ All), 4.66 (1H, d, $J=12.2$ Hz, PhCH), 4.73 (1H, d, $J=12.1$ Hz, PhCH), 4.80–4.84 (3H, m, 2×PhCH, H-1 Gal), 5.15 (1H, at, $J=5.9$ Hz, H-2 All), 5.31 (1H, at, $J=4.8$ Hz, H-3 All), 5.60 (1H, s, $PhCHO_2$), 6.49 (1H, d, $J_{1,2}=6.1$ Hz, H-1 All), 7.07–7.45 (20H, m, 20×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 56.0 (q, OCH_3), 63.8 (d, C-3 All), 65.0 (d, C-5 All), 68.6 (t, C-6 All), 70.4 (d, C-5 Gal), 72.8, 73.7, 74.9 (3×t, 3×$PhCH_2$), 75.5, 75.6, 78.1 (3×d, C-2 Gal, C-3 Gal, C-4 All), 77.5 (d, C-4 Gal), 98.3 (d, C-2 All), 99.2 (d, C-1 Gal), 101.9 (d, $PhCHO_2$), 126.2, 127.0, 127.3, 127.4, 127.5, 127.8, 128.2, 128.2, 128.4, 129.2 (10×d, 20×Ar-C), 137.0, 138.3, 138.6, 138.8 (4×s, 4×Ar-C), 147.6 (d, C-1 All), 168.3 (s, C-6 Gal); *m/z* 1447 ($2M+NH_4^+ + CH_3CN$, 7), 753 ($M+NH_4^+ + CH_3CN$, 100%). (ES^+) Calcd for $C_{41}H_{46}NO_{10}$ ($M+NH_4^+$) 712.3122. Found, 712.3132).

4.3.10. Methyl 1,5-anhydro-6-*O*-(4′,6′-*O*-benzylidene-3′-yl-D-allal)-7-deoxy-2,3,4-tri-*O*-benzyl-α-D-*gluco*-hept-6-enopyranose 14. *General procedure B*. Ester **11** (R_f 0.2 (petrol/ethyl acetate, 4:1), 170 mg, 0.24 mmol), Tebbe reagent (0.5 M, 2.0 ml, 0.98 mmol) in THF (8 ml) and pyridine (2 ml) gave enol ether **14** (138 mg, 82%) as a pale yellow foam; (R_f 0.2 petrol/ethyl acetate, 4:1). This unstable compound was used in the next step without further, purification; ν_{max} (thin film) 1634 (sh, C=C–O) cm^{-1}; δ_H (400 MHz, C_6D_6) 3.16 (3H, s, OCH_3), 3.44–3.52 (2H, m, H-5 All, H-6 All), 3.58 (1H, dd, $J_{1,2}=3.5$ Hz, $J_{2,3}=9.5$ Hz, H-2 Glc), 4.08 (1H, at, $J=9.3$ Hz, H-4 Glc), 4.19 (1H, dd, $J_{5,6'}=5.4$ Hz, $J_{6,6'}=10.5$ Hz, H-6′ All), 4.22–4.27 (2H, m, H-3 Glc, C=C*H*H′), 4.31 (1H, d, $J_{4,5}=9.9$ Hz, H-5 Glc), 4.36, 4.48 (2H, 2×d, $J=11.8$ Hz, $PhCH_2$), 4.38–4.44 (3H, m, H-3 All, H-4 All, C=CH*H*′), 4.65 (1H, d, H-1 Glc), 4.74 (1H, at, $J=5.9$ Hz, H-2 All), 4.87, 4.98 (2H, 2×d, $J=11.2$ Hz, $PhCH_2$), 4.92, 4.95 (2H, 2×d, $J=11.3$ Hz, $PhCH_2$), 5.28 (1H, s, $PhCHO_2$), 6.04 (1H, d, $J_{1,2}=5.9$ Hz, H-1 All), 7.03–7.65 (20H, m, 20×Ar-H); δ_C (100.6 MHz, C_6D_6) 55.1 (q, OCH_3), 65.3, 65.9 (2×d, C-3 All, C-4 All), 68.8 (t, C-6 All), 73.1, 74.9, 75.9 (3×t, 3×$PhCH_2$), 74.1 (d, C-5 Glc), 77.3 (d, C-5 All), 80.1 (d, C-4 Glc), 81.3 (d, C-2 Glc), 82.2 (d, C-3 Glc), 89.1 (t, C=*C*H_2), 98.8, 98.8 (2×d, C-1 Glc, C-2 All), 101.9 (d, $PhCHO_2$), 127.1, 127.5, 127.6, 127.7, 127.9, 127.9, 128.1, 128.3, 128.4, 128.4, 128.5, 128.6, 129.1 (13×d, 20×Ar-C), 138.5, 139.5, 140.0, 140.0 (4×s, 4×Ar-C), 146.7 (d, C-1 All), 158.5 (s, C-6 Glc); *m/z* (ES^+) 751 ($M+NH_4^+ + CH_3CN$, 100%). (HRMS (ES^+) Calcd for $C_{42}H_{48}NO_9$ ($M+NH_4^+$) 710.3329. Found, 710.3338).

4.3.11. Methyl 1,5-anhydro-2,3,4-tri-*O*-benzyl-6-*O*-(4′,6′-*O*-benzylidene-3′-yl-D-allal)-7-deoxy-α-D-*manno*-hept-6-enopyranoside 15. *General procedure B*. Ester **12** (R_f 0.2 (petrol/ethyl acetate, 4:1), 331 mg, 0.48 mmol), Tebbe reagent (0.5 M, 3.8 ml, 1.9 mmol) in THF (12 ml) and pyridine (3 ml) gave enol ether **15** (252 mg, 76%) as a pale yellow oil; (R_f 0.25, petrol/ethyl acetate, 4:1). This unstable compound was used in the next step without further, purification; ν_{max} (thin film) 1634 (m, C=C–O) cm^{-1}; δ_H (400 MHz, C_6D_6) 3.22 (3H, s, OCH_3), 3.59 (1H, at, $J=10.5$ Hz, H-6 All), 3.64 (1H, dd, $J_{3,4}=3.7$ Hz, $J_{4,5}=10.5$ Hz, H-4 All), 3.93 (1H, at, $J=2.5$ Hz, H-2 Man), 4.15 (1H, dd, $J_{2,3}=3.0$ Hz, $J_{3,4}=9.3$ Hz, H-3 Man), 4.30 (1H, dd, $J_{5,6'}=5.3$ Hz, $J_{6,6'}=10.3$ Hz, H-6′ All), 4.36 (1H, d, $J_{4,5}=9.5$ Hz, H-5 Man), 4.42 (1H, d, $J=1.7$ Hz, C=C*H*H′), 4.54 (1H, dat, $J=5.3$, 10.4, 10.4 Hz, H-5 All), 4.57–4.70 (6H, m, H-3 All, H-4 Man, C=CH*H*′, 3× PhCH), 4.78 (1H, d, $J=12.3$ Hz, PhCH), 4.88 (1H, d, $J_{1,2}=1.6$ Hz, H-1 Man), 4.91 (1H, at, $J=6.0$ Hz, H-2 All), 5.01 (2H, s, $PhCH_2$), 5.40 (1H, s, $PhCHO_2$), 6.16 (1H, d, H-1 All), 7.14–7.80 (20H, m, 20×Ar-H); δ_C (100.6 MHz, C_6D_6) 54.7 (q, OCH_3), 65.2 (d, C-5 All), 66.0 (d, C-3 All), 69.0 (t, C-6 All), 72.8, 73.1, 75.0 (3×t, 3×$PhCH_2$), 75.5 (d, C-5 Man), 76.2 (d, C-2 Man), 77.3 (d, C-4 Man), 77.6 (d, C-4 All), 80.5 (d, C-3 Man), 89.1 (t, C=*C*H_2), 99.0 (d, C-2 All), 100.0 (d, C-1 Man), 102.1 (d, $PhCHO_2$), 127.3, 127.5, 127.7, 127.7, 128.1, 128.4, 128.6, 128.7, 129.1 (9×d, 20× Ar-C), 138.6, 139.5, 139.7, 140.3 (4×s, 4×Ar-C), 146.6 (d, C-1 All), 159.1 (s, *C*=CH_2); *m/z* (ES^+) 710 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd for $C_{42}H_{48}NO_9$ ($M+NH_4^+$) 710.3329. Found, 710.3329).

4.3.12. Methyl 8,12-anhydro-2,3,4-tri-*O*-benzyl-11,13-*O*-benzylidene-9,10-didehydro-6-oxo-7,9,10-trideoxy-α-D-*glycero*-D-*ido*-α-D-glucopyranoside 16. Enol ether **14** (125 mg, 0.18 mmol) was dissolved in xylene (3 ml) and stirred at 185 °C in a sealed tube under an atmosphere of argon. After 12 h, TLC (petrol/ethyl acetate, 4:1) indicated consumption of starting material (R_f 0.25) and formation of a major product (R_f 0.20). The solution was concentrated in vacuo, and the residue was purified by flash column chromatography (petrol/ethyl acetate, 4:1) to afford α-*C*-disaccharide **16** (83 mg, 66%) as a white foam; $[\alpha]_D^{21}$ +18.7 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film) 1728 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.66 (1H, dd, $J_{7,7'}=17.2$ Hz, $J_{7,8}=4.9$ Hz, H-7), 3.14 (1H, dd, $J_{7',8}=8.2$ Hz, H-7′), 3.43 (3H, s, OCH_3), 3.51–3.57 (2H, m, H-2, H-12), 3.67 (1H, at, $J=9.3$ Hz, H-4), 3.75 (1H, at, $J=10.4$ Hz, H-13), 4.04 (1H, at, $J=9.4$ Hz, H-3), 4.12–4.17 (1H, m, H-11), 4.17 (1H, d, $J_{4,5}=10.0$ Hz, H-5), 4.21 (1H, dd, $J_{12,13'}=4.6$ Hz, $J_{13,13'}=10.4$ Hz, H-13′), 4.63 (1H, d, $J_{1,2}=3.3$ Hz, H-1), 4.64 (1H, d, $J=10.6$ Hz, PhCH), 4.68 (1H, d, $J=12.1$ Hz, PhCH), 4.82–4.87 (4H, m, H-8, 3×PhCH), 5.00 (1H, d, $J=10.9$ Hz, PhCH), 5.59 (1H, s, $PhCHO_2$), 5.70 (1H, dat, $J=2.6$, 2.6, 10.5 Hz, H-10), 6.03 (1H, d, $J_{9,10}=10.4$ Hz, H-9),

7.25–7.53 (20H, m, 20×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 43.8 (t, C-7), 55.8 (q, OCH_3), 65.7 (d, C-12), 69.5 (t, C-13), 69.9 (d, C-8), 73.6, 75.1, 75.9 (3×t, 3×$PhCH_2$), 74.2, 75.0 (2×d, C-5, C-11), 78.7 (d, C-4), 79.4 (d, C-2), 81.7 (d, C-3), 98.7 (d, C-1), 101.9 (d, $PhCHO_2$), 126.2, 127.5, 127.7, 127.9, 127.9, 128.1, 128.1, 128.2, 128.3, 128.4, 128.5, 129.1 (12×d, C-9, 20×Ar-C), 129.6 (d, C-10), 137.4, 137.8, 137.9, 138.5 (4×s, 4×Ar-C), 203.8 (s, C-6); *m/z* (ES^+) 751 ($M+NH_4^+ +CH_3CN$, 100%). (HRMS (ES^+) Calcd for $C_{42}H_{48}NO_9$ ($M+NH_4^+$) 710.3329. Found, 710.3328).

4.3.13. Methyl 8,12-anhydro-2,3,4-tri-*O*-benzyl-11,13-*O*-benzylidene-9,10-didehydro-6-oxo-7,9,10-trideoxy-α-D-*glycero*-D-*ido*-α-D-mannopyranoside 17. Enol ether **15** (151 mg, 0.22 mmol) was dissolved in xylene (3 ml) and stirred at 185 °C in a sealed tube under an atmosphere of argon. After 12 h, TLC (petrol/ethyl acetate, 2:1) indicated no change (R_f 0.5), but crude NMR indicated complete consumption of starting material and formation of a major product. The solution was concentrated in vacuo, and the residue was purified by flash column chromatography (toluene/ether, 19:1) to afford α-*C*-disaccharide **17** (125 mg, 83%) as a colourless oil; $[\alpha]_D^{21}$ +41.5 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film) 1730 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.73 (1H, dd, $J_{7,7'}=17.2$ Hz, $J_{7,8}=5.0$ Hz, H-7), 3.26 (1H, dd, $J_{7',8}=8.6$ Hz, H-7′), 3.38 (3H, s, OCH_3), 3.56–3.62 (1H, m, H-12), 3.76 (1H, at, $J=10.4$ Hz, H-13), 3.79 (1H, at, $J=2.7$ Hz, H-2), 3.92 (1H, dd, $J_{2,3}=3.1$ Hz, $J_{3,4}=8.5$ Hz, H-3), 4.05–4.18 (3H, m, H-4, H-5, H-11), 4.27 (1H, dd, $J_{12,13'}=4.7$ Hz, $J_{13,13'}=10.2$ Hz, H-13′), 4.62, 4.66 (2H, 2×d, $J=11.9$ Hz, $PhCH_2$), 4.68, 4.81 (2H, 2×d, $J=9.9$ Hz, $PhCH_2$), 4.73, 4.79 (2H, 2×d, $J=12.0$ Hz, $PhCH_2$), 4.81 (1H, d, $J_{1,2}=2.3$ Hz, H-1), 4.89–4.93 (1H, m, H-8), 5.60 (1H, s, $PhCHO_2$), 5.75 (1H, dat, $J=2.4$, 2.4, 10.4 Hz, H-10), 6.03 (1H, d, $J_{9,10}=10.4$ Hz, H-9), 7.18–7.53 (20H, m, 20×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 42.8 (t, C-7), 55.5 (q, OCH_3), 65.8 (d, C-12), 69.7 (t, C-13), 70.1 (d, C-8), 72.5, 73.0, 74.9 (3×t, 3×$PhCH_2$), 74.5 (d, C-2), 75.1, 75.1, 76.8 (3×d, C-4, C-5, C-11), 79.4 (d, C-3), 99.8 (d, C-1), 102.0 (d, $PhCHO_2$), 125.4, 126.4, 127.4, 127.7, 127.8, 127.9, 127.9, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 129.2 (14×d, C-9, 20×Ar-C), 129.2 (d, C-10), 137.6, 138.2, 138.2, 138.4 (4×s, 4×Ar-C), 204.4 (s, C-6); *m/z* (ES^+) 1443 ($2M+NH_4^+ +CH_3CN$, 3), 751 ($M+NH_4^+ +CH_3CN$, 100%). (HRMS (ES^+) Calcd for $C_{42}H_{48}NO_9$ ($M+NH_4^+$) 710.3329. Found, 710.3315).

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References and notes

1. (a) Varki, A. *Glycobiology* **1993**, *3*, 97–130. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720.
2. For a review see: Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300–2324.
3. (a) Witczak, Z. J. *Curr. Med. Chem.* **1995**, *1*, 392–405. (b) Mulvey, G.; Kitov, P. I.; Marcato, P.; Bundle, D. R.; Armstrong, G. D. *Biochimie* **2001**, *83*, 841–847. (c) Drinnan, N. B.; Vari, F. *Mini Rev. Med. Chem.* **2003**, *3*, 633–649.
4. For a selection of approaches to *C*-disaccharide synthesis see: (a) Rouzaud, D.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1353–1354. (b) Dawson, I. M.; Johnson, T.; Paton, R. M.; Rennie, R. A. C. *J. Chem. Soc., Chem. Commun.* **1988**, 1339–1340. (c) Lay, L.; Nicotra, F.; Panza, L.; Russo, G.; Caneva, E. *J. Org. Chem.* **1992**, *57*, 1304–1306. (d) Chénedé, A.; Perrin, E.; Rekai, E. D.; Sinaÿ, P. *Synlett* **1994**, 420–422. (e) Mazéas, D.; Skrydstrup, T.; Doumeix, O.; Beau, J.-M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1383–1386. (f) Khan, A. T.; Sharma, P.; Schmidt, R. R. *J. Carbohydr. Chem.* **1995**, *14*, 1353–1367. (g) Dondoni, A.; Boscarato, A.; Zuurmond, H. *Tetrahedron Lett.* **1996**, *37*, 7587–7590. (h) Lei, L.; McKee, M.; Postema, M. H. D. *Curr. Org. Chem.* **2001**, 1133–1167.
5. Reports of biological activity of *C*-disaccharides and *C*-oligosaccharides have been scarce. See: (a) Wei, A.; Boy, K. M.; Kishi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9432–9436. (b) Helmboldt, A.; Mallet, J.-M.; Petitou, M.; Sinaÿ, P. *Bull Soc. Chim. Fr.* **1997**, *134*, 1057–1067. (c) Xin, Y.-C.; Zhang, Y.-M.; Mallet, J.-M.; Glaudemans, C. P. J.; Sinaÿ, P. *Eur. J. Org. Chem.* **1999**, 471–476.
6. (a) Godage, H. Y.; Fairbanks, A. J. *Tetrahedron Lett.* **2000**, *41*, 7589–7593. (b) Godage, H. Y.; Fairbanks, A. J. *Tetrahedron Lett.* **2003**, *44*, 3631–3635. (c) Godage, H. Y.; Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Org. Biomol. Chem.* **2003**, *1*, 3772–3786. (d) Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 45–55.
7. (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613. (b) Hartley, R. C.; McKiernan, G. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2763–2793.
8. For pioneering use of stereospecific sigmatropic rearrangements in carbohydrate chemistry see: (a) Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, *18*, 1625–1626. (b) Fleet, G. W. J.; Spensley, C. R. C. *Tetrahedron Lett.* **1982**, *23*, 109–112. (c) Fleet, G. W. J.; Gough, M. J. *Tetrahedron Lett.* **1982**, *23*, 4509–4512. (d) Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Tetrahedron Lett.* **1983**, *24*, 3661–3664.
9. For approaches to *C*-glycosides by Claisen rearrangement see: (a) Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S.; Vanier, R. *Can. J. Chem.* **1979**, *57*, 1743–1745. (b) Fraser-Reid, B.; Dawe, R. D.; Tulshian, D. B. *Can. J. Chem.* **1979**, *57*, 1746–1749. (c) Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205–3207. (d) Ireland, R. E.; Anderson, R. C.; Badoub, R.; Fitzsimmons, B. J.; McGarvey, G.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988–2006. (e) Tulshian, D. B.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 518–522. (f) Curran, D. P.; Suh, Y. G. *Carbohydr. Res.* **1987**, *111*, 161–191. (g) Colombo, L.; Casiraghi, G.; Pittalis, A.; Rassu, G. *J. Org. Chem.* **1991**, *56*, 3897–3900. (h) Vidal, T.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 5677–5680. (i) Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145–4152.
10. The products of the Tebbe/Claisen approach detailed here, actually require ketone reduction and alkene dihydroxylation in order to be formally classified as *C*-disaccharides. These functional group transformations have been achieved on a

model α-*C*-glycoside (derived from esterification of allal **1** with benzoic acid and then Tebbe methylenation and Claisen rearrangement) as follows. Complete ketone reduction was achieved via a three step reaction sequence involving; (a) reduction with sodium borohydride in ethanol to give a diastereomeric mixture of alcohols; (b) formation of a diastereomeric mixture of imidazole xanthates by subsequent reaction with thiocarbonyldiimidazole; (c) free radical reduction with triphenyltin hydride and AIBN in toluene at 80 °C. Diastereoselective *cis* dihydroxylation to give the *manno* configured product was then achieved by treatment with catalytic $K_2OsO_4 \cdot 2H_2O$ in an acetone/water mixture in the presence of quinuclidine, and methyl sulphonamide, with *N*-methyl morpholine *N*-oxide as stoichiometric oxidant.

11. (a) Sharma, M.; Brown, R. K. *Can. J. Chem.* **1968**, *46*, 757–766. (b) For data see: Guthrie, R. D.; Irvine, R. W. *Carbohydr. Res.* **1979**, *6*, 285–268. See also Ref. 6a,b.
12. The reaction sequence involved tritylation of OH-6 of methyl glucopyranoside, benzylation of the remaining hydroxyls, and finally, acid catalysed removal of the trityl group.
13. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
14. (a) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999–5001. (b) Desai, R. N.; Blackwell, L. F. *Synlett* **2003**, 1981–1984. (c) Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293–295. (d) Sofia, M. J.; Hunter, R.; Chan, T. Y.; Vaughan, A.; Dulina, R.; Wang, H.; Gange, D. *J. Org. Chem.* **1998**, *63*, 2802–2803.
15. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
16. (a) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825–4830. (b) Lindgren, B. O.; Hilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890.
17. Petitou, M.; Coudert, C.; Level, M.; Lormeau, J.-C.; Zuber, M.; Simenel, C.; Fournier, J.-C.; Choay, J. *Carbohydr. Res.* **1992**, *236*, 107–119.
18. Hassan, H. H. A. M.; Spies, H. S.; Bredenkamp, M. W. *Pol. J. Chem.* **2000**, *74*, 1589–1598.
19. Chung, M.-K.; Orlova, G.; Goddard, J. D.; Schlaf, M.; Harris, R.; Beveridge, T. J.; White, G.; Hallet, F. R. *J. Am. Chem. Soc.* **2002**, *124*, 10508–10518.
20. Verduyn, R.; Douwes, M.; van der Klein, P. A. M.; Mösinger, E. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1993**, *49*, 7301–7316.
21. It is known that the Tebbe reagent is sensitive to steric effects [for examples, see Ref. 7b] and so one possible explanation for the failure of this reaction is that the axial configuration of the 4-substituent in the case of the *galacto* ester means that the ester is simply too hindered for reaction to occur.
22. In these previous studies Lewis acid catalysed Claisen rearrangements, or the use of other solvents such as PhCN, had resulted in the undesired formation of amounts of the thermodynamically more stable β-*C*-glycoside products, presumably via retro-Michael type reaction of the α-*C*-glycoside products. See Ref. 6b.
23. Hashimoto, H.; Asano, K.; Fujii, F.; Yoshimura *J. Carbohydr. Res.* **1982**, *104*, 87–104.
24. Boren, H. B.; Eklind, K.; Garegg, P. J.; Lindberg, B.; Pilotti, A. *Acta Chim. Scand.* **1972**, *26*, 4143–4146.

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Investigation into the regioselective C-deuteriation of α-keto esters

Claude Grison,* Sylvain Petek and Philippe Coutrot

Laboratoire de Chimie Organique Biomoléculaire, UMR 7565 CNRS-UHP Nancy 1, BP 239, 54506 Vandoeuvre-lès-Nancy cédex, France

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Abstract—Results are reported on the efficient regioselective C-mono and C-dideuteriation of iodomagnesium enolates derived from α-ketoesters in aliphatic and glucidic series using [D_4]acetic acid as the best deuterium donor.

1. Introduction

The synthesis of partially labelled compounds is a very useful approach to study the mechanistic details of biosynthetic pathways. Analysis of the kinetic isotope effect and the isotope distribution provide details about the enzymatic mechanism and the relative properties of transition states.

Higher 3-deoxy-D-*manno*-2-octulosonic acid (KDO), and 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH) are glucidic α-ketoacids, which are involved in biosynthetic pathways of bacteria and consequently, are important targets for the design of new antibacterial agents.[1] In order to increase the knowledge of the mechanism of these biosynthetic pathways, it is interesting and useful to develop new synthetic methods for incorporation of isotopic labels in these structures. Thus, C-8 deuteriated glycosides of KDO have been prepared upon reduction of an aldehyde group using a deuteriated borane complex.[2] Incorporation of isotopic labels onto phosphoenolpyruvate (PEP), the natural precursor of the α-ketoacid group, has also been reported: in particular, the stereocontrolled syntheses of (*E*)- and (*Z*)-3-deuteriophosphoenolpyruvate have been described in view to study the stereochemistry of the formations of UDP-*N*-acetylmuramic acid, 3-deoxy-D-*manno*-2-octulosonic acid 8-phosphate (KDO8P) and 3-deoxy-D-*arabino*-2-heptulosonic acid 7-phosphate (DAH7P).[3] [^{18}O]-phosphoenol pyruvate specifically labelled in the enolic oxygen has also been prepared to study the key-step of the biosynthesis of KDO8P.[4]

To our knowledge, despite the biological interest of the α-ketoacid group, no example of deuterium incorporation in this moiety has been described.

We report here the preparation of β-C-mono and -dideuteriated α-ketocarboxylic esters, in aliphatic and glucidic series, in order to prepare 3-deuteriated KDO and DAH.

2. Results and discussion

To introduce deuterium regioselectively at the α-C of a carbonyl group, based- or acid-catalyzed H/D exchange via the corresponding enol is a popular method, which usually uses a large excess of a deuterium donor (D_2O or CD_3OD) under thermodynamic control.[5] Long reaction time and/or increased temperature are often needed to insure a complete C-deuteriation.[6] Other difficulties arise with this protocol, such as overall D-incorporation, and the problem associated with product separation.[7]

C-deuteriation of enolates under kinetic control is also well documented but presents also difficulties to achieve complete deuteriation.[8] In particular, the choice of the base for the kinetic enolate generation is very important to drive the deuteriation to completion for the conjugate acid of the base produced during the enolate formation behaves as a competitive proton donor during the deuteriation step and decreases the deuterium incorporation.[9] For instance, competitive internal proton return with diisopropylamine is well known to suffer from this drawback.[10] Attempts to

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* Corresponding author. Present address: Laboratoire de Chimie Biomoléculaire, FRE CNRS-UM II-5032-ERT 5, Université Montpellier II, ENSCM, 8 Rue de l'Ecole Normale, 34296 Montpellier, France. Tel.: +33 467 144342; e-mail: cgrison@univ-montp2.fr

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solve this problem have been proposed by using a double deprotonation strategy to form a lithium enolate–lithium amide complex[11,12] or by ensuring the formation of a less basic amine,[12] or by using C-deuteriation of 'base-free'-enolates with a carbonyl-chelating deuterium donor such as [D_4]acetic acid.[13]

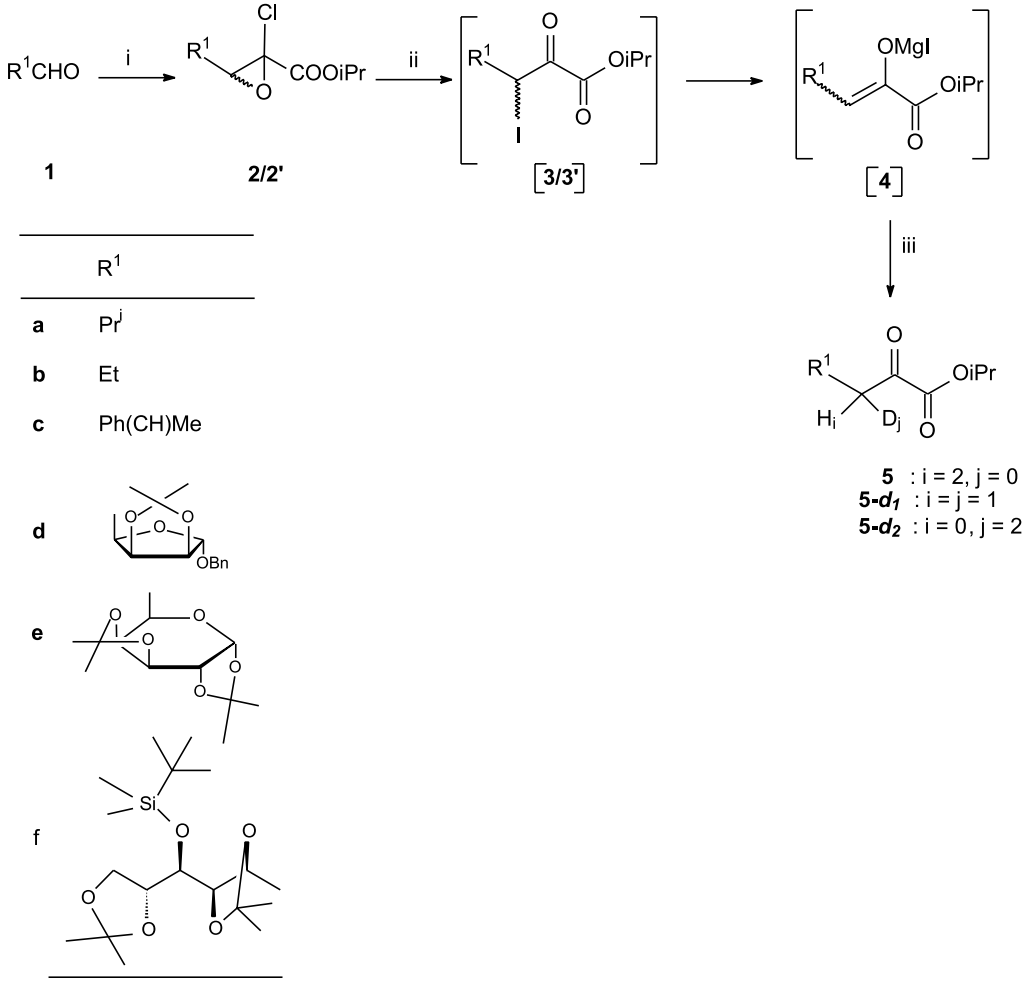
Thus, it appears from the literature data that the best method for the C-deuteriation under kinetic control would involve the use of enolates in the absence of any competitive base, coupled with the use of an efficient C-deuteriating reagent. The structural nature and D-acidity of the D-source is an important factor. Indeed, the efficient regioselective C-deuteriation of enolates is essential to obtain satisfactory deuterium-incorporation ratio. Incomplete D-incorporation can effectively occured from competitive deuterium exchange resulting in *O*-deuteriation leading to the corresponding D-enol, tautomerisation of, which in the presence of water (wet atmosphere or water traces) would allow the D-label to be exchanged and lost.[14]

As a result, our strategy was based on the preparation of the enolate derived from an α-ketoester without any deprotonation step involving a base formed from the reaction between the β-iodo-α-ketoester precursor **3** and active magnesium (like to prepare the corresponding Grignard reagent) (Scheme 1).

The β-iodo-α-ketoester precursor **3** was obtained from the reaction between the α-chloroglycidic ester **2** and magnesium di-iodine in ether. The β-iodo-α-ketoester **3** was not isolated and was completely transformed in situ into the iodomagnesium enolate **4** with the active magnesium produced during the preparation of MgI_2 (magnesium was intentionally used in a ratio $Mg/I_2=2:1$ in the preparation of MgI_2).[15]

Deuteriations of the enolate **4** with different deuterium sources known to afford efficient regioselective C-deuteriation, as D_2O, MeOH-d_4 and acetic acid-d_4,[16] were studied and led to β-C-deuteriated α-ketocarboxylic esters **5**-d_1 and **5**-d_2 with moderate to excellent overall deuterium-incorporation ratio (Table 1). Attempts were also realized with acetic acid-d_4 diluted with MeOH-d_4 to avoid the degradation of the glucidic substrates.

All deuteriolyses were carried out under an inert atmosphere and scrupulously anhydrous conditions to minimize the D/H enol exchange and the lost of the D-label. When D_2O was used as the cheap deuterium source, an excess of D_2O was added at room temperature with vigorous stirring of the mixture. After 15 min, the organic and aqueous layers were separated by filtration under nitrogen pressure. With acetic acid-d_4 or acetic acid-d_4 1.22 M in methanol-d_4, the mixture was maintained under stirring at ambient temperature for



Scheme 1. Reagents and conditions: (i) $CHCl_2COOiPr/Et_2O/iPrOK/iPrOH/0\ ^\circ C$; (ii) $Mg/MgI_2/Et_2O-35\ ^\circ C$; (iii) ZOD Z=D, CD_3, CD_3CO.

Table 1. Deuteriation of enolates [**4**] with different deuterium donors

Attempt	Deuterium source	R[1]	**5**	**5**-d_1	**5**-d_2	**5**-d_1+**5**-d_2
1	D_2O	**a**	27	54	19	73
2	AcOH-d_4	**a**	8	36	56	92
3	AcOH-d_4 1.22 M in MeOH-d_4	**a**	5	55	40	95
4	D_2O	**b**	20	59	21	80
5	AcOH-d_4	**b**	1	16	83	99
6	AcOH-d_4 1.22 M in MeOH-d_4	**b**	11	70	19	89
7	D_2O	**c**	22	61	17	78
8	AcOH-d_4	**c**	6	35	59	94
9	AcOH-d_4 1.22 M in MeOH-d_4	**c**	7	66	27	93
10	D_2O	**d**	38	55	7	62
11	AcOH-d_4 1.22 M in MeOH-d_4	**d**	11	85	4	89
12	D_2O	**e**	44	46	10	56
13	AcOH-d_4 1.22 M in MeOH-d_4	**e**	12	79	9	88
14	AcOH-d_4 1.22 M in MeOH-d_4	**f**	20	57	23	80

4 h, before it was centrifuged under nitrogen to separate the insoluble magnesium salt.

In these conditions, it appeared that the reaction could give up to six different detectable products in ^{1}H NMR: β-C-tautomerisation of which, β-C-dideuterio-α-ketoester **5**-d_2, *O*-deuterioenol, *C*-deuterioenol, no-labeled enol and keto-ester **5**. For example, the ^{1}H NMR spectrum of the crude product obtained in the deuteriation of the enolate **4a** was depicted in Figure 1. The complexity of such a mixture involved difficulties in the ^{1}H NMR estimation of the deuterium incorporation, the principal difficulty being the presence of the enolic forms. Previous works in our laboratory have shown that the enolic forms of α-ketoesters are the major products obtained in the preparation of α-ketoesters. These enols can be completely transformed into the corresponding thermodynamic keto form after a rapid purification on a silicagel chromatographic column. As a consequence, we verified that such a treatment of the precedent deuteriation crude mixture only yielded the α-ketoester **5a**, but, as it was to be feared, with a total loss of the label.

An increase in the deuteriation time or a temperature increase of the reaction medium to favor the enol transformation towards the thermodynamic C-deuteriation[17] was also studied but was unsuccessful, the mixture degraded.

Finally, we found that the heating of the ^{1}H NMR sample of the crude product in $CDCl_3$ at 55 °C for 1 h allowed the total transformation of the enol into the α-keto form without any degradation. Only three compounds **5a**, **5a**-d_1 and **5a**-d_2 were then detected (Fig. 2). The CHD group in **5a**-d_1 appeared as a doublet of triplet and CH_2 in **5a** as a doublet. The **5a**/**5a**-d_1 ratio was evaluated by integration of H(3) signals in **5a** and **5a**-d_1. The proportion of **5a**-d_2 that contains the sample was estimated by the difference in the integration of the H(6) signal present in **5a**, **5a**-d_1 and **5a**-d_2 and the H(3) signal only present in **5a** and **5a**-d_1. The presence of the dideuterated product was confirmed by mass spectroscopy. However, ^{13}C NMR data did not allow to easily distinguish mono and dideuterated compounds. In most cases, ^{13}C NMR spectra of the mixture of mono and dideuterated products only presented a triplet of low

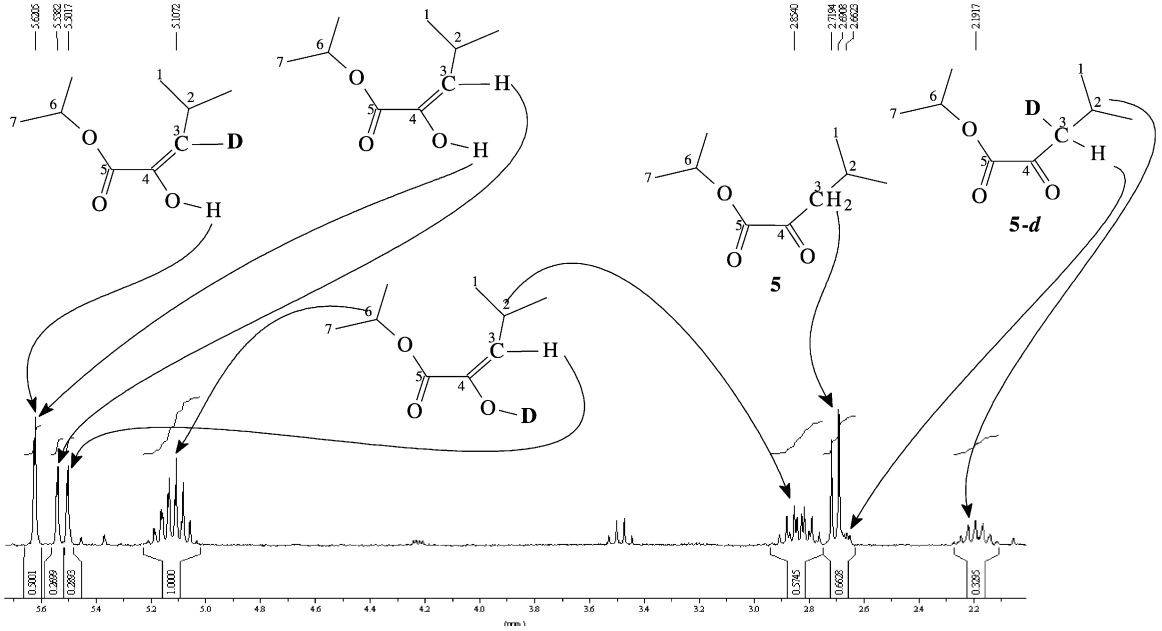


Figure 1.

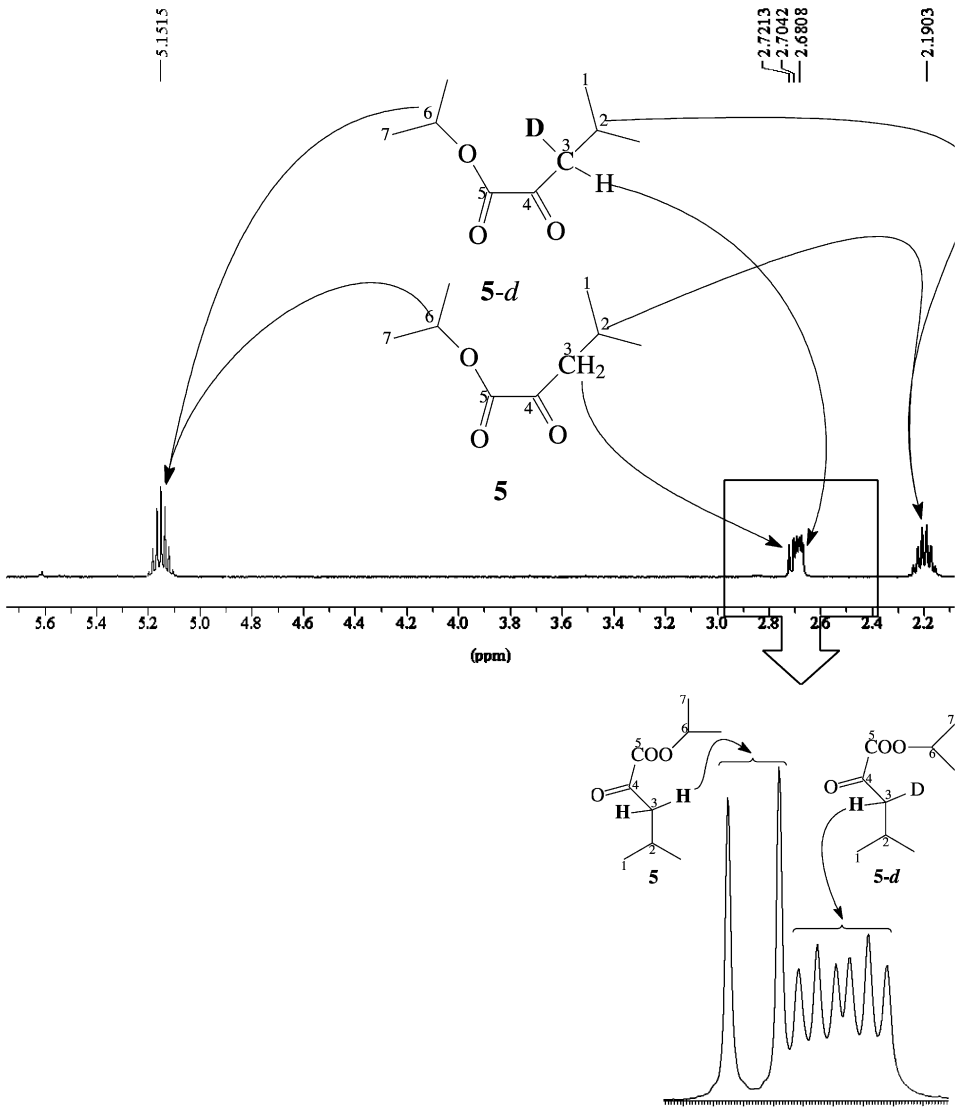


Figure 2.

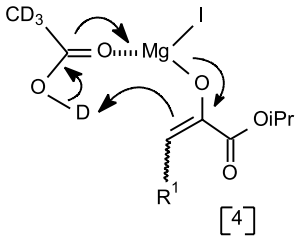
intensity in the range 38–47 ppm with *J* couplings of around 20 Hz assigned to the associated CHD signal. We would have expected also a quintet (1:2:3:2:1) for the CD_2 signal. This last resonance was only observed in the case of **5a**-d_2 (Table 1, attempt 2) as a triplet-like signal of low intensity at a closely downfield resonance to the CHD signal with a *J* coupling of around 20 Hz. In other cases, the feeble amount of the dideuterated product in the mixture and the low intensity of the ^{13}C NMR signal associated with a quaternary carbon involved either the disappearance of the CD_2 quintet in the back-ground noise or its superimposition with the CHD triplet.

Otherwise, it was note worthy that when a new stereogenic center was created (**5c**-d_1, **5d**-d_1, **5e**-d_1, **5f**-d_1), only one diastereomer was observed in ^1H and ^{13}C NMR. Nevertheless, it was difficult to rationalize this fact as far as the *E*/*Z* structure of the enolate **4** was still unknown.

High incorporation was obtained with acetic acid-d_4 or acetic acid-d_4 1.22 M in methanol-d_4 (80–99%). The best results were obtained with aliphatic substrates and acetic acid-d_4 (94–99%), whereas reaction with D_2O led only to a partial deuteriation (56–80%).

Similar observations have been reported by Eames, Coumbarides et al.[16] These authors have found that the best method of synthesis of deuteriated tetralones required the preparation of lithium enolates and using only acetic acid-d_4 as the cheap deuterium source. The carbonyl chelation of acetic acid-d_4 with the lithium cation was responsible for the direct C-deuteriation and allowed a complete incorporation of deuterium. With D_2O and MeOH-d_4, the incorporation of deuterium was partial.[16]

A closely related process could explain our results. The presence of the Lewis acid magnesium cation could give a complex with acetic acid-d_4 and favor the regioselective C-deuteriation (Scheme 2). This regiocontrol of deuteriation allowed to avoid the formation of the *O*-deuteriated enol, which was very sensitive to water and could led to the loss of the deuterium label through tautomerisation to give the unlabelled ketoester **5**.



Scheme 2.

The incorporation of a second deuterium atom gave the dideuterio product **5**-d_2. The acidity of the mixture favored the dideuteriation. Acetic acid-d_4 gave the best **5**-d_2/**5**-d_1 ratios (83/16 with **4b**). This excess D-incorporation must come from the subsequent enolisation of the **5**-d_1 keto form followed by H/D exchange to give **5**-d_2. However, the presence of the magnesium cation was essential to afford the C-dideuteriation since without it, when **5**-d_1 was stirred in acetic acid-d_4, no deuterium incorporation was observed.

In summary, this study has shown that an efficient regioselective C-deuteriation of α-ketoesters is possible via the preparation of the corresponding iodomagnesium enolate under 'base-free' conditions and with acetic acid-d_4 as the best deuterium donor.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR were run at 250 or 400 and 62.5 MHz, respectively. NMR spectra were obtained in $CDCl_3$. Chemical shifts are given in parts per million (δ ppm) from TMS as an internal standard. Infrared spectra were obtained using a Nicolet 205 spectrometer and are given in cm^{-1}. Mass spectra were obtained on an Autospec Fited Cesium Gun (Micromass, Manchester). Organic solvents were purified according to the methods described by Armarego and Perrin.[18] All no aqueous reactions were performed in oven-dried glassware under nitrogen atmosphere.

α-Chloroglycidic esters **2** were easily prepared from aldehydes **1** according our previous works.[1g,19]

3.1.1. Typical procedure for the preparation of the magnesium enolate 4. In a typical experiment to obtain **4**, iodine (10.15 mmol) was added to Mg (powder 325 mesh, 20.3 mmol) in anhydrous ether (65 ml). After stirring at 35 °C for 3 h in obscurity to avoid a possible substitution of ether with iodine, the mixture MgI_2-activated Mg was allowed to warm to room temperature and was added dropwise at −60 °C, under stirring to the α-chloroglycidic ester **2** (10.15 mmol, 0.05 M in ether/toluene 4:1). The mixture was allowed to warm up to −30 °C and stirring was pursued for 120 min at this temperature.

3.1.2. Typical procedure for deuteriation with deuterium oxide. D_2O (10.0 ml, 52 equiv, 500.0 mmol, 99.97%, ref. Eurisotop: D215-EP) was added with a syringe, to the magnesium enolate **4** prepared as above under inert atmosphere. After 15 min stirring, the organic layer was separated by filtration under inert atmosphere. The D_2O layer was extracted with diethylether (3×20.0 ml) and the organic layer was siphoned in the same way as previously. The joined organic layers were dried on anhydrous sodium sulfate, then filtered under nitrogen. The solvent was evaporated under reduced pressure. The obtained residue was kept under nitrogen.

3.1.3. Typical procedure for deuteriation using an excess of acetic acid-d_4, or with a solution of 1.22 M acetic acid-d_4 in methanol-d_4. Acetic acid-d_4 (10.0 ml, 18 equiv, 174.9 mmol, 99.5%, ref. Eurisotop: D012-EA) or acetic acid-d_4 (10.75 ml, 1.22 M, 13.1 mmol, 1.35 equiv, 99.5%, ref. Eurisotop: D012-BB) in methanol-d_4 (10 ml, 246.2 mmol, 25 equiv, 99.8%, ref. Eurisotop: D024-ES) was added with a syringe to the magnesium enolate **4** under inert atmosphere. The mixture was maintained under stirring at room temperature for 4 h, and then transferred with a syringe, towards a centrifugal under nitrogen. The four neck flask was rinsed with diethylether (20.0 ml), which was transferred in the same way to the centifugal. After 20 min of centrifugation at 2500 rpm, the yellow clearly and limpid supernatant was transferred using a syringe towards a two neck flask under nitrogen. The diethylether was distillated, which allowed to convert the enol form to the ketone form. When the majority of the solvent was recovered, the residue was evaporated under vacuum for 1 h. The obtained residue was kept under nitrogen.

3.1.4. 4-Methyl-2-oxo-pentanoic acid iso propyl ester 5a. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 1740, 1727 (C=O). ^{1}H NMR (400 MHz), δ (ppm): 5.14 (h, J=6.3 Hz, 1H, OC*H*$(CH_3)_2$); 2.70 (d, J=7.0 Hz, 2H, H-3); 2.18 (m, 1H, H-4); 1.35 (d, J=6.3 Hz, 6H, CH(C*H*$_3)_2$); 0.97 (d, J=6.7 Hz, 6H, CH(C*H*$_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 194.4 (C-2); 160.7 (C-1); 70.0 (O*C*H$(CH_3)_2$); 47.5 (*C*H$_2$); 23.8 (*C*H$(CH_3)_2$); 22.0 (OCH(*C*H$_3)_2$); 21.2 (CH(*C*H$_3)_2$). MS (FAB+): m/z calculated for $C_9H_{16}O_3$ $[M]^+$ 172.2, found $[M+1, 100\%]^+$ 173.

3.1.5. 4-Methyl-3-deuterio-2-oxo-pentanoic acid iso-propyl ester 5a-d_1. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 2100 (C–D); 1740, 1727 (C=O). ^{1}H NMR (400 MHz), δ (ppm): 5.14 (h, J=6.3 Hz, 1H, OC*H*$(CH_3)_2$); 2.66–2.70 (m, 1H, H-3); 2.18 (m, 1H, H-4); 1.35 (d, J=6.3 Hz, 6H, CH(C*H*$_3)_2$); 0.97 (d, J=6.7 Hz, 6H, CH(C*H*$_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 194.4 (C-2); 160.7 (C-1); 70.0 (*C*H$(CH_3)_2$); 47.1 (t, $J_{(C-D)}$=20.0 Hz, *C*HD); 23.8 (*C*H$(CH_3)_2$); 22.0 (OCH(*C*H$_3)_2$); 21.2 (CH(*C*H$_3)_2$). MS (FAB+): m/z calculated for $C_9H_{15}DO_3$ $[M]^+$ 173.1, found $[M+1, 100\%]^+$ 174.

3.1.6. 4-Methyl-3,3-dideuterio-2-oxo-pentanoic acid iso-propyl ester 5a-d_2. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 2100 (C–D); 1740, 1727 (C=O). ^{1}H NMR (400 MHz), δ (ppm): 5.14 (h, J=6.3 Hz, 1H, C*H*$(CH_3)_2$); 2.18 (m, 1H, H-4); 1.35 (d, J=6.3 Hz, 6H, CH(C*H*$_3)_2$); 0.97 (d, J=6.7 Hz, 6H, CH(C*H*$_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 194.4 (C-2); 160.7 (C-1); 70.0 (*C*H$(CH_3)_2$); 46.7 (t, $J_{(C-D)}$=19.5 Hz, *C*D$_2$); 23.8 (*C*H$(CH_3)_2$); 22.0 (OCH(*C*H$_3)_2$); 21.2

($CH(CH_3)_2$). MS (FAB+): *m/z* calculated for $C_9H_{14}D_2O_3$ $[M]^+$ 174.2, found $[M+1, 100\%]^+$ 175.

3.1.7. 2-Oxo-pentanoic acid isopropyl ester 5b. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 1740, 1724 (C=O). ^1H NMR (400 MHz), δ (ppm): 5.15 (h, $J=6.3$ Hz, 1H, $CH(CH_3)_2$); 2.82 (t, $J=7.3$ Hz, 2H, H-3); 1.60–1.80 (m, 2H, H-4); 1.35 (d, $J=6.3$ Hz, 6H, $CH(CH_3)_2$); 0.97 (t, $J=7.5$ Hz, 3H, H-5). ^{13}C NMR (100 MHz), δ (ppm): 194.8 (C-2); 160.6 (C-1); 70.2 ($CH(CH_3)_2$); 40.7 (C-3); 21.2 ($CH(CH_3)_2$); 17.3 (C-4); 10.9 (C-5). MS (FAB+): *m/z* calculated for $C_8H_{14}O_3$ $[M]^+$ 158.2, found $[M+1, 100\%]^+$ 159.

3.1.8. 3-Deuterio-2-oxo-pentanoic acid isopropyl ester 5b-d_1. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 2070 (C–D); 1740, 1724 (C=O). ^1H NMR (400 MHz), δ (ppm): 5.15 (h, $J=6.3$ Hz, 1H, $CH(CH_3)_2$); 2.75–2.82 (m, 1H, H-3); 1.60–1.80 (m, 2H, H-4); 1.35 (d, $J=6.3$ Hz, 6H, $CH(CH_3)_2$); 0.97 (t, $J=7.5$ Hz, 3H, H-5). ^{13}C NMR (100 MHz), δ (ppm): 194.8 (C-2); 160.6 (C-1); 70.2 ($CH(CH_3)_2$); 40.7 (C-3); 40.4 (t, $J=19.6$ Hz, C-3); 21.2 ($CH(CH_3)_2$); 17.3 (C-4); 10.9 (C-5). MS (FAB+): *m/z* calculated for $C_8H_{13}DO_3$ $[M]^+$ 159.2, found $[M+1, 100\%]^+$ 160.

3.1.9. 3,3-Dideuterio-2-oxo-pentanoic acid isopropyl ester 5b-d_2. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 2070 (C–D); 1740, 1724 (C=O). ^1H NMR (400 MHz), δ (ppm): 5.15 (h, $J=6.3$ Hz, 1H, $CH(CH_3)_2$); 1.60–1.80 (m, 2H, H-4); 1.35 (d, $J=6.3$ Hz, 6H, $CH(CH_3)_2$); 0.97 (t, $J=7.5$ Hz, 3H, H-5). ^{13}C NMR (100 MHz), δ (ppm): 194.8 (C-2); 160.6 (C-1); 70.2 (C-6); 40.4 (t, $J=19.6$ Hz, C-3); 21.2 ($CH(CH_3)_2$); 17.3 (C-4); 10.9 (C-5). MS (FAB+): *m/z* calculated for $C_8H_{12}D_2O_3$ $[M]^+$ 160.2, found $[M+1, 100\%]^+$ 161.

3.1.10. 2-Oxo-4-phenyl-pentanoic acid isopropyl ester 5c. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 2070 (C–D); 1750, 1725 (C=O). ^1H NMR (400 MHz), δ (ppm): 7.20–7.40 (m, 5H); 5.10 (h, $J=6.0$ Hz, 1H, $CH(CH_3)_2$); 3.37 (m, 1H, H-4); 3.02–3.25 (ddd, 2H, H-3); 1.31 (d, $J=6.0$ Hz, 3H, $CH(CH_3)_2$); 1.33 (d, $J=6.0$ Hz, 3H, $CH(CH_3)_2$); 1.32 (d, $J=7.0$ Hz, 3H, H-5). ^{13}C NMR (100 MHz), δ (ppm): 178.9 (C-2); 160.6 (C-1); 145.3 (C-8); 126.4, 126.7, 128.5 (C-9,10,11); 70.7 (C-6); 47.3 (C-3); 34.9 (C-4); 21.7, 21.8 (C-5,5′); 21.5 ($CH(CH_3)_2$). MS (FAB+): *m/z* calculated for $C_{14}H_{18}O_3$ $[M]^+$ 234.3, found $[M+1, 90\%]^+$ 235.

3.1.11. 3-Deutero-2-oxo-4-phenyl-pentanoic acid isopropyl ester 5c-d_1. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 2070 (C–D); 1750, 1725 (C=O). ^1H NMR (400 MHz), δ (ppm): 7.20–7.40 (m, 5H); 5.10 (h, $J=6.0$ Hz, 1H, $CH(CH_3)_2$); 3.37 (m, 1H, H-4); 3.02–3.07, 3.14–3.20 (m, 1H, H-3); 1.31 (d, $J=6.0$ Hz, 3H, $CH(CH_3)_2$); 1.33 (d, $J=6.0$ Hz, 3H, $CH(CH_3)_2$); 1.32 (d, $J=7.0$ Hz, 3H, H-5). ^{13}C NMR (100 MHz), δ (ppm): 178.9 (C-2); 160.6 (C-1); 145.3 (C-8); 126.4, 126.7, 128.5 (C-9,10,11); 70.7 (C-6); 46.9 (t, $J=19.6$ Hz, C-3); 34.9 (C-4); 21.7, 21.8 (C-5,5′); 21.5 ($CH(CH_3)_2$). MS (FAB+): *m/z* calculated for $C_{14}H_{17}DO_3$ $[M]^+$ 235.3, found $[M+1, 90\%]^+$ 236.

3.1.12. 3,3-Dideuterio-2-oxo-4-phenyl-pentanoic acid isopropyl ester 5c-d_2. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 2070 (C–D); 1750, 1725 (C=O). ^1H NMR (400 MHz), δ (ppm): 7.20–7.40 (m, 5H); 5.10 (h, $J=6.0$ Hz, 1H, $CH(CH_3)_2$); 3.37 (m, 1H, H-4); 1.31 (d, $J=6.0$ Hz, 3H, $CH(CH_3)_2$); 1.33 (d, $J=6.0$ Hz, 3H, $CH(CH_3)_2$); 1.32 (d, $J=7.0$ Hz, 3H, H-5). ^{13}C NMR (100 MHz), δ (ppm): 178.9 (C-2); 160.6 (C-1); 145.3 (C-8); 126.4; 126.7, 128.5 (C-9,10,11); 70.7 (C-6); 46.9 (t, $J=19.6$ Hz, C-3); 34.9 (C-4); 21.7, 21.8 (C-5,5′); 21.5 ($CH(CH_3)_2$). MS (FAB+): *m/z* calculated for $C_{14}H_{16}D_2O_3$ $[M]^+$ 236.3, found $[M+1-Ph, 88\%]^+$ 159.2.

3.1.13. Isopropyl 5-deoxy-6-oxo-1-*O*-benzyl-2,3-*O*-isopropylidene-α-D-*lyxo*-heptofuranuronate 5d. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 1748, 1726 (C=O). ^1H NMR (400 MHz), δ (ppm): 7.30–7.40 (m, 5H); 5.16 (h, $J=6.3$ Hz, $CH(CH_3)_2$); 5.06 (s, 1H, H-1); 4.80 (dd, $J=5.8$, 3.8 Hz, 1H, H-3); 4.68 (d, $J=11.7$ Hz, 1H, OCH_2Ph); 4.67 (d, $J=5.8$ Hz, 1H, H-2); 4.49 (dd, $J=3.8$, 6.3 Hz, 1H, H-4); 4.46 (d, $J=11.7$ Hz, 1H, OCH_2Ph); 3.22–3.42 (m, 2H, H-5); 1.36 (d, $J=6.3$ Hz, 6H, $CH(CH_3)_2$); 1.30 (s, 3H, $C(CH_3)_2$), 1.49 (s, 3H, $C(CH_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 191.9 (C-6); 159.8 (C-7); 137.0 (C-11); 127.7, 128.0, 128.3 (C-12,13,14); 112.4 (C-15); 104.5 (C-1); 84.8 (C-2); 79.6 (C-3); 74.9 (C-4); 70.6 (C-8); 68.5 (C-10); 38.6 (C-5); 24.6, 25.8 ($C(CH_3)_2$); 21.4 ($CH(CH_3)_2$). MS (FAB+): *m/z* calculated for $C_{20}H_{26}O_7$ $[M]^+$ 378.4, found $[M+1, 100\%]^+$ 379.

3.1.14. Isopropyl 5-deoxy-5-deuterio-6-oxo-1-*O*-benzyl-2,3-*O*-isopropylidene-α-D-*galacto*-heptofuranuronate or Isopropyl 5-deoxy-5-deuterio-6-oxo-1-*O*-benzyl-2,3-*O*-isopropylidene-α-D-*talo*-hepto furanuronate 5d-d_1. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 2255 (C–D); 1748, 1726 (C=O). ^1H NMR (400 MHz), δ (ppm): 7.30–7.40 (m, 5H); 5.16 (h, $J=6.3$ Hz, $CH(CH_3)_2$); 5.06 (s, 1H, H-1); 4.80 (dd, $J=5.8$, 3.8 Hz, 1H, H-3); 4.68 (d, $J=11.7$ Hz, 1H, OCH_2Ph); 4.67 (d, $J=5.8$ Hz, 1H, H-2); 4.49 (dd, $J=3.8$, 6.3 Hz, 1H, H-4); 4.46 (d, $J=11.7$ Hz, 1H, OCH_2Ph); 3.22–3.27 (m, 0.5H, H-5); 3.32–3.38 (m, 0.5H, H-5); 1.36 (d, $J=6.3$ Hz, 6H, $CH(CH_3)_2$); 1.30 (s, 3H, $C(CH_3)_2$), 1.49 (s, 3H, $C(CH_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 191.9 (C-6); 159.8 (C-7); 137.0 (C-11); 127.7, 128.0, 128.3 (C-12,13,14); 112.4 (C-15); 104.5 (C-1); 84.8 (C-2); 79.6 (C-3); 74.9 (C-4); 70.6 (C-8); 68.5 (C-10); 38.3 (t, $J=19.6$ Hz, C-5); 24.6, 25.8 ($C(CH_3)_2$); 21.4 ($CH(CH_3)_2$). MS (FAB+): *m/z* calculated for $C_{20}H_{25}DO_7$ $[M]^+$ 379.4, found $[M+1, 88\%]^+$ 380.

3.1.15. Isopropyl 5-deoxy-5,5-dideuterio-6-oxo-1-*O*-benzyl-2,3-*O*-isopropylidene-D-*lyxo*-heptofuranuronate 5d-d_2. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 2255 (C–D); 1748, 1726 (C=O). ^1H NMR (400 MHz), δ (ppm): 7.30–7.40 (m, 5H); 5.16 (h, $J=6.3$ Hz, $CH(CH_3)_2$); 5.06 (s, 1H, H-1); 4.80 (dd, $J=5.8$, 3.8 Hz, 1H, H-3); 4.68 (d, $J=11.7$ Hz, 1H, OCH_2Ph); 4.67 (d, $J=5.8$ Hz, 1H, H-2); 4.49 (dd, $J=3.8$, 6.3 Hz, 1H, H-4); 4.46 (d, $J=11.7$ Hz, 1H, OCH_2Ph); 1.36 (d, $J=6.3$ Hz, 6H, $CH(CH_3)_2$); 1.30 (s, 3H, $C(CH_3)_2$), 1.49 (s, 3H, $C(CH_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 191.9 (C-6); 159.8 (C-7); 137.0 (C-11); 127.7, 128.0, 128.3 (C-12,13,14); 112.4 (C-15); 104.5 (C-1); 84.8 (C-2); 79.6 (C-3); 74.9 (C-4); 70.6 (C-8); 68.5 (C-10); 38.3 (t, $J=19.6$ Hz, C-5); 24.6, 25.8 ($C(CH_3)_2$); 21.4 ($CH(CH_3)_2$). MS (FAB+): *m/z* calculated for $C_{20}H_{24}D_2O_7$ $[M]^+$ 380.4, found $[M+1, 100\%]^+$ 381.

3.1.16. Isopropyl 6-deoxy-7-oxo-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-octo pyranuronate 5e. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 1740, 1726 (C=O). ^1H NMR (400 MHz), δ (ppm): 5.48 (d, $J=5.0$ Hz, 1H, H-1); 5.15 (h, $J=6.5$ Hz, 1H, C*H*$(CH_3)_2$); 4.65 (dd, $J=2.5$, 7.8 Hz, 1H, H-3); 4.38 (dd, $J=1.7$, 7.1 Hz, 1H, H-5); 4.33 (dd, $J=5.0$, 2.5 Hz, 1H, H-2); 4.27 (dd, $J=7.8$, 1.7 Hz, 1H, H-4); 3.04–3.32 (m, 2H, H-6); 1.34 (s, 3H, C(C*H*$_3)_2$); 1.35 (s, 3H, C(C*H*$_3)_2$); 1.47 (s, 3H, C(C*H*$_3)_2$); 1.60 (s, 3H, C(C*H*$_3)_2$); 1.35 (d, $J=6.5$ Hz, 3H, CH(C*H*$_3)_2$, 1.36 (d, $J=6.5$ Hz, 3H, CH(C*H*$_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 191.7 (C-7); 159.8 (C-8); 108.4, 108.9 (C-11,12); 95.9 (C-1); 71.7 (C-4); 70.4 (C-3); 70.1 (C-2); 69.9 (C-9); 63.3 (C-5); 39.8 (C-6); 24.1, 24.6, 25.5, 25.6 (C(*C*H$_3)_2$); 21.2 (CH(*C*H$_3)_2$). MS (FAB+): *m/z* calculated for $C_{17}H_{26}O_8$ $[M]^+$ 358.4, found $[M+1, 88\%]^+$ 359.

3.1.17. Isopropyl 6-deoxy-6-deuterio-7-oxo-1,2:3,4-di-*O*-isopropylidene-D or L-*glycero*-α-D-*galacto*-octopyranuronate 5e-d_1. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 2256 (C–D); 1740, 1726 (C=O). ^1H NMR (400 MHz), δ (ppm): 5.48 (d, $J=5.0$ Hz, 1H, H-1); 5.15 (h, $J=6.5$ Hz, 1H, C*H*$(CH_3)_2$); 4.65 (dd, $J=2.5$, 7.8 Hz, 1H, H-3); 4.38 (dd, $J=1.7$, 7.1 Hz, 1H, H-5); 4.33 (dd, $J=5.0$, 2.5 Hz, 1H, H-2); 4.27 (dd, $J=7.8$, 1.7 Hz, 1H, H-4); 3.04–3.08 (m, 0.5H, H-6); 3.24–3.29 (m, 0.5H, H-6); 1.34 (s, 3H, C(C*H*$_3)_2$); 1.35 (s, 3H, C(C*H*$_3)_2$); 1.47 (s, 3H, C(C*H*$_3)_2$); 1.60 (s, 3H, C(C*H*$_3)_2$); 1.35 (d, $J=6.5$ Hz, 3H, CH(C*H*$_3)_2$), 1.36 (d, $J=6.5$ Hz, 3H, CH(C*H*$_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 191.7 (C-7); 159.8 (C-8); 108.4, 108.9 (C-11,12); 95.9 (C-1); 71.7 (C-4); 70.4 (C-3); 70.1 (C-2); 69.9 (C-9); 63.3 (C-5); 39.5 (t, $J=19.5$ Hz, C-6); 24.1, 24.6, 25.5, 25.6 (C(*C*H$_3)_2$); 21.2 (CH(*C*H$_3)_2$). MS (FAB+): *m/z* calculated for $C_{17}H_{25}DO_8$ $[M]^+$ 359.4, found $[M+1, 88\%]^+$ 360.

3.1.18. Isopropyl 6-deoxy-6,6-dideuterio-7-oxo-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-octopyranuronate 5e-d_2. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 2256 (C–D); 1740, 1726 (C=O). ^1H NMR (400 MHz), δ (ppm): 5.48 (d, $J=5.0$ Hz, 1H, H-1); 5.15 (h, $J=6.5$ Hz, 1H, C*H*$(CH_3)_2$); 4.65 (dd, $J=2.5$, 7.8 Hz, 1H, H-3); 4.38 (dd, $J=1.7$, 7.1 Hz, 1H, H-5); 4.33 (dd, $J=5.0$, 2.5 Hz, 1H, H-2); 4.27 (dd, $J=7.8$, 1.7 Hz, 1H, H-4); 1.34 (s, 3H, C(C*H*$_3)_2$); 1.35 (s, 3H, C(C*H*$_3)_2$); 1.47 (s, 3H, C(C*H*$_3)_2$); 1.60 (s, 3H, C(C*H*$_3)_2$); 1.35 (d, $J=6.5$ Hz, 3H, CH(C*H*$_3)_2$); 1.36 (d, $J=6.5$ Hz, 3H, CH(C*H*$_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 191.7 (C-7); 159.8 (C-8); 108.4, 108.9 (C-11,12); 95.9 (C-1); 71.7 (C-4); 70.4 (C-3); 70.1 (C-2); 69.9 (C-9); 63.3 (C-5); 39.5 (t, $J=19.5$ Hz, C-6); 24.1, 24.6, 25.5, 25.6 (C(*C*H$_3)_2$); 21.2 (CH(*C*H$_3)_2$). MS (FAB+): *m/z* calculated for $C_{17}H_{24}D_2O_8$ $[M]^+$ 360.4, found $[M+1, 88\%]^+$ 361.

3.1.19. Isopropyl 3-deoxy-2-oxo-6-*O*-dimethyl-*tert*-butylsilyl-4,5:7,8-di-*O*-iso propylidene-D-*gluco*-octuronate 5f. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 1726 (C=O). ^1H NMR (400 MHz), δ (ppm): 5.08 (h, $J=6.2$ Hz, 1H, C*H*$(CH_3)_2$); 4.40 (m, 1H, H-4); 3.70–4.10 (m, 5H, H-5,6,7,8); 3.01–3.22 (m, 2H, H-3); 1.28 (d, $J=6.2$ Hz, 6H, CH(C*H*$_3)_2$); 1.23 (s, 3H, C(C*H*$_3)_2$); 1.29 (s, 3H, C(C*H*$_3)_2$); 1.31 (s, 3H, C(C*H*$_3)_2$); 1.32 (s, 3H, C(C*H*$_3)_2$); 0.84 (s, 9H, SiC(C*H*$_3)_3$); 0.07 (s, 3H, Si(C*H*$_3)_2$; 0.08 (s, 3H, Si(C*H*$_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 191.9 (C-2); 160.3 (C-1); 108.7, 108.8 (C-12,13); 73.3, 76.2, 82.8 (C-5,6,7); 71.9 (C-4); 70.5 (C-9); 66.8 (C-8); 43.1 (C-3); 25.8 (SiC(*C*H$_3)_3$); 25.1, 26.2, 26.7, 26.8 (C(*C*H$_3)_2$); 21.4 (CH(*C*H$_3)_2$); 18.1 (Si*C*(CH$_3)_3$); −4.6, −4.1 (Si(*C*H$_3)_2$). MS (FAB+): *m/z* calculated for $C_{23}H_{42}O_8Si$ $[M]^+$ 474.7, found $[M, 5\%]^+$ 474; $[M-Me, 10\%]^+$ 459.

3.1.20. Isopropyl 3-deuterio-2-oxo-6-*O*-dimethyl-*tert*-butylsilyl-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*ido*-octuronate or isopropyl 3-deuterio-2-oxo-6-*O*-dimethyl-*tert*-butylsilyl-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*gulo*-octuronate 5f-d_1. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 1726 (C=O). ^1H NMR (400 MHz), δ (ppm): 5.08 (h, $J=6.2$ Hz, 1H, C*H*$(CH_3)_2$); 4.40 (m, 1H, H-4); 3.70–4.10 (m, 5H, H-5,6,7,8); 3.00–3.06 (m, 0.5H, H-3); 3.13–3.17 (m, 0.5H, H-3); 1.28 (d, $J=6.2$ Hz, 6H, CH(C*H*$_3)_2$); 1.23 (s, 3H, C(C*H*$_3)_2$); 1.29 (s, 3H, C(C*H*$_3)_2$); 1.31 (s, 3H, C(C*H*$_3)_2$); 1.32 (s, 3H, C(C*H*$_3)_2$); 0.84 (s, 9H, SiC(C*H*$_3)_3$); 0.07 (s, 3H, Si(C*H*$_3)_2$; 0.08 (s, 3H, Si(C*H*$_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 191.9 (C-2); 160.3 (C-1); 108.7, 108.8 (C-12,13); 73.3, 76.2, 82.8 (C-5,6,7); 71.9 (C-4); 70.5 (C-9); 66.8 (C-8); 42.8 (t, $J=19.4$ Hz, C-3); 25.8 (SiC(*C*H$_3)_3$); 25.1, 26.2, 26.7, 26.8 (C(*C*H$_3)_2$); 21.4 (CH(*C*H$_3)_2$); 18.1 (Si*C*(CH$_3)_3$); −4.6, −4.1 (Si(*C*H$_3)_2$). MS (FAB+): *m/z* calculated for $C_{23}H_{41}DO_8Si$ $[M]^+$ 475.7, found $[M, 10\%]^+$ 475; $[M-Me, 10\%]^+$ 460.

3.1.21. Isopropyl 3,3-dideuterio-2-oxo-6-*O*-dimethyl-*tert*-butylsilyl-4,5:7,8-di-*O*-isopropylidene-D-*gluco*-octuronate 5f-d_2. Yellow oil. IR (NaCl, ν_{max}, cm^{-1}) 1726 (C=O). ^1H NMR (400 MHz), δ (ppm): 5.08 (h, $J=6.2$ Hz, 1H, C*H*$(CH_3)_2$); 4.40 (m, 1H, H-4); 3.70–4.10 (m, 5H, H-5,6,7,8); 1.28 (d, $J=6.2$ Hz, 6H, CH(C*H*$_3)_2$); 1.23 (s, 3H, C(C*H*$_3)_2$); 1.29 (s, 3H, C(C*H*$_3)_2$); 1.31 (s, 3H, C(C*H*$_3)_2$); 1.32 (s, 3H, C(C*H*$_3)_2$); 0.84 (s, 9H, SiC(C*H*$_3)_3$); 0.07 (s, 3H, Si(C*H*$_3)_2$); 0.08 (s, 3H, Si(C*H*$_3)_2$). ^{13}C NMR (100 MHz), δ (ppm): 191.9 (C-2); 160.3 (C-1); 108.7, 108.8 (C-12,13); 73.3, 76.2, 82.8 (C-5,6,7); 71.9 (C-4); 70.5 (C-9); 66.8 (C-8); 42.8 (t, $J=19.4$ Hz, C-3); 25.8 (SiC(*C*H$_3)_3$); 25.1, 26.2, 26.7, 26.8 (C(*C*H$_3)_2$); 21.4 (CH(*C*H$_3)_2$); 18.1 (Si*C*(CH$_3)_3$); −4.6, −4.1 (Si(*C*H$_3)_2$). MS (FAB+): *m/z* calculated for $C_{23}H_{40}D_2O_8Si$ $[M]^+$ 476.7, found $[M, 10\%]^+$ 476; $[M-Me, 10\%]^+$ 461.

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References and notes

1. (a) Belakhov, V.; Dovgolevsky, E.; Rabkin, E.; Shulami, S.; Shoham, Y.; Baasov, T. *Carbohydr. Res.* **2004**, *339*, 385–392. (b) Xu, X.; Wang, J.; Grison, C.; Petek, S.; Coutrot, P.; Birck, M.; Woodard, R. W.; Gatti, D. L. *Drug Des. Discov.* **2003**, *18*, 1–9. (c) Baasov, T.; Thack, R.; Sheffer-Dee-Noor, S.; Raetz, C. R.; Whifield, C. *Annu. Rev. Biochem.* **2002**, *71*, 635–700. (d) Birck, M. R.; Woodard, R. W. *J. Mol. Evol.* **2001**, *52*, 205–214. (e) Belakhov, V. *Curr. Org. Chem.* **2001**, *5*, 127–138. Radaev, S.; Dastidar, P.; Patel, M.; Woodard, R. W. *J. Biol.*

Chem. **2000**, *275*, 9476–9484. (f) Subramaniam, P. S; Xie, G.; Xia, T.; Jensen, R. A. J. *Bacteriol.* **1998**, *180*, 119–127. (g) Coutrot, P.; Dumarcay, S.; Finance, C.; Tabyaoui, M.; Tabyaoui, B.; Grison, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 949–952. (h) Du, S.; Faiger, H.; Belakhov, V.; Baasov, T. *Bioorg. Med. Chem.* **1999**, *7*, 2671–2682. Jenson, R. A. *J. Bacteriol.* **1998**, *180*, 119–127. (i) Raetz, C. R. *Annu. Rev. Biochem.* **1990**, *59*, 129–170. (j) Haslam, E. *Shikimic Acid. Metabolism and Metabolites*; Wiley: New York, 1993. (k) Walsh, C. T.; Liu, J.; Rusnak, F.; Sakaitani, M. *Chem. Rev.* **1990**, *90*, 1105–1129. (l) Bentley, R. *Crit. Rev. Biochem. Mol. Biol.* **1990**, *25*, 307–384. (m) Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323–389. (n) IP, K.; Doy, C. H. *Eur. J. Biochem.* **1979**, *98*, 431–440. (o) Simpson, R. J.; Davidson, B. E. *Eur. J. Biochem.* **1976**, *70*, 501–507 and references cited therein.

2. Kosma, P.; Strobl, M.; Hofinger, A.; Duus, J. O.; Petersen, B. O.; Bock, K.; Brade, H. *Monatsh. Chem.* **2002**, *133*, 211–220.
3. Gore, M. P.; Nanjappan, P.; Hoops, G. C.; Woodard, R. W. *J. Org. Chem.* **1990**, *55*, 758–760.
4. Hedstrom, L.; Abeles, R. *Biochem. Biophys. Res. Commun.* **1988**, *157*, 816.
5. (a) Wilson, C. L. *J. Chem. Soc.* **1936**, 1550. (b) Hsu, S. K.; Ingold, C. K.; Wilson, C. L. *J. Chem. Soc.* **1938**, 78. (c) Ives, D. J. G.; Wilson, C. L. *J. Chem. Soc.* **1938**, 81.
6. (a) El Nemr, A.; Tsuchiya, T. *Tetrahedron Lett.* **1998**, 3543–3546. (b) Crombie, L.; Dove, R. V. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1695. (c) Murray, R. W.; Shiang, D. L.; Singh, M. *J. Org. Chem.* **1991**, *56*, 3677. (d) Guthrie, R. D.; Nicolas, E. C. *J. Am. Chem. Soc.* **1981**, *103*, 4637–4638.
7. (a) Armanath, V.; Armanath, K. *J. Org. Chem.* **1995**, *60*, 301–307. (b) Kenar, J. A.; Nickon, A. *Tetrahedron* **1997**, *53*, 14871–14874.
8. (a) Vedejs, E.; Kruger, A. W.; Lee, N.; Sakata, S. T.; Stec, M.; Suna, E. *J. Am. Chem. Soc.* **2000**, *122*, 4602–4607. (b) Yangagisawa, A.; Kikuchi, T.; Kuribayashi, T.; Yamamoto, H. *Tetrahedron* **1998**, *54*, 10253–10264. (c) Pfeffer, P. E.; Silbert, L. S.; Chrinko, J. M., Jr. *J. Org. Chem.* **1972**, *37*, 451.
9. Berté-Verrando, S.; Nief, F.; Patois, C.; Savignac, P. *J. Chem. Soc, Perkin Trans. 1* **1994**, 821–824.
10. Seebach, D.; Boes, M.; Naet, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398.
11. (a) Krause, N.; Ebert, S.; Haubrich, A. *Liebigs Ann. Recl.* **1997**, 2409–2418. (b) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373–1393.
12. Gerlach, U.; Hünig, S. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1283–1285.
13. Eames, J.; Weerasooriya, N.; Coumbarides, G. S. *Eur. J. Org. Chem.* **2002**, 181–187.
14. Eames, J.; Coumbarides, G. S.; Suggate, M. J.; Weerasooriya, N. *Eur. J. Org. Chem.* **2003**, 634–641.
15. Grison, C.; Petek, S.; Coutrot, P. *Synlett* **2005**, 331–333.
16. Coumbarides, G. S.; Eames, J.; Weerasooriya, N. *Tetrahedron Lett.* **2000**, *41*, 5753–5756.
17. Bodepudi, V. R.; Le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3265–3269.
18. Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1998.
19. (a) Czernecki, S.; Valéry, J. M. *J. Chem. Soc., Chem. Commun.* **1988**, 1515–1516. (b) Coutrot, P.; Grison, C.; Tabyaoui, M. *Tetrahedron Lett.* **1993**, *34*, 5089–5092.

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The novel hydrogen bonding motifs and supramolecular patterns in 2,4-diaminopyrimidine–nitrobenzoate complexes

N. Stanley,[a] P. T. Muthiah,[a,*] S. J. Geib,[b] P. Luger,[c] M. Weber[c] and M. Messerschmidt[c]

[a]*School of Chemistry, Bharathidasan University, Tiruchirappalli 620 024, India*
[b]*Department of Chemistry, University of Pittsburgh, PA 15260, USA*
[c]*Institute of Chemistry/Crystallography, Free University of Berlin, Berlin, Germany*

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Abstract—The crystal structures of the hydrogen-bonded, 1:1 molecular complexes of nitro (*ortho*, *meta* and *para*) benzoic acids with two 2,4-diaminopyrimidine derivatives (trimethoprim and pyrimethamine) have been investigated in detail (**1**–**5**). In all the crystal structures except pyrimethamine *o*-nitrobenzoate (**3**), the carboxylate group of the respective anions interacts with the protonated trimethoprim or pyrimethamine moiety in a linear fashion through a pair of N–H···O hydrogen bonds to form a cyclic hydrogen-bonded motif. This cyclic hydrogen-bonded motif is self-organized in different ways to get the novel types of hydrogen bonding motifs and supramolecular patterns. In the crystal structure of pyrimethamine *o*-nitrobenzoate (**3**), the chelating type of hydrogen bonding motif is self-organized to get a helical supramolecular pattern. In the crystal structures of both pyrimethamine *m*-nitrobezoate (**4**) and pyrimethamine *p*-nitrobenzoate (**5**), a novel type of an alternate arrangement of DADA (D represents donor and A represents acceptor) and DDAA arrays is present, resulting in the formation of hydrogen-bonded ladders.

1. Introduction

Supramolecular chemistry and crystal engineering are closely related fields.[1–3] Both involve non-covalent interactions as their basis and have expanded the frontiers of chemical science dealing with many physical and biological phenomena.[4–7] Non-covalent interactions are of great biological interest because of the fact that the biomolecules are usually made from loose aggregates that are held together by weak interactions. These interactions are dynamic in nature and are responsible for most of the processes occurring in living systems.[4] Among non-covalent interactions, hydrogen bonding plays the most important role in chemistry, biology and material science.[8,9] Identifying hydrogen-bonded motifs or supramolecular synthons is clearly very important to crystal engineering.[4,10] Hydrogen bonding is the most important interaction in molecular recognition because of its strength and directional properties. In many self-assembling structures,[11] the components are held together by arrays of double (for instance the AT base pair), triple (for instance, the GC base pair), quadruple (for instance, 2-ureido-4-pyrimidones) and quintuple hydrogen bonds.[8,12] More stable structures of self-complementary modules that dimerize through the formation of up to six hydrogen bonds have been synthesized. The infinite hydrogen-bonded structures (self assemblies) are the nanotubes based on cyclic peptides synthesized by Ghadiri and co-workers.[13] These peptide nanotubes have antibiotic properties. Pyrimidine and aminopyrimidine derivatives are biologically very important compounds and they occur in nature as components of nucleic acids (cytosine, uracil and thymine). The carboxyl group and also the carboxylate anion can be involved in hydrogen bonding interactions with aminopyrimidines.[14] These interactions play a vital role in protein–nucleic acid interactions. Such interactions are involved in many drug–protein recognition processes.[15] A lot of monoaminopyrimidine (2-amino-pyrimidine)-carboxyl group interactions have been reported.[16–20] Some reports on triaminopyrimidine (2,4,6-triaminopyrimidine)-carboxylate interactions are also available in the literature.[21] The diaminopyrimidines [trimethoprim (TMP) and pyrimethamine(PMN)] have been used in this study. They are very good antifolate drugs, which selectively inhibit the bacterial dihydrofolate reductase enzyme (DHFR) through several hydrogen bonds.[22] We have already reported a number of diamino-pyrimidine–carboxylate complexes from our lab.[23–31,34–38,51]

Keywords: Aminopyrimidine–carboxylate interactions; Crystal engineering; Supramolecular chemistry; Non-covalent interactions; Self-organization.
* Corresponding author. Tel.: +91 431 2407053; fax: +91 431 2407045; e-mail: tommtrichy@yahoo.co.in

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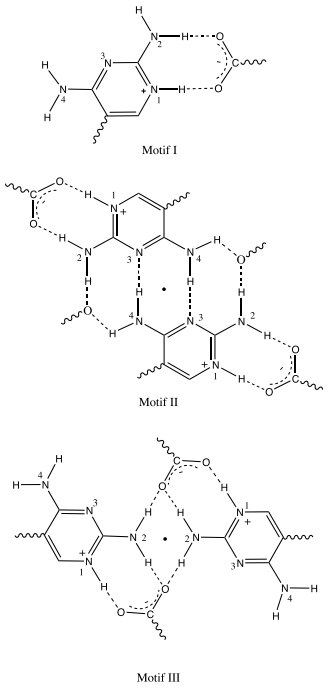
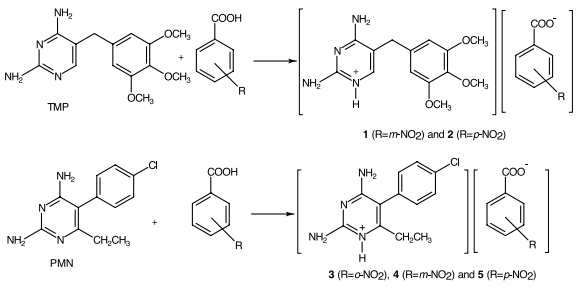


Figure 1. Most predominant hydrogen bonding motifs in 2,4-diaminopyrimidine–carboxylate complexes.

We believe that two types of hydrogen bonding motifs, DADA (D represents donor and A represents acceptor) array and DDAA array, play a predominant role in stabilizing the crystal structures (motifs II and III) (Fig. 1). The variation of the supramolecular organization depending upon the nature of the 2,4-diaminopyrimidine substituents (trimethoxybenzyl or *p*-chlorophenyl) and nature of the side chain R, attached to the COOH group resulting in the formation of different kinds of supramolecular motifs and supramolecular patterns have been studied. It has been observed that benzoic acid only forms the O-mediated hydrogen-bonded motif (motif II) with base pairing and oxygen bridging in the crystal structure of TMP benzoate benzoic acid.[33] In order to investigate the type of hydrogen bonding patterns formed in the 2,4-diaminopyrimidine-nitrobenzoates, crystals were prepared and their structures were analysed. In this paper, we present the new types of hydrogen-bonded motifs and the novel hydrogen-bonded supramolecular patterns in the crystal structures of diaminopyrimdines with nitrobenzoate structures (Scheme 1) [diaminopyrimdine = TMP or PMN], namely TMP-*m*-nitrobenzoate (**1**), TMP-*p*-nitrobenzoate (**2**), PMN-*o*-nitrobenzoate (**3**), PMN-*m*-nitrobenzoate (**4**) and PMN-*p*-nitrobenzoate (**5**).



Scheme 1.

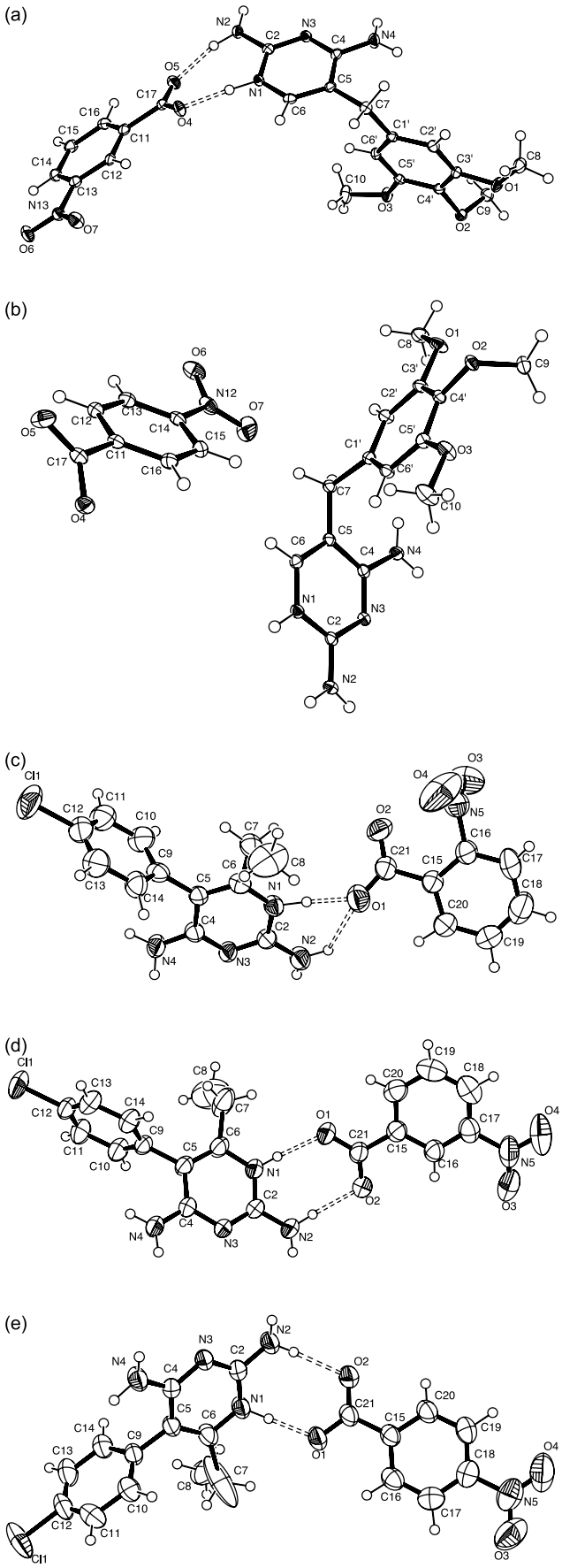


Figure 2. ORTEP view of compounds **1–5** (a–e). Ellipsoids are drawn at the 30% probability level: dashed lines represent hydrogen bonds.

2. Results and discussion

The ORTEP views of the compounds **1–5** are shown in Figure 2. In all the crystal structures (**1–5**), the TMP and PMN moieties are protonated at N1, as evident from the increase in the ring angle at N1 [from 115.46(5)° in neutral TMP[39] to 119.2(2)° in the compound (**1**), the corresponding angle in compound **2** is 119.8(1)°; from 116.3(2)° (molecule A) and 116.1(2)° (molecule B) in neutral[40] PMN to 121.3(5)° in compound **3**, 120.8(3)° in compound **4** and 120.5(3)° in compound **5**]. These protonated hydrogen atoms were located from the difference Fourier map and were refined isotropically. The conformation of the TMP molecule is described by two torsion angles [(τ_1) C4–C5–C7–C1′ and (τ_2) C5–C7–C1′–C2′] and a dihedral angle between the phenyl and pyrimidine rings. The torsion angles observed in this study have been compared with the corresponding angles observed in other related TMP salts in Table 1. The dihedral angles observed in this study have been compared with the corresponding angles observed in other related TMP salts in Table 2. The 3D structures of DHFR–TMP complexes[41] indicate that the torsion angles of TMP play an important role in inhibiting the active sites of the enzymes.

The conformation of the PMN moieties is described by two angles. The first is the dihedral angle between the 2,4-diaminopyrimidine and the *p*-chlorophenyl planes. The

Table 1. Comparison of torsion angles (°) describing the conformation adopted by TMP moiety in related structures

S. No.	Compound		τ_1(C4–C5–C7–C1′)/(°)	τ_2(C5–C7–C1′-2′)/(°)	Reference
1	TMP neutral (form I)		−89.4(1)	153.3(1)	39
2	TMP nitrate		77.1(3)	−158.8(2)	23
3	TMP salicylate dihydrate		−74.3(6)	154.3(4)	24
4	TMP hydrogen maleate		−70.1(5)	144.2(4)	25
5	TMP formate		−70.2(2)	123.2(2)	26
6	TMP perchlorate		78.4(2)	−157.5(1)	27
7	TMP sulfate trihydrate	Mol I	−73.3(2)	−120.6(5)	28
		Mol II	−94.5(2)	158.3(7)	
8	TMP hydrogen glutarate		73.06(6)	127.3(4)	29
9	TMP salicylate methanol solvate		−74.6(3)	155.2(2)	30
10	TMP *p*-toluenesulfonate		−153.8(2)	−76.4(3)	31
11	TMP sulfanilate mono hydrate		66.1(4)	−135.0(3)	31
12	TMP 3-caryboxy-4-hydroxybenzene sulfonate dihydrate		175.8(5)	89.4(7)	31
13	TMP acetate		−77.5(1)	157.2(1)	32
14	TMP benzoate benzoic acid	Mol I	−74.4(5)	157.0(4)	33
		Mol II	−78.2(1)	149.2(3)	
15	TMP trifluoroacetate		−81.61(3)	160.01(2)	34
16	TMP terephthalate terephthalic acid		86.8(2)	−153.8(1)	35
17	TMP *m*-chlorobenzoate		−72.4(4)	28.3(3)	36
18	TMP *m*-chlorobenzoate dihydrate		167.4(3)	−103.4(3)	36
19	TMP sorbate dehydrate		68.2(2)	−154.6(2)	51
20	TMP *o*-nitrobenzoate		72.4(4)	−144.1(3)	51
21	TMP *m*-nitrobenzoate (**2**)		−73.6(2)	158.2(2)	Present study
22	TMP *p*-nitrobenzoate (**3**)		−75.79(1)	151.3(1)	Present study

Table 2. Comparison of dihedral angles (°) between the pyrimidine and phenyl rings of TMP in the related structures

S. No.	Compound	Dihedral angle	Reference
1	TMP neutral (form I)	71.33(2)	39
2	TMP nitrate	93.8(1)	23
3	TMP salicylate dihydrate	89.5(4)	24
4	TMP hydrogen maleate	92.0(2)	25
5	TMP formate	97.8(1)	26
6	TMP perchlorate	83.7(2)	27
7	TMP sulfate trihydrate	758(9)	28
		69.9(6)	
8	TMP hydrogen glutarate	97.5(2)	29
9	TMP salicylate methanol solvate	89.5(4)	30
10	TMP p-toluenesulfonate	70.9(1)	31
11	TMP sulfanilate mono hydrate	87.0(1)	31
12	TMP 3-caryboxy-4-hydroxybenzene sulfonate dihydrate	79.4(3)	31
13	TMP benzoate benzoic acid	69.8(4)	33
14	TMP trifluoroacetate	83.7(3)	34
15	TMP terephthalate terephthalic acid	72.3(1)	35
16	TMP *m*-chlorobenzoate	74.2(2)	36
17	TMP *m*-chlorobenzoate dihydrate	71.3(1)	36
18	TMP sorbate dihydrate	81.7(8)	51
19	TMP *o*-nitrobenzoate	87.2(2)	51
18	TMP *m*-nitrobenzoate (**2**)	85.6(1)	Present study
19	TMP *p*-nitrobenzoate (**3**)	86.0(2)	Present study

Table 3. Comparison of the dihedral angles (°) involving related PMN moieties

S. No.	Compound		Dihedral angle/(°)	Reference
1	PMN neutral	Mol I	74.4(1)	40
		Mol II	82.4(1)	
2	PMN formate		76.7(1)	37
3	PMN hydrogen maleate		72.1(2)	38
4	PMN hydrogen succinate		72.9(1)	38
5	PMN hydrogen phthalate		75.2(1)	38
6	PMN hydrogen glutarate		74.8(1)	37
7	PMN *o*-nitrobenzoate		88.7(3)	Present study
8	PMN *m*-nitrobenzoate		86.9(2)	Present study
9	PMN *p*-nitrobenzoate		86.0(2)	Present study

second one is the deviation of the ethyl group from the pyrimidine plane. The angle between pyrimidine and phenyl ring is 88.7(3)° in compound **3**, and the corresponding angle in compound **4** is 86.9(2)° and compound **5** is 86.0(2)°. These values are close to the value observed in the modelling studies on the DHFR–PMN complexes.[42] The dihedral angles observed in this study have been compared with the corresponding angles observed in other PMN salts in Table 3. The torsion angle [C5–C6–C7–C8] is 88.7(3)° in compound **3**, and the corresponding angle in compound **4** is 86.9(2)° and compound **5** is 92.7(6)°. Modelling studies of the DHFR–PMN complexes[42] indicate that the dihedral angle plays an important role in proper docking of the drug molecule in the active site of the enzyme and that the change in the torsion angle representing the orientation of the ethyl group does not affect the overall binding energy of the enzyme–drug complex.

Three types of base pairings are possible in 2,4-diaminopyrimidine motifs (Fig. 3). The schematic representation of the hydrogen-bonded motifs observed in this study is shown in Figure 4. In the crystal structure of neutral TMP, the 2,4-diaminopyrimidine motifs (TMP) are centrosymmetrically paired through a pair of N–H···N hydrogen bonds involving 2-amino and N1 of the pyrimidine moiety on one side (motif IV). On the other side also, pyrimidine motifs are centrosymmetrically paired through a pair of N–H···N hydrogen bonds involving 4-amino and N3 of the pyrimidine moiety (motif V). These two types of base-pairs lead to a hydrogen-bonded supramolecular ribbon like pattern. Since N1 is protonated in 2,4-diaminopyrimidine-carboxylate salts (**1**–**5**), the N2–H···N1 base-pair (motif IV) has not been observed. As expected, in all the crystal structures (**1**,**2**,**4** and **5**), the carboxylate group of the

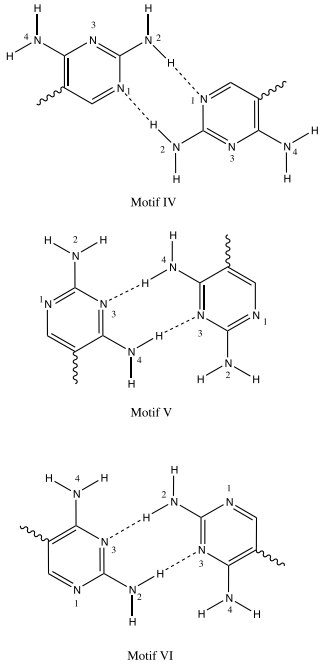


Figure 3. Three types of base pairings possible in 2,4-diaminopyrimidine motifs.

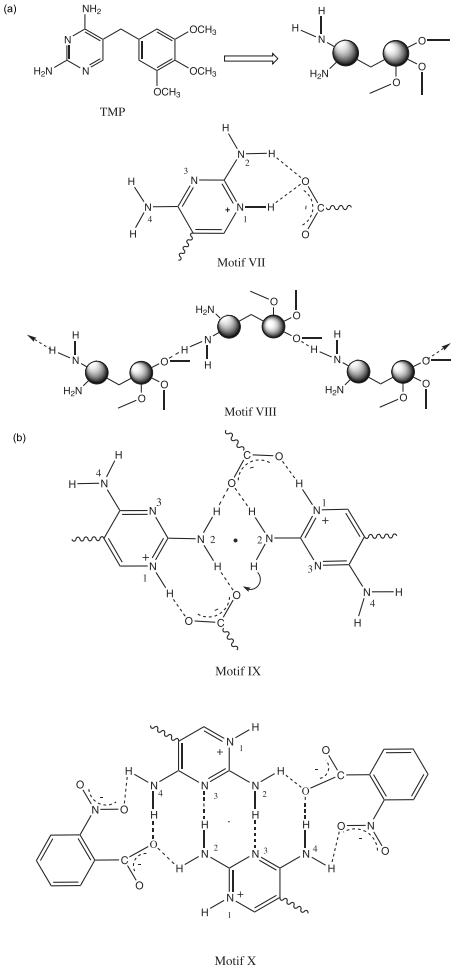


Figure 4. New types of hydrogen bonding motifs in 2,4-diaminopyrimidine motifs.

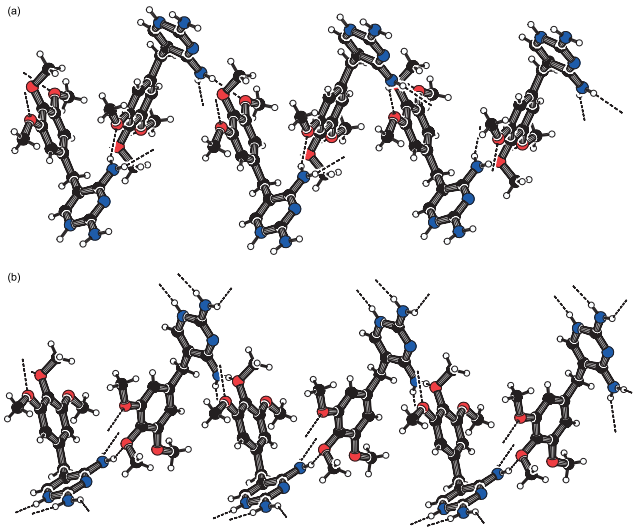


Figure 5. Head-to-tail arrangement of v-shaped TMP moieties resulting in the formation of spiral motif in compounds **1** and **2** (a and b).

respective anions (*o*-nitrobenzoate, *m*-nitrobenzoate and *p*-nitrobenzoate) interacts with the protonated TMP or PMN moiety in a linear fashion through a pair of N–H···O hydrogen bonds to form a cyclic hydrogen-bonded motif (motif I). This motif is a well known supramolecular synthon in aminopyrimidine-carboxylate salts and it is one of the 24 most frequently observed bimolecular cyclic hydrogen-bonded motifs in organic crystal structures.[43] It can be designated by the graph-set notation[44,45] $R_2^2(8)$. It is also observed in the crystal structure of DHFR–TMP complex[41] involving ASP-27 and TMP. The least-squares planes passing through the carboxylate group and the pyrimidine ring atoms involved in the specific hydrogen-bond interaction make an angle of 28.3(1)° in compound **1**,

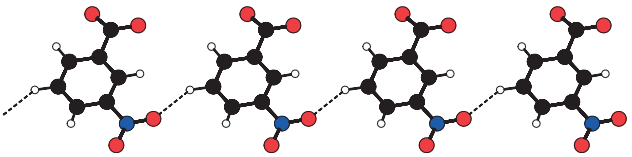


Figure 7. Hydrogen-bonded supramolecular chain involving nitrobenzoate ions in compound **1**.

and the corresponding angle in compound **2** is 16.9(3)°, in compound **4** is 43.94(1)° and in compound **5** is 46.37(1)°. In general, the cyclic hydrogen-bonded motif is a unique part of the motif in the diaminopyrimidine salts. Very interestingly, in the crystal structure of compound **3**, one of the oxygen atoms of the carboxylate group interacts with the protonated ring nitrogen (N1) and 2-amino group of the pyrimidine moiety through a pair of N–H···O hydrogen bonds. Here, the oxygen atom acts as a bifurcated acceptor, as shown in motif VII [with graph-set notation $R_2^1(6)$]. This type of motif has not been identified in the reported diaminopyrimidine salts. Figure 5a and b show a spiral hydrogen bonding pattern (motif VIII) as observed in the lattice of compounds **1** and **2**, respectively. Motif VIII, a helix, is formed with the head to tail arrangement of v-shaped TMP moieties via N–H···O hydrogen bonds. In compound **1**, the cyclic hydrogen-bonded motifs (I) are further bridged via N–H···O hydrogen bonds to form a hydrogen-bonded open helix motif (IX) [with graph-set notation $C_4^2(8)$]. The O–H···O hydrogen bonds responsible for this open helix have been observed recently.[46] This pattern is shown in Figure 6. The *m*-nitrobenzoate ions (syn-oriented) form a hydrogen-bonded supramolecular chain along the *c* axis, via C–H···O hydrogen bonds involving benzene hydrogen and one of the oxygen atoms of the nitro group. This pattern is shown in Figure 7. In compound **2**, the cyclic hydrogen-bonded motifs (motif I) are centrosymmetrically paired via N–H···O hydrogen bonds to form

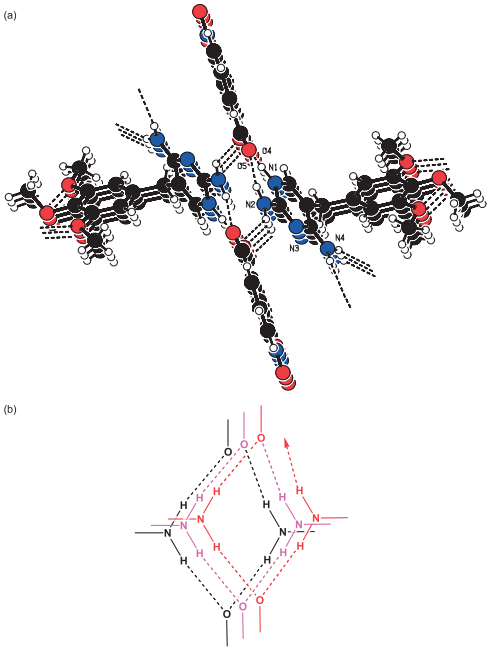


Figure 6. Hydrogen-bonded helical motif and its schematic diagram (a and b) in compound **1**.

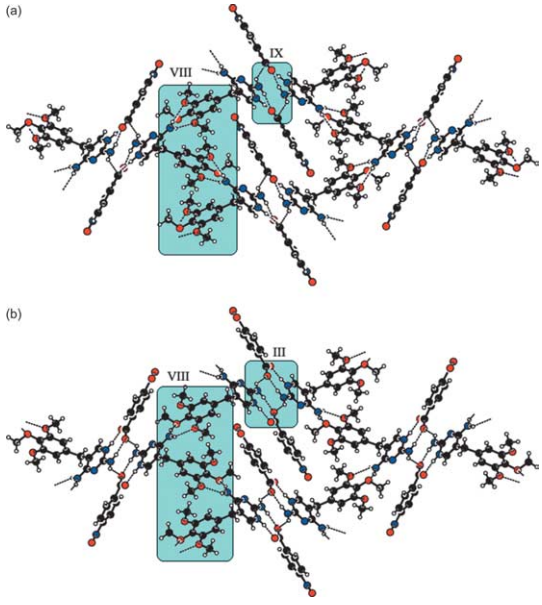


Figure 8. 2D sheet structures in compounds **1** and **2** (a and b) (motifs are highlighted).

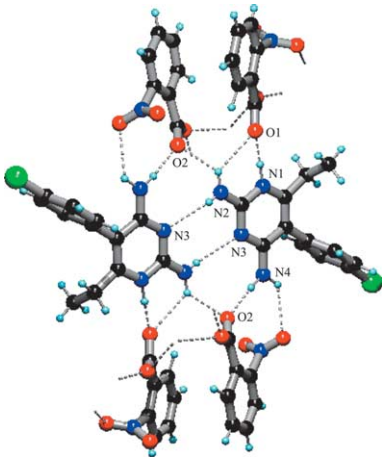


Figure 9. Multiple hydrogen bonding motif (X) in compound **3**.

a complementary DDAA arrays of quadruple hydrogen bonding, motif (III). This DDAA array can be represented by the graph-set notation $R_2^2(8)$, $R_4^2(8)$ and $R_2^2(8)$. The interactions between motif VIII, motif IX and C–H···O hydrogen bonds (supramolecular chain involving *m*-nitrobenzoate ions) form a 2D array in compound **1** (Fig. 8a). The interactions between motif III and motif VIII form a supramolecular 2D array in compound **2** (Fig. 8b). Usually, in the diaminopyrimidine–carboxylate complexes that have been reported, the pyrimidine moieties are centrosymmetrically paired through a pair of N–H···N hydrogen bonds [graph-set designation $R_2^2(8)$] involving the 4-amino group and the N3 atom of the pyrimidine moieties (motif V). But interestingly, in the crystal structure of compound **3**, the pyrimidine moieties are centrosymmetrically paired through a pair of N–H···N hydrogen bonds involving the 2-amino group and the N3 atom of the PMN moieties [with graph-set notation $R_2^2(8)$] (motif VI). The 2-amino group of the one member of the pair and the 4-amino group of the other member are bridged by an O atom of the carboxylate group, using a pair of N–H···O hydrogen bonds to form a eight-membered ring. This can be designated by the graph-set notation $R_3^1(8)$. This combination of hydrogen bonds results in the complementary DADA arrays of quadruple hydrogen-bonded patterns. This type of DADA array (involving N2 and N3 base pair) has not been identified in diaminopyrimidine-carboxylate salts. Normally DADA arrays (motif II) involving N4 and N3 base pairs has been observed in the reported diaminopyrimidine-carboxylate salts.[23–25,27,30–34,36–38] In compound **3**, the oxygen atom of the nitro group interacts with the 4-amino group of the DADA array motif through N–H···O hydrogen bond leading to the formation of a nine-membered ring [with graph-set notation $R_2^2(9)$]. The combination of DADA array and nine-membered rings results in the formation of a multiple hydrogen bonding pattern (motif X) (Fig. 9). The multiple hydrogen bonding motif can be represented in the form of five fused rings with graph-set notations $R_2^2(9)$, $R_3^2(8)$, $R_2^2(8)$, $R_3^2(8)$ and $R_2^2(9)$ in order. The multiple hydrogen bonding motifs are further extended through N–H···O hydrogen bonds leading to the formation of hydrogen-bonded supramolecular helical pattern. Here, one of the N4 hydrogen atoms is involved in the bifurcated hydrogen bonding. This type of hydrogen bonding pattern is shown in Figure 10. The hydrogen-bonded helical patterns extend to form a grid-like hydrogen bonding pattern. In the crystal structures of compounds **4** and **5**, two of the motifs(I) are paired through a pair of N–H···N hydrogen bonds involving N3 atom and 4-amino group of inversion related pyrimidine rings. This type of base pairing has been observed in many diaminopyrimidine-carboxylate salts. In addition to the base pairing, a hydrogen-bonded acceptor (O2) bridges the 4-amino and 2-amino groups on both sides of pairing leading to a complementary linear DADA array (motif II) of quadruple hydrogen bonds with the rings having the graph-set notations $R_3^2(8)$, $R_2^2(8)$ and $R_3^2(8)$. The two motifs(I) interact sidewise to produce the DDAA array of quadruple hydrogen bonds (motif III). In general, only any one of the motifs (DADA or DDAA array) has been identified in diaminopyrmidine-carboxylate salts. But interestingly, both DADA (motif II) and DDAA (motif III) array motifs are arranged in an alternate manner to form a hydrogen-bonded supramolecular ladder. This type of hydrogen bonding pattern is shown in Figure 11. The comparison of the hydrogen-bonded motifs in diaminopyrimidine salts are listed in Table 4. The hydrogen bonding geometries of compounds **1**–**5** are given in Table 5. In all the

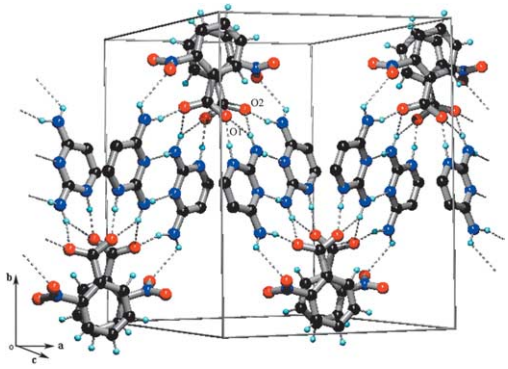


Figure 10. Hydrogen-bonded supramolecular helical pattern made up of multiple hydrogen bonding motif (X) in compound **3** (*p*-chlorophenyl moieties are omitted for clarity).

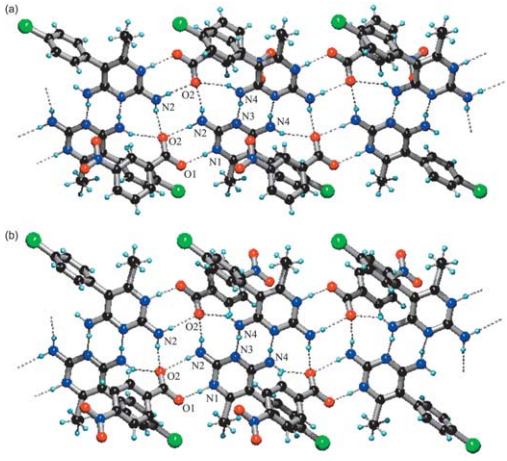


Figure 11. The alternate arrangement of DADA (II) and DDAA (III) arrays resulting in the formation of supramolecular ladder in compounds **4** and **5** (a and b).

Table 4. Hydrogen-bonded motifs in diaminopyrimdine salts

S. No.	Compound	Space group	Hydrogen-bonded motif	Functional group (O-bridging)	Reference
1	TMP nitrate	$P\bar{1}$	II	$-NO_3$	23
2	TMP salicylate dihydrate	$P\bar{1}$	II	H_2O	24
3	TMP hydrogen maleate	$P2_1/n$	II	–COOH	25
4	TMP formate	$C2/c$	III	–COOH	26
5	TMP perchlorate	$P\bar{1}$	II	$-OCH_3$	27
6	TMP sulfate trihydrate	$P2_1/c$	—	—	28
7	TMP hydrogen glutarate	$P\bar{1}$	III	–COOH	29
8	TMP salicylate methanol solvate	$P\bar{1}$	II	$-CH_3OH$	30
9	TMP *p*-toluenesulfonate	$P2_1/n$	II	$-SO_3^-$	31
10	TMP acetate	$P2_1/a$	II	$-OCH_3$	32
11	TMP benzoate benzoic acid	$P\bar{1}$	II	–COOH	33
12	TMP trifluoroacetate	$P2_1/a$	II	$-OCH_3$	34
13	TMP terephthalate terephthalic acid	$P\bar{1}$	—	—	35
14	TMP *m*-chlorobenzoate	$P2_1/n$	II and VIII	–COOH	36
15	TMP *m*-chlorobenzoate dihydrate	$P\bar{1}$	—	—	36
16	TMP sulfanilate mono hydrate	$P2_1/c$	—	—	31
17	TMP 3-caryboxy-4-hydroxybenzene sulfonate dihydrate	$P2_1/c$	—	—	31
18	TMP sorbate dehydrate	$P\bar{1}$	II	H_2O	51
19	TMP *o*-nitrobenzoate	*Pbca*	—	—	51
20	TMP *m*-nitrobenzoate	*Fdd*2	Open helix (IX) and VIII	—	Present study
21	TMP *p*-nitrobenzoate	$P2_1/n$	III and VIII	–COOH	Present study
22	PMN formate	$P2_1/n$	II	–COOH	37
23	PMN hydrogen maleate	$P2_1/c$	II	–COOH	38
24	PMN hydrogen succinate	$P2_1/c$	II	–COOH	38
25	PMN hydrogen phthalate	$P\bar{1}$	II	–COOH	38
26	PMN hydrogen glutarate	$P2_1/c$	II	–COOH	37
27	PMN *o*-nitrobenzoate	C2/*c*	DADA involving N2 and N3 type of pair (X)	–COOH	Present study
28	PMN *m*-nitrobenzoate	$P\bar{1}$	II and III	–COOH	Present study
29	PMN *p*-nitrobenzoate	$P\bar{1}$	II and III	–COOH	Present study

crystal structures (**1**–**5**), π–π stacking interactions are also playing an important role in stabilizing the crystal structures. Especially the two respective nitrobenzoate ions are overlapping one another. The centroid to centroid distance between the overlapping nitrobenzoate moieties is 3.753(2) Å in compound **1**. The corresponding distance in compound **2** is 3.562(1) Å, in compound **3** is 3.642(7) Å, in compound **4** is 3.744(2) Å and in compound **5** is 3.682(3) Å. In compound **3**, two such pyrimidine moieties are overlapping one another. The centroid to centroid distance between two pyrimidine rings is 3.732(7) Å.

The DADA array motif is a robust synthon in 2,4-diaminopyrimidine salts. Interestingly in the present study, different types of hydrogen bonding motifs and hydrogen-bonded supramolecular patterns have been observed. This may be due to two reasons. The first is the position (*ortho* or *meta* or *para*) and orientation of the nitro group, which plays an important role in crystal packing. The second reason is the effect the substituents present on 2,4-diaminopyrimidine (trimethoxylbenzyl and *p*-chlorophenyl). The trimethoxybenzyl group contains three O atoms. It has a very good hydrogen bond acceptor capability. In the trimethoprim salts reported already,[23–26,51] the trimethoxybenzyl substituent bridges two such motifs (DADA or DDAA). Recently, Thallapally and Nangia have analysed C–H···Cl hydrogen bonds using CSD (Cambridge Structural Database).[47] They have concluded that C–H···Cl^- and C–H···Cl–M(Metal) often behave as hydrogen bonds but C–H···Cl–C is generally a van der Waals interaction. We have a similar inference in the present study, also in that the Cl atom of the *p*-chlorophenyl substituent is not involved in hydrogen bonding interactions. Here, supramolecular motifs and supramolecular patterns are defined by the nature of the 2,4-diaminopyrimidine substituents and the R group attached to the COOH group.

3. Conclusion

The salts of novel hydrogen-bonded, 1:1 molecular complexes of nitro (*ortho*, *meta* and *para*) benzoic acids with 2,4-diaminopyrimidine derivatives (TMP and PMN) have been investigated in detail (**1**–**5**). As expected, in all the crystal structures except pyrimethamine *o*-nitrobenzoate (**3**), the carboxylate group of the respective anions interacts with the protonated TMP or PMN moiety in a linear fashion through a pair of N–H···O hydrogen bonds to form a cyclic hydrogen-bonded motif. This cyclic hydrogen-bonded motif is self-organized in different ways to get the novel types of hydrogen bonding motifs and supramolecular patterns. In the crystal structure of pyrimethamine *o*-nitrobenzoate, the chelating type of hydrogen bonding motif is self-organized to get a helical supramolecular pattern. In general, the DADA array motif is a robust synthon in 2,4-diaminopyrimidine salts. In the present study, new types of hydrogen bonding motifs and hydrogen-bonded supramolecular patterns have been observed. Here,

Table 5. Geometries of the hydrogen bonds in **1–5**

S. No.	D–H···A	d(H···A)/Å	d(D···A)/Å	∠(DH···A)/°
1	N1–H1···O4	1.72(2)	2.739(2)	177(3)
	N2–H2A···O4[a]	2.26(3)	3.036(2)	140.8(19)
	N2–H2B···O5	1.82(3)	2.722(2)	167(2)
	N4–H4A···O1[b]	2.30(3)	3.079(2)	153(2)
	N4–H4B···O3[c]	2.14(2)	2.930(2)	147(2)
	C14–H14···O6	2.38(3)	2.719(3)	102(2)
	C15–H15···O7[d]	2.34(3)	3.263(3)	142.5(18)
2	N1–H1···O4[e]	1.75(2)	2.6875(15)	173.6(18)
	N2–H2A···O5[e]	1.90(2)	2.8055(16)	172.6(18)
	N2–H2B···O5[f]	2.177(19)	2.8617(17)	135.9(16)
	N4–H4A···O2[g]	2.178(19)	2.9800(16)	152.4(18)
	N4–H4B···O3[h]	2.39(2)6	3.1310(15)	142.7(17)
	C7–H7B···O7	2.455(17)	3.3146(18)	149.1(14)
	C9–H9A···O1	2.58(2)	3.081(2)	112.4(14)
3	N1–H1···O1	1.61(8)	2.651(8)	178(5)
	N2–H2A···O1	2.48(7)	3.136(9)	128(6)
	N2–H2A···O2[i]	2.15(8)	2.844(9)	130(6)
	N2–H2B···N3[j]	2.42(7)	3.119(8)	171(8)
	N4–H4A···O2[k]	1.85(6)	2.812(8)	162(6)
	N4–H4B···O4[k]	2.46(7)	2.985(11)	114(5)
	C13–H13···O1[l]	2.33(9)	3.320(10)	173(6)
	C20–H20···O1	2.30(8)	2.773(9)	106(5)
4	N1–H1···O2	1.78(4)	2.662(4)	167(3)
	N2–H2A···O1	1.99(4)	2.924(4)	177(3)
	N2–H2B···O1[m]	2.08(4)	2.876(4)	167(4)
	N4–H4A···N3[n]	2.25(4)	3.100(4)	160(4)
	N4–H4B···O1[o]	2.59(4)	3.273(4)	134(3)
	C16–H16···O1	2.50(4)	2.804(4)	101(2)
	C20–H20···O2	2.42(3)	2.789(5)	105(2)
5	N1–H1···O1[p]	1.70(4)	2.663(4)	157(3)
	N2–H2A···O2[p]	2.06(3)	2.944(3)	174(3)
	N2–H2B···O2[q]	2.04(4)	2.906(4)	166(3)
	N4–H4A···N3[q]	2.50(4)	3.243(4)	144(3)
	N4–H4B···O2	2.21(5)	3.011(4)	138(3)

[a] $-x, 1/2-y, 1/2+z$.
[b] $-1/4+x, 1/4-y, 3/4+z$.
[c] $-1/4+x, 1/4-y, -1/4+z$.
[d] $x, y, 1+z$.
[e] $2-x, -y, 3-z$.
[f] $1+x, y, -1+z$.
[g] $1/2+x, 1/2-y, -1/2+z$.
[h] $-1/2+x, 1/2-y, -1/2+z$.
[i] $-x, y, 3/2-z$.
[j] $-x, -y, 2-z$.
[k] $x, -y, 1/2+z$.
[l] $1/2-x, 1/2+y, 3/2-z$.
[m] $-x, 2-y, -z$.
[n] $-x, 1-y, -z$.
[o] $x, -1+y, z$.
[p] $-1+x, y, z$.
[q] $-x, 1-y, 1-z$.

supramolecular motifs and supramolecular patterns are defined by the nature of the 2,4-diaminopyrimidine substituents and the R group attached to the COOH group.

4. Experimental

Infrared spectra were recorded neat in KBr cells with a FT-IR spectrometer (Perkin Elmer). The wave numbers (γ) are given in cm^{-1}.

4.1. Synthesis of 1–5

Compounds **1–5** were prepared by the mixing of hot methanolic solutions of TMP (Shilpa Antibiotics Ltd, India) or PMN (Lupin Pharma Ltd, India) and the corresponding acids [*o*-nitro benzoic acid (SD Fine Chemicals, India), *m*-nitro benzoic acid (SD Fine Chemicals, India) and *p*-nitro benzoic acid (SD Fine Chemicals, India)] in a 1:1 molar ratio. The resultant mixtures were warmed over a water bath at 70 °C for 10 min, allowed to cool slowly and kept at room temperature for crystallization. After a few days, crystals of **1–5** were obtained.

4.1.1. Trimethoprim *m*-nitrobenzoate 1. Type: pale yellow block crystals; IR: γ (C–H) str in CH_3 2848; γ (C–H) str aromatic 3040; γ (N–H) str 3459(s), 3312(w); γ (C–N) str aromatic 1682(s); γ (C–O–C) str 1238; γ (N═O) str nitro 1532(s).

4.1.2. Trimethoprim *p*-nitrobenzoate 2. Type: pale yellow prismatic crystals; IR: γ (C–H) str in CH_3 2852; γ (C–H) str

Table 6. Crystallographic parameters for **1**–**5**.

Properties	1	2	3	4	5
Empirical formula	$C_{14}H_{19}N_4O_3$ $C_7H_4NO_4$	$C_{14}H_{19}N_4O_3$, $C_7H_4NO_4$	$C_{12}H_{14}ClN_4$, $C_7H_4NO_4$	$C_{12}H_{14}ClN_4$, $C_7H_4NO_4$	$C_{12}H_{14}ClN_4$, $C_7H_4NO_4$
Molecular weight	457.44	457.44	415.83	415.83	415.83
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Triclinic	Triclinic
Temperature (K)	100(2)	100(2)	293(2)	293(2)	293(2)
Space group	Fdd2	$P2_1/n$	$C2/c$	$P\bar{1}$	$P\bar{1}$
Diffractometer	Bruker Smart Apex CCD	Bruker Smart Apex CCD	STOE four circle	STOE four circle	STOE four circle
a (Å)	20.7616(11)	6.2029(3)	19.04(3)	9.581(4)	9.8959(14)
b (Å)	56.841(3)	29.3162(15)	16.281(9)	10.350(4)	10.2871(15)
c (Å)	7.0764(4)	11.5972(6)	13.258(6)	10.946(5)	10.7218(15)
α (°)	90	90	90	66.80(3)	88.714(3)
β (°)	90	99.8990(10)	93.25(8)	81.89(4)	65.157(3)
γ (°)	90	90	90	74.25(4)	78.079(3)
V (Å^3)	8350.9(8)	2079.18(18)	4103(7)	959.5(8)	966.6(2)
Z	16	4	8	2	2
μ (mm^{-1})	0.111	0.112	0.221	0.237	0.235
$F(000)$	3840	960	1728	432	432
Reflections collected	17259	17063	4604	3996	5139
Observed reflections [$I>2\sigma(I)$]	4168	5076	1480	2432	2258
Final R_1 on observed data	0.0475	0.0518	0.0615	0.0524	0.0579
Final wR_2 on observed data	0.1008	0.1264	0.2758	0.1591	0.1740
Structure solution	SHELXS97[48]	SHELXS97	SHELXS97	SHELXS97	SHELXS97
Structure refinement	SHELXL97[48]	SHELXL97	SHELXL97	SHELXL97	SHELXL97
Graphics	ORTEP3[49] PLATON97[50]	ORTEP3 PLATON97	ORTEP3 PLATON97	ORTEP3 PLATON97	ORTEP3 PLATON97

aromatic 3044; γ (N–H) str 3463(s), 3305(w); γ (C–N) str aromatic 1679(s); γ (C–O–C) str 1243; γ (N═O) str nitro 1524(s).

4.1.3. Pyrimethamine *o*-nitrobenzoate 3. Type: pale yellow prismatic crystals; IR: γ (C–H) str in CH_3 2839; γ (C–H) str aromatic 3038; γ (N–H) str 3463(s), 3317(w); γ (C–N) str aromatic 1685(s); γ (N═O) str nitro 1529(s).

4.1.4. Pyrimethamine *m*-nitrobenzoate 4. Type: pale yellow crystals; IR: γ (C–H) str in CH_3 2859; γ (C–H) str aromatic 3026; γ (N–H) str 3447(s), 3320(w); γ (C–N) str aromatic 1683(s); γ (N═O) str nitro 1524(s).

4.1.5. Pyrimethamine *p*-nitrobenzoate 5. Type: pale yellow crystals; IR: γ (C–H) str in CH_3 2843; γ (C–H) str aromatic 3033; γ (N–H) str 3458(s), 3298(w); γ (C–N) str aromatic 1675(s); γ (N═O) str nitro 1522(s).

4.2. X-ray crystallography

Data for compounds **1** and **2** were collected at 100 K on a Bruker Smart Apex CCD diffractometer. The data for compounds **3**–**5** were collected at 293 K on a STOE four circle diffractometer. The crystal data and the details of structure determination parameters are listed in Table 6 [(Deposition numbers: CCDC 185205 and 185206 for compounds **1** and **2**, CCDC 210444-21446 for compounds **3**–**5**)].

Acknowledgements

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References and notes

1. Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.
2. Desiraju, G. R. *Crystal Engineering: The Design of Organic Solids*; Elsevier: Amsterdam, 1989.
3. Moulton, B.; Zaworotko, M. J. *Chem. Rev.* **2001**, *101*, 1629–1658.
4. Desiraju, G. R. *Nature* **2001**, *412*, 397–400.
5. Desiraju, G. R. *Curr. Sci.* **2001**, *81*, 1038–1042.
6. Rodríguez-Spong, B.; Price, C. P.; Jayasankar, A.; Matzger, A. J.; Rodríguez-Hornedo, N. *Adv. Drug Deliv. Rev.* **2004**, *56*, 241–274.
7. Desiraju, G. R. *J. Mol. Struct.* **2004**, *656*, 5–15.
8. Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382–2426.
9. Jeffrey, G. A. *Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.
10. Aakeröy, C. B. *Acta Crystallogr., Sect. B* **1997**, *53*, 569–586.
11. Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer: Berlin, 1991.
12. Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761–6769.
13. Fernandez-Lopez, S.; Kim, H.-S.; Choi, E. C.; Delgado, M.; Granja, J. R.; Khasanov, A.; Kraehenbuehl, K.; Long, G.; Weinberger, D. A.; Wilcoxen, K. M.; Ghadiri, M. R. *Nature* **2001**, *412*, 452–455.
14. Vallee, B. L.; Auld, D. S. *Acc. Chem. Res.* **1993**, *26*, 543–551.

15. Kuyper, L. F. In *Crystallographic and Modelling Methods in Molecular Design*; Bugg, C. E., Ealick, S. E., Eds.; Springer: New York, 1990; p 56.
16. Etter, M. C.; Adsmond, D. A. *J. Chem. Soc., Chem. Commun.* **1990**, 589–591.
17. Etter, M. C. *J. Phys. Chem.* **1991**, *95*, 4601–4610.
18. Goswami, S.; Mahapatra, A. K.; Nigam, G. D.; Chinnakali, K.; Fun, H.-K.; Razak, I. A. *Acta Crystallogr., Sect. C* **1999**, *55*, 583–585.
19. Goswami, S.; Mahapatra, A. K.; Ghosh, K.; Nigam, G. D.; Chinnakali, K.; Fun, H.-K. *Acta Crystallogr.* **1999**, *155*, 87–89.
20. Shan, N.; Bond, A. D.; Jones, W. *Tetrahedron Lett.* **2002**, *43*, 3101–3104.
21. Pedireddi, V. R.; Chatterjee, S.; Renganathan, A.; Rao, C. N. R. *Tetrahedron* **1998**, *54*, 9457–9474.
22. Hitchings, G. H.; Burchall, J. J. In Nord, F., Ed.; Advances in Enzymology; Interscience: New York, 1965; Vol. 27, p 417.
23. Murugesan, S.; Muthiah, P. T. *Acta Crystallogr., Sect. C* **1997**, *53*, 763–764.
24. Murugesan, S.; Muthiah, P. T. Academic Discussion Meeting on Frontiers in Structural Chemistry, I.I.T., Chennai, India, 1996; Abstract No. 3.4.
25. Prabakaran, P.; Robert, J. J.; Muthiah, P. T.; Bocelli, G.; Righi, L. *Acta Crystallogr., Sect. C* **2001**, *57*, 459–461.
26. Umadevi, B.; Prabakaran, P.; Muthiah, P. T. *Acta Crystallogr., Sect. C* **2002**, *58*, 510–512.
27. Muthiah, P. T.; Umadevi, B.; Stanley, N.; Bocelli, G.; Cantoni, A. *Acta Crystallogr., Sect. E* **2002**, *58*, o59–o61.
28. Muthiah, P. T.; Umadevi, B.; Stanley, N.; Shui, N.; Eggleston, D. S. *Acta Crystallogr., Sect. C* **2001**, *57*, o1179–o1182.
29. Robert, J. J.; Raj, S. B.; Muthiah, P. T. *Acta Crystallogr., Sect. E* **2001**, *59*, o1206–o1208.
30. Panneerselvam, P.; Stanley, N.; Muthiah, P. T. *Acta Crystallogr., Sect. E* **2002**, *58*, o180–o182.
31. Raj, S. B.; Sethuraman, V.; Francis, S.; Hemamalini, M.; Muthiah, P. T.; Bocelli, G.; Cantoni, A.; Rychlewska, U.; Warzajtis, B. *CrystEngComm.* **2003**, *5*, 70–76.
32. Bryan, R. F.; Haltiwanger, C. R. *Acta Crystallogr., Sect. C* **1987**, *43*, 2412–2415.
33. Giuseppetti, G.; Tadini, C.; Bettinetti, G. P.; Giordano, F.; Manna, A.-L. *Acta Crystallogr., Sect. C* **1988**, *44*, 856–860.
34. Francis, S.; Muthiah, P. T.; Bocelli, G.; Righi, L. *Acta Crystallogr., Sect. E* **2002**, *58*, o717–o719.
35. Hemamalini, M.; Muthiah, P. T.; Bocelli, G.; Cantoni, A. *Acta Crystallogr., Sect. E* **2003**, *59*, o14–o17.
36. Raj, S. B.; Muthiah, P. T.; Rychlewska, U.; Warzajtis, B. *CrystEngComm* **2003**, *5*, 48–53.
37. Stanley, N.; Sethuraman, V.; Muthiah, P. T.; Luger, P.; Weber, M. *Cryst. Growth Des.* **2002**, *2*, 631–635.
38. Sethuraman, V.; Stanley, N.; Muthiah, P. T.; Sheldrick, W. S.; Winter, M.; Luger, P.; Weber, M. *Cryst. Growth Des.* **2003**, *3*, 823–828.
39. Koetzle, T. F.; Williams, G. J. B. *J. Am. Chem. Soc.* **1976**, *98*, 2074–2078.
40. Sethuraman, V.; Muthiah, P. T. *Acta Crystallogr., Sect. E* **2002**, *58*, o817–o818.
41. Hitchings, G. H.; Kuyper, L. F.; Baccananari, D. P. In *Design of Enzyme Inhibitors as Drugs*; Sandler, M., Smith, H. J., Eds.; Oxford University Press: New York, 1988.
42. Sansom, C. E.; Schwalbe, C. H.; Lambert, P. A.; Griffn, R. J.; Stevens, M. F. G. *Biochem. Biophys. Acta* **1989**, *995*, 21–27.
43. Allen, F. H.; Raithby, P. R.; Shields, G. P.; Taylor, R. *Chem. Commun.* **1998**, 1043–1044.
44. Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–126.
45. Bernstein, J.; Davis, R. E.; Shimoni, L.; Chang, N.-L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1555–1573.
46. Aitipamula, S.; Thallapally, P. K.; Thaimattam, R.; Jaskólski, M.; Desiraju, G. R. *Org. Lett.* **2002**, *4*, 92–924.
47. Thallapally, P. K.; Nangia, A. *CrystEngComm* **2001**, *3*, 114–119.
48. Sheldrick, G. M. *SHELXS97 and SHELXL97*; University of Göttingern, Germany, 1997.
49. Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.
50. Spek, A. L. *PLATON97*; Utrecht University: The Netherlands, 1997.
51. Raj, B. S.; Stanley, N.; Muthiah, P. T.; Bocelli, G.; Olla, R.; Cantoni, A. *Cryst. Growth Des.* **2003**, *3*, 567–571.

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Efficient total synthesis of bastadin 6, an anti-angiogenic brominated tyrosine-derived metabolite from marine sponge

Naoyuki Kotoku, Hiroaki Tsujita, Atsushi Hiramatsu, Chinatsu Mori, Noriko Koizumi and Motomasa Kobayashi*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan

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Abstract—An efficient total synthesis of bastadin 6 (**1**), a cyclic tetramer of brominated tyrosine derivatives from the marine sponge, *Ianthella basta*, with selective anti-angiogenic activity, was accomplished. We developed a novel Ce(IV)-mediated oxidative coupling reaction of 2,6-dibromophenols to give the diaryl ether derivatives, the characteristic segment of **1**. Condensation of two segments and subsequent intramolecular macrocyclization gave bastadin 6 (**1**) in nine steps, 26% overall yield.

1. Introduction

Angiogenesis, a formation of new blood capillaries from pre-existing blood vessels, is critical for tumor growth and metastasis. A growing tumor needs an extensive network of capillaries to provide nutrients and oxygen, etc. In addition, the new blood vessels provide a way for tumor cells to enter the circulation system and to metastasize to another organ. Therefore, substances that inhibit angiogenesis have considerable potential to be novel therapeutic agents for the treatment of cancer.[1]

In the course of our study on the bioactive substances from marine organisms, we focused on a search for anti-angiogenic substances and isolated bastadins[2] from the Indonesian marine sponge, *Ianthella basta*. We found that bastadin 6 (**1**), a major constituent, showed anti-angiogenic activity in vitro and in vivo, through the induction of selective apoptosis to endothelial cells.[3] Bastadins are cyclic or acyclic tetramers of brominated-tyrosine derivative and have been known to show some interesting biological activities, such as antibacterial[2a] and cytotoxic activities,[2b] inhibition of inositol-5′-phosphate dehydrogenase[2h] and lipoxygenases,[4] and interaction with intracellular ryanodine receptor-1 (RyR-1) calcium channel complex.[2i,j] For further mechanistic study of the anti-angiogenic effect and chemical study from the viewpoint of medicinal chemistry, we aimed to develop a practical synthetic method of bastadins. Here, we present full details of the concise total synthesis of bastadin 6 (**1**) through novel Ce(IV)-mediated oxidative coupling of 2,6-dibromophenol derivatives.

2. Results and discussion

2.1. Synthetic strategy

So far, two total syntheses of bastadin 6 (**1**) have been reported. Yamamura and co-workers reported the first total synthesis of **1** using Tl(III)-mediated oxidative coupling of bromophenols as a key step, although the overall yield was marginal.[5] Recently, Sih and co-workers have developed a novel method for oxidative coupling of *o*,*o*′-dihalophenols using peroxidase and applied it in an improved total synthesis of **1**.[6] Although their synthetic route was a convergent and short-step sequence, it left much room for more improvement. Namely, the key reaction needs rather expensive peroxidase as a catalyst and is not suitable for large-scale synthesis. Furthermore, the overall yield was not so satisfactory. Then, we planned to synthesize bastadin 6 (**1**) by using a similar strategy as shown in Figure 1, with more practical method for the synthesis of two diaryl ether derivatives **2** and **3**, the key structural elements of **1**.[7]

2.2. Preparation of the left segment of bastadin 6

We first investigated the synthesis of **2**, the left segment of bastadin 6 (**1**). It has been reported that the oxidative coupling of *N*-Boc-3,5-dibromotyramine (**4**) using soybean

Keywords: Total synthesis; Bastadin; Oxidative coupling; Angiogenesis; Marine sponge.
* Corresponding author. Tel.: +81 6 6879 8215; fax: +81 6 6879 8219; e-mail: kobayasi@phs.osaka-u.ac.jp

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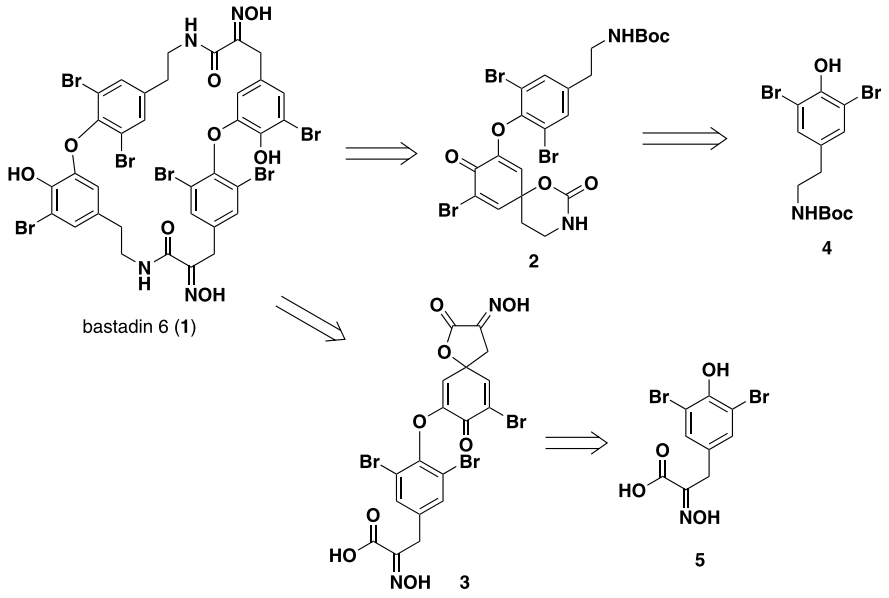
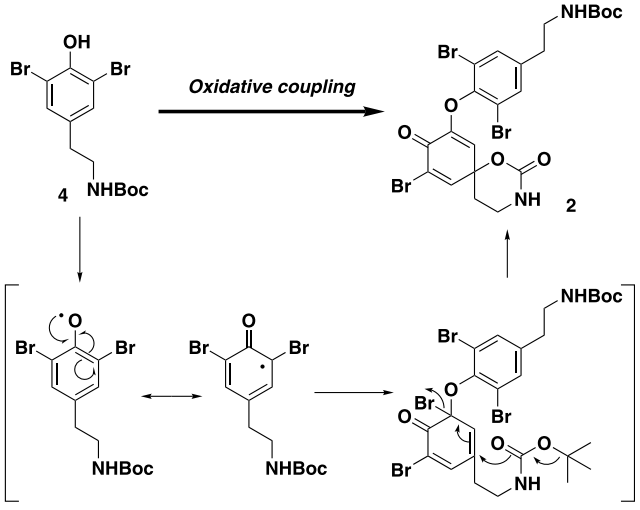


Figure 1. Synthetic strategy of bastadin 6 (**1**).

peroxidase (SPO) proceeded to give the cyclic carbamate **2** as shown in Scheme 1, with concomitant discrimination of the two amino groups which is important for the total synthesis of **1**.[6a] We examined some other oxidants, which are used for phenolic oxidation, for this coupling reaction (Table 1). In most cases, using Fe (III), Tl (III), and Pb (IV) as oxidants, no desired product **2** was obtained at all, and oxidation with phenyliodine bis(trifluoroacetate) (PIFA) gave only a trace amount of **2**. Among the oxidants tested, cerium (IV) diammonium nitrate (CAN) in aqueous CH_3CN afforded the cyclic carbamate **2** as the major product. Under optimum conditions (2 equiv of CAN, aqueous CH_3CN at 0 °C), the yield (53%) was acceptable and similar with that obtained by SPO.



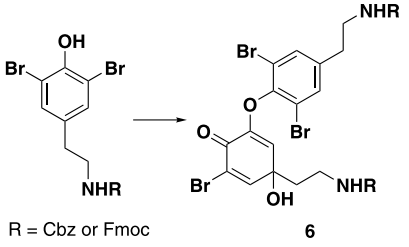
Scheme 1. Reaction mechanism of the oxidative coupling of **4**.

Table 1. Oxidative coupling of **2**

Reagent	Condition	Yield
$K_3Fe(CN)_6$	CH_3CN/H_2O, rt	n. r.
Fremy's salt[a]	MeOH, 0 °C–rt	n. r.
$Tl(ONO_2)_3$	MeOH	Decomp.
$Pb(OAc)_4$	Benzene, rt	Decomp.
PIFA[b]	$(CF_3)_2CHOH$, rt	Trace
CAN[c] (1 equiv)	CH_3CN/H_2O, rt	33%
CAN[c] (2 equiv)	CH_3CN/H_2O, rt	40%
CAN[c] (2 equiv)	CH_3CN/H_2O, 0 °C	53%

[a] $(KSO_3)_2NO$.
[b] Phenyliodine bis(trifluoroacetate).
[c] Cerium ammonium nitrate.

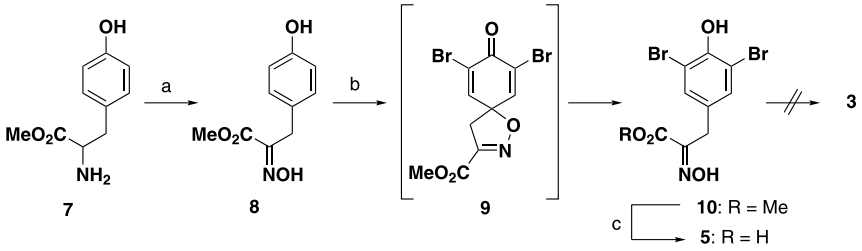
When the protecting group in **4** was changed from the Boc group to a benzyloxycarbonyl (Cbz) or 9-fluorenylmethoxycarbonyl (Fmoc) group, the coupling reaction gave a complex mixture. Each major product was **6** that was formed by similar C–O coupling and subsequent nucleophilic attack of water, instead of an intramolecular carbonyl group (Scheme 2). In this case, the two amino groups in **6** could not be discriminated. As shown in Scheme 1, nucleophilic attack of the Boc carbonyl should be derived from the producibility of the *tert*-butyl cation.[8]



Scheme 2.

2.3. Preparation of the right segment of bastadin 6

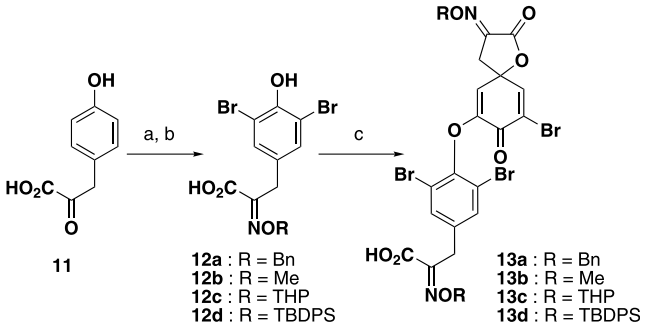
Next, the synthesis of the right segment **3** through the oxidative coupling of 3,5-dibromotyrosine derivative (**5**) was attempted. Since the reported method for the synthesis of **5** was unsatisfactory,[6a,9] we developed an improved method according to other literature,[10] as shown in Scheme 3. Thus, oxidation of tyrosine methyl ester (**7**) with Na_2WO_4/H_2O_2 afforded an oxime **8** in good yield.



Scheme 3. Reagents and conditions: (a) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2, EtOH, 74%. (b) NBS, DMF; aq. $Na_2S_2O_4$, Et_2O, two steps 90%. (c) KOH, THF/H_2O, quant.

O,*o*′-Dibrominated phenol **10** was obtained by the treatment of **8** with 3.5 equiv of *N*-bromosuccinimide (NBS) and subsequent reductive aromatization of the resulting spiroisoxazole **9** with $Na_2S_2O_4$.[11] Hydrolysis of the ester moiety in **10** proceeded quantitatively to give the coupling substrate **5**. However, oxidative coupling of **5** did not proceed to afford the desired diaryl ether derivative under the reaction conditions developed above.

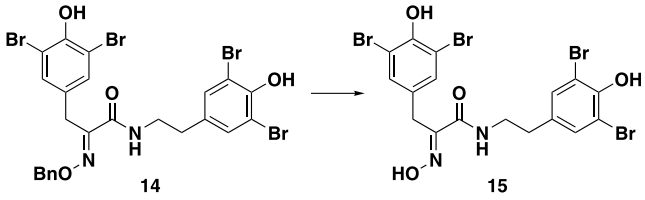
We supposed that the nucleophilic oxime moiety in **5** would interrupt the oxidative coupling, and then coupling reaction using the oxime-protected phenol **12** was investigated (Scheme 4). Since selective protection of the oxime group in **5** is not easy, **12** was prepared through condensation of 4-hydroxyphenylpyruvic acid (**11**) with *O*-protected hydroxylamine[12] and subsequent bromination by NBS. To our delight, the coupling reaction of **12** mediated by CAN proceeded smoothly to give the desired biaryl ether **13** in good yield. As shown in Scheme 4, various protecting groups were compatible. The acid-sensitive THP group also survived in this reaction condition,[13] although the yield was relatively low. The yield of the coupling reaction was up to 65%, in the case of **13d** with the TBDPS-protecting group.



Scheme 4. Reagents and conditions: (a) $RONH_2$, NaOAc; NBS, DMF, two steps 91% for **12a**; two steps quant. for **12b**; two steps 97% for **12c**; two steps 44% for **12d**. (b) CAN (2 equiv), aq. CH_3CN, 0 °C, 52% for **13a**; 61% for **13b**; 42% for **13c**; 65% for **13d**.

2.4. Model study

In order to choose a suitable protecting group of the oxime moiety for the total synthesis of bastadin 6 (**1**), preliminary experiments using model compounds were executed to obtain the following information. THP or TBDPS groups were susceptible to trifluoroacetic acid (TFA), which is used for deprotection of the Boc group at the late stage of the total synthesis, while the Me group could not be removed by some conventional reagents such as iodotrimethylsilane.[14] Fortunately, as shown in Table 2, the benzyl group of the model compound **14** was inert to the TFA treatment and was selectively removed to give **15**, by the hydrogenolysis using Pd-black[5c,15] in moderate yield, or by the treatment with $BCl_3 \cdot SMe_2$[16] in quantitative yield (Scheme 5). Thus, we decided to use **13a** as the right segment of bastadin 6 (**1**).



Scheme 5. Deprotection of model compound **14**.

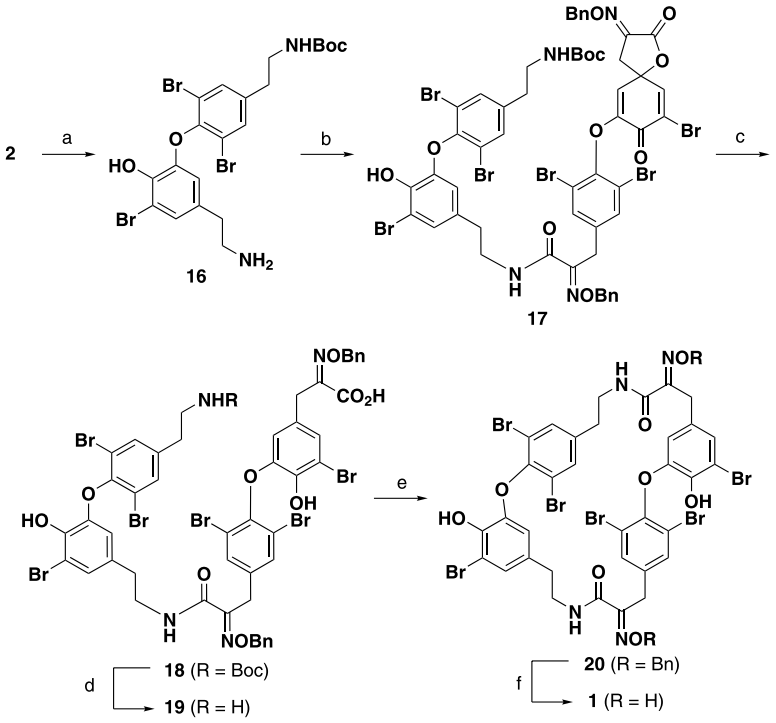
Table 2. Debenzylation of **14**

Reagent	Condition	Yield
H_2/Pd–C	MeOH	—[a]
H_2/Pd-black	Dioxane	Trace
H_2/Pd-black	Dioxane:AcOH=3:1	31%
H_2/Pd-black	Dioxane: AcOH=1:1	52%
$AlCl_3$	CH_2Cl_2:EtSH=1:1, 0 °C	n.r.
$BF_3 \cdot Et_2O$	EtSH, 0 °C	Decomp.
BCl_3	CH_2Cl_2, 0 °C	n.r.
BCl_3	CH_2Cl_2:EtSH=1:1, 0 °C	33%
$BCl_3 \cdot Me_2S$	CH_2Cl_2, 0 °C	Quant.

[a] Debrominated product was obtained.

2.5. Total synthesis of bastadin 6

As we obtained with the required two segments **2** and **13a** in hand, total synthesis of bastadin 6 (**1**) was investigated (Scheme 6). Cyclic carbamate **2** was reduced with $Na_2S_2O_4$ to give an amine **16** in almost quantitative yield. Condensation of **16** with the right segment **13a** by 1-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (EDCI·HCl) in the presence of 1-hydroxybenzotriazole hydrate (HOBt) afforded the desired amide **17**. In the case of using **3** as the coupling substrate, the oxime moiety might react with EDCI to give a considerable amount of byproducts, instead of the desired amide bond formation. Reduction of the spirodienone part in **17** with $Na_2S_2O_4$ gave a carboxylic acid **18**. Removal of the Boc group in **18** using TFA and subsequent treatment with HCl/Et_2O afforded a HCl salt of amine **19**, and then intramolecular macrocycle formation was accomplished by the EDCI/HOBt treatment to give a Bn-protected bastadin 6 (**20**) in good yield. Deprotection of the oxime group in the final step was also crucial. Selective deprotection of the two benzyl groups in **20** succeeded by the treatment with $BCl_3 \cdot SMe_2$ in CH_2Cl_2, the same condition found in the model study, to afford



Scheme 6. Reagents and conditions: (a) $Na_2S_2O_4$, THF/H_2O, quant. (b) **13a**, EDCI, HOBt, THF, 82%. (c) $Na_2S_2O_4$, CH_3CN/H_2O, 99%. (d) TFA, CH_2Cl_2; HCl/Et_2O. (e) EDCI, HOBt, Et_3N, THF, two steps 86%. (f) $BCl_3 \cdot SMe_2$, CH_2Cl_2, 76%.

bastadin 6 (**1**) in 76% yield. Physical properties of the synthetic bastadin 6 (**1**) were identical with those of natural product.[2a]

3. Summary

In summary, we have developed a highly efficient synthetic method of bastadin 6 (**1**), through the novel oxidative coupling of the 2,6-dibromophenol derivatives mediated by CAN, in the overall yield of 26% (nine steps, the longest linear sequence). The synthetic sequence is short-step, high-yielding, and convergent. The mechanistic study of bastadin and the structure–activity relationship study, to develop a novel anti-angiogenic drug candidate, are now in progress.

4. Experimental

4.1. General

The following instruments were used to obtain physical data: a JASCO FT/IR-5300 infrared spectrometer for IR spectra; a JEOL JMS SX-102 mass spectrometer for FAB MS; a Micromass Q-Tof Ultima API mass spectrometer for ESI-Q-TOF MS; a JEOL JNM AL-500 NMR spectrometer for ^1H (500 MHz) and ^{13}C (125 MHz) NMR using tetramethylsilane as an internal standard. Silica gel (Fuji Silysia BW-200) and pre-coated thin layer chromatography (TLC) plates (Merck, $60F_{254}$) were used for column chromatography and TLC. Spots on TLC plates were detected by spraying ninhydrin solution (2 g ninhydrin in 100 mL of sat. *n*-BuOH aquous) and acidic *p*-anisaldehyde solution (*p*-anisaldehyde: 25 mL, *c*-H_2SO_4: 25 mL, AcOH: 5 mL, EtOH: 425 mL) with subsequent heating. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy.

4.1.1. *tert*-Butyl [2-(3,5-dibromo-4-hydroxyphenyl)-ethyl]carbamate (4). To a solution of tyramine (10 g, 70 mmol) in AcOH (200 mL), Br_2 (25 g, 156 mmol) was added and stirred overnight at 50 °C. The reaction mixture was diluted with Et_2O, and the precipitate was collected by filtration and washed with Et_2O to give HBr-salt of 3,5-dibromotyramine.

The salt was dissolved in MeOH (240 mL), and Et_3N (40 mL, 287 mmol) and $(Boc)_2O$ (18 mL, 70 mmol) was added with stirring at rt. After 2 h, 5% HCl was added and extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the residue was purified by SiO_2 column (*n*-hexane/AcOEt =4:1) to give **4** (24 g, 92% in two steps) as a white solid. FAB MS: *m/z* 394/396/398 $(M+H)^+$. HR-FAB MS: *m/z* 395.9633, calcd for $C_{13}H_{18}{}^{79}Br^{81}BrNO_3$. Found: 395.9608. IR ν_{max} (KBr) cm^{-1}: 3345, 2976, 1691. ^1H NMR ($CDCl_3$) δ: 7.26 (2H, s), 5.77 (1H, br s), 4.51 (1H, br s), 3.29 (2H, q, J=6.5 Hz), 2.68 (2H, t, J=6.5 Hz), 1.42 (9H, s). ^{13}C NMR ($CDCl_3$) δ: 156.0, 148.2, 133.9, 132.4 (2C), 110.0 (2C), 79.7, 41.8, 35.0, 28.6 (3C). Anal. Calcd for $C_{13}H_{17}Br_2NO_3$: C, 39.52; H, 4.34; Br, 40.45; N, 3.55. Found: C, 39.48; H, 4.25; Br, 40.31; N, 3.51.

4.1.2. *tert*-Butyl {2-[3,5-dibromo-4-(10-bromo-2,9-dioxo-1-oxa-3-azaspiro[5.5]undeca-7,10-dien-8-yloxy)phenyl]-ethyl}carbamate (2). To a cooled (0 °C) solution of **4** (3.0 g, 7.6 mmol) in CH_3CN (400 mL) and H_2O (135 mL), a solution of CAN (8.3 g, 15 mmol) in H_2O (65 mL) was added dropwise. After stirring for 1 h, brine was added and extracted with AcOEt. The organic phase was dried over

$MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column ($CHCl_3$/MeOH=20:1) to give **2** (1.3 g, 53%) as a white powder. FAB MS: *m/z* 671/673/675/677 $(M+Na)^+$. HR-FAB MS: *m/z* 676.8943, calcd for $C_{22}H_{23}{}^{81}Br_3N_2O_6Na$. Found: 676.8945. IR ν_{max} (KBr) cm^{-1}: 3464, 3346, 1738, 1687, 1676. ^1H NMR (DMSO-d_6) δ: 7.91 (1H, d, J=3.0 Hz), 7.59 (2H, s), 7.57 (1H, s), 6.87 (1H, t, J=5.5 Hz), 5.77 (1H, d, J=3.0 Hz), 3.37–3.31 (1H, m), 3.19–3.15 (3H, m), 2.71 (2H, t, J=6.5 Hz), 2.06–2.02 (2H, m), 1.33 (9H, s). ^{13}C NMR (DMSO-d_6) δ: 171.9, 155.5, 150.5, 147.9, 145.4, 144.8, 141.2, 133.6 (2C), 122.8, 119.8, 116.1 (2C), 77.5, 76.9, 40.5, 36.5, 34.0, 29.8, 28.2 (3C).

4.1.3. Methyl 2-hydroxyimino-3-(4-hydroxyphenyl)propionate (8). To a cooled (0 °C) solution of tyrosine methyl ester (**7**) (0.50 g, 2.6 mmol) in EtOH (5.8 mL), $Na_2WO_4\cdot 2H_2O$ (0.86 g, 2.6 mmol), 30% H_2O_2 (2.6 mL), H_2O (4.5 mL) was added, and stirred for 4 h at rt. The reaction was quenched with sat. aqueous NH_4Cl and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue was purified by SiO_2 column (*n*-hexane/AcOEt =1:1) to give **8** (0.56 g, 74%) as a white powder. FAB MS: *m/z* 210 $(M+H)^+$. HR-FAB MS: *m/z* 210.0766, calcd for $C_{10}H_{12}NO_4$. Found: 210.0764. IR ν_{max} (KBr) cm^{-1}: 3481, 1714. ^1H NMR (acetone-d_6) δ: 11.35 (1H, br s), 8.12 (1H, br s), 7.10 (2H, d, J=8.0 Hz), 6.72 (2H, d, J=8.0 Hz), 3.83 (2H, s), 3.71 (3H, s). ^{13}C NMR (DMSO-d_6) δ: 164.3, 155.8, 150.1, 129.6 (2C), 126.4, 115.2 (2C), 52.1, 29.2.

4.1.4. Methyl 3-(3,5-dibromo-4-hydroxyphenyl)-2-(hydroxyimino)propionate (10). To a cooled (0 °C) solution of **8** (40 mg, 0.19 mmol) in DMF (1.0 mL), NBS (0.12 g, 0.66 mmol) in DMF (0.90 mL) was added and stirred for 1 h at rt, then $Na_2S_2O_4$ (0.50 g, 2.9 mmol) in H_2O (3.0 mL) was added and stirred for an additional hour. The reaction was diluted with Et_2O and the organic layer was separated. The aqueous phase was further extracted with Et_2O, and the combined organic phase was washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue was purified by SiO_2 column (*n*-hexane/AcOEt =1:1) to give **10** (63 mg, 90%) as a white powder. FAB MS: *m/z* 366/368/370 $(M+H)^+$. HR-FAB MS: *m/z* 367.8956, calcd for $C_{10}H_{10}{}^{79}Br^{81}BrNO_4$. Found: 367.8958. IR ν_{max} (KBr) cm^{-1}: 3412, 1732. ^1H NMR (acetone-d_6) δ: 11.80 (1H, br s), 8.52 (1H, br s), 7.45 (2H, s), 3.84 (2H, s), 3.74 (3H, s). ^{13}C NMR (acetone-d_6) δ: 164.0, 149.2, 149.0, 132.2 (2C), 130.8, 111.8 (2C), 52.3, 28.5.

4.1.5. 3-(3,5-Dibromo-4-hydroxyphenyl)-2-(hydroxyimino)propionic acid (5). To a solution of **10** (0.85 g, 2.3 mmol) in THF (46 mL), 3.3 M KOH (10 mL) was added and stirred for 30 min at rt. The reaction was quenched with 5% HCl and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo to give **5** (0.81 g, 99%) as a white powder. FAB MS: *m/z* 352/354/356 $(M+H)^+$. HR-FAB MS: *m/z* 353.8800, calcd for $C_9H_8{}^{79}Br^{81}BrNO_4$. Found: 353.8801. IR ν_{max} (KBr) cm^{-1}: 3256, 1703. ^1H NMR (acetone-d_6) δ: 11.05 (1H, br s), 7.47 (2H, s), 3.85 (2H, s), 2.57 (2H, s). ^{13}C NMR (acetone-d_6) δ: 164.9, 150.9, 150.2, 133.6 (2C), 132.0, 111.2 (2C), 29.1.

4.1.6. 2-Benzyloxyimino-3-(3,5-dibromo-4-hydroxyphenyl)propionic acid (12a, R=Bn). To a solution of 4-hydroxyphenylpyruvic acid (**11**) (1.0 g, 5.6 mmol) and *O*-benzylhydroxylamine hydrochloride (1.3 g, 8.3 mmol) in EtOH (55 mL) was added NaOAc (1.4 g, 17 mmol), and the mixture was stirred for 6 h at rt. After 5% HCl was added, the aqueous phase was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 4-hydroxyphenylpyruvic acid *O*-benzyloxime (1.7 g, quant.) as a white powder. FAB MS: *m/z* 286 $(M+H)^+$. HR-FAB MS: *m/z* 286.1080, calcd for $C_{16}H_{16}NO_4$. Found: 286.1076. IR ν_{max} (KBr) cm^{-1}: 3329, 3030, 1712. ^1H NMR (DMSO-d_6) δ: 13.09 (1H, br s), 9.22 (1H, s), 7.37–7.30 (5H, m), 6.94 (2H, d, J=8.0 Hz), 6.32 (2H, d, J=8.0 Hz), 5.23 (2H, s), 3.69 (2H, s). ^{13}C NMR (DMSO-d_6) δ: 164.3, 155.9, 151.7, 137.0, 129.6 (2C), 128.3 (2C), 128.0 (3C), 125.8, 115.2 (2C), 76.4, 29.8.

To a solution of oxime (22 mg, 0.070 mmol) in DMF (0.7 mL), NBS (49 mg, 0.27 mmol) was added portionwise at 0 °C and stirred for 2 h. The reaction mixture was diluted with Et_2O, and $Na_2S_2O_4$ (0.14 g, 0.79 mmol) in H_2O (1.0 mL) was added dropwise with vigorous stirring. The organic layer was separated, and the aqueous phase was extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column (*n*-hexane/AcOEt =7:3) to give dibrominated phenol **12a** (32 mg, 91%) as a white powder. FAB MS: *m/z* 442/444/446 $(M+H)^+$. HR-FAB MS: *m/z* 443.9269, calcd for $C_{16}H_{14}{}^{79}Br^{81}BrNO_4$. Found: 443.9286. IR ν_{max} (KBr) cm^{-1}: 3493, 2939, 1701. ^1H NMR (DMSO-d_6) δ: 13.29 (1H, br s), 9.82 (1H, br s), 7.36–7.30 (7H, m), 5.25 (2H, s), 3.72 (2H, s). ^{13}C NMR (DMSO-d_6) δ: 164.1, 150.6, 149.3, 136.8, 132.3 (2C), 130.3, 128.4 (2C), 128.1 (2C), 128.0, 111.8 (2C), 76.7, 29.2.

4.1.7. 3-(3,5-Dibromo-4-hydroxyphenyl)-2-(methoxyimino)propionic acid (12b, R=Me). In the same procedure as **12a**, **11** (0.20 g, 1.1 mmol) was converted to **12b** (0.41 g, quant.). White powder. FAB MS: *m/z* 366/368/370 $(M+H)^+$. HR-FAB MS: *m/z* 367.8956, calcd for $C_{10}H_{10}{}^{79}Br^{81}BrNO_4$. Found: 367.8956. IR ν_{max} (KBr) cm^{-1}: 3497, 1703. ^1H NMR (acetone-d_6) δ: 7.41 (2H, s), 4.05 (3H, s), 3.80 (2H, s). ^{13}C NMR (acetone-d_6) δ: 164.3, 150.4, 150.3, 133.6 (2C), 131.5, 111.3 (2C), 63.7, 29.7.

4.1.8. 3-(3,5-Dibromo-4-hydroxyphenyl)-2-(tetrahydropyran-2-yloxyimino)propionic acid (12c, R=THP). In the same procedure as **12a**, **11** (10 mg, 0.050 mmol) was converted to **12c** (21 mg, 97%). Colorless oil. FAB MS: *m/z* 436/438/440 $(M+H)^+$. HR-FAB MS: *m/z* 437.9374, calcd for $C_{14}H_{16}{}^{79}Br^{81}BrNO_5$. Found: 437.9349. IR ν_{max} (KBr) cm^{-1}: 3347, 2945, 1722. ^1H NMR (acetone-d_6) δ: 7.52 (2H, s), 5.41 (1H, s), 3.89 (1H, d, J=14.0 Hz), 3.85 (1H, d, J=14.0 Hz), 3.60 (1H, td, J=10.5, 2.5 Hz), 3.54–3.51 (1H, m), 1.89–1.54 (6H, m). ^{13}C NMR (DMSO-d_6) δ: 164.4, 151.4, 149.3, 132.5 (2C), 130.5, 111.8 (2C), 100.8, 61.0, 29.4, 28.0, 24.6, 18.2.

4.1.9. 2-(*tert*-Butyldiphenylsilyloxyimino)-3-(3,5-dibromo-4-hydroxyphenyl)propionic acid (12d, R=TBDPS). In the same procedure as **12a**, **11** (0.10 g, 0.55 mmol) was converted to **12d** (0.14 g, 44%). Colorless oil. FAB MS: *m/z* 590/592/594 $(M+H)^+$. HR-FAB MS: *m/z* 591.9978, calcd for $C_{25}H_{26}{}^{79}Br^{81}BrNO_4Si$. Found: 591.9957. IR ν_{max} (KBr) cm^{-1}: 3488, 3051, 1703. ^1H NMR (acetone-d_6) δ: 7.69–7.67 (4H, m), 7.56 (2H, s), 7.47–7.39 (6H, m), 4.06 (2H, s), 1.11 (9H, s). ^{13}C NMR (acetone-d_6) δ: 164.8, 156.7, 150.3, 136.1 (4C), 133.6 (2C), 133.3 (2C), 131.7, 130.9 (2C), 128.6 (4C), 111.4 (2C), 30.2, 27.3 (3C), 19.9.

4.1.10. 2-Benzyloxyimino-3-[4-(3-benzyloxyimino-9-bromo-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-7-yloxy)-3,5-dibromophenyl]propionic acid (13a, R=Bn). As the same procedure in the synthesis of **2**, **12a** (332 mg, 0.75 mmol) was converted to **13a** (152 mg, 52%). White powder. FAB MS: *m/z* 801/803/805/807 $(M+H)^+$. HR-FAB MS: *m/z* 804.9042, calcd for $C_{32}H_{24}{}^{79}Br^{81}Br_2N_2O_8$. Found: 804.9050. IR ν_{max} (KBr) cm^{-1}: 3065, 3036, 1784, 1695, 1658. ^1H NMR (DMSO-d_6) δ: 13.37 (1H, br s), 7.94 (1H, d, $J=2.5$ Hz), 7.51 (2H, s), 7.37–7.32 (10H, m), 6.29 (1H, d, $J=2.5$ Hz), 5.27 (4H, s), 3.84 (2H, s), 3.29 (1H, d, $J=19.5$ Hz), 2.94 (1H, d, $J=19.5$ Hz). ^{13}C NMR (DMSO-d_6) δ: 171.9, 164.0, 163.2, 149.8, 148.4, 146.4, 145.4, 144.9, 137.3, 136.6, 136.5, 133.2 (2C), 128.5, 128.4 (4C), 128.2 (2C), 128.1 (2C), 122.1 (2C), 120.2, 116.5 (2C), 78.2, 77.3, 76.9, 33.8, 29.6.

4.1.11. 3-[4-(9-Bromo-3-methoxyimino-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-7-yloxy)-3,5-dibromophenyl]-2-(methoxyimino)propionic acid (13b, R=Me). As the same procedure in the synthesis of **2**, **12b** (0.30 g, 0.83 mmol) was converted to **13b** (0.16 g, 61%). White powder. FAB MS: *m/z* 649/651/653/655 $(M+H)^+$. HR-FAB MS: *m/z* 650.8437, calcd for $C_{20}H_{16}{}^{79}Br_2{}^{81}BrN_2O_8$. Found: 650.8463. IR ν_{max} (KBr) cm^{-1}: 3231, 3061, 1776, 1703. ^1H NMR (acetone-d_6) δ: 9.86 (1H, br s), 7.79 (1H, d, $J=2.5$ Hz), 7.58 (2H, s), 6.19 (1H, d, $J=2.5$ Hz), 4.06 (3H, s), 4.02 (3H, s), 3.88 (2H, s), 3.42 (1H, d, $J=19.5$ Hz), 3.17 (1H, d, $J=19.5$ Hz). ^{13}C NMR (acetone-d_6) δ: 172.4, 164.3, 163.6, 149.7, 148.2, 146.9, 146.7, 146.0, 138.4, 134.6 (2C), 124.1, 120.1, 117.6 (2C), 79.0, 64.3, 63.9, 34.8, 30.2.

4.1.12. 3-{4-[9-Bromo-2,8-dioxo-3-(tetrahydropyran-2-yloxyimino)-1-oxaspiro[4.5]deca-6,9-dien-7-yloxy]-3,5-dibromophenyl}-2-(tetrahydropyran-2-yloxyimino)propionic acid (13c, R=THP). As the same procedure in the synthesis of **2**, **12c** (657 mg, 1.50 mmol) was converted to **13c** (249 mg, 42%) as a mixture of four diastereomers. White powder. FAB MS: *m/z* 809/811/813/815 $(M+Na)^+$. IR ν_{max} (KBr) cm^{-1}: 2947, 1695, 1660. ^1H NMR (acetone-d_6) δ: 7.86, 7.82 (1H, both d, $J=2.5$ Hz), 7.70 (2H, s), 6.23–6.17 (1H, m), 5.41–5.38 (2H, m), 3.97–3.86 (2H, m), 3.80–3.69 (1H, m), 3.63–3.50 (4H, m), 3.33–3.22 (1H, m), 1.87 (12H, m). ^{13}C NMR (DMSO-d_6) δ: 172.4, 164.5, 163.6, 150.7, 148.3, 148.2, 147.4, 147.0, 146.8, 138.6, 134.9, 133.8, 124.1, 120.2, 117.6, 103.2, 103.1, 102.8, 102.7, 79.1 (2C), 62.9, 62.7, 62.5, 62.4, 34.9, 34.8, 30.7, 29.0, 25.7, 19.6, 19.5, 19.4, 19.3.

4.1.13. 3-{4-[9-Bromo-3-(*tert*-butyldiphenylsilyloxyimino)-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-7-yloxy]-3,5-dibromophenyl}-2-(*tert*-butyldiphenylsilyloxyimino)propionic acid (13d, R=TBDPS). As the same procedure in the synthesis of **2**, **12d** (26 mg, 0.043 mmol) was converted to **13d** (15 mg, 65%). Colorless oil. ESI-Q-TOF MS: *m/z* 1119/1121/1123/1125 $(M+Na)^+$. HR-ESI-Q-TOF MS: *m/z* 1121.0298, calcd for $C_{50}H_{47}{}^{79}Br_2{}^{81}BrN_2O_8Si_2Na$. Found: 1121.0313. IR ν_{max} (KBr) cm^{-1}: 3072, 1697, 1658. ^1H NMR (acetone-d_6) δ: 7.86 (1H, d, $J=2.5$ Hz), 7.73 (2H, s), 7.70–7.66 (8H, m), 7.46–7.38 (12H, m), 6.18 (1H, d, $J=2.5$ Hz), 4.16 (2H, s), 3.83 (1H, d, $J=20.0$ Hz), 3.49 (1H, d, $J=20.0$ Hz), 1.09 (9H, s), 1.08 (9H s). ^{13}C NMR (acetone-d_6) δ: 165.9, 164.7, 156.0, 153.1, 148.3, 148.3, 147.0, 146.9, 138.8, 136.2 (4C), 136.2 (4C), 134.7, 133.2, 133.1 (2C), 131.1 (4C), 129.7, 129.0, 128.7 (4C), 128.6 (4C), 124.1, 120.0, 117.8 (2C), 79.3, 35.4, 30.3, 27.4 (3C), 27.2 (3C), 19.9 (2C).

4.1.14. *tert*-Butyl (2-{4-[5-(2-aminoethyl)-3-bromo-2-hydroxyphenoxy]-3,5-dibromophenyl}ethyl)carbamate (16). To a solution of **2** (0.60 g, 0.92 mmol) in THF (20 mL), $Na_2S_2O_4$ (0.96 g, 5.5 mmol) in H_2O (6.0 mL) was added and stirred for 10 min at rt. Brine was added and extracted with AcOEt. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was treated with *n*-hexane, and the precipitate was collected by filtration to give **16** (0.59 g, quant.) as a white powder. FAB MS: *m/z* 607/609/611/613 $(M+H)^+$. HR-FAB MS: *m/z* 608.9422, calcd for $C_{21}H_{26}{}^{79}Br_2{}^{81}BrN_2O_4$. Found: 608.9419. IR ν_{max} (KBr) cm^{-1}: 3522, 3335, 1680. ^1H NMR (DMSO-d_6) δ: 7.87 (1H, br s), 7.62 (2H, s), 7.11 (1H, d, $J=1.5$ Hz), 6.94 (1H, t, $J=6.0$ Hz), 6.11 (1H, d, $J=1.5$ Hz), 3.19 (2H, q, $J=6.0$ Hz), 2.83 (2H, t, $J=7.5$ Hz), 2.73 (2H, t, $J=6.0$ Hz), 2.62 (2H, t, $J=7.5$ Hz), 1.34 (9H, s). ^{13}C NMR (DMSO-d_6) δ: 155.5, 146.0, 144.9, 142.7, 140.7, 133.4 (2C), 129.0, 126.1, 117.2 (2C), 112.6, 110.6, 77.5, 40.6, 40.3, 34.0, 32.4, 28.2 (3C).

4.1.15. *tert*-Butyl (2-{4-[5-(2-{2-benzyloxyimino-3-[4-(3-benzyloxyimino-9-bromo-2,8-dioxo-1-oxaspiro[4.5]-deca-6,9-dien-7-yloxy)-3,5-dibromophenyl]propionyl-amino}ethyl)-3-bromo-2-hydroxyphenoxy]-3,5-dibromophenyl}ethyl)carbamate (17). To a stirred solution of **13a** (8.8 mg, 0.010 mmol), **16** (7.0 mg, 0.010 mmol), and HOBt (1.7 mg, 0.011 mmol) in THF (0.10 mL), EDCI (2.7 mg, 0.010 mmol) was added at 0 °C. The reaction mixture was stirred for 6 h. HCl (5%) was added and aqueous phase was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column ($CHCl_3$) to give **17** (13.2 mg, 82%) as a white powder. ESI-Q-TOF MS: *m/z* 1411/1413/1415/1417/1419/1421/1423 $(M+Na)^+$. HR-ESI-Q-TOF MS: *m/z* 1416.8100, calcd for $C_{53}H_{46}{}^{79}Br_3{}^{81}Br_3N_4O_{11}Na$. Found: 1416.8112. IR ν_{max} (KBr) cm^{-1}: 3414, 2976, 1784, 1697, 1666. ^1H NMR (DMSO-d_6) δ: 9.93 (1H, s), 8.12 (1H, t, $J=5.5$ Hz), 7.95 (1H, d, $J=2.5$ Hz), 7.61 (2H, s), 7.51 (2H, s), 7.37–7.32 (10H, m), 7.05 (1H, s), 6.90 (1H, t, $J=5.5$ Hz), 6.28 (1H, d, $J=2.5$ Hz), 6.07 (1H, s), 5.28 (2H, s), 5.24 (2H, s), 3.79 (2H, s), 3.30 (1H, d, $J=19.5$ Hz), 3.22–3.19 (4H, m), 2.95 (1H, d, $J=19.5$ Hz), 2.73 (2H, t, $J=5.0$ Hz), 2.54 (2H, t, $J=5.0$ Hz), 1.33 (9H, s). ^{13}C NMR (DMSO-d_6) δ: 171.8, 163.2, 161.8, 155.5, 151.0, 148.3, 146.4, 146.0, 145.2, 144.9, 144.7, 142.0, 140.6, 137.4 (2C), 136.5 (4C), 133.4 (2C), 130.8, 128.4 (4C), 128.3, 128.2 (2C), 128.1

(2C), 126.0, 122.1, 120.1, 117.2 (2C), 116.4 (2C), 112.6, 110.4, 78.1, 77.5, 77.3, 76.7, 40.5 (2C), 34.0, 33.8, 33.6, 28.8, 28.2 (3C).

4.1.16. 2-Benzyloxyimino-3-(3-{4-[2-benzyloxyimino-2-(2-{3-bromo-5-[2,6-dibromo-4-(2-*tert*-butoxycarbonylaminoethyl)phenoxy]-4-hydroxyphenyl}ethylcarbamoyl)-ethyl]-2,6-dibromophenoxy}-5-bromo-4-hydroxyphenyl)-propionic acid (18). To a solution of **17** (170 mg, 0.12 mmol) in CH_3CN (8.0 mL), $Na_2S_2O_4$ (58 mg, 0.33 mmol) in 4.0 mL of H_2O was added and stirred for 30 min at rt. Brine was added and extracted with AcOEt. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column to give **18** (170 mg, 99%) as a white powder. ESI-Q-TOF MS: *m/z* 1413/1415/1417/1419/1421/1423/1425 $(M+Na)^+$. HR-ESI-Q-TOF MS: *m/z* 1416.8277, calcd for $C_{53}H_{48}{}^{79}Br_4{}^{81}Br_2N_4O_{11}Na$. Found: 1416.8274. IR ν_{max} (KBr) cm^{-1}: 3508, 3319, 1724, 1684. ^1H NMR (DMSO-d_6) δ: 13.16 (1H, br s), 10.04 (1H, s), 9.93 (1H, s), 8.11 (1H, t, $J=5.5$ Hz), 7.61 (2H, s), 7.51 (2H, s), 7.37–7.20 (10H, m), 7.03 (1H, s), 6.96 (1H, s), 6.91 (1H, t, $J=5.5$ Hz), 6.17 (1H, s), 6.06 (1H, s), 5.22 (2H, s), 5.06 (2H, s), 3.79 (2H, s), 3.55 (2H, s), 3.20 (2H, q, $J=6.5$ Hz), 3.16 (2H, q, $J=6.5$ Hz), 2.73 (2H, t, $J=6.5$ Hz), 2.50 (2H, t, $J=6.5$ Hz), 1.33 (9H, s). ^{13}C NMR (DMSO-d_6) δ: 164.0, 161.8, 155.5, 151.2, 150.9, 146.4, 146.0, 144.7, 144.6, 142.3, 142.0, 140.7, 137.1, 136.7 (2C), 136.4 (2C), 133.4 (2C), 133.3 (2C), 130.8, 128.5 (4C), 128.3, 128.0 (2C), 127.9, 127.8 (2C), 127.5, 117.3 (2C), 117.2 (2C), 113.1, 112.6, 110.4, 110.2, 77.5, 76.7, 76.3, 40.5 (2C), 34.0, 33.6, 29.6, 28.9, 28.2 (3C).

4.1.17. Bn-bastadin 6 (20). To a stirred solution of **18** (130 mg, 0.090 mmol) in CH_2Cl_2 (9.0 mL), TFA (1.0 mL) was added and stirred for 10 min at rt. The solvent was removed in vacuo to give TFA salt of **19**. The TFA salt was converted to HCl salt by HCl–Et_2O treatment/evaporation for three times. The HCl salt was dissolved in THF (9 mL), and Et_3N (10 μL, 0.10 mmol) was added and stirred for 30 min at 0 °C, then HOBt (30 mg, 0.29 mmol) and EDCI (20 mg, 0.10 mmol) was added, and the reaction mixture was stirred for 3 h at rt. HCl (5%) was added and the aqueous phase was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column (*n*-hexane/EtOAc =2:1) to give **20** (99 mg, 86% in two steps) as a white powder. FAB MS: *m/z* 1273/1275/1277/1279/1281/1283/1285 $(M+H)^+$. HR-FAB MS: *m/z* 1278.7807, calcd for $C_{48}H_{39}{}^{79}Br_3{}^{81}Br_3N_4O_8$. Found: 1278.7858. IR ν_{max} (KBr) cm^{-1}: 3508, 3319, 1724, 1684. ^1H NMR (DMSO-d_6) δ: 10.03 (1H, s), 9.89 (1H, s), 8.14 (1H, t, $J=6.0$ Hz), 8.09 (1H, t, $J=6.0$ Hz), 7.62 (2H, s), 7.60 (2H, s), 7.34–7.29 (6H, m), 7.25 (2H, d, $J=6.5$ Hz), 7.22 (2H, d, $J=6.5$ Hz), 7.04 (1H, d, $J=1.5$ Hz), 7.01 (1H, d, $J=1.5$ Hz), 6.22 (1H, d, $J=1.5$ Hz), 6.14 (1H, d, $J=1.5$ Hz), 5.18 (2H, s), 5.04 (2H, s), 3.68 (2H, s), 3.57 (2H, s), 3.28–3.22 (4H, m), 2.68 (2H, t, $J=8.0$ Hz), 2.60 (2H, t, $J=6.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 162.3, 162.1, 151.9, 150.7, 147.0 (2C), 144.0, 143.9, 141.5 (2C), 139.7 (2C), 136.7 (2C), 136.2, 134.0 (2C), 133.6 (2C), 130.9, 128.8, 128.6 (4C), 128.3, 128.2 (2C), 128.1 (2C), 127.9, 126.8, 118.2 (2C), 117.8 (2C), 113.1, 112.3, 109.3 (2C), 77.7, 77.4, 40.6, 39.1, 34.9, 34.1, 29.3, 28.7. Anal. Calcd for $C_{48}H_{38}Br_6N_4O_8$: C, 45.10; H, 3.00; N, 4.38. Found: C, 44.74; H, 2.97; N, 4.03.

4.1.18. Bastadin 6 (1). To a solution of **20** (21 mg, 0.016 mmol) in CH_2Cl_2 (0.30 mL), $BCl_3\cdot SMe_2$ (2.0 M in CH_2Cl_2, 0.16 mL, 0.32 mmol) was added. After stirring for 3 h at rt, sat. aqueous $NaHCO_3$ was added and stirred vigorously for 1 h. The mixture was neutralized by 5% HCl and extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the resulting crude product was purified by SiO_2 column (*n*-hexane/AcOEt =2:3) to give bastadin 6 (**1**, 13 mg, 76%) as a white powder. ESI-Q-TOF MS: *m/z* 1115/1117/1119/1121/1123/1125/1127 $(M+Na)^+$. HR-ESI-Q-TOF MS: *m/z* 1120.6687, calcd for $C_{34}H_{26}{}^{79}Br_3{}^{81}Br_3N_4O_8$. Found: 1120.6656. IR ν_{max} (KBr) cm^{-1}: 3051, 2868, 1664, 1626. ^1H NMR (DMSO-d_6) δ: 11.86 (1H, s), 11.65 (1H, s), 9.98 (1H, s), 9.87 (1H, s), 8.06 (1H, t, $J=5.5$ Hz), 7.95 (1H, t, $J=5.5$ Hz), 7.63 (4H, s), 7.07 (1H, d, $J=1.0$ Hz), 7.02 (1H, d, $J=2.0$ Hz), 6.21 (1H, d, $J=1.0$ Hz), 6.14 (1H, d, $J=2.0$ Hz), 3.65 (2H, s), 3.55 (2H, s), 3.27–3.22 (4H, m), 2.71–2.68 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 163.3, 163.1, 151.4, 150.5, 146.1 (2C), 144.8, 144.7, 141.9, 141.6, 140.2, 137.7, 133.7 (2C), 133.3 (2C), 130.8, 128.2, 126.9, 126.3, 117.5 (2C), 117.1 (2C), 112.7, 111.7, 110.2, 109.8, 40.4, 38.4, 33.9, 32.8, 28.7, 27.4.

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References and notes

1. Carmeliet, P.; Jain, R. K. *Nature* **2000**, *407*, 249–257.
2. (a) Kazlauskas, R.; Lidgard, R. O.; Murphy, P. T.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1981**, *34*, 765–786. (b) Pordesimo, E. O.; Schmitz, F. J. *J. Org. Chem.* **1990**, *55*, 4704–4709. (c) Miao, S.; Andersen, R. J. *J. Nat. Prod.* **1990**, *53*, 1441–1446. (d) Butler, M. S.; Lim, T. K.; Capon, R. J.; Hammond, L. S. *Aust. J. Chem.* **1991**, *44*, 287–296. (e) Carney, J. R.; Scheuer, P. J.; Kelly-Borges, M. *J. Nat. Prod.* **1993**, *56*, 153–157. (f) Dexter, A. F.; Garson, M. J.; Hemling, M. E. *J. Nat. Prod.* **1993**, *56*, 782–786. (g) Park, S.-K.; Jurek, J.; Carney, J. R.; Scheuer, P. J. *J. Nat. Prod.* **1994**, *57*, 407–410. (h) Jaspars, M.; Rali, T.; Laney, M.; Schatzman, R. C.; Diaz, M. C.; Schmitz, F. J.; Pordesimo, E. O.; Crews, P. *Tetrahedron* **1994**, *50*, 7367–7374. (i) Mack, M. M.; Molinski, T. F.; Buck, E. D.; Pessah, I. N. *J. Biol. Chem.* **1994**, *269*, 23236–23249. (j) Franklin, M. A.; Penn, S. G.; Lebrilla, C. B.; Lam, T. H.; Pessah, I. N.; Molinski, T. F. *J. Nat. Prod.* **1996**, *59*, 1121–1127. (k) Coll, J. C.; Kearns, P. S.; Rideout, J. A.; Sankar, V. *J. Nat. Prod.* **2002**, *65*, 753–756.
3. Aoki, S.; Cho, S.; Ono, M.; Kuwano, T.; Nakao, S.; Kuwano, M.; Nakagawa, S.; Gao, J.-Q.; Mayumi, T.; Shibuya, M.; Kobayashi, M. Submitted for publication.
4. Segraves, E. N.; Shah, R. R.; Segraves, N. L.; Johnson, T. A.;

Whitman, S.; Sui, J. K.; Kenyon, V. A.; Cichewicz, R. H.; Crews, P.; Holman, T. R. *J. Med. Chem.* **2004**, *47*, 4060–4065.
5. (a) Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1982**, *23*, 1281–1284. (b) Nishiyama, S.; Suzuki, T.; Yamamura, S. *Tetrahedron Lett.* **1982**, *23*, 3699–3702. (c) Nishiyama, S.; Suzuki, T.; Yamamura, S. *Chem. Lett.* **1982**, 1851–1852.
6. (a) Guo, Z. W.; Machiya, K.; Salamonczyk, G. M.; Sih, C. J. *J. Org. Chem.* **1998**, *63*, 4269–4276. (b) Guo, Z. W.; Salamonczyk, G. M.; Han, K.; Machiya, K.; Sih, C. J. *J. Org. Chem.* **1997**, *62*, 6700–6701.
7. (a) Couladouros, E. A.; Pitsinos, E. N.; Moutsos, V. I.; Sarakinos, G. *Chem. Eur. J.* **2005**, *11*, 406–421. (b) Couladouros, E. A.; Moutsos, V. I.; Pitsinos, E. N. *ARKIVOC* **2003**, *15*, 92–101. (c) Couladouros, E. A.; Moutsos, V. I. *Tetrahedron Lett.* **1999**, *40*, 7023–7026. (d) Couladouros, E. A.; Moutsos, V. I. *Tetrahedron Lett.* **1999**, *40*, 7027–7030. (e) Bailey, K. L.; Molinski, T. F. *Tetrahedron Lett.* **2002**, *43*, 9657–9661. For a recent review in diaryl ether synthesis, see: (f) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045–5065.
8. CAN-catalyzed deprotection of Boc group has been reported. Hwu, J. R.; Jain, M. L.; Tsay, S. C.; Hakimelahi, G. H. *Tetrahedron Lett.* **1996**, *37*, 2035–2038.
9. (a) Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1987**, *28*, 4969–4972. (b) Shiba, T.; Cahnmann, H. J.; Matsuura, T.; Nishinaga, A.; Sakamoto, H. *J. Org. Chem.* **1964**, *29*, 3061–3063. (c) Forrester, A. R.; Thomson, R. H.; Woo, S.-O. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2340–2348.
10. Boehlow, T. R.; Harburn, J. J.; Spilling, C. D. *J. Org. Chem.* **2001**, *66*, 3111–3118.
11. Parker, K. A.; Coburn, C. A.; Johnson, P. D.; Aristoff, P. *J. Org. Chem.* **1992**, *57*, 5547–5550.
12. (a) Ting, P. C.; Lee, J. F.; Anthes, J. C.; Shih, N. Y.; Piwinski, J. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2333–2335. (b) Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4978–4984. (c) Denmark, S. E.; Dappen, M. S.; Sear, N. L.; Jacobs, R. T. *J. Am. Chem. Soc.* **1990**, *112*, 3466–3474.
13. DattaGupta, A.; Singh, R.; Singh, V. K. *Synlett* **1996**, 69–71.
14. Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761–3764.
15. Nishiyama, S.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3453–3456.
16. Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. E. *Synlett* **1993**, 663.

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Asymmetric synthesis of cytotoxic sponge metabolites *R*-strongylodiols A and B and an analogue

James E. D. Kirkham, Timothy D. L. Courtney, Victor Lee* and Jack E. Baldwin*

Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, UK

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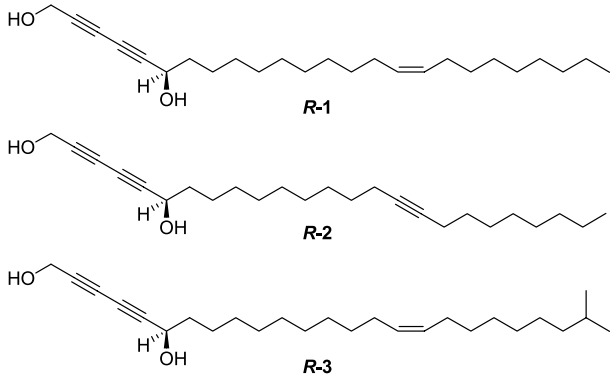
Abstract—The asymmetric synthesis of the marine sponge natural products *R*-strongylodiols A *R*-**1** and B *R*-**2**, using a minimum protection strategy, is described. Two approaches were examined and the Noyori asymmetric reduction of ynones was found to be successful for installing the chirality of the natural products. Analogue *R*-**32** was also prepared. In addition, asymmetric alkynylation of aldehydes is briefly reviewed.

1. Introduction

Research on marine natural products over the last two decades has revealed that sponges are prolific sources of novel and diverse long-chain, polyacetylenic metabolites.[1] Many exhibit potent and varied bioactivities, as well as important ecological roles.[2] Strongylodiols A **1**, B **2** and C **3** are three such natural products isolated from the Okinawan marine sponge of the genus *Strongylophora* by Iguchi and co-workers.[3] Interestingly, compounds **1**–**3** were found to exist as enantiomeric mixtures (*R*/*S* ratio 91:9 for **1**, 97:3 for **2** and 84:16 for **3**) with the *R*-enantiomer as the major component in each compound. The enantiomeric mixtures of **1**–**3** were found to be cytotoxic towards MOLT-4, IMR-90 and DLD-1 cells. The gross structures of **1**–**3** were determined by a combination of NMR and mass spectrometry analysis and through the application of the modified Mosher's method. Four related compounds, strongylodiols D–G, were subsequently found from the same source.[4]



The first total synthesis of strongylodiol A *R*-**1** was reported by Yadav et al.[5] The key step in Yadav's synthesis involved the use of strongly basic conditions to effect the β-elimination of a chiral epoxychloride to install the requisite acetylenic alcohol. Hence, their method is unsuitable in the synthesis of strongylodiol B *R*-**2** due to the likelihood of triple bond isomerization. Their choice of 1,10-decanediol as starting material and sequential chain extension at either end resulted in the heavy use of protecting group chemistry. Thus Yadav's synthesis is rather complicated for a compound with a relatively simple molecular structure. Recently Carreira[6] completed the synthesis of *R*-**1** and *R*-**2** via the asymmetric alkynylation of aldehydes. Carreira's synthesis is succinct, however, the ee of their asymmetric addition products were only approximately 80%. We have previously communicated our results[7] and herein we disclose the full details of our investigation into the asymmetric synthesis of *R*-**1** and *R*-**2** based on a minimal protection strategy. We first investigated the synthesis of *R*-**2** due to its simpler structure.

2. Results and discussion

The retrosynthetic analysis of strongylodiol B *R*-**2** is outlined in Figure 1. This investigation was initiated prior

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* Corresponding authors. Tel.: +44 1865 275653; fax: +44 1865 275674. (V.L.); e-mail addresses: victor.lee@chem.ox.ac.uk; jack.baldwin@chem.ox.ac.uk

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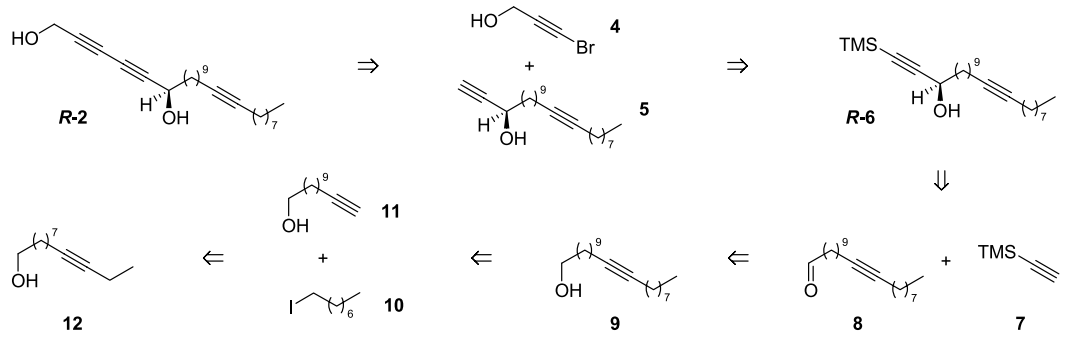


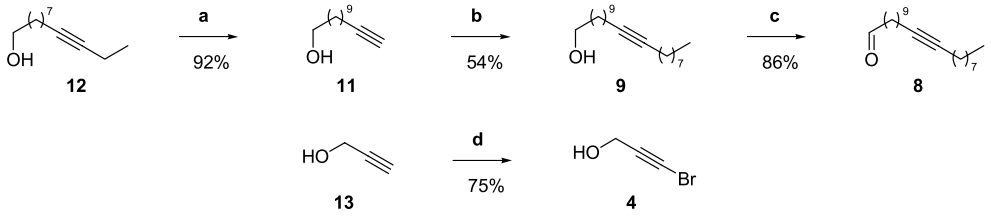
Figure 1. Retrosynthetic analysis of strongylodiol B **2**.

to the publication of Carreira's results.[6] It was anticipated that fragments **4** and **5** would be coupled by a Cadiot–Chodkiewicz[8] reaction via a copper alkynylide derived from **4**. Fragment **4** would be prepared by bromination of propargyl alchol **13**.[9] Fragment **5** would be constructed from protected acetylene *R*-**6**, itself derived from the enantioselective addition of commercially available trimethylsilylacetylene **7** to aldehyde **8** using the conditions of Carreira et al.[10] Aldehyde **8** would be formed by oxidation[11] of the corresponding alcohol **9**, itself synthesized by the nucleophilic displacement of alkyl iodide **10** by the dianion of alkynol **11**.[12] Alkynol **11** would be derived from commercially available 9-dodecyn-1-ol **12** by a zipper reaction.[13]

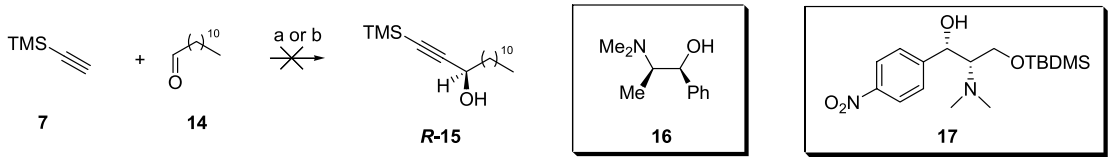
Alcohol **11** was prepared by isomerization of commercially available **12** using lithium 3-aminopropanamide in the presence of potassium *tert*-butoxide in 92% yield, following the protocol of Abrahams et al.[14] This method was reported to be more convenient than other literature protocols.[15] Double deprotonation of **11** with 2 equiv of *n*-BuLi in DMPU/THF generated the corresponding dianion, which was subsequently quenched with 1-iodooctane **10** to afford alcohol **9**. A difficulty with this step was that the dianion had a tendency to cause the reaction to 'freeze out'. Therefore the reaction was occasionally removed from the cold bath to thaw out the frozen mixture. Notwithstanding this minor problem the alkylation product was obtained in 54% yield. Oxidation of alcohol **9** was effected with *o*-iodoxybenzoic acid (IBX) in THF/DMSO[11] to deliver aldehyde **8** in 86% yield. 3-Bromoprop-2-yn-1-ol **4** was prepared in 75% yield by the addition of propargyl alcohol **13** to a solution of bromine and KOH in water (Scheme 1). Although literature[9] described the instability of **4** towards shock and heat we found that **4** could be purified by flash chromatography without any difficulty.

We initially investigated the Carreira method of asymmetric addition of alkynylides to aldehydes. It is documented that simple unbranched aliphatic aldehydes are not highly effective substrates in the Carreira reaction. However, the concomitant formation of a carbon–carbon bond and a chiral centre was deemed to offset the aforementioned disadvantage. The Carreira reaction was examined with trimethylsilylacetylene **7** and dodecanal **14** by treatment with an amine base and chiral ligand (+)-*N*-methylephedrine **16** in the presence of $Zn(OTf)_2$ (Scheme 2).

A mixture of $Zn(OTf)_2$ and (+)-*N*-methylephedrine in toluene was stirred at 23 °C for 2 h resulting in a white suspension. A solution of **7** in toluene was added via cannula and the mixture stirred for a further 18 h in an attempt to solubilize the reagents. However, no further solubilization was observed. Aldehyde **14** was added leading to isolation of adduct **15** in <5% yield containing impurities and with variable reproducibility. It was



Scheme 1. Synthesis of aldehyde **8** and fragment **4**. Reagents and conditions: (a) $LiHN(CH_2)_3NH_2$, KO^{t}Bu, $H_2N(CH_2)_3NH_2$, rt; (b) *n*-BuLi (2 equiv), THF, DMPU, then **10**, −20 °C; (c) IBX, DMSO, THF, rt; (d) $Br_{2(liq)}$, KOH, H_2O, −12 °C.



Scheme 2. Attempted asymmetric addition reaction using the conditions of Carreira et al. and Jiang et al. Reagents and conditions: (a) $Zn(OTf)_2$ (2.0 equiv), triethylamine (2.1 equiv), **16** (2.1 equiv), toluene; (b) $Zn(OTf)_2$ (1.0 equiv), **17** (1.0 equiv), triethylamine (1.1 equiv), toluene.

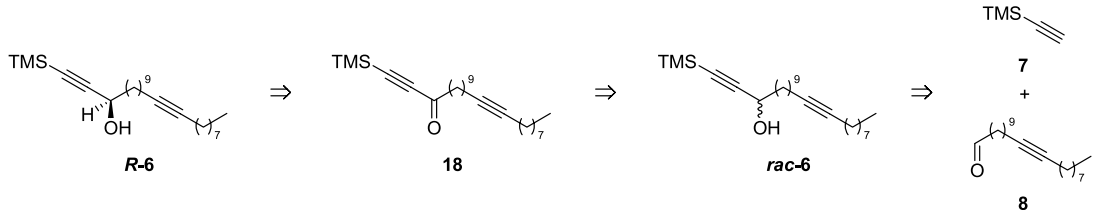


Figure 2. Second retrosynthetic analysis of strongylodiol B *R*-**2**.

conceived that the failure of the reaction might have been attributed to the facile enolisation of the aldehyde and so use of a weaker base than triethylamine was attempted. However, neither 2,6-lutidine nor pyridine was found to be effective in mediating the desired reaction. Marshall et al.[16] later reported an unsuccessful attempt in modifying the Carreira reaction with Hünig's base.

Subsequent attempts to form a homogeneous mixture were made in which the $Zn(OTf)_2$ was thoroughly powdered and dried before addition to a mixture of **7** and **16**.[17] Toluene was added and the mixture stirred for 2 h, again resulting in a white suspension. Addition of triethylamine and **14** to the suspension and heating at 60 °C did not lead to a homogeneous mixture and no product formation was observed.

A literature survey[16,18] revealed examples of failed Carreira reactions on aliphatic aldehydes which consolidated our belief that this reaction was not suitable in our synthesis. We were then attracted by a similar method recently reported by Jiang et al.[19] in which the asymmetric alkynylation of an aliphatic aldehyde using chiral ligand **17** were described in excellent yields and enantioselectivities. Amino-alcohol **17** was therefore synthesized according to literature procedure[20] and the enantioselective addition of trimethylsilylacetylene **7** to dodecanal **14** was attempted as described by Jiang et al.[19] (Scheme 2).

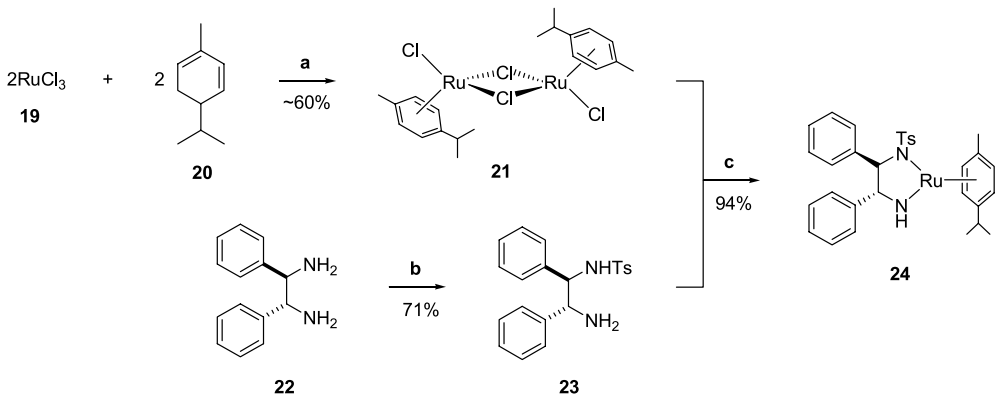
Jiang et al. had described the mixture of $Zn(OTf)_2$ and chiral ligand **17** in toluene as a 'solution' and that the enantioselective addition reaction took place in a 'homogeneous phase'. However, we observed great difficulty in forming a solution of $Zn(OTf)_2$ and chiral ligand **17** in toluene: a yellow suspension always resulted. Sonification and heating of the suspension led to coagulation into an insoluble gum and addition of triethylamine led to no change in the physical state of the reactants. Addition of trimethylsilylacetylene **7** and aldehyde **14** to the reaction mixture and stirring overnight resulted in no reaction. On subsequent attempts THF was added to the heterogeneous mixture in an effort to solubilize the gum; this was successful. Unfortunately, no reaction was observed.

Several further attempts were made to form a homogeneous solution by varying the commercial source of $Zn(OTf)_2$, by further powdering and drying the $Zn(OTf)_2$, and by allowing the $Zn(OTf)_2$ and chiral ligand **17** to congeal before stirring and heating. Unfortunately, all attempts were unsuccessful.

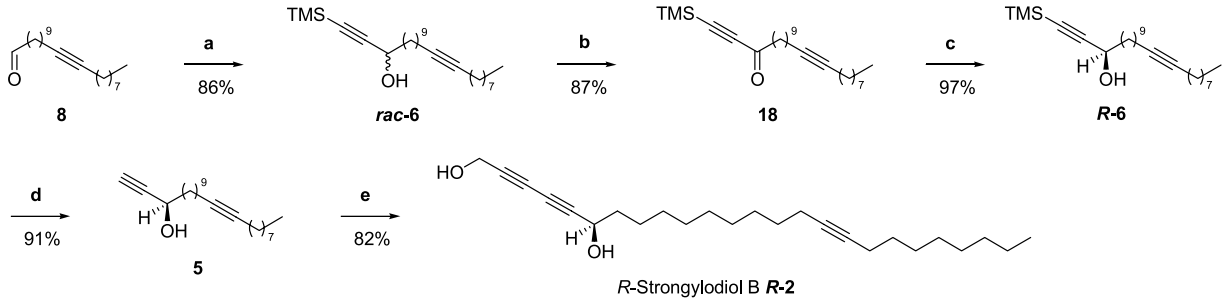
Consequently, a different approach to the synthesis of strongylodiols A *R*-**1** and B *R*-**2** was adopted. During the course of our new investigation we were pleasantly surprised that the Carreira group reported the successful synthesis of strongylodiols A *R*-**1** and B *R*-**2** using the chiral alkynylide addition approach, albeit an excess of $Zn(OTf)_2$, chiral ligand and base (4 equiv each) were required to deliver the products in acceptable ee and yields.[6] Therefore it would appear that these types of chiral zinc acetylide addition reactions are highly substrate sensitive.[21,22]

2.1. Revised synthetic route

Our revised synthetic route involved introducing the chiral centre at C-6 via the asymmetric reduction of ynone **18** (Fig. 2). It was anticipated that *R*-**6** could be obtained by performing a Noyori asymmetric transfer hydrogenation reaction on ynone **18** using chiral ruthenium catalyst **24** in propan-2-ol. Ynone **18** could be obtained by oxidation of racemic alcohol *rac*-**6**, itself obtained by the nucleophilic addition of trimethylsilylacetylene **7** to aldehyde **8**. Chiral



Scheme 3. Synthesis of chiral ruthenium catalyst **24**. Reagents and conditions: (a) EtOH, 120 °C under reflux; (b) *p*-TsCl (1 equiv), Et_3N, THF, 0 °C; (c) KOH, DCM, rt.



Scheme 4. Synthesis of strongylodiol B *R*-**2**. Reagents and conditions: (a) trimethylsilylacetylene **7**, *n*-BuLi, THF, −12 °C; (b) IBX, DMSO, THF, rt; (c) **24**, *i*-PrOH, 30 °C, rt; (d) NH_4F, MeOH, 67 °C; (e) **4**, CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, MeOH, rt.

ruthenium catalyst **24** was therefore synthesized according to literature procedure.

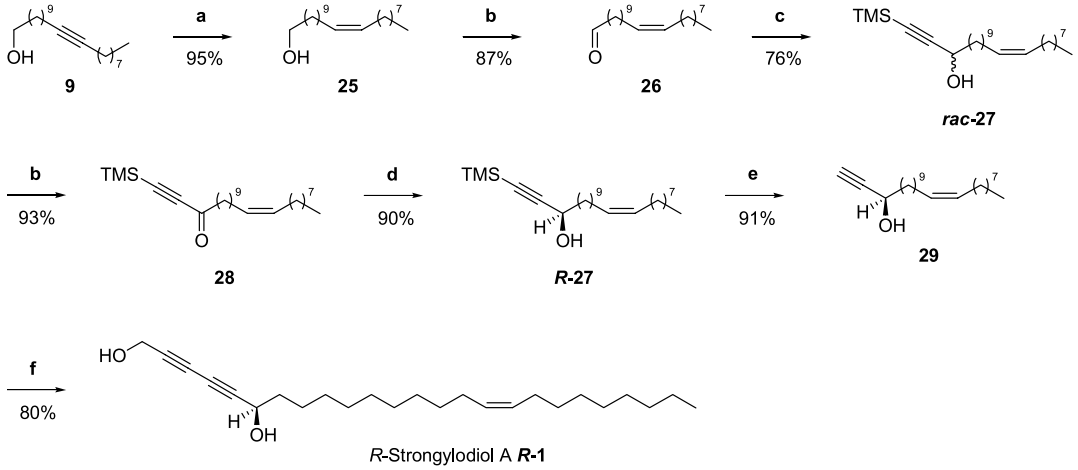
Formation of bis-arene complex **21** was achieved in approximately 60% yield by heating ruthenium (III) chloride **19** and α-phellandrene **20** in EtOH under reflux, as described by Bennet et al.[23] It was observed that the expected aromatic double-doublet signal in the ^1H NMR spectrum of **21** was nearly 1 ppm downfield of the literature value. Subsequent X-ray diffraction studies confirmed the structure of **21** and that the literature data is incorrect. Formation of chiral ligand **23** was achieved in 71% yield by the selective mono-tosylation of **22**, as described by Tietze et al.[24] Synthesis of chiral ruthenium catalyst **24** was achieved in 94% yield following the protocol of Noyori et al.[25] (Scheme 3). We observed that the preparation of chiral ruthenium catalyst **24** did not require the use of a Schlenk technique. Although catalyst **24** contained some impurities it was subsequently proven that the **24** we prepared was highly effective in asymmetric reduction reactions.

Synthesis of strongylodiol *R*-**2** continued by the addition of lithium trimethylsilylalkynide to aldehyde **8** to give *rac*-**6** in 86% yield, which was subjected to IBX oxidation to give ynone **18** in 87% yield. Asymmetric reduction of **18** with catalyst **24** in propan-2-ol delivered *R*-**6** in 97% yield.[26] The ee of *R*-**6** was >95% as determined by ^{19}F NMR analysis of its Mosher's esters.[27] The terminal trimethylsilyl group in *R*-**6** was removed by ammonium fluoride in methanol to afford **5** in 91% yield.[28] Cadiot–Chodkiewicz coupling[8] of **5** and 2-bromopropyn-1-ol **4** delivered *R*-**2** in 82% yield (Scheme 4).

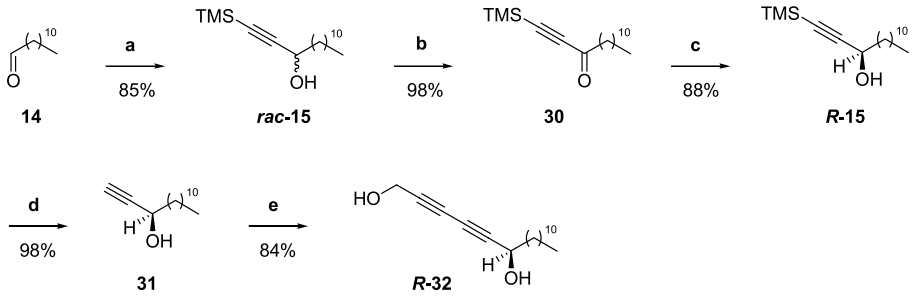
The synthesis of strongylodiol *R*-**1** commenced with a Lindlar hydrogenation[29] of **9** in benzene to afford **25** in 95% yield, which was oxidised to aldehyde **26** in 87% yield by IBX in THF/DMSO. Reaction of aldehyde **26** with lithium trimethylsilylacetylide delivered *rac*-**27** in 76% yield. Oxidation of *rac*-**27** with IBX afforded a 93% yield of ynone **28** and subsequent chiral reduction of **28** with catalyst **24** in propan-2-ol gave *R*-**27** in 97% yield with >95% ee. Removal of the trimethylsilyl group from *R*-**27** was effected with ammonium fluoride in methanol to deliver terminal acetylenic alcohol **29** in 91% yield, which was coupled with **4** to afford *R*-**1** in 80% yield (Scheme 5).

2.2. Synthesis of an analogue of strongylodiols A, B and C

An analogue of the strongylodiols, *R*-**32**, was prepared since reactions subsequent to the formation of **8** in the synthesis of strongylodiol B *R*-**2** were first tested on a model system based on commercially available dodecanal **14**. Aldehyde **14** was converted to *rac*-**15** in 85% yield, which was oxidised to **30** in 98% yield. **30** was subject to an asymmetric reduction to yield *R*-**15** in >95% ee and 88% yield, which was deprotected to give **31** in 98% yield. Cadiot–Chodkiewicz coupling of **31** and **4** afforded *R*-**32** in 84% yield (Scheme 6). Comparison of the optical rotation



Scheme 5. Synthesis of strongylodiol A *R*-**1**. Reagents and conditions: (a) Lindlar's catalyst, quinoline, H_2, benzene, rt; (b) IBX, DMSO, THF, rt; (c) trimethylsilylacetylene **7**, *n*-BuLi, THF, −12 °C; (d) **24**, *i*-PrOH, 30 °C, rt; (e) NH_4F, MeOH, 67 °C; (f) **4**, CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, MeOH, rt.



Scheme 6. Test reactions of the model system. Reagents and conditions: (a) trimethylsilylacetylene **7**, *n*-BuLi, THF, −12 °C; (b) IBX, DMSO, THF, rt; (c) **24**, *i*-PrOH, 30 °C, rt; (d) NH_4F, MeOH, 67 °C; (e) **4**, CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, MeOH, rt.

data of *R*-**1**, *R*-**2** and *R*-**32** indicated that the magnitude and sign of the rotation is almost independent of both chain length and chain functionality.

3. A comment on the Carreira asymmetric alkynylation reaction

Since Carreira's initial report of the asymmetric alkynylation of aldehydes the synthetic community has expressed mixed opinion about the effectiveness of this reaction. There are research groups that have successfully applied this reaction to synthesis,[30] yet the number of failed Carreira reactions reported is considerable.[16,18]

Literature survey has revealed clues to the apparent discrepancies of the Carreira reactions as observed by various groups. Firstly, the Garcia group noticed that the source and particle size of the $Zn(OTf)_2$ can have an effect on the yield of the reaction.[17b] Secondly, the Tanaka group[22,30b,c,h–j] and Garcia group[17] deemed it necessary to vigorously dry the $Zn(OTf)_2$ prior to reaction. This is in contrast to Carreira who reported that the asymmetric alkynylation reaction is reasonably tolerant to moisture.[10,31]

Since the Carreira reaction is essentially a heterogeneous mixture[32] it is tempting to speculate that the reaction takes place on the surface of the $Zn(OTf)_2$ particles. The surface morphology and particle size of $Zn(OTf)_2$ may vary from source to source, methods of preparation and degree of dryness. All these factors can affect the outcome of the reaction. Since the mechanism of this reaction is not well understood, it is impossible to predict the applicability of this reaction to target synthesis with a great degree of confidence.

4. Conclusion

In conclusion, we have developed an efficient synthesis of *R*-**1** and *R*-**2** without the deliberate use of protecting groups. The spectral data and specific rotation values of both *R*-**1** and *R*-**2** are in excellent agreement with their corresponding literature values. We have also demonstrated that the Noyori reduction of ynones **18**, **28** and **30** were achieved with high ee and high yields. In addition, compound **11** could be a useful intermediate in the syntheses of other members of the strongylodiols.[4]

5. Experimental

5.1. General

^1H NMR and ^{13}C NMR spectra were recorded on Varian Gemini 200 (200 MHz), Brüker DPX200 (200 MHz), Brüker DPX400 (400 MHz) and Brüker AMX500 (500 MHz) spectrometers at ambient temperatures and are reported in parts per million (ppm). ^1H NMR coupling constants (*J*) are recorded to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded on Varian Gemini 200 (50.3 MHz), Brüker DPX200 (50.3 MHz), Brüker DPX400 (100.6 MHz) and Brüker AMX500 (125.8 MHz) spectrometers at ambient temperatures and are reported in parts per million (ppm). A combination of COSY, HMQC and DEPT experiments were utilized when necessary for the assignment of ^1H and ^{13}C chemical shifts. ^{19}F spectra were recorded on Brüker DPX250 (235 MHz) and Brüker DPX400 (376 MHz) spectrometers at ambient temperatures and are reported in parts per million (ppm). ^1H, ^{13}C and ^{19}F NMR spectra are referenced to the residual solvent peak.

Low resolution mass spectra were recorded using a TRIO-1 GCMS spectrometer, Micromass Platform (APCI) spectrometer, Micromass Autospec spectrometer (CI^+) and a Micromass ZAB spectrometer (CI^+, EI); only molecular ions (M^+), fragments from molecular ions and other major peaks are reported. High resolution spectra were recorded on a Micromass Autospec spectrometer and are accurate to ± 10 ppm.

All melting points were determined using a Cambridge Instruments Gallen™ III hot stage melting point apparatus and are uncorrected.

Optical rotations were recorded on a Perkin–Elmer 241 polarimeter using a 10 cm path length cell.

Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer as a thin film between NaCl plates, a nujol emulsion between NaCl plates or KBr disks; absorption maxima (ν_{max}) of the major peaks are reported in cm^{-1}.

Elemental analyses were performed by Elemental Analysis Limited.

Thin layer chromatography (TLC) was performed using Merck aluminium foil backed plates pre-coated with silica

gel 60 F_{254} (1.05554). Visualisation was effected by quenching of UV fluorescence ($\lambda_{max}=254$ nm), staining with 10% w/v ammonium molybdate in 1 M H_2SO_4, followed by heating. Retention factors (R_f) are reported to two decimal places. Column chromatography refers to flash chromatography and was performed on ICN silica 32–63, 60 Å.

All operations involving air-sensitive reagents were performed under an inert atmosphere of dry argon using syringes, oven-dried glassware. Anhydrous tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl under nitrogen. Anhydrous dichloromethane (DCM) was distilled from calcium hydride under nitrogen. Triethylamine, dimethyl formamide (DMF), toluene, chloroform and dimethyl sulfoxide (DMSO) were distilled from calcium hydride under argon or reduced pressure and stored over 4 Å molecular sieves under argon. Propane-1,3-diamine was stirred over barium oxide, distilled under reduced pressure and stored over 4 Å molecular sieves under argon. α-Phellandrene was distilled under reduced pressure and stored over 4 Å molecular sieves under argon. Commercial solutions of *n*-BuLi were titrated against 1,3-diphenylacetone-*p*-toluenesulfonylhydrazone in THF prior to use. PE 30–40 refers to the fraction of light petroleum ether boiling between 30 and 40 °C, and was distilled before use. All water used was distilled except where otherwise indicated. Solvents were evaporated on a Büchi R110 Rotavaporator.

5.2. Synthesis of chiral ligands 34 and 24

5.2.1. (1*S*,2*S*)-2-(Dimethylamino)-1-(4-nitrophenyl)propane-1,3-diol. A mixture of (1*S*,2*S*)-2-amino-3-(*p*-nitrophenyl)propane-1,3-diol (1.01 g, 4.76 mmol), aqueous formaldehyde (37–40%, 1.5 ml) and formic acid (98%, 2.0 ml) was heated under reflux at 110 °C under argon with continuous stirring for 22 h. An effervescence of CO_2 was observed almost immediately. Removal of solvent in vacuo afforded a yellow residue, which was neutralized with $NaOH_{(aq)}$ (1 M, 6 ml) and extracted with DCM (3×15 ml). The organic phases were combined and washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (90% DCM, 10% MeOH) on a basic alumina column to yield (1*S*,2*S*)-2-*N*,*N*-dimethylamino-1-*p*-nitrophenyl-propane-1,3-diol (1.02 g, 4.25 mmol, 89%) as a yellow crystalline solid.[20]

5.2.2. (1*S*,2*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-(dimethylamino)-1-(4-nitrophenyl)propan-1-ol (17). To a stirred solution of (1*S*,2*S*)-2-*N*,*N*-dimethylamino-1-*p*-nitrophenyl-propane-1,3-diol (0.946 g, 3.95 mmol, 1 equiv) and imidazole (0.338 g, 4.96 mmol, 1.26 equiv) in DCM (6 ml) under argon and immersed in a salt-ice bath at −12 °C was added a solution of TBDMSCl (0.621 g, 4.12 mmol, 1.04 equiv) in DCM (2 ml, 2×2 ml wash) via cannula. The reaction was stirred at ambient temperature for 3 h, diluted with DCM (20 ml) and quenched with $NH_4Cl_{(aq)}$ (5 ml sat. in 40 ml H_2O) before being extracted with DCM (3×10 ml). The combined organic phases were washed with $NaHCO_{3(aq)}$ (sat., 10 ml), $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (95% DCM, 5% MeOH) on a silica column to yield (1*S*,2*S*)-3-*tert*-butyldimethylsilyloxy-2-*N*,*N*-dimethylamino-1-*p*-nitrophenyl-propan-1-ol (0.658 g, 1.86 mmol, 47%) as a yellow oil.[20]

5.2.3. Di-μ-chloro-bis[chloro(η^6-1-isopropyl-4-methylbenzene)ruthenium (II)] (21). A solution of ruthenium (III) chloride hydrate **19** (35–40% Ru) (3.00 g, approximately 13 mmol) in EtOH (150 ml) was treated with α-phellandrene **20** (15 ml) and heated under reflux at 120 °C for 4 h. The solution was allowed to cool to ambient temperature and the red-brown crystalline product was filtered off. Additional product was obtained by concentrating the orange-yellow filtrate under reduced pressure to approximately half-volume, refrigerating overnight and filtering off the crystals. Drying in vacuo afforded **21** (2.39 g, 3.90 mmol, approximately 60%) as deep-purple crystals; decomp. >200 °C; ν_{max}/cm^{-1} (nujol) 319 (s), 287 (s), 266 (s), 247 (s), 232 (s), 204 (s), 169 (w), 154 (m), 139 (m), 123 (m), 108 (m); *m*/*z* Probe EI$^+$ 576.9 ($[M(-Cl)]^+$, $Ru_2Cl_3C_{20}H_{28}$, 100%); δ_H (400 MHz, $CDCl_3$) 1.25 (12H, d, $J=7.0$ Hz, –CH(CH_3)$_2$), 2.13 (6H, s, Ar-CH_3), 2.89 (2H, septet, $J=7.0$ Hz, –CH(CH_3)$_2$), 5.32 (4H, d, $J=5.0$ Hz, –C_6H_4), 5.44 (4H, d, $J=5.0$ Hz, –C_6H_4); δ_C (100.6 MHz, $CDCl_3$) 18.91 (2C, Ar-CH_3), 22.12 (2C, Ar-CH(CH_3)$_2$), 30.58 (2C, Ar-CH(CH_3)$_2$), 80.48 (4C, Ar*C*-H), 81.26 (4C, Ar*C*-H), 96.70 (2C, Ar*C*-C), 101.1 (2C, Ar*C*-C); microanalysis found C=39.20, H=4.60, $Ru_2Cl_2C_{20}H_{28}$ requires C=39.23, H=4.61.

5.2.4. *N*-((1*R*,2*R*)-2-Amino-1,2-diphenylethyl)-4-methylbenzenesulfonamide (23). To a solution of **22** (0.805 g, 3.79 mmol, 1 equiv) in anhydrous THF (32 ml) at 0 °C was added anhydrous triethylamine (1.6 ml) via syringe. A solution of *p*-TsCl (0.725 g, 3.80 mmol, 1 equiv) in anhydrous THF (8 ml) at 0 °C was added over 30 min via syringe pump and the mixture stirred overnight at 0 °C. Removal of solvent in vacuo afforded a white solid, which was quenched with $NaHCO_{3(aq)}$ (sat., 60 ml) and extracted with DCM (4×15 ml). The combined organic layers were washed with $NaCl_{(aq)}$ (sat., 20 ml), dried over $Na_2SO_{4(s)}$ and concentrated to dryness in vacuo to afford the crude product, which was purified by flash chromatography (EtOAc) on a silica column to yield **23**[†] (0.983 g, 2.69 mmol, 71%) as a white solid; mp 125–125.5 °C, lit. mp 125–126 °C[33]; $[\alpha]_D^{25}=-36.7$ (*c* 1.0, $CHCl_3$), lit. $[\alpha]_D^{25}$ vary considerably; ν_{max}/cm^{-1} (KBr) 3349 (m), 3284 (m), 3151 (m, br), 2919 (w), 2864 (m), 1599 (m), 1495 (m), 1455 (m), 1322 (m), 1155 (s), 1094 (m), 1062 (m), 1019 (m), 937 (w), 898 (m), 838 (w), 813 (m), 767 (s), 699 (s), 670 (m); *m*/*z* Probe ES$^+$ 367.1 ($[MH]^+$, 100%), HRMS found $[MH]^+$=367.1469, $C_{21}H_{23}N_2O_2S$ requires 367.1480; δ_H (400 MHz, $CDCl_3$) 1.51 (2H, br s, –NH_2), 2.33 (3H, s, –$pC_6H_4CH_3$), 4.14 (1H, d, $J=5.5$ Hz, –$CH$$NH_2$), 4.40 (1H, d, $J=5.5$ Hz, –$CH$$NHSO_2pC_6H_4CH_3$), 6.98 (2H, d, $J=8.0$ Hz, –$pC_6H_4CH_3$), 7.05–7.25 (10H, m, –C_6H_5), 7.32 (2H, d, $J=8.0$ Hz, –$pC_6H_4CH_3$); δ_C (100.6 MHz, $CDCl_3$) 21.38 (1C, –$pC_6H_4CH_3$), 60.52 (1C, –$CHNH_2$), 63.24 (1C, –$CHNHSO_2pC_6H_4CH_3$), 126.5 (2C, Ar*C*-H), 126.8 (2C, Ar*C*-H), 127.0 (2C, Ar*C*-H), 127.3 (1C, Ar*C*-H), 127.4 (1C,

[†] A small amount of ditosylated product was also observed.

Ar*C*-H), 128.2 (2C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 129.1 (2C, Ar*C*-H), 137.2 (1C, Ar*C*-C), 139.3 (1C, Ar*C*-C), 141.4 (1C, Ar*C*-C), 142.5 (1C, Ar*C*-C); microanalysis found C=69.17, H=6.08, N=7.74, $C_{21}H_{22}N_2O_2S$ requires C=68.82, H=6.05, N=7.64.

5.2.5. (1*R*,2*R*)-(−)-*N*-Tosyl-1,2-diphenylethane-1,2-diamine[(η^6-1-isopropyl-4-methylbenzene)ruthenium (II)] (24). A mixture of **21** (0.306 g, 0.500 mmol, 1 equiv), **23** (0.366 g, 1.00 mmol, 2 equiv) and KOH (0.411 g, 7.33 mmol, 15 equiv) in anhydrous DCM (7 ml) was stirred under argon at ambient temperature for 5 min. On addition of water (7 ml) the colour changed from orange to deep purple. The purple organic layer was washed with water (7 ml), dried over CaH_2 and concentrated to dryness in vacuo to yield **24** (0.564 g, 0.941 mmol, 94%) as deep purple crystals; decomp. >80 °C; ν_{max}/cm^{-1} (KBr) 3441 (m, br), 3287 (s), 3064 (m), 2965 (m), 2928 (m), 2861 (m), 1800 (w), 1597 (m), 1449 (m), 1388 (m), 1261 (s), 1130 (s), 1087 (s), 939 (m), 862 (m), 808 (m), 771 (m), 694 (s), 640 (m), 547 (m), 506 (w); *m/z* Probe ES$^+$601.0 ($[MH]^+$, $C_{31}H_{35}N_2O_2SRu$, 100%); HRMS found $[MH]^+$=601.1486, $C_{31}H_{35}N_2O_2S^{102}Ru$ requires 601.1463; δ_H (400 MHz, toluene-d_8) 1.04, 1.09 (3H, d, J=7.0 Hz, –CH(C*H*$_3$)$_2$), 1.89 (3H, s, –C*H*$_3$ in *p*-Ts), 2.05 (3H, s, –C*H*$_3$ in *p*-cymene), 2.37 (1H, m, –C*H*(CH$_3$)$_2$), 3.91 (1H, d, J=4.0 Hz, –C*H*NH), 4.71 (1H, s, –C*H*N-*p*-Ts), 4.94, 5.06, 5.11, 5.22 (4H, d, J=5.0 Hz, –C$_6$*H*$_5$ in *p*-cymene), 6.42 (1H, br. s, –CHN*H*), 6.70 (2H, d, J=8.0 Hz, –C$_6$*H*$_5$ in *p*-Ts), 7.00–7.23 (10H, m, *p*-TsNCH(C$_6$*H*$_5$)CH(C$_6$*H*$_5$)NH), 7.49 (2H, d, J=8.0 Hz, –C$_6$*H*$_5$ in *p*-Ts); microanalysis found C=61.76, H=5.69, N=4.78, $C_{31}H_{34}N_2O_2SRu$ requires C=62.08, H=5.71, N=4.78.

5.3. Synthesis of common intermediates 4 and 9

5.3.1. 3-Bromoprop-2-yn-1-ol (4). *Caution*. 1-Halopropynes are potentially explosive. Do not heat these compounds. Perform these operations behind a blast shield. Do not distil.

Molecular bromine (1.54 ml, 30 mmol, 1 equiv) was added to a vigorously stirred solution of KOH (4.51 g, 80.3 mmol, 2.67 equiv) in water (12 ml) at −12 °C. The resultant yellow solution was kept at −12 °C and added dropwise to a stirred solution of propargyl alcohol **13** (1.80 ml, 30 mmol, 1 equiv) in water (3.9 ml) maintaining a temperature of <5 °C. Addition took approximately 1 h, after which the mixture was stirred for 1 h, allowed to warm to ambient temperature and stirred again for 1 h. The mixture was then extracted with Et_2O (4×20 ml), washed with $Na_2S_2O_{3(aq)}$ (sat., 1×10 ml) and dried over $K_2CO_{3(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (EtOAc) on a silica column to yield **4** (3.03 g, 22.4 mmol, 75%) as a pale yellow oil; R_f=0.19 (65% PE 30–40, 35% Et_2O); ν_{max}/cm^{-1} (thin film) 3334 (s, br), 2921 (m), 2867 (m), 2218 (s), 1710 (w), 1630 (w), 1424 (m), 1359 (m), 1226 (m), 1050 (s), 990 (s), 607 (m); δ_H (400 MHz, $CDCl_3$) 3.50 (1H, t, J=5.5 Hz, –O*H*), 4.26 (2H, d, J=5.5 Hz, H-1); δ_C (100.6 MHz, $CDCl_3$) 45.68 (1C, C-3), 51.52 (1C, C-1), 78.18 (1C, C-2).

5.3.2. Dodec-11-yn-1-ol (11). To a two-necked flask containing lithium (0.52 g, 74.6 mmol, 3.2 mm wire washed with petrol) was added propane-1,3-diamine (36 ml, previously distilled from barium oxide). The mixture was stirred at ambient temperature for 30 min before heating at 75 °C until the deep blue colour had discharged to afford a white suspension of the lithium amide. The reaction mixture was allowed to cool to ambient temperature and KO^{t}Bu (5.88 g, 52.4 mmol) was added to afford a pale yellow solution which was stirred for 20 min. To this solution was added **12** (2.5 ml, 2.137 g, 11.7 mmol, 1.0 equiv) in propane-1,3-diamine (10 ml, 120 mmol, 10 equiv) dropwise via cannula. The reddish-brown mixture was stirred for 30 min and poured into 100 ml water and 100 g ice before being extracted with PE 30–40 (3×100 ml), washed with water (100 ml), $KHSO_{4(aq)}$ (10%, 100 ml) and $NaCl_{(aq)}$ (sat., 100 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (50% PE 30–40, 50% Et_2O) to **11** (1.96 g, 10.76 mmol, 92%) as a waxy solid; R_f=0.31 (50% PE 30–40, 50% Et_2O); mp=28 °C; ν_{max}/cm^{-1} (KBr) 3287 (s, br), 2919 (s), 2850 (s), 2114 (w), 1487 (m), 1472 (s), 1462 (s), 1434 (m), 1421 (m), 1356 (m), 1322 (m), 1124 (m); *m/z* Probe CI$^+$ (NH_3) 200.2 ($[MNH_4]^+$, 100%), 183.2 ($[MH]^+$, 17%); HRMS found $[MNH_4]^+$=200.2011, $C_{12}H_{26}NO$ requires 200.2014; δ_H (400 MHz, $CDCl_3$) 1.24–1.62 (16H, m, H-2,3,4,5,6,7,8,9), 1.94 (1H, t, J=2.5 Hz, H-12), 2.18 (2H, dt, J_1=7.0 Hz, J_2=2.5 Hz, H-10), 3.64 (2H, t, J=6.5 Hz, H-1); δ_C (100.6 MHz, $CDCl_3$) 18.37 (1C, C-10), 25.70 (1C, *C*H$_2$), 28.45 (1C, *C*H$_2$), 28.71 (1C, *C*H$_2$), 29.05 (1C, *C*H$_2$), 29.37 (1C, *C*H$_2$), 29.38 (1C, *C*H$_2$), 29.50 (1C, *C*H$_2$), 32.77 (1C, C-2), 63.05 (1C, C-1), 68.02 (1C, C-12), 84.77 (1C, C-11).

5.3.3. Icos-11-yn-1-ol (9). To a solution of **11** (0.160 g, 0.89 mmol) in THF (1 ml) and DMPU (1.15 ml) was added dropwise a solution of *n*-BuLi in hexanes (0.83 ml, 2.51 M, 2.08 mmol) via syringe, while cooling to −20 °C. The pale yellow solution was stirred for 30 min at 0 °C before 1-iodooctane **10** (0.32 ml, 1.80 mmol) was added via syringe. The reaction mixture sometimes 'froze out' and therefore was temporarily removed from the cold bath to thaw out. The solution was allowed to warm to ambient temperature and stirred for a further 30 min before being poured into $NH_4Cl_{(aq)}$ (sat., 40 ml) to quench and extracted with a 1:1 mixture of PE 30–40 and Et_2O (3×20 ml). The combined organics were washed with $NaCl_{(aq)}$ (sat., 20 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (96% PE 30–40, 4% Et_2O) on a silica column to yield **9** (0.142 g, 0.480 mmol, 54%) as a waxy solid; R_f=0.26 (80% benzene, 20% Et_2O); mp=40 °C; ν_{max}/cm^{-1} (KBr) 3289 (s, br), 2920 (s), 2852 (s), 2019 (w), 1460 (s), 1356 (s), 1295 (m), 1260 (m), 1208 (w), 1058 (s), 1021 (s), 998 (m), 967 (m), 919 (m), 860 (w), 724 (s); *m/z* Probe CI$^+$ (NH_3) 312.3 ($[MNH_4]^+$, 100%); HRMS found $[MNH_4]^+$=312.3255, $C_{20}H_{42}NO$ requires 312.3266; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, J=7.0 Hz, H-20), 1.12–1.80 (28H, m, H-2,3,4,5,6,7,8,9,14,15,16,17,18,19), 2.13 (4H, t, J=7.0 Hz, H-10,13), 3.63 (2H, t, J=6.5 Hz, H-1); δ_C (100.6 MHz, $CDCl_3$) 14.07 (1C, C-20), 18.73 (2C, C-10,13), 22.63 (1C, *C*H$_2$), 25.71 (1C, *C*H$_2$), 28.82 (1C, *C*H$_2$), 28.84 (1C, *C*H$_2$), 29.11 (1C, *C*H$_2$), 29.14 (1C, *C*H$_2$), 29.15 (1C, *C*H$_2$), 29.16 (1C, *C*H$_2$), 29.20 (1C, *C*H$_2$), 29.38

(1C, CH_2), 29.45 (1C, CH_2), 29.54 1C, CH_2), 31.82 (1C, CH_2), 32.78 (1C, CH_2) 63.04 (1C, C-1), 80.18, 80.23 (2C, C-11,12).

5.4. Synthesis of strongylodiol B *R*-2

5.4.1. Icos-11-ynal (8). To a stirred solution of IBX (0.281 g, 1.00 mmol, 2 equiv) in DMSO (3 ml) under argon was added **9** (0.142 g, 0.481 mmol, 1 equiv) in anhydrous THF (1 ml, 2×0.5 ml wash) via cannula. The reaction mixture was stirred for 3 h, after which water (12 ml) was added. In a few minutes a white precipitate had formed which was removed by filtration through a sintered glass funnel. The residue was washed with cold EtOAc (6 ml). The combined organics were extracted with EtOAc (4×10 ml), washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (96% PE 30–40, 4% Et_2O) on a silica column to yield **8** (0.121 g, 0.415 mmol, 86%) as a white solid; mp 25–25.5 °C; R_f=0.14 (96% PE 30–40, 4% Et_2O); ν_{max}/cm^{-1} (KBr) 2952 (s), 2930 (s), 2848 (s), 2746 (m), 2359 (w), 1709 (s), 1466 (m), 1424 (w), 1407 (m), 1393 (m), 1302 (w), 1231 (w), 1062 (w), 892 (w), 724 (m), 696 (m), 668 (w), 527 (w); *m/z* Probe CI^+ (NH_3) 310.3 ($[MNH_4]^+$, 100%); HRMS found $[MNH_4]^+$=310.3112, $C_{20}H_{40}NO$ requires 310.3110; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J*=6.5 Hz, H-20), 1.18–1.40 (20H, m, H-4,5,6,7,8,15,16,17,18,19), 1.60 (2H, qui, *J*=7.0 Hz, H-3), 1.40–1.50 (4H, m, H-9,14), 2.11 (4H, t, *J*=7.0 Hz, H-10,13), 2.39 (2H, dt, J_1=7.5 Hz, J_2=2.0 Hz, H-2), 9.75 (1H, t, *J*=2.0 Hz, H-1); δ_C (100.6 MHz, $CDCl_3$) 14.06 (1C, C-20), 18.70, 18.71 (2C, C-10,13), 22.03 (1C, CH_2), 22.62 (1C, CH_2), 28.76 (1C, CH_2), 28.83 (1C, CH_2), 29.04 (1C, CH_2), 29.09 (2C, CH_2), 29.10 (1C, CH_2), 29.11 (1C, CH_2), 29.13 (1C, CH_2), 29.19 (1C, CH_2), 29.27 (2C, CH_2), 31.81 (1C, CH_2), 43.86 (1C, C-2), 80.09, 80.21 (2C, C-11,12), 202.8 (1C, C-1).

5.4.2. 1-(Trimethylsilyl)docosa-1,13-diyn-3-ol (*rac*-6). To a stirred solution of trimethylsilylacetylene **7** (0.120 ml, 0.865 mmol, 1.03 equiv) in anhydrous THF (4 ml) at −12 °C was added *n*-BuLi (2.12 M in hexanes, 0.410 ml, 0.865 mmol, 1.03 equiv) under argon. After stirring for 1 h at −12 °C a pre-cooled solution of **8** (0.246 g, 0.840 mmol, 1 equiv) in anhydrous THF (1 ml, 2×0.5 ml wash) at −12 °C was added dropwise via cannula. The reaction mixture was stirred for 1.5 h, then quenched with $NH_4Cl_{(aq)}$ (sat., 5 ml) and water (5 ml) before being extracted with Et_2O (3×20 ml). The combined organic phases were washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (90% PE 30–40, 10% Et_2O) on a silica column to yield *rac*-**6** (0.283 g, 0.724 mmol, 86%) as a colourless oil; R_f= 0.27 (90% PE 30–40, 10% Et_2O); ν_{max}/cm^{-1} (thin film) 3350 (w, br), 2928 (s), 2855 (s), 2360 (w), 2171 (w), 1465 (m), 1332 (m), 1250 (m), 1022 (m), 843 (s), 760 (m), 721 (w), 699 (w); *m/z* Probe CI^+ (NH_3) 408.4 ($[MNH_4]^+$, 32%) 373.3 (55%), 310.3 (100%); HRMS found $[MNH_4]^+$= 408.3663, $C_{25}H_{50}NOSi$ requires 408.3662; δ_H (400 MHz, $CDCl_3$) 0.18 (9H, s, –Si(CH_3)$_3$), 0.89 (3H, t, *J*=7.0 Hz, H-22), 1.22–1.42 (m, 20H, H-6,7,8,9,10,17,18,19,20,21), 1.42–1.54 (6H, m, H-5,11,16), 1.63–1.76 (2H, m, H-4), 1.80 (1H, d, *J*=5.5 Hz, –O*H*), 2.14 (4H, t, *J*=7.0 Hz, H-12,15), 4.35 (1H, apparent q, *J*=5.5 Hz, H-3); δ_C (100.6 MHz, $CDCl_3$) −0.14 (3C, Si(CH_3)$_3$), 14.09 (1C, C-22), 18.74 (2C, C-12,15), 22.65 (1C, CH_2), 25.08 (1C, C-5), 28.84 (1C, CH_2), 28.85 (1C, CH_2), 29.11 (1C, CH_2), 29.13 (1C, CH_2), 29.15 (1C, CH_2), 29.19 (1C, CH_2), 29.21 (1C, CH_2), 29.41 (1C, CH_2), 29.44 (1C, CH_2), 31.83 (1C, CH_2), 37.69 (1C, C-4), 62.90 (1C, C-3), 80.19, 80.24 (2C, C-13.14), 89.26, 106.90 (2C, C-1,2).

5.4.3. 1-(Trimethylsilyl)docosa-1,13-diyn-3-one (18). To a stirred solution of IBX (0.038 g, 0.135 mmol, 1.5 equiv) in DMSO (3 ml) under argon was added *rac*-**6** (0.035 g, 0.090 mmol, 1 equiv) in anhydrous THF (0.5 ml, 2×0.5 ml wash) via cannula. The reaction mixture was stirred for 3 h, after which water (12 ml) was added. In a few minutes a white precipitate had formed which was removed by filtration through a sintered glass funnel. The residue was washed with cold EtOAc (6 ml). The combined organics were extracted with EtOAc (4×10 ml), washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (94% PE 30–40, 6% Et_2O) on a silica column to yield **18** (0.030 g, 0.078 mmol, 87%) as a colourless oil; R_f=0.53 (90% PE 30–40, 10% Et_2O); ν_{max}/cm^{-1} (KBr) 2929 (s), 2855 (s), 2151 (w), 1680 (s), 1466 (m), 1406 (w), 1352 (w), 1332 (w), 1252 (s), 1217 (w), 1116 (m), 1081 (m), 847 (s),762 (m), 723 (w), 704 (w), 621 (w); *m/z* Probe CI^+ (NH_3) 406.4 ($[MNH_4]^+$, 100%) 389.3 ($[MH]^+$, 88%); HRMS found $[MNH_4]^+$=406.3466, $C_{25}H_{48}NOSi$ requires 406.3505; δ_H (400 MHz, $CDCl_3$) 0.25 (9H, s, −(CH_3)$_3$), 0.88 (3H, t, *J*=7.0 Hz, H-22), 1.15–1.42 (m, 20H, H-6,7,8,9,10,17,18,19,20,21), 1.42–1.52 (4H, m, H-11,16), 1.66 (2H, quintet, *J*=7.0 Hz, H-5), 2.14 (4H, t, *J*=7.0 Hz, H-12,15), 2.55 (2H, t, *J*=7.5 Hz, H-4); δ_C (100.6 MHz, $CDCl_3$) −0.80 (3C, –Si(CH_3)$_3$), 14.06 (1C, C-22), 18.71 (2C, C-12,15), 22.62 (1C, CH_2), 23.88 (1C, C-5), 28.77 (1C, CH_2), 28.82 (1C, CH_2), 28.88 (1C, CH_2), 29.05 (1C, CH_2), 29.09 (1C, CH_2), 29.13 (1C, CH_2), 29.18 (1C, CH_2), 29.23 (1C, CH_2), 29.27 (1C, CH_2), 29.65 (1C, CH_2), 31.80 (1C, CH_2), 45.25 (1C, C-4), 80.12, 80.22 (2C, C-13,14), 97.48, 102.0 (2C, C-1,2), 188.0 (1C, C-3).

5.4.4. (*R*)-1-(Trimethylsilyl)docosa-1,13-diyn-3-ol (*R*-6). To a solution of **18** (0.132 g, 0.340 mmol, 1 equiv) in degassed isopropyl alcohol (1 ml) was added catalyst **24** (0.003 g, 0.005 mmol, 0.15 equiv) in one portion. The mixture was stirred for 18 h at 30 °C under argon before being concentrated to dryness in vacuo to afford the crude product. The crude product was purified by flash chromatography (90% PE 30–40, 10% Et_2O) on a silica column to yield *R*-**6** (0.129 g, 0.330 mmol, 97%, >95% ee) as a colourless oil; R_f=0.18 (90% PE 30–40, 10% Et_2O); $[\alpha]_D^{25}$=−1.1 (*c* 0.95, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3389 (m), 2928 (s), 2855 (s), 2358 (m), 2360 (m), 2172 (w), 1456 (m), 1333 (w), 1249 (m), 1026 (m), 843 (s), 760 (m); *m/z* Probe CI^+ (NH_3) 408.4 ($[MNH_4]^+$, 100%); HRMS found $[MNH_4]^+$=408.3592, $C_{25}H_{50}NOSi$ requires 408.3662; δ_H (400 MHz, $CDCl_3$) 0.18 (9H, s, –Si(CH_3)$_3$), 0.89 (3H, t, *J*=7.0 Hz, H-22), 1.22–1.42 (m, 20H, H-6,7,8,9,10,17,18,19,20,21), 1.42–1.54 (6H, m, H-5,11,16), 1.63–1.76 (2H, m, H-4), 1.80 (1H, d, *J*=5.0 Hz, –O*H*), 2.14 (4H, t, *J*=5.0 Hz, H-12,15), 4.35 (1H, apparent

q, $J=6.0$ Hz, H-3); δ_C (100.6 MHz, $CDCl_3$) −0.14 (3C, –Si(CH_3)$_3$), 14.10 (1C, C-22), 18.74 (2C, C-12,15), 22.65 (1C, CH_2), 25.09 (1C, C-5), 28.85 (1C, CH_2), 28.86 (1C, CH_2), 29.11 (1C, CH_2), 29.12 (1C, CH_2), 29.13 (1C, CH_2), 29.15 (1C, CH_2), 29.19 (1C, CH_2), 29.22 (1C, CH_2), 29.42 (1C, CH_2), 29.45 (1C, CH_2), 31.84 (1C, CH_2), 37.69 (1C, C-4), 62.90 (1C, C-3), 80.19, 80.25 (2C, C-13.14), 89.26, 106.9 (2C, C-1,2).

5.4.5. (*R*)-Docosa-1,13-diyn-3-ol (5). To a solution of *R*-**6** (0.123 g, 0.315 mmol, 1 equiv) in MeOH (1.5 ml) was added NH_4F (0.117 g, 3.15 mmol, 10 equiv) in one portion. The mixture was stirred overnight at 67 °C under argon before being diluted with water (10 ml) and extracted with Et_2O (4×10 ml). The combined organic layers were washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (80% PE 30–40, 20% Et_2O) on a silica column to yield **5** (0.091 g, 0.287 mmol, 91%) as a white solid; $R_f=0.19$ (80% PE 30–40, 20% Et_2O); mp 44–44.5 °C; $[\alpha]_D^{25}=+1.0$ (*c* 0.74, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3340 (s, br), 3278 (s), 2956 (s), 2930 (s), 2949 (s), 2848 (s), 2360 (w), 1636 (w), 1466 (s), 1426 (w), 1384 (w), 1312 (w), 1262 (w), 1102 (m), 1059 (m), 1021 (m), 977 (m), 935 (w), 898 (w), 856 (w), 803 (w), 723 (m), 685 (m), 668 (m), 553 (w), 470 (w); *m/z* Probe CI^+ (NH_3) 336.3 ($[MNH_4]^+$, 100%); HRMS found $[MH]^+=319.2999$, $C_{22}H_{39}O$ requires 319.3001; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, $J=6.5$ Hz, H-22), 1.22–1.42 (m, 20H, H-6,7,8,9,10,17,18,19,20,21), 1.42–1.54 (6H, m, H-5,11,16), 1.63–1.76 (2H, m, H-4), 1.81 (1H, d, $J=$ 5.5 Hz, −O*H*), 2.14 (4H, t, $J=7.0$ Hz, H-12,15), 2.47 (1H, d, $J=2.0$ Hz, H-1), 4.38 (1H, apparent dq, $J_1=6.0$ Hz, $J_2=$ 2.0 Hz, H-3); δ_C (100.6 MHz, $CDCl_3$) 14.10 (1C, C-22), 18.74 (2C, C-12,15), 22.65 (1C, CH_2), 24.98 (1C, C-5), 28.82 (1C, CH_2), 28.85 (1C, CH_2), 29.11 (1C, CH_2), 29.12 (1C, CH_2), 29.13 (1C, CH_2), 29.15 (1C, CH_2), 29.19 (1C, CH_2), 29.21 (1C, CH_2), 29.41 (1C, CH_2), 29.44 (1C, CH_2), 31.83 (1C, CH_2), 37.63 (1C, C-4), 62.33 (1C, C-3), 72.82 (1C, C-1), 80.19, 80.26 (2C, C-13.14), 84.98 (1C, C-2).

5.4.6. (*R*)-Pentacosa-2,4,16-triyne-1,6-diol (*R*-2). To a mixture of **5** (0.079 g, 0.247 mmol, 1 equiv), anhydrous CuCl powder (0.003 g, 0.030 mmol, 0.12 equiv, cat.), 33% methanolic ethylamine (0.325 ml, 1.88 mmol, 7.5 equiv) and hydroxylamine hydrochloride (0.010 g, 0.144 mmol, 0.58 equiv) in MeOH (0.5 ml) was added **4** (0.047 g, 0.35 mmol, 1.40 equiv) via cannula over 30 min. The yellow suspension was stirred at ambient temperature for 3 h before being diluted with water (10 ml) and extracted with Et_2O (3×20 ml). The combined organic layers were washed with $NaHSO_{4(aq)}$ (1%, 10 ml) and $NaCl_{(aq)}$ (sat., 10 ml), and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (50% PE 30–40, 50% Et_2O) on a silica column to yield *R*-**2** (0.076 g, 0.20 mmol, 82%) as a white solid; $R_f=0.19$ (50% PE 30–40, 50% Et_2O); mp 58–58.5 °C; $[\alpha]_D^{25}=-7.1$ (*c* 0.90, $CHCl_3$), lit. $[\alpha]_D^{22}=-7.1$ (*c* 0.42, $CHCl_3$)[3]; ν_{max}/cm^{-1} (KBr) 3305 (s, br), 2931 (s), 2848 (s), 2361 (w), 2343 (w), 1463 (s), 1439 (m), 1428 (m), 1354 m), 1320 (m), 1292 (w), 1280 (w), 1265 (w), 1222 (w), 1224 (w), 1104 (w), 1064 (s), 1049 (m), 1030 (s), 980 (w), 964 (m), 934 (m), 900 (w), 856 (m); *m/z* Probe CI^+ (NH_3) 390.4 ($[MNH_4]^+$, 17%); HRMS found $[MNH_4]^+=390.3379$, $C_{25}H_{44}NO_2$ requires 390.3372; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, $J=7.0$ Hz, H-25), 1.18–1.52 (26H, m, H-8,9,10,11,12,13,14,19,20,21,22,23,24), 1.64–1.80 (2H, m, H-7), 2.13 (4H, t, $J=7.0$ Hz, H-15,18), 2.49 (2H, br s, –O*H*), 4.34 (2H, s, H-1), 4.42 (1H, t, $J=6.5$ Hz, H-6); δ_C (100.6 MHz, $CDCl_3$) 14.09 (1C, C-25), 18.73 (2C, C-15,18), 22.64 (1C, CH_2), 25.01 (1C, CH_2), 28.83 (1C, CH_2), 28.84 (1C, CH_2), 29.10 (2C, CH_2), 29.14 (2C, CH_2), 29.16 (1C, CH_2), 29.20 (1C, CH_2), 29.41 (1C, CH_2), 29.42 (1C, CH_2), 31.82 (1C, CH_2), 37.40 (1C, C-7), 51.29 (1C, C-1), 62.76 (1C, C-6), 68.82, 69.73 (2C, C-3,4), 77.53, 80.24, 80.30, 80.46 (4C, C-2,5,16,17); microanalysis found C=80.74, H=10.95, $C_{25}H_{40}O_2$ requires C=80.59, H=10.82.

5.5. Synthesis of strongylodiol A *R*-1

5.5.1. (*Z*)-Icos-11-en-1-ol (25). To a solution of **9** (0.128 g, 0.436 mmol) and anhydrous benzene (2 ml) were added Lindlar's catalyst (0.053 g) and quinoline (0.040 ml) under argon. The mixture was stirred under $H_{2(g)}$ (1 atm, balloon) at ambient temperature for 2 h. The mixture was filtered through cellulose and washed with benzene (50 ml). The combined filtrate was washed with $KHSO_{4(aq)}$ (1%, 10 ml), neutralised with $NaHCO_{3(aq)}$ (sat., 10 ml), washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $MgSO_{4(s)}$. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (80% PE 30–40, 20% Et_2O) on a silica column to yield **25** (0.124 g, 0.417 mmol, 95%) as a colourless oil; $R_f=0.38$ (50% PE 30–40, 50% Et_2O); ν_{max}/cm^{-1} (thin film) 3338 (m, br), 3005 (m), 2924 (s), 2853 (s), 1656 (w), 1465 (m), 1378 (m), 1058 (m), 967 (m), 722 (m); *m/z* Probe CI^+ (NH_3) 314.3 ($[MNH_4]^+$, 100%); HRMS found $[MNH_4]^+=314.3408$, $C_{20}H_{44}NO$ requires 314.3423; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, $J=6.5$ Hz, H-20), 1.18–1.40 (26H, m, H-3,4,5,6,7,8,9,14,15,16,17,18,19), 1.57 (2H, qui, $J=7.0$ Hz, H-2), 1.94–2.09 (4H, m, H-10,13), 3.64 (2H, t, $J=6.5$ Hz, H-1), 5.31–5.42 (2H, m, H-11,12); δ_C (100.6 MHz, $CDCl_3$) 14.07 (1C, C-20), 22.65, (1C, CH_2), 25.72 (2C, CH_2), 27.18 (2C, C-10,13), 29.14 (1C, CH_2), 29.29 (1C, CH_2), 29.41 (1C, CH_2), 29.50 (1C, CH_2), 29.54 (1C, CH_2), 29.58 (1C, CH_2), 29.63 (1C, CH_2), 29.67 (1C, CH_2), 29.74 (1C, CH_2), 31.88 (1C, CH_2), 32.79 (1C, C-2), 63.05 (1C, C-1), 129.8, 129.9 (2C, C-11,12).

5.5.2. (*Z*)-Icos-11-enal (26). To a stirred solution of IBX (0.463 g, 1.65 mmol, 2 equiv) in DMSO (3 ml) under argon was added **25** (0.232 g, 0.781 mmol, 1 equiv) in anhydrous THF (2 ml, 2×0.5 ml wash) via cannula. The reaction mixture was stirred for 3 h, after which water (12 ml) was added. In a few minutes a white precipitate had formed which was removed by filtration through a sintered glass funnel. The residue was washed with cold EtOAc (6 ml). The combined organics were extracted with EtOAc (4× 10 ml), washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (96% PE 30–40, 4% Et_2O) on a silica column to yield **26** (0.201 g, 0.682 mmol, 87%) as a white solid; $R_f=0.12$ (96% PE 30–40, 4% Et_2O; ν_{max}/cm^{-1} (thin film) 3004 (w), 2925 (s), 2854 (s), 2112 (w), 1728 (m), 1465 (m), 1409 (w), 1378 (w),

1302 (w), 968 (w), 722 (w); *m/z* Probe CI^+ (NH_3) 312.3 ($[MNH_4]^+$); HRMS found $[MNH_4]^+=312.3253$, $C_{20}H_{42}NO$ requires 312.3266; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, $J=6.5$ Hz, H-20), 1.18–1.40 (24H, m, H-4,5,6,7,8,9,14,15,16,17,18,19), 1.63 (2H, qui, $J=$ 7.0 Hz, H-3), 2.01–2.07 (4H, m, H-10,13), 2.42 (2H, dt, $J_1=7.5$ Hz, $J_2=2.0$ Hz, H-2), 5.28–5.21 (2H, m, H-11,12), 9.77 (1H, t, $J=2.0$ Hz, H-1); δ_C (100.6 MHz, $CDCl_3$) 14.08 (1C, C-20), 22.06 (1C, C-3), 22.66 (1C, CH_2), 27.16, 27.18 (2C, C-10,13), 29.14 (1C, CH_2), 29.23 (1C, CH_2), 29.30 (1C, CH_2), 29.32 (1C, CH_2), 29.37 (1C, CH_2), 29.44 (1C, CH_2), 29.50 (1C, CH_2), 29.72 (1C, CH_2), 29.74 (1C, CH_2), 31.88 (1C, CH_2), 32.56 (1C, CH_2), 43.89 (1C, C-2), 129.8, 129.9 (2C, C-11,12), 202.9 (1C, C-1).

5.5.3. (*Z*)-1-(Trimethylsilyl)docos-13-en-1-yn-3-ol (*rac*-27). To a stirred solution of trimethylsilylacetylene **7** (0.098 ml, 0.708 mmol, 1.03 equiv) in anhydrous THF (4 ml) at −12° was added *n*-BuLi (1.28 M in hexanes, 0.553 ml, 0.708 mmol, 1.03 equiv) under argon. After stirring for 1 h at −12 °C a pre-cooled solution of **26** (0.201 g, 0.687 mmol, 1 equiv) in anhydrous THF (1 ml, 2×0.5 ml wash) at −12 °C was added dropwise via cannula. The reaction mixture was stirred for 1.5 h, then quenched with $NH_4Cl_{(aq)}$ (sat., 5 ml) and water (5 ml) before being extracted with Et_2O (3×20 ml). The combined organic phases were washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (90% PE 30–40, 10% Et_2O) on a silica column to yield *rac*-**27** (0.283 g, 0.721 mmol, 76%) as a colourless oil; $R_f=0.16$ (90% PE 30–40), 10% Et_2O; ν_{max}/cm^{-1} (thin film) 3326 (w, br), 3005 (m), 2925 (s), 2854 (s), 2172 (w), 1466 (m), 1406 (w), 1378 (w), 1250 (s), 1017 (m), 909 (w), 844 (s), 760 (m), 735 (m), 700 (m); *m/z* Probe CI^+ (NH_3) 410.4 ($[MNH_4]^+$); HRMS found $[MNH_4]^+=410.3827$, $C_{25}H_{52}NOSi$ requires 410.3818; δ_H (400 MHz, $CDCl_3$) 0.18 (9H, s, –Si(CH_3)$_3$), 0.89 (3H, t, $J=7.0$ Hz, H-22), 1.22–1.38 (m, 24H, H-6,7,8,9,10,11,16,17,18,19,20,21), 1.38–1.50 (2H, m, H-5), 1.63–1.76 (2H, m, H-4), 1.81 (1H, d, $J=5.5$ Hz, –O*H*), 1.93–2.08 (4H, m, H-12,15), 4.35 (1H, apparent q, $J=4.5$ Hz, H-3) 5.29–3.41 (2H, m, H-13,14); δ_C (100.6 MHz, $CDCl_3$) −0.14 (3C, –Si(CH_3)$_3$), 14.09 (1C, C-22), 22.66 (1C, CH_2), 25.08 (1C, C-5), 27.19 (2C, C-12,15), 29.20 (1C, CH_2), 29.30 (1C, CH_2), 29.48 (1C, CH_2), 29.50 (1C, CH_2), 29.63 (1C, CH_2), 29.75 (1C, CH_2), 31.89 (1C, CH_2), 32.59 (1C, CH_2), 37.69 (1C, C-4), 62.90 (1C, C-3), 89.24, 106.9 (2C, C-1,2), 129.8, 129.9 (2C, C-13,14).

5.5.4. (*Z*)-1-(Trimethylsilyl)docos-13-en-1-yn-3-one (28). To a stirred solution of IBX (0.292 g, 1.04 mmol, 2 equiv) in DMSO (3 ml) under argon was added *rac*-**27** (0.205 g, 0.522 mmol, 1 equiv) in anhydrous THF (1 ml, 2×0.5 ml wash) via cannula. The reaction mixture was stirred for 3 h, after which water (12 ml) was added. In a few minutes a white precipitate had formed which was removed by filtration through a sintered glass funnel. The residue was washed with cold EtOAc (6 ml). The combined organics were extracted with EtOAc (4×10 ml), washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (95% PE 30–40, 5% Et_2O) on a silica column to yield **28** (0.189 g, 0.485 mmol, 93%) as a colourless oil; $R_f=0.38$ (95% PE 30–40, 5% Et_2O); ν_{max}/cm^{-1} (thin film) 3004 (m), 2925 (s), 2854 (s), 2151 (w), 1681 (s), 1465 (m), 1406 (m), 1353 (w), 1252 (s), 1217 (w), 1112 (m), 1082 (m), 846 (s), 761 (m), 722 (w), 665 (w); *m/z* Probe CI^+ (NH_3) 408.4 ($[MNH_4]^+$, 100%); HRMS found $[MNH_4]^+=408.3654$, $C_{25}H_{50}NOSi$ requires 408.3662; δ_H (400 MHz, $CDCl_3$) 0.25 (9H, s, –Si(CH_3)$_3$), 0.89 (3H, t, $J=7.0$ Hz, H-22), 1.24–1.42 (m, 24H, H-6,7,8,9,10,11,16,17,18,19,20,21), 1.58–1.73 (m, 2H, H-5), 1.92–2.10 (4H, m, H-12,15), 2.55 (2H, t, $J=7.5$ Hz, H-4), 5.30–5.41 (m, 2H, H-13,14); δ_C (100.6 MHz, $CDCl_3$) −0.78 (3C, –Si(CH_3)$_3$), 14.09 (1C, C-22), 22.66 (1C, CH_2), 23.91 (1C, C-5), 27.18 (2C, CH_2), 28.92 (1C, CH_2), 29.26 (1C, CH_2), 29.30 (3C, CH_2), 29.38 (1C, CH_2), 29.46 (1C, CH_2), 29.50 (1C, CH_2), 29.74 (2C, CH_2), 31.89 (1C, CH_2), 45.29 (1C, C-4), 97.51, 102.4 (2C, C-1,2), 129.8, 129.9 (2C, C-13,14), 188.1 (1C, C-3).

5.5.5. (*R*,*Z*)-1-(Trimethylsilyl)docos-13-en-1-yn-3-ol (*R*-27). To a solution of **28** (0.028 g, 0.072 mmol, 1 equiv) in de-gassed isopropyl alcohol (1 ml) was added catalyst **24** (0.0024 g, 0.004 mmol, 0.06 equiv) in one portion. The mixture was stirred overnight at 30 °C under argon before removal of solvent in vacuo and purification by flash chromatography (90% PE 30–40, 10% Et_2O) on a silica column to yield *R*-**27** (0.027 g, 0.070 mmol, 97%, >95% ee) as a colourless oil; $R_f=0.28$ (80% PE 30–40, 20% Et_2O); $[\alpha]_D^{25}=-1.2$ (*c* 1.02, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3324 (w, br), 3005 (w), 2925 (s), 2854 (m), 2172 (w), 1466 (m), 1406 (w), 1378 (w), 1333 (w), 1250 (s), 1019 (m), 843 (s), 760 (m), 722 (w), 700 (w); *m/z* Probe CI^+ (NH_3) 393.4 ($[MH]^+$, 100%); HRMS found $[MH]^+=393.3553$, $C_{25}H_{49}OSi$ requires 393.3553; δ_H (400 MHz, $CDCl_3$) 0.18 (9H, s, –Si(CH_3)$_3$), 0.89 (3H, t, $J=7.0$ Hz, H-22), 1.22–1.39 (m, 24H, H-6,7,8,9,10,11,16,17,18,19,20,21), 1.39–1.54 (2H, m, H-5), 1.65–1.75 (2H, m, H-4), 1.79 (1H, d, $J=$ 5.0 Hz, –O*H*), 1.99–2.03 (4H, m, H-12,15), 4.36 (1H, apparent q, $J=5.5$ Hz, H-3), 5.31–5.41 (2H, m, H-13,14); δ_C (100.6 MHz, $CDCl_3$) −0.13 (3C, –Si(CH_3)$_3$), 14.11 (1C, C-22), 22.67 (1C, CH_2), 25.09 (1C, C-5), 27.19 (2C, C-10,13), 29.20 (1C, CH_2), 29.31 (3C, CH_2), 29.48 (1C, CH_2), 29.51 (3C, CH_2), 29.76 (2C, CH_2), 31.89 (1C, CH_2), 37.69 (1C, C-4), 62.91 (1C, C-3), 89.26, 106.9 (2C, C-1,2), 129.9[‡] (2C, C-13,14).

5.5.6. (*R*,*Z*)-Docos-13-en-1-yn-3-ol (29). To a solution of *R*-**27** (0.125 g, 0.318 mmol, 1 equiv) in MeOH (2 ml) was added NH_4F (0.117 g, 3.18 mmol, 10 equiv) in one portion. The mixture was stirred for 18 h at 67 °C under argon before being diluted with water (10 ml) and extracted with Et_2O (4×10 ml). The combined organic layers were washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (80% PE 30–40, 20% Et_2O) on a silica column to yield **29** (0.091 g, 0.287 mmol, 91%) as a white solid; $R_f=0.19$ (80% PE 30–40, 20% Et_2O); mp 44–44.5 °C; $[\alpha]_D^{25}=+1.6$ (*c* 1.60, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3311 (s), 3005 (m), 2924 (s), 2853 (s), 2361 (w), 2341 (w), 1653 (w), 1465 (m), 1404 (m), 1378 (m), 1308 (m), 1025 (m), 722 (m), 655 (m), 627 (m), 556 (w),

[‡] Can be resolved as 129.85 and 129.90.

496 (w), 474 (m), 460 (m); *m/z* Probe CI$^+$ (NH_3) 338.3 ($[MNH_4]^+$, 100%); HRMS found $[MNH_4]^+=338.3411$, $C_{22}H_{44}NO$ requires 338.3423; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, $J=6.5$ Hz, H-22), 1.22–1.40 (m, 24H, H-6,7,8,9,10,11,16,17,18,19,20,21), 1.40–1.52 (2H, m, H-5), 1.67–1.76 (2H, m, H-4), 1.83 (1H, s, –O*H*), 2.02 (4H, apparent q, $J=6.0$ Hz, H-12,15), 2.47 (1H, d, $J=2.0$ Hz, H-1), 4.37 (1H, apparent q, $J=6.0$ Hz, H-3), 5.31–5.40 (2H, m, H-13,14); δ_C (100.6 MHz, $CDCl_3$) 14.09 (1C, C-22), 22.66 (1C, *C*H_2), 24.98 (1C, *C*H_2), 27.18 (2C, *C*H_2), 29.21 (1C, *C*H_2), 29.27 (1C, *C*H_2), 29.30 (2C, *C*H_2), 29.49 (5C, *C*H_2), 29.75 (2C, *C*H_2), 31.88 (1C, *C*H_2), 37.64 (1C, C-4), 62.33 (1C, C-3), 72.79 (1C, C-1), 85.00 (1C, C-2), 129.8, 129.9 (2C, C-13,14).

5.5.7. (*R,Z*)-Pentacosa-16-en-2,4-diyne-1,6-diol (*R*-1). To a mixture of **29** (0.042 g, 0.132 mmol, 1 equiv), anhydrous CuCl powder (0.003 g, 0.030 mmol, 0.12 equiv, cat.), methanolic ethylamine (2.03 M, 0.470 ml, 0.954 mmol, 7.5 equiv) and hydroxylamine hydrochloride (0.050 g, 0.730 mmol, 5.5 equiv) in MeOH (0.5 ml) was added **4** (0.037 g, 0.270 mmol, 2.0 equiv) via cannula over 30 min. The yellow suspension was stirred at ambient temperature for 3 h before being diluted with water (10 ml) and extracted with Et_2O (3×20 ml). The combined organic layers were washed with $NaHSO_{4(aq)}$ (1%, 10 ml) and $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (50% PE 30–40, 50% Et_2O) on a silica column to yield *R*-**1** (0.039 g, 0.105 mmol, 80%) as a white solid; $R_f=0.25$ (50% PE 30–40, 50% Et_2O); mp 56–56.5 °C; $[\alpha]_D^{25}=-7.1$ (*c* 1.04, $CHCl_3$), lit. $[\alpha]_D^{22}=-7.2$ (*c* 1.11, $CHCl_3$)[3]; ν_{max}/cm^{-1} (KBr) 3296 (m, br), 3003 (m), 2920 (s), 2847 (s), 1463 (s), 1442 (m), 1406 (m), 1352 (m), 1318 (m), 1064 (s), 1031 (s), 965 (m), 901 (m), 806 (m); *m/z* Probe CI$^+$ (NH_3) 392.4 ($[MNH_4]^+$, 100%), 312.3 (76%); HRMS found $[MNH_4]^+=392.3532$, $C_{25}H_{46}NO_2$ requires 392.3529; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t $J=7.0$ Hz, H-25), 1.22–1.39 (24H, m, H-9,10,11,12,13,14,19, 20,21,22,23,24), 1.39–1.50 (2H, m, H-8), 1.65–1.80 (2H, m, H-7), 1.90–2.10 (6H, m, 2×-O*H*, H-15,18), 4.35 (2H, s, H-1), 4.39–4.47 (1H, m, H-6), 5.31–5.41 (m, 2H, H-16,17); δ_C (100.6 MHz, $CDCl_3$) 14.11 (1C, C-25), 22.67 (1C, *C*H_2), 25.00 (1C, *C*H_2), 27.19 (1C, *C*H_2), 29.19 (1C, *C*H_2), 29.28 (1C, *C*H_2), 29.30 (2C, *C*H_2), 29.47 (1C, *C*H_2), 29.50 (3C, *C*H_2), 29.75 (3C, *C*H_2), 31.89 (1C, *C*H_2), 37.44 (1C, C-7), 51.41 (1C, C-1), 62.82 (1C, C-6), 68.80, 69.80 (2C, C-3,4), 77.48, 80.51 (2C, C-2,5), 129.9[§] (2C, C-16,17); microanalysis found C=79.73, H=10.93, $C_{25}H_{42}O_2$ requires C=80.16, H=11.30.

5.6. Synthesis of *R*-32, an analogue of strongylodiol B *R*-2

5.6.1. 1-Trimethylsilyl-tetradec-1-yn-3-ol (*rac*-15). To a stirred solution of **7** (0.750 ml, 5.42 mmol, 1 equiv) in anhydrous THF (2 ml) at −12 °C was added *n*-BuLi (2.02 M in hexanes, 2.68 ml, 5.41 mmol, 1 equiv) under argon. After stirring for 1 h at −12 °C a pre-cooled solution of **14** (1.20 ml, 5.44 mmol, 1 equiv) in anhydrous THF (2 ml, 2×0.5 ml wash) at −12 °C was added via cannula. The reaction mixture was maintained at −78 °C for 30 min, and then at −12 °C for 1 h, before being quenched with $NH_4Cl_{(aq)}$ (sat., 25 ml) and extracted with Et_2O (3×20 ml). The combined organic layers were washed with $NaCl_{(aq)}$ (sat., 20 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (90% PE 30–40, 10% Et_2O) on a silica column to yield *rac*-**15** (1.30 g, 4.61 mmol, 85%) as a pale yellow oil; $R_f=0.22$ (90% PE 30–40, 10% Et_2O); ν_{max}/cm^{-1} (thin film) 3326 (m, br), 2924 (s), 2855 (s), 2173 (m), 1466 (m), 1407 (m), 1378 (m), 1334 (m), 1250 (s), 1128 (m), 1028 (m), 843 (s), 760 (m), 721 (m), 699 (m), 666 (m); *m/z* Probe CI$^+$ (NH_3) 300.3 ($[MNH_4]^+$, 20%), 282.2 ($[MH]^+$, 31%), 265.2 (42%), 191.2 (79%), 90.1 (61%), 73.0 (100%); HRMS found $[MNH_4]^+=300.2711$, $C_{17}H_{38}NOSi$ requires 300.2723; δ_H (400 MHz, $CDCl_3$) 0.18 (9H, s, –Si(CH_3)$_3$), 0.88 (3H, t, $J=7.0$ Hz, H-14), 1.18–1.38 (16H, m, H-6,7,8,9,10,11,12,13), 1.38–1.52 (2H, m, H-5), 1.60–1.78 (2H, m, H-4), 1.87 (1H, d, $J=5.5$ Hz, –O*H*), 4.35 (1H, apparent q, $J=6.0$ Hz, H-3); δ_C (100.6 MHz, $CDCl_3$) −0.14 (3C, –Si(*C*H_3)$_3$), 14.10 (1C, C-14), 22.67 (1C, *C*H_2), 25.08 (1C, C-5), 29.19 (1C, *C*H_2), 29.33 (1C, *C*H_2), 29.48 (1C, *C*H_2), 29.52 (1C, *C*H_2), 29.62 (1C, *C*H_2), 29.63 (1C, *C*H_2), 31.90 (1C, *C*H_2), 37.68 (1C, C-4), 62.89 (1C, C-3), 89.24, 106.93 (2C, C-1,2).

5.6.2. 1-Trimethylsilyl-tetradec-1-yn-3-one (30). To a stirred solution of IBX (0.151 g, 0.541 mmol, 1.5 equiv) in DMSO (3 ml) under argon was added *rac*-**15** (0.101 g, 0.356 mmol, 1 equiv) in anhydrous THF (0.5 ml, 2×0.5 ml wash) via cannula. The reaction mixture was stirred for 3 h, after which water (12 ml) was added. In a few minutes a white precipitate had formed which was removed by filtration through a sintered glass funnel. The residue was washed with cold EtOAc (6 ml). The combined organics were extracted with EtOAc (4×10 ml), washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (97% PE 30–40, 3% Et_2O) on a silica column to yield **30** (0.099 g, 0.352 mmol, 98%) as a colourless oil; $R_f=0.38$ (97% PE 30–40, 3% Et_2O); ν_{max}/cm^{-1} (thin film) 2926 (s), 2856 (s), 2151 (w), 1679 (s), 1462 (m), 1408 (w), 1358 (w), 1253 (m), 1219 (w), 1334 (m), 1096 (m), 851 (s), 762 (m), 709 (w), 620 (w); *m/z* Probe CI$^+$ (NH_3) 298.3 ($[MNH_4]^+$, 100%), 281.2 ($[MH]^+$, 65%); HRMS found $[MH]^+=281.2295$, $C_{17}H_{33}OSi$ requires 281.2301; δ_H (400 MHz, $CDCl_3$) 0.25 (9H, s, –Si(CH_3)$_3$), 0.88 (3H, t, $J=7.0$ Hz, H-14), 1.20–1.36 (16H, m, H-6,7,8,9,10,11,12,13), 1.66 (2H, quintet, $J=7.0$ Hz, H-5), 2.55 (2H, t, $J=7.5$ Hz, H-4); δ_C (100.6 MHz, $CDCl_3$) −0.78 (3C, –Si(*C*H_3)$_3$), 14.08 (1C, C-14), 22.65 (1C, *C*H_2), 23.92 (1C, C-5), 28.91 (1C, *C*H_2), 29.29 (1C, *C*H_2), 29.30 (1C, *C*H_2), 29.39 (1C, *C*H_2), 29.56 (1C, *C*H_2), 29.57 (1C, *C*H_2), 31.88 (1C, *C*H_2), 45.28 (1C, C-4), 97.50, 102.03 (2C, C-1,2), 188.1 (1C, C-3).

5.6.3. (3*R*)-1-Trimethylsilyl-tetradec-1-yn-3-ol (*R*-15). To a solution of **30** (0.069 g, 0.244 mmol, 1 equiv) in degassed isopropyl alcohol (2.5 ml) was added catalyst **24** (0.0015 g, 0.0025 mmol, 0.01 equiv) in one portion. The mixture was stirred for 18 h at 30 °C under argon before being concentrated to dryness in vacuo to afford the crude product. The crude product was purified by flash chromatography (85% PE 30–40, 15% Et_2O) on a silica column to

[§] Can be resolved as 129.85 and 129.93.

yield *R*-**15** (0.061 g, 0.215 mmol, 88%, >95% ee) as a pale yellow oil; R_f=0.24 (85% PE 30–40, 15% Et_2O); $[\alpha]_D^{25}=-1.6$ (*c* 1.29, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3333 (m, br), 2926 (s), 2856 (s), 2172 (m), 1462 (m), 1251 (m), 1027 (m), 845 (s), 760 (m), 700 (w); *m/z* Probe CI^+ (NH_3) 300.3 ($[MNH_4]^+$, 100%); HRMS found $[MNH_4]^+$= 300.2723, $C_{17}H_{38}NOSi$ requires 300.2723; δ_H (400 MHz, $CDCl_3$) 0.18 (9H, s, $-Si(CH_3)_3$), 0.89 (3H, t, *J*=7.0 Hz, H-14), 1.20–1.38 (16H, m, H-6,7,8,9,10,11,12,13), 1.38–1.52 (2H, m, H-5), 1.64–1.76 (2H, m, H-4), 1.81 (1H, d, *J*= 5.5 Hz, –O*H*), 4.36 (1H, apparent q, *J*=6.5 Hz, H-3); δ_C (100.6 MHz, $CDCl_3$) −0.15 (3C, $-Si(CH_3)_3$), 14.08 (1C, C-14), 22.65 (1C, CH_2), 25.07 (1C, C-5), 29.19 (1C, CH_2), 29.31 (1C, CH_2), 29.47 (1C, CH_2), 29.51 (1C, CH_2), 29.61 (1C, CH_2), 29.63 (1C, CH_2), 31.89 (1C, CH_2), 37.70 (1C, C-4), 62.91 (1C, C-3), 89.25, 106.93 (2C, C-1,2).

5.6.4. (3*R*)-Tetradec-1-yn-3-ol (31). To a solution of *R*-**15** (0.026 g, 0.092 mmol, 1 equiv) in MeOH (1.5 ml) was added NH_4F (0.034 g, 0.920 mmol, 10 equiv) in one portion. The mixture was stirred for 18 h at 67 °C under argon before being diluted with water (10 ml) and extracted with Et_2O (4×10 ml). The combined organic layers were washed with $NaCl_{(aq)}$ (sat., 10 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (85% PE 30–40, 15% Et_2O) on a silica column to yield **31** (0.019 g, 0.090 mmol, 98%) as a white solid; mp 28–28.5 °C; R_f = 0.34 (70% PE 30–40, 30% Et_2O); $[\alpha]_D^{25}=+1.2$ (*c* 0.95, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3299 (m), 3280 (s), 2954 (m), 2917 (s), 2872 (m), 2848 (s), 2117 (w), 1470 (m), 1428 (w), 1376 (w), 1305 (w), 1262 (w), 1128 (w), 1085 (m), 1062 (m), 1036 (m), 998 (m), 964 (m), 928 (w), 892 (w), 855 (w), 809 (w), 719 (m), 679 (m), 658 (m); *m/z* Probe CI^+ (NH_3) 228.2 ($[MNH_4]^+$, 100%); HRMS found $[MNH_4]^+$= 228.2319, $C_{14}H_{30}NO$ requires 228.2327; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=7.0 Hz, H-14), 1.20–1.38 (16H, m, H-6,7,8,9,10,11,12,13), 1.38–1.52 (2H, m, H-5), 1.64–1.76 (2H, m, H-4), 1.84 (1H, d, *J*=5.0 Hz, −O*H*), 2.47 (1H, d, *J*=2.0 Hz, H-1), 4.37 (1H, apparent q, *J*=6.0 Hz, H-3); δ_C (100.6 MHz, $CDCl_3$) 14.06 (1C, C-14), 22.63 (1C, CH_2), 24.96 (1C, C-5), 29.18 (1C, CH_2), 29.29 (1C, CH_2), 29.46 (1C, CH_2), 29.50 (1C, CH_2), 29.57 (1C, CH_2), 29.59 (1C, CH_2), 31.86 (1C, CH_2), 37.62 (1C, C-4), 62.32 (1C, C-3), 72.76 (1C, C-1), 85.00 (1C, C-2).

5.6.5. (6*R*)-Heptadeca-2,4-diyne-1,6-diol (*R*-32). To a mixture of **31** (0.040 g, 0.190 mmol, 1 equiv), anhydrous CuCl powder (0.003 g, 0.030 mmol, 0.16 equiv, cat.), 33% methanolic ethylamine (0.260 ml, 1.33 mmol, 7 equiv) and hydroxylamine hydrochloride (0.003 g, 0.043 mmol, 0.23 equiv) in MeOH (0.5 ml) was added **4** (0.036 g, 0.267 mmol, 1.41 equiv) via cannula over 30 min. The yellow suspension was stirred at ambient temperature for 3 h before being diluted with water (10 ml) and extracted with Et_2O (3×20 ml). The combined organic layers were washed with $NaHSO_{4(aq)}$ (1%, 10 ml) and $NaCl_{(aq)}$ (sat., 10 ml), and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (50% PE 30–40, 50% Et_2O) on a silica column to yield *R*-**32** (0.042 g, 0.159 mmol, 84%) as a white solid; R_f=0.19 (50% PE 30–40, 50% Et_2O); mp 28–28.5 °C; $[\alpha]_D^{25}=-7.0$ (*c* 0.99, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3307 (s, br), 2926 (s), 2848 (s), 2361 (m), 2342 (m), 1636 (w), 1559 (w), 1540 (w), 1507 (w), 1463 (m), 1354 (w), 1316 (w), 1086 (m), 1060 (m), 1030 (s), 964 (w), 668 (m); *m/z* Probe CI^+ (NH_3) 282.2 ($[MNH_4]^+$, 24%), 264.2 ($[MH^+]$, 41%); HRMS found $[MNH_4]^+$=282.2440, $C_{17}H_{32}NO_2$ requires 282.2433; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=7.0 Hz, H-17), 1.20–1.38 (16H, m, H-9,10,11,12,13,14,15,16), 1.38–1.50 (2H, m, H-8), 1.64–1.80 (3H, m, H-7, –O*H* of C-1), 1.90 (1H, d, *J*=5.5 Hz, –O*H* of C-6), 4.36 (2H, d, *J*=5.5 Hz, H-1), 4.44 (1H, apparent q, *J*=6.0 Hz, H-6); δ_C (125.7 MHz, $CDCl_3$) 13.97 (1C, C-17), 22.55 (1C, CH_2), 24.89 (1C, C-8), 29.08 (1C, CH_2), 29.21 (1C, CH_2), 29.35 (1C, CH_2), 29.41 (1C, CH_2), 29.48 (1C, CH_2), 29.50 (1C, CH_2), 31.78 (1C, CH_2), 37.37 (1C, C-7), 51.34 (1C, C-1), 62.75 (1C, C-6), 68.70, 69.74, 77.38, 80.47 (4C, C-2,3,4,5).

5.7. General procedure for the preparation of MTPA esters

To a solution of (*R*)-(+)-MTPA or (*S*)-(−)-MTPA (0.048 g, 0.190 mmol, 4 equiv) in anhydrous hexane (2 ml) was added DMF (0.015 ml, 0.190 mmol, 4 equiv) and oxalyl chloride (0.065 ml, 0.760 mmol, 16 equiv). The solution was stirred under argon for 2 h at ambient temperature. The organic layer was transferred to another flask and the solvent removed in vacuo. The residue was dissolved in anhydrous $CHCl_3$ (1 ml) and a solution of DMAP (0.035 g, 0.285 mmol, 6 equiv) and alcohol (0.048 mmol, 1 equiv) in $CHCl_3$ (1 ml, 1×0.5 ml wash) was added via cannula. The reaction was stirred under argon overnight at ambient temperature before being diluted with DCM (3 ml). The organic layer was washed with $KHSO_{4(aq)}$ (sat., 5 ml) followed by $NaCl_{(aq)}$ (sat., 5 ml) and dried over $Na_2SO_{4(s)}$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (98% PE 30–40, 2% Et_2O) to yield the Mosher's ester.

5.7.1. (*S*)-MTPA ester of (3*R*)-1-trimethylsilyl-docosa-1,13-diyn-3-ol. *R*-**6** (0.010 g, 0.025 mmol) was used following the general procedure for the preparation of an (*S*)-MTPA ester to yield (*S*)-((*R*)-1-(trimethylsilyl)docosa-1,13-diyn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate (0.014 g, 0.024 mmol, 96%); δ_H (400 MHz, $CDCl_3$) 0.17 (9H, s, –Si(CH_3)$_3$), 0.89 (3H, t, *J*=7.0 Hz, H-22), 1.22–1.42 (20H, m, H-6,7,8,9,10,17,18,19,20,21), 1.42–1.54 (6H, m, H-5,11,16), 1.77–1.92 (2H, m, H-4), 2.15 (4H, t, *J*=7.0 Hz, H-12,15), 3.57 (3H, s, –OCH_3), 5.51 (1H, t, *J*=7.0 Hz, H-3), 7.39–7.44 (3H, m, –C_6H_5), 7.52–7.57 (2H, m, –C_6H_5); δ_F (376.6 MHz, $CDCl_3$) −71.84 (F, s).

5.7.2. (*S*)-MTPA ester of 1-trimethylsilyl-docosa-1,13-diyn-3-ol. *rac*-**6** (0.010 g, 0.025 mmol) was used following the general procedure for the preparation of an (*S*)-MTPA ester to yield (*S*)-1-(trimethylsilyl)docosa-1,13-diyn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (0.014 g, 0.024 mmol, 96%); δ_H (400 MHz, $CDCl_3$) 0.16 (50% of 9H, s, –Si(CH_3)$_3$), 0.18 (50% of 9H, s, –Si(CH_3)$_3$), 0.89 (3H, t, *J*=7.0 Hz, H-22), 1.22–1.42 (m, 20H, H-6,7,8,9,10,17,18,19,20,21), 1.42–1.54 (6H, m, H-5,11,16), 1.70–1.92 (2H, m, H-4), 2.15 (4H, t, *J*= 7.0 Hz, H-12,15), 3.57 (50% of 3H, s, −OCH_3), 3.61 (50% of 3H, s, –OCH_3), 5.51 (50% of 1H, t, *J*=6.5 Hz, H-3), 5.56

(50% of 1H, t, $J=6.5$ Hz, H-3), 7.37–7.45 (3H, m, $-C_6H_5$), 7.52–7.60 (2H, m, $-C_6H_5$); δ_F (376.6 MHz, $CDCl_3$) −71.84 (F, s), −71.51 (F, s).

5.7.3. (*S*)-MTPA ester of (3*R*)-1-trimethylsilyl-docosa-13-en-1-yn-3-ol. *R*-**27** (0.010 g, 0.025 mmol) was used following the general procedure for the preparation of an (*S*)-MTPA ester to yield (*S*)-((*R*,*Z*)-1-(trimethylsilyl)-docos-13-en-1-yn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (0.013 g, 0.021 mmol, 85%); δ_H (400 MHz, $CDCl_3$) 0.16 (9H, $-Si(CH_3)_3$), 0.89 (3H, t, $J=7.0$ Hz, H-22), 1.22–1.50 (26H, m, H-5,6,7,8,9,10,11,16,17,18,19,20,21), 1.77–1.92 (2H, m, H-4), 2.15 (4H, t, $J=7.0$ Hz, H-12,15), 3.57 (3H, s, $-OCH_3$), 5.31–5.42 (2H, m, H-13,14), 5.51 (1H, t, $J=7.0$ Hz, H-3), 7.37–7.45 (3H, m, $-C_6H_5$), 7.52–7.58 (2H, m, $-C_6H_5$); δ_F (376.6 MHz, $CDCl_3$) −71.85 (3F, s, $-CF_3$).

5.7.4. (*S*)-MTPA ester of 1-trimethylsilyl-docosa-13-en-1-yn-3-ol. *rac*-**27** (0.011 g, 0.028 mmol) was used following the general procedure for the preparation of an (*S*)-MTPA ester to yield (2′*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid 1-trimethylsilylethynyl-eicos-22-enyl ester (0.017 g, 0.028 mmol, 100%); δ_H (500 MHz, $CDCl_3$) 0.17 (50% of 9H, $-Si(CH_3)_3$), 0.18 (50% of 9H, $-Si(CH_3)_3$), 0.89 (3H, t, $J=7.0$ Hz, H-22), 1.22–1.50 (26H, m, H-5,6,7,8,9,10,11,16,17,18,19,20,21), 1.77–1.92 (2H, m, H-4), 2.03 (4H, apparent q, $J=7.0$ Hz, H-12,15), 3.57 (50% of 3H, s, $-OCH_3$), 3.61 (50% of 3H, s, $-OCH_3$), 5.31–5.42 (2H, m, H-13,14), 5.51 (50% of 1H, t, $J=7.0$ Hz, H-3), 5.56 (50% of 1H, t, $J=7.0$ Hz, H-3), 7.37–7.44 (3H, m, $-C_6H_5$), 7.53–7.59 (2H, m, $-C_6H_5$); δ_F (235.4 MHz, $CDCl_3$) −71.96 (50% of 3F, s, $-CF_3$), −72.29 (50% of 3F, s, $-CF_3$).

5.7.5. (*R*)-MTPA ester of (3*R*)-1-trimethylsilyl-tetradec-1-yn-3-ol. *R*-**15** (0.011 g, 0.039 mmol) was used following the general procedure for the preparation of an (*R*)-MTPA ester to yield (*S*)-((*R*)-1-(trimethylsilyl)tetradec-1-yn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (0.017 g, 0.034 mmol, 87%); δ_H (400 MHz, $CDCl_3$) 0.18 (3H, s, $-Si(CH_3)_3$), 0.89 (3H, t, $J=6.5$ Hz, H-14), 1.18–1.38 (18H, m, H-5,6,7,8,9,10,11,12,13), 1.74–1.86 (2H, m, H-4), 3.61 (3H, s, $-OCH_3$), 5.56 (1H, t, $J=6.5$ Hz, H-3), 7.36–7.44 (3H, m, $-C_6H_5$), 7.55–7.61 (2H, m, $-C_6H_5$); δ_F (376.6 MHz, $CDCl_3$) −71.50 (F, s).

5.7.6. (*R*)-MTPA ester of 1-trimethylsilyl-tetradec-1-yn-3-ol. *rac*-**15** (0.010 g, 0.035 mmol) was used following the general procedure for the preparation of an (*R*)-MTPA ester to yield (*S*)-1-(trimethylsilyl)tetradec-1-yn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (0.009 g, 0.018 mmol, 51%); δ_H (400 MHz, $CDCl_3$) 0.16 (50% of 9H, s, $-Si(CH_3)_3$), 0.18 (50% of 9H, s, $-Si(CH_3)_3$), 0.89 (3H, t, $J=7.0$ Hz, H-14), 1.18–1.38 (18H, m, H-5,6,7,8,9,10,11,12,13), 1.73–1.92 (2H, m, H-4), 3.57 (50% of 3H, s, $-OCH_3$), 3.61 (50% of 3H, s, $-OCH_3$), 5.51 (50% of 1H, t, $J=7.0$ Hz, H-3), 5.56 (50% of 1H, t, $J=7.0$ Hz, H-3), 7.36–7.44 (3H, m, $-C_6H_5$), 7.52–7.60 (2H, m, $-C_6H_5$); δ_F (376.6 MHz, $CDCl_3$) −71.84 (F, s), −71.51 (F, s).

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References and notes

1. Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, R. *Nat. Prod. Rep.* **2004**, *21*, 1–49 and previous papers in this series.
2. (a) Fusetani, N.; Sugano, M.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1987**, *28*, 4311–4312. (b) Wright, A. E.; McConnell, O. J.; Kohmoto, S.; Lui, M. S.; Thompson, W.; Snader, K. M. *Tetrahedron Lett.* **1987**, *28*, 1377–1379. (c) Gunasekera, S. P.; Faircloth, G. T. *J. Org. Chem.* **1990**, *55*, 6223–6225. (d) Patil, A. D.; Kokke, W. C.; Cochran, S.; Francis, T. A.; Tomszek, T.; Westley, J. W. *J. Nat. Prod.* **1992**, *55*, 1170–1177. (e) Isaacs, S.; Kashman, Y.; Loya, S.; Hizi, A.; Loya, Y. *Tetrahedron* **1993**, *49*, 10435–10438. (f) Fusetani, N.; Li, H.-Y.; Tamura, K.; Matsunaga, S. *Tetrahedron* **1993**, *49*, 1203–1210. (g) Li, H.-Y.; Matsunaga, S.; Fusetani, N. *J. Nat. Prod.* **1994**, *57*, 1464–1467. (h) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *J. Nat. Prod.* **1997**, *60*, 126–130.
3. Watanabe, K.; Tsuda, Y.; Yamane, Y.; Takahashi, H.; Iguchi, K.; Naoki, H.; Fujita, T.; Van Soest, R. W. M. *Tetrahedron Lett.* **2000**, *41*, 9271–9276.
4. Watanabe, K.; Tsuda, Y.; Yamane, Y.; Takahashi, K.; Iguchi, K.; Naoki, H.; Fujita, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **2000**, 42nd ed., Nippon Kagakkai.
5. Yadav, J. S.; Mishra, R. K. *Tetrahedron Lett.* **2002**, *43*, 1739–1741.
6. Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813–6817.
7. Kirkham, J. E. D.; Courtney, T. D. L.; Lee, V.; Baldwin, J. E. *Tetrahedron Lett.* **2004**, *45*, 5645–5647.
8. (a) Brandsma, L. *Preparative Acetylene Chemistry*, 2nd ed.; Elsevier: Oxford, 1998. (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632–2657.
9. Polt, R.; Sames, D.; Churma, J. *J. Org. Chem.* **1999**, *64*, 6147–6158.
10. Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.
11. (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022. (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276. (c) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.
12. Mori, K.; Qian, Z.-H. *Liebigs Ann. Chem.* **1994**, 291–295.
13. Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891–892.
14. Abrahams, S. R.; Shaw, A. G. *Org. Synth. Coll.* **1993**, *8*, 146–148.
15. (a) Hommes, H.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1997**, *96*, 160. (b) Macaulay, S. R. *J. Org. Chem.* **1980**, *45*, 734–735.
16. Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 3197–3199.
17. (a) Amador, M.; Ariza, X.; Garcia, J.; Oritz, J. *Tetrahedron Lett* **2002**, *43*, 2691–2694. See: Ref. 16 therein. Ortiz, J.; Garcia, J. Departament de Qui'mica Orga'nica, Universitat de

Barcelona. Personal communication. (Note: Carreira previously stated that these enantioselective addition reactions are relatively insensitive to the presence of moisture. See: Ref. 31. However, Garcia et al. deemed it necessary to thoroughly dry the $Zn(OTf)_2$ to effect a successful reaction. In addition, Garcia et al. observed that the source of $Zn(OTf)_2$ affects the yield of reaction and that the reaction worked best when the $Zn(OTf)_2$ is in powder form).

18. (a) Ariza, X.; Garcia, J.; López, M.; Montserrat, L. *Synlett* **2001**, 120–122. (b) Gung, B. W.; Dickson, H.; Shockley, S. *Tettrahedron Lett.* **2001**, *42*, 4761–4763. (c) Gung, B. W.; Dickson, H. D.; Seggerson, S.; Bluhm, K. *Synth. Commun.* **2002**, *32*, 2733–2740. (d) Ahmed, A.; Crawford, T.; Gould, S.; Ha, Y. S.; Hollrah, M.; Noor-E-Ain, F.; Dickman, M. B.; Dussault, P. H. *Phytochemistry* **2003**, *63*, 47–52. (e) Ariza, X.; Fernández, N.; Garcia, J.; López, M.; Montserrat, L.; Ortiz, J. *Synthesis* **2004**, 128–134. (f) Alcaide, B.; Almendros, P.; Alonso, J. M. *J. Org. Chem.* **2004**, *69*, 993–996. (g) Fenster, M. D. B.; Dake, G. R. *Chem. Eur. J.* **2005**, *11*, 639–649. (h) López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2005**, *7*, 287–290.
19. Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* **2002**, 1524–1525.
20. Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451–3453.
21. Rozners, E.; Xu, Q. *Org. Lett.* **2003**, *5*, 3999–4001.
22. Kojima, N.; Maezaki, N.; Tominaga, H.; Asai, M.; Yanai, M.; Tanaka, T. *Chem. Eur. J.* **2003**, *9*, 4980–4990.
23. Bennet, M. A.; Huang, T. N.; Matheson, T. W.; Smith, A. K. *Inorg. Synth.* **1982**, *21*, 74–78.
24. Tietze, L. F.; Zhou, Y.; Töpken, E. *Eur. J. Org. Chem.* **2000**, 2247–2252.
25. Haak, K.-J.; Hashiguchi, S.; Akio, F.; Ikariya, F.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285–288.
26. Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.
27. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
28. Kalogerakis, A.; Groth, U. *Synlett* **2003**, 1886–1888.
29. Poulain, S.; Noiret, N.; Nugier-Chauvin, C.; Patin, H. *Liebigs Ann. Chem.* **1997**, 35–40.
30. (a) . For contributions outside the Carreira group see: Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855–3858. (b) Maezaki, N.; Kojima, N.; Asai, M.; Tominaga, H.; Tanaka, T. *Org. Lett.* **2002**, *4*, 2977–2980. (c) Maezaki, N.; Kojima, N.; Tominaga, H.; Yanai, M.; Tanaka, T. *Org. Lett.* **2003**, *5*, 1411–1414. (d) Oritz, J.; Ariza, X.; Garcia, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1127–1131. (e) Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 1737–1739. (f) More, J. D.; Finney, N. S. *Synlett* **2003**, 1307–1310. (g) García-Fortanet, J.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron* **2004**, *60*, 12261–12267. (h) Kojima, N.; Maezaki, N.; Tominaga, H.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Eur. J.* **2004**, *10*, 672–680. (i) Maezaki, N.; Hirose, Y.; Tanaka, T. *Org. Lett.* **2004**, *6*, 2177–2180. (j) Maezaki, N.; Tominaga, H.; Kojima, N.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Commun.* **2004**, 406–407. (k) Arndt, H.-D.; Welz, R.; Müller, S.; Ziemer, B.; Koert, U. *Chem. Eur. J.* **2004**, *10*, 3945–3962. (l) Georges, Y.; Allenbach, Y.; Ariza, X.; Campagne, J.-M.; Garcia *J. Org. Chem.* **2004**, *69*, 7387–7390. (m) Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313–10318. (n) Davidson, M. H.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 1601–1603. Trost, B. M.; Ameriks, M. K. *Org. Lett.* **2004**, *6*, 1601–1603. (o) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790–12791. (p) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348–15349. (q) Franchini, L.; Compostella, F.; Donda, A.; Mori, L.; Colombo, D.; De Libero, G.; Matto, P.; Ronchetti, F.; Panza, L. *Eur. J. Chem.* **2004**, 4755–4761. (r) Archambaud, S.; Aphecetche-Julienne, K.; Guingant, A. *Synlett* **2005**, 139–143. (s) Strand, D.; Rein, T. *Org. Lett.* **2005**, *7*, 199–202.
31. (a) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688. (Note: it is interesting that in this reference the experimental procedure details drying of the $Zn(OTf)_2$ under heat and vacuum overnight, whereas it is stated within the body of the text that the reaction is tolerant to moisture.). (b) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605–2606.
32. Most documented protocols described the reaction as a 'mixture'. Three further described the reaction as a 'slurry'. (See: Refs. 30e,t,q). Only a single reference described the formation of a 'nearly homogeneous' mixture of $Zn(OTf)_2$, *N*-methylephedrine and alkyne. (See: Ref. 17a). Interestingly, the same authors subsequently described the reaction as a slurry. (See: Ref. 30e).
33. Meuzelaar, G. J.; Van-Vliet, M. C. A.; Maat, L.; Sheldon, R. A. *Eur. J. Org. Chem.* **1999**, 2315–2321.

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A general synthesis of five, six and seven-membered silasultones via dehydrative cyclisation

D. Christopher Braddock* and Jérôme J.-P. Peyralans

Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, UK

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Abstract—Five, six and seven-membered silasultones can be conveniently prepared in good yield by dehydrative cyclisation of siloxane disulphonic acids. The siloxanes are prepared by protodesilylation of the corresponding phenylsilane sulphonic acids. The sulphonate group is introduced either by free-radical sulphonation of vinyl silanes, or by S_N2 sulphite displacement of a long chain alkyl chloride.

1. Introduction

Silasultones are alicyclic structures containing the –Si–O–SO_2– molecular fragment. Silasultones have potential as monomers in polymer chemistry and are the cyclic equivalents of useful aliphatic reagents and catalysts such as trimethylsilyl trifluoromethanesulphonate.[1] However, the silasultones as a class of compounds has been little explored, and synthetic routes to them are severely limited. Pre-existing methods for the preparation of silasultones include only the formal insertion of SO_3 into silacyclobutanes,[2a–f] or the rearrangement of 1-silacyclopent-3-enes and 3-silabicyclo[3.2.1]hexanes mediated by Me_3SiOSO_2-Cl.[2g] The former method is restricted to the preparation of six-membered silasultones from silacyclobutanes† since attempted SO_3 insertion into larger non-strained sila-rings results in competitive attack at *exo*-Si–C bonds.[1c] The latter method generally results in mixtures of compounds, and necessarily leaves a(n) (unwanted) pendant alkene chain in the silasultone product. Herein, we describe the first general synthetic approach to silasultones of ring sizes of 5–7.‡

Keywords: Silasultone; Cyclisation; Siloxane; Protodesilylation; Sulphonation.
* Corresponding author. Tel.: +44 20 7594 5772; fax: +44 20 7594 5805; e-mail: c.braddock@imperial.ac.uk
† It seems reasonable to assume that the insertion of SO_3 into silacyclopropanes would yield 5-membered silasultones. To date, however, this approach has not been demonstrated.
‡ Two isolated examples in the patent literature make reference to the synthesis of a six-membered silasultone via dehydration of a disulphonic acid siloxane. Only one example is given in each case, the generality and scope is not demonstrated, limited experimental details are available and no characterising spectroscopic data is given. See: Ryan, J. W. (Dow Corning Corporation, U.S.A.) September 6th, **1966**, Patent no.: CA742243 and Hager, R.; Wolferseder, J.; Deubzer, B. (Wacker-Chemie, Gmbh) October 24th, **1991**, Patent no.: DE4135170.

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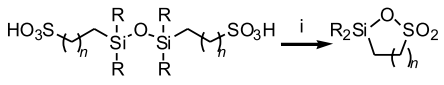
2. Results and discussion

Silasultones **1–6** were prepared by dehydrative cyclisation of disulphonic acid siloxanes (**7–12**) via vacuum sublimation (Scheme 1). This method provides the silasultones **1–6** in good-to-moderate yields (ca. 65–45%). It was found to be superior to attempted dehydrative cyclisation of the disulphonic acids by azeotropic removal of water in refluxing toluene which consistently generated a mixture of silasultones and the corresponding unreacted diacids even after extended heating (48 h).

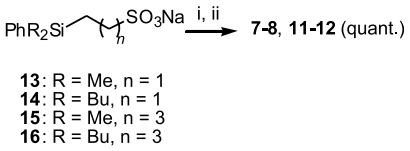
With the exception of disulphonic acids **9** and **10**, the diacids **7–8**, **11–12** were prepared by *ipso*-protodesilylation of the corresponding phenylsilanes **13–16** followed by treatment with a strong acid ion-exchange resin to ensure complete protonation of the sulphonates. This two-step procedure delivered the disulphonic acids in essentially quantitative yields (Scheme 2). Aqueous hydrochloric acid was a sufficiently acidic medium for *ipso*-protodesilylation of methylsilanes **13** and **15**, but the more sterically hindered butylsilanes **14** and **16** required the use of a more powerful acidic medium: aqueous hydrobromic acid was employed. Presumably this is a reflection of the increased steric clash



7: R = Me, n = 1
8: R = Bu, n = 1
9: R = Me, n = 2
10: R = Bu, n = 2
11: R = Me, n = 3
12: R = Bu, n = 3

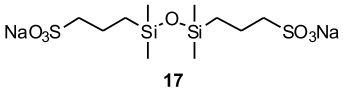
1: R = Me, n = 1 (67%)
2: R = Bu, n = 1 (67%)
3: R = Me, n = 2 (65%)
4: R = Bu, n = 2 (46%)
5: R = Me, n = 3 (48%)
6: R = Bu, n = 3 (45%)

Scheme 1. Reagents and conditions: (i) 0.02 mmHg, up to 250 °C.



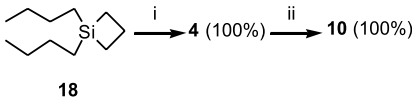
Scheme 2. Reagents and conditions: (i) aq. HX (X=Cl: **13**, **15**; X=Br **14**, **16**), reflux 24–36 h; (ii) Proton exchange resin, MeOH, H_2O.

between the butyl groups and the phenyl ring in the Wheland intermediate as the phenyl group undergoes *ipso*-protonation. Methylsiloxane **9**[1b] was prepared by Dowex-H mediated acid exchange of disodium disulphonate **17** obtained directly from a sulphonation reaction (vide infra). Butylsiloxane **10**[1b] was most conveniently prepared by hydrolysis of silasultone **4**, which can be obtained directly by sulphur trioxide insertion[1a] into butylsilacyclobutane **18**[3] using trimethylsilylchlorosulphonate (Scheme 3). Silasultone **4** formed in this manner is not pure, but hydrolysis to diacid **10** followed by diethyl ether washes removes the impurities and subsequent dehydrative cyclisation delivers pure **4**.

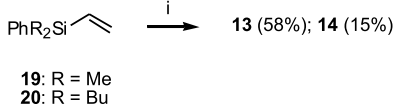


Two distinct methods were employed for the preparation of phenylsilanes **13**–**16**. Free-radical sulphonation of vinylsilanes **19** and **20** allowed access to silanes **13** and **14**. For the preparation of phenylsilanes **15** and **16**, S_N2 displacement of an appropriate alkylchloride with sulphite anion was employed. Vinyl silanes **19** and **20** were prepared by the Grignard reactions of phenylmagnesium bromide with chlorodimethylvinylsilane and double addition of butylmagnesium bromide to dichlorophenylvinylsilane,[4] respectively. Using a modified method of Weinreb,[5] regioselective free-radical sulphonation of dimethylvinylsilane **19** in a methanol/water mixture proceeded smoothly to give sodium sulphonate **13** in good yield (58%) (Scheme 4).[§] Under identical conditions, dibutylvinylsilane **20** failed to undergo sulphonation and starting material was recovered along with diphenyltetrabutylsiloxane (from vinyl protodesilylation). Attempts to perform this sulphonation instead under microwave conditions or sonication failed. Sulphonation in an *n*-propanol/water mixture proceeded to some degree giving a 15% isolated yield of sodium salt **14**. Clearly, the extra lipophilicity of the dibutyl substrate is problematic under the aqueous regime required for sodium hydrogen sulphite solubility. As a solution to this problem, we set about preparing a water-soluble dibutylvinylsilane substrate for the sulphonation reaction. We chose to functionalise the phenyl substituent since it is to be ultimately eliminated from the substrate during the protodesilylation reaction after the crucial free-radical sulphonation step. Accordingly, addition of the Grignard reagent of tertiary amine, (4-bromobenzyl)dimethylamine (**21**),[6] to dibutylmethoxyvinylsilane (**22**) gave phenylsilane **23** (81%) (Scheme 5). Quaternisation with methyliodide gave ammonium salt **24**

[§] In an initial approach to the preparation of silasultones, the direct extrusion of benzene via intramolecular *ipso*-protodesilylation of the acid of sodium sulphonate **13** was explored. After much experimentation only 2% of the desired silasutone **1** could be isolated by sublimation.



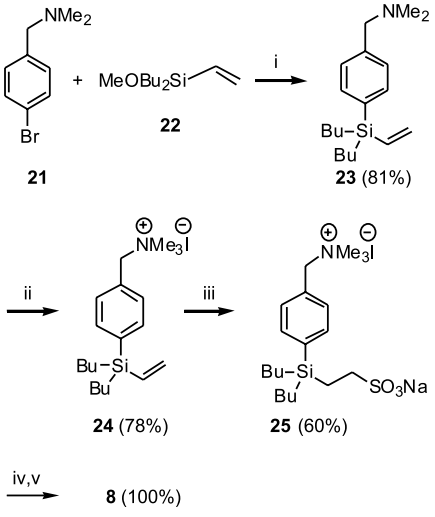
Scheme 3. Reagents and conditions: (i) Me_3SiOSO_2Cl, CH_2Cl_2, −78→−20 °C, 16 h; (ii) H_2O, 20 °C, 1 h.



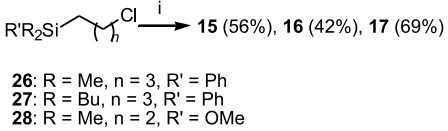
Scheme 4. Reagents and conditions: (i) $NaHSO_3$, cat. $PhCO_3{}^tBu$, H_2O, $R'OH$ (R'=Me: **19**; R'=Pr: **20**), reflux, 72 h.

(78%). Subsequent free-radical sulphonation using the original conditions gave the new sulphonate salt **25** in a pleasing 60% yield. Protodesilylation with aqueous HBr, followed by treatment with Dowex-H furnished the disulphonic acid **8** in quantitative yield.

For the longer chain sulphonates **15**–**17**, the sulphonate groups were introduced by nucleophilic displacement of chlorides **26**–**28**, respectively, with sodium sulphite (Scheme 6). Chloride **26** was prepared by the addition of Negishi's 1-chloro-4-lithiobutane reagent[7] to chlorodimethylphenylsilane. Dibutyl chloride **27** was obtained in good yield (85%) by the reaction of the alkyllithium with dibutylphenylsilyl triflate **29**. The latter was prepared by the action of triflic acid on dibutyldiphenylsilane[8] applying Matyjaszewski's method for the preparation of dimethylphenylsilyl triflate.[9] Commercially available methoxysilane **28** underwent smooth substitution reaction with sodium



Scheme 5. Reagents and conditions: (i) Mg, THF, reflux, 72 h; (ii) MeI, EtOH, 20 °C, 48 h; (iii) $NaHSO_3$, cat. $PhCO_3{}^tBu$, H_2O, MeOH, reflux, 72 h; (iv) aq. HBr, reflux, 32 h; (v) proton exchange resin, MeOH, H_2O.



Scheme 6. Reagents and conditions: (i) Na_2SO_3.

sulphite in refluxing water to give the disulphonate salt **17** directly (69%). The corresponding reaction of dimethylsilane **26** required the addition of a co-solvent (ethanol) for reasonable yields (56%). The more lipophilic dibutylsilane **27** gave only poor yields (ca. 14%) under these conditions, but the application of microwave irradiation (150 °C, 11250 mmHg, 1.5 h) gave the desired product in moderate yield (42%).

3. Conclusion

In conclusion we have shown that silasultones **1–6** can be prepared by a dehydrative cyclisation of the corresponding disulphonic acid siloxanes. In general, the latter compounds can be approached synthetically by *ipso*-protodesilylation of the corresponding phenylsilanes. The phenylsilanes can either be prepared by free-radical sulphonation of vinylsilanes or sulphite displacement of alkylchlorides as appropriate. These procedures allow for a general method for the synthesis of silasultones.

4. Experimental

4.1. General

Dichlorocyclobutasilane,[10] dichlorophenylvinylsilane,[4] bromobenzyldimethylamine (**21**),[6] 4-chloro-1-iodobutane[11] and dibutyldiphenylsilane[9] were prepared according to the published procedures. Trimethylsilylchlorosulfonate was distilled immediately before use. *N*′,*N*′,*N*,*N*-Tetramethylethane-1,2-diamine was dried over NaOH pellets and distilled immediately before use. DOWEX®50WX4-400 was activated using aqueous hydrochloric acid (1 M) and washed with water immediately before use. All other chemicals were used as received.

All reactions were performed under N_2 in dry solvents unless used in combination with water. Et_2O and THF were distilled from sodium and potassium, respectively, in the presence of benzophenone. EtOH, used during the synthesis of ammonium iodide **24**, was dried over sodium and distilled.

4.2. General procedure for silasultone formation

Disulphonic siloxane was placed in a sublimation apparatus under reduced pressure (0.02 mmHg) and gradually heated to 250 °C. The sublimed product was collected under N_2.

4.2.1. 3,3-Dimethyl-3-sila-1,3-propanesultone (1). Following the general procedure, silasultone **1** (0.11 g, 0.69 mmol, 67%) was obtained from disulphonic diacid **7** (0.18 g, 0.51 mmol) as a white solid: mp 95–105 °C; IR (CH_2Cl_2) ν_{max} 1344, 1257, 1172, 1070 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) δ 3.35–3.27 (m, 2H, –C$H_2$$CH_2$Si), 1.53–1.44 (m, 2H, –CH_2Si), 0.51 (s, 6H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 47.4 (–C$H_2$$CH_2$Si), 11.8 (–C$H_2$Si), −0.1 ($H_3C$–Si) ppm; ^{29}Si NMR (99 MHz; $CDCl_3$) δ 32.9 ppm; MS (CI^+) *m*/*z* 184 $[M+NH_4]^+$; HRMS (CI^+) *m*/*z* calculated for $C_4H_{14}NO_3SiS$ $[M+NH_4]^+$ 184.0464, found 184.0466; MS (EI^+) *m*/*z* 151 $[M-CH_3]^{+\cdot}$; HRMS (EI^+) *m*/*z* calculated for $C_3H_7O_3SiS$ $[M-CH_3]^{+\cdot}$ 150.9885, found 150.9893.

4.2.2. 3,3-Dibutyl-3-sila-1,3-propanesultone (2). Following the general procedure, silasultone **2** (97 mg, 0.58 mmol, 67%) was obtained from disulphonic diacid **8** (0.15 g, 0.29 mmol) as a colourless oil: IR (CH_2Cl_2) ν_{max} 1344, 1170, 1082 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) δ 3.28 (t, 2H, ^3J=7.9 Hz, O_3SCH_2–), 1.46 (t, 2H, ^3J=7.9 Hz, $O_3SCH_2CH_2$–), 1.50–1.18 (m, 8H, alk), 0.96–0.77 (m, 10H, alk) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 47.5 (O_3SCH_2–), 26.0, 24.3, 13.7, 13.7, 7.7 ($O_3SCH_2CH_2$–) ppm; ^{29}Si NMR (99 MHz; $CDCl_3$) δ 34.8 ppm; MS (CI^+) *m*/*z* 268 $[M+NH_4]^+$; HRMS (CI^+) *m*/*z* calculated for $C_{10}H_{26}NO_3SiS$ $[M+NH_4]^+$ 268.1403, found 268.1407; MS (EI^+) *m*/*z* 193 $[M-C_4H_9]^{+\cdot}$; HRMS (EI^+) *m*/*z* calculated for $C_6H_{13}O_3SiS$ $[M-C_4H_9]^{+\cdot}$ 193.0355, found 193.0364.

4.2.3. 4,4-Dimethyl-4-sila-1,4-butanesultone (3). Following the general procedure, silasultone **3** (0.20 g, 1.11 mmol, 65%) was obtained from disulphonic diacid **9** (0.32 g, 0.86 mmol) as a white solid: mp ~40–50 °C; IR (CH_2Cl_2) ν_{max} 1349, 1257, 1169 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) δ 3.10–3.00 (m, 2H, O_3SCH_2–), 2.30–2.15 (m, 2H, –CH_2–), 0.85–0.75 (m, 2H, –CH_2Si), 0.33 (s, 6H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 50.7 (O_3SCH_2–), 19.0 (–CH_2–), 11.0 (–CH_2Si), −1.0 (H_3C–Si) ppm; ^{29}Si NMR (99 MHz; $CDCl_3$) δ 37.9 ppm; MS (CI^+) *m*/*z* 198 $[M+NH_4]^+$; HRMS (CI^+) *m*/*z* calculated for $C_5H_{16}NO_3SiS$ $[M+NH_4]^+$ 198.0620, found 198.0617; MS (EI^+) *m*/*z* 165 $[M-CH_3]^{+\cdot}$; HRMS (EI^+) *m*/*z* calculated for $C_4H_9O_3SiS$ $[M-CH_3]^{+\cdot}$ 165.0042, found 165.0044.

4.2.4. 4,4-Dibutyl-4-sila-1,4-butanesultone (4).[1a,b] Following the general procedure, silasultone **4** (95 mg, 0.36 mmol, 46%) was obtained from disulphonic diacid **10** (0.21 g, 0.39 mmol) as a colourless oil: IR (CH_2Cl_2) ν_{max} 1344, 1172, 1076 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) δ 3.13–3.05 (m, 2H, O_3SCH_2–), 2.37–2.23 (m, 2H, $O_3SCH_2CH_2$–), 1.50–1.20 (m, 8H, alk), 1.00–0.75 (m, 12H, alk and $O_3SCH_2CH_2CH_2$–) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 50.9 (O_3SCH_2–), 26.1, 24.3, 19.3 ($O_3SCH_2CH_2$–), 13.7, 13.5, 8.3 ($O_3SCH_2CH_2CH_2$–) ppm; ^{29}Si NMR (99 MHz; $CDCl_3$) δ 36.1 ppm; MS (CI^+) *m*/*z* 282 $[M+NH_4]^+$; HRMS (CI^+) *m*/*z* calculated for $C_{11}H_{28}NO_3SiS$ $[M+NH_4]^+$ 282.1559, found 282.1559; MS (EI^+) *m*/*z* 207 $[M-C_4H_9]^{+\cdot}$; HRMS (EI^+) *m*/*z* calculated for $C_7H_{15}O_3SiS$ $[M-C_4H_9]^{+\cdot}$ 207.0511, found 207.0518. *Alternative synthesis of silasultone* **4**: to neat silacyclobutane **18** (2.0 g, 7.56 mmol) at −20 °C, trimethylsilylchlorosulfonate (1.17 mL, 7.56 mmol) was added dropwise over 10 min. The light orange mixture was allowed to warm to room temperature, stirred for 6 h at room temperature and the volatiles were removed under reduced pressure (0.02 mmHg) at 60–80 °C for 30 min to leave silasultone **4** (2.0 g, 7.56 mmol, 100%) as a colourless oil: data as reported above.

4.2.5. 5,5-Dimethyl-5-sila-1,5-pentanesultone (5). Following the general method, silasultone **5** (80 mg, 0.41 mmol, 48%) was obtained from disulphonic diacid **11** (0.18 g, 0.43 mmol) as a colourless oil: IR (CH_2Cl_2) ν_{max} 1351, 1257, 1171, 1070 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$)

δ 3.28–3.18 (m, 2H, O_3SCH_2–), 2.05–1.91 (m, 2H, $O_3SCH_2CH_2$–), 1.88–1.76 (m, 2H, –CH_2CH_2Si), 1.11–1.00 (m, 2H, –CH_2Si), 0.33 (s, 6H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 53.6 (O_3SCH_2–), 26.0 ($O_3SCH_2CH_2$–), 21.6 (–CH_2CH_2Si), 16.7 (–CH_2Si), −1.2 (CH_3Si) ppm; ^{29}Si NMR (99 MHz; $CDCl_3$) δ 29.7 ppm; MS (CI^+) *m/z* 212 $[M+NH_4]^+$; HRMS (CI^+) *m/z* calculated for $C_6H_{14}NO_3SiS$ $[M+NH_4]^+$ 212.0777, found 212.0783; MS (EI^+) *m/z* 179 $[M-CH_3]^+$; HRMS (EI^+) *m/z* calculated for $C_5H_{11}O_3SiS$ $[M-CH_3]^+$ 179.0198, found 179.0206.

4.2.6. 5,5-Dibutyl-5-sila-1,5-pentanesultone (6). Following the general method, silasultone **6** (52 mg, 0.19 mmol, 45%) was obtained from disulphonic diacid **12** (0.12 g, 0.21 mmol) as a colourless oil: IR (CH_2Cl_2) ν_{max} 1376, 1160 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) δ 3.27–3.17 (m, 2H, O_3SCH_2–), 2.04–1.90 (m, 2H, $O_3SCH_2CH_2$–), 1.90–1.75 (m, 2H, $O_3SCH_2CH_2CH_2$–), 1.44–1.26 (m, 8H, alk), 1.08–0.97 (m, 2H, $O_3SCH_2CH_2CH_2CH_2$–), 0.93–0.69 (m, 10H, alk) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 53.7 (O_3SCH_2–), 26.3, 26.0 ($O_3SCH_2CH_2$–), 24.7, 22.1 ($O_3SCH_2CH_2CH_2$–), 14.2 ($O_3SCH_2CH_2CH_2CH_2$–), 13.7, 13.6 ppm; ^{29}Si NMR (99 MHz; $CDCl_3$) δ 27.7 ppm; MS (CI^+) *m/z* 296 $[M+NH_4]^+$; HRMS (CI^+) *m/z* calculated for $C_{12}H_{30}NO_3SiS$ $[M+NH_4]^+$ 296.1716, found 296.1705; MS (EI^+) *m/z* 221 $[M-C_4H_9]^{+\cdot}$; HRMS (EI^+) *m/z* calculated for $C_8H_{17}O_3SiS$ $[M-C_4H_9]^{+\cdot}$ 221.0668, found 221.0677.

4.3. General procedure for the formation of disulphonic acids

(A) A solution of arylsilane (1/50, w/v) in an aqueous solution of HCl (12 M) (**13**, **15**) or HBr (12 M) (**14**, **16**) was heated at reflux. After 24 h (**13**, **15**) or 32 h (**14**, **16**) the mixture was allowed to cool to room temperature and concentrated. The resulting di-sodium salts were extracted with PrOH and the resultant liquor was concentrated to dryness. (B) A solution of the sodium salt (typically ~10% w/v) in MeOH:H_2O (1:1) was passed through a DOWEX®50WX4-400 proton exchange resin packed column (typically ~100 times as much mass of wet resin as sodium salt) at room temperature. The column was eluted further with MeOH:H_2O (1:1) (typically ~10 times as much volume as sodium salt solution) and H_2O (typically ~10 times as much volume as sodium salt solution). The eluate was concentrated to afford quantitatively the expected acid as a pale yellow oil. Chemical shifts of the protons from the sulphonic acid groups are not reported since they range variously and unpredictably between 13 and 7 ppm irrespective of the solvent or the sulphonic acid. These compounds also displayed two very broad, intense absorbances in their IR spectra at 3600–2500 and 2000–1500 wavenumbers.

4.3.1. 3,3,5,5-Tetramethyl-4-oxa-3,5-disilaheptane-1,7-disulphonic diacid (7). Following the general procedure above (Part A and Part B) using sodium sulphonate **13** (1.23 g, 4.62 mmol) gave disulphonic diacid **7** (0.84 g, 2.22 mmol, 96%) as a pale yellow oil: ^1H NMR (270 MHz; DMSO-d_6) δ 2.65–2.53 (m, 4H, HO_3SCH_2–), 0.93–0.80 (m, 4H, –CH_2Si), 0.03 (s, 12H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 46.7 (HO_3SCH_2–), 13.5 (–CH_2Si), 0.7 (H_3C–Si) ppm; ^1H NMR (270 MHz; $CDCl_3$) δ 3.16–3.02 (m, 4H), 1.13–1.02 (m, 4H), 0.13 (s, 12H) ppm; MS (CI^+) *m/z* 350 $[M-H_2O+NH_4]^+$; HRMS (CI^+) *m/z* calculated for $C_8H_{24}NO_6Si_2S_2$ $[M-H_2O+NH_4]^+$ 350.0584, found 350.0579.

4.3.2. 3,3,5,5-Tetrabutyl-4-oxa-3,5-disilaheptane-1,7-disulphonic diacid (8). Following the general procedure above (Part A and Part B) using sodium sulphonate **14** (0.46 g, 1.31 mmol) or {2-[dibutyl-(*p*-trimethylammoniumiodide)-benzyl]-silyl}ethane sulfonate (**25**) (0.72 g, 1.31 mmol) gave disulphonic diacid **8** (0.34 g, 0.66 mmol, 100%) as a pale yellow oil: ^1H NMR (270 MHz; DMSO-d_6) δ 2.61–2.38 (m, 4H, HO_3SCH_2–), 1.35–1.17 (m, 16H, alk), 0.93–0.75 (m, 16H, alk and $HO_3SCH_2CH_2$–), 0.61–0.41 (m, 8H, alk) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 46.7 (HO_3SCH_2–), 26.4, 25.4, 15.1, 14.1, 11.0 ($HO_3SCH_2CH_2$–) ppm; ^1H NMR (270 MHz; $CDCl_3$) δ 2.96–2.75 (m, 4H), 1.45–1.16 (m, 16H), 1.09–0.92 (m, 4H), 0.92–0.76 (m, 12H), 0.66–0.45 (m, 8H) ppm; MS (CI^+) *m/z* 518 $[M-H_2O+NH_4]^+$; HRMS (CI^+) *m/z* calculated for $C_{20}H_{48}NO_6Si_2S_2$ $[M-H_2O+NH_4]^+$ 518.2462, found 518.2462.

4.3.3. 4,4,6,6-Tetramethyl-5-oxa-4,6-disilanonane-1,9-disulphonic diacid (9).[1b] Following the general procedure above (Part B only) using disodium disulfonate **17** (1.54 g, 3.64 mmol), gave disulphonic diacid **9** (1.38 g, 3.64 mmol, 100%) as a pale yellow oil: ^1H NMR (270 MHz; DMSO-d_6) δ 2.69 (br t, 4H, $^3J=7.6$ Hz, HO_3SCH_2–), 1.70–1.55 (m, 4H, –CH_2–), 0.55 (br t, 4H, $^3J=8.5$ Hz, –CH_2Si), 0.01 (s, 12H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 54.9 (HO_3SCH_2–), 19.0 (–CH_2–), 17.4 (–CH_2Si), 0.8 (H_3C–Si) ppm; ^1H NMR (270 MHz; $CDCl_3$) δ 3.08–2.88 (m, 4H), 1.83–1.65 (m, 4H), 0.60–0.46 (m, 4H), −0.04 (s, 12H); MS (CI^+) *m/z* 378 $[M-H_2O+NH_4]^+$; HRMS (CI^+) *m/z* calculated for $C_{10}H_{28}O_6Si_2S_2$ $[M-H_2O+NH_4]^+$ 378.0897 found 378.0899.

4.3.4. 4,4,6,6-Tetrabutyl-5-oxa-4,6-disilanonane-1,9-disulphonic diacid (10).[1b] To silasultone **4** (2.0 g, 7.56 mmol) at room temperature was added H_2O (10 mL). The resulting solution was stirred for 1 h, and washed with Et_2O (3× 10 mL). The resulting mixture was dissolved in MeOH and concentrated to give disulphonic diacid **10** (2.1 g, 3.78 mmol, 100%) as an orange oil: ^1H NMR (270 MHz; DMSO-d_6) δ 2.66 (br t, 4H, $^3J=7.6$ Hz, HO_3SCH_2–), 1.73–1.54 (m, 4H, $HO_3SCH_2CH_2$–), 1.37–1.16 (m, 20H, alk and $HO_3SCH_2CH_2CH_2$–), 0.94–0.78 (m, 12H, alk), 0.65–0.40 (m, 8H, alk) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 55.3 (HO_3SCH_2–), 26.6, 25.4, 19.0 ($HO_3SCH_2CH_2$–), 15.4, 15.1 ($HO_3SCH_2CH_2CH_2$–), 14.1(H_3C–) ppm; ^1H NMR (270 MHz; $CDCl_3$) δ 3.01–2.83 (m, 4H), 1.91–1.66 (m, 4H), 1.52–1.18 (m, 20H), 1.02–0.71 (m, 12H), 0.70–0.45 (m, 8H) ppm; MS (CI^+) *m/z* 546 $[M-H_2O+NH_4]^+$, 281 $[M-C_{11}H_{25}O_4SSi]^+$; HRMS (CI^+) *m/z* calculated for $C_{22}H_{52}O_6NSi_2S_2$ $[M-H_2O+NH_4]^+$ 546.2775, found 546.2780.

4.3.5. 5,5,7,7-Tetramethyl-6-oxa-5,7-disilaundecane-1,11-disulphonic diacid (11). Following the general procedure above (Part A and Part B) using sodium sulphonate **15** (1.21 g, 4.11 mmol) gave disulphonic diacid

11 (0.84 g, 2.05 mmol, 100%) as a pale yellow oil: ^{1}H NMR (270 MHz; DMSO-d_6) δ 2.60–2.45 (m, 4H, HO_3SCH_2–), 1.71–1.49 (m, 4H, $HO_3SCH_2CH_2$–), 1.38–1.24 (m, 4H, –CH_2CH_2Si), 0.56–0.36 (m, 4H, –CH_2Si), 0.00 (s, 12H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 51.9 (HO_3SCH_2–), 28.8 ($HO_3SCH_2CH_2$–), 22.8 (–CH_2CH_2Si), 18.4 (–CH_2Si), 1.0 (H_3C–Si) ppm; ^{1}H NMR (270 MHz; $CDCl_3$) δ 3.02–2.88 (m, 4H), 1.85–1.70 (m, 4H), 1.54–1.33 (m, 4H), 0.55–0.45 (m, 4H), 0.03 (s, 12H) ppm; MS (CI^+) m/z 406 $[M-H_2O+NH_4]^+$; HRMS (CI^+) m/z calculated for $C_{12}H_{32}NO_6Si_2S_2$ $[M-H_2O+NH_4]^+$ 406.1210, found 406.1201.

4.3.6. 5,5,7,7-Tetrabutyl-6-oxa-5,7-disilaundecane-1,11-disulphonic diacid (12). Following the general procedure above (Part A and Part B) using sodium sulphonate **16** (0.16 g, 0.42 mmol) gave disulphonic diacid **12** (0.12 g, 0.21 mmol, 100%) as a pale yellow oil: ^{1}H NMR (270 MHz; DMSO-d_6) δ 2.62–2.50 (m, 4H, HO_3SCH_2–), 1.68–1.55 (m, 4H, $HO_3SCH_2CH_2$–), 1.48–1.12 (m, 20H, alk and $HO_3SCH_2CH_2CH_2$–), 0.98–0.72 (m, 12H, alk), 0.63–0.35 (m, 12H, alk and $HO_3SCH_2CH_2CH_2CH_2$–) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 51.7 (HO_3SCH_2–), 29.0 ($HO_3SCH_2CH_2$–), 26.6, 25.6, 22.6 ($HO_3SCH_2CH_2CH_2$–), 15.7 ($HO_3SCH_2CH_2CH_2CH_2$–), 15.4, 14.2 (H_3C–) ppm; ^{1}H NMR (270 MHz; $CDCl_3$) δ 3.02–2.88 (m, 4H), 1.89–1.60 (m, 4H), 1.58–1.11 (m, 20H), 0.98–0.71 (m, 12H), 0.67–0.35 (m, 12H) ppm; MS (CI^+) m/z 574 $[M-H_2O+NH_4]^+$; HRMS (CI^+) m/z calculated for $C_{24}H_{56}NO_6Si_2S_2$ $[M-H_2O+NH_4]^+$ 574.3088, found 574.3090.

4.3.7. Sodium 2-(dimethylphenylsilyl)ethanesulfonate (13). An aqueous solution of HCl (3.3 mL, 12 M, 40 mmol) and then a solution of vinylsilane **19** (3.6 mL, 20 mmol) in MeOH (8 mL) followed by *t*-butylbenzoic peroxide (0.25 mL, 1.3 mmol) were added dropwise to a solution of Na_2SO_3 (5.0 g, 40 mmol) in H_2O (4 mL) over 10 min. The resulting biphasic suspension was heated at reflux. After 72 h, the mixture was allowed to cool to room temperature, washed with Et_2O (3×15 mL), and concentrated to dryness. The resulting salts were extracted with EtOH (5×20 mL) and the resultant liquor was concentrated to dryness to afford sodium sulfonate **13** (3.1 g, 11.6 mmol, 58%) as a white solid: mp 185–187 °C (decomp.); IR (DRIFTS) ν_{max} 1191 cm^{-1}; ^{1}H NMR (270 MHz; DMSO-d_6) δ 7.56–7.42 (m, 2H, Ar), 7.42–7.30 (m, 3H, Ar), 2.42–2.30 (m, 2H, NaO_3SCH_2–), 1.13–1.02 (m, 2H, –CH_2Si), 0.23 (s, 6H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 138.8, 133.9, 129.6, 128.4, 40.9 (NaO_3SCH_2–), 11.6 (–CH_2Si), −2.7 (H_3C–Si) ppm; MS (FAB^-) m/z 243 $[M-Na]^-$. Sodium salt **13** could be converted to the corresponding monosulphonic acid (a yellow oil) using Part B of the general procedure above: ^{1}H NMR (270 MHz; DMSO-d_6) δ 7.53–7.42 (m, 2H, Ar), 7.40–7.29 (m, 3H, Ar), 2.93–2.78 (m, 2H, HO_3SCH_2–), 1.34–1.09 (m, 2H, –CH_2Si), 0.27 (s, 6H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 138.4, 133.9, 129.7, 128.4, 47.3 (HO_3SCH_2–), 11.1 (–CH_2Si), −2.8 ppm (H_3C–Si); MS (CI^+) m/z 184 $[M-C_6H_6+NH_4]^+$. *ipso*-Desilylation–cyclisation was attempted: the sulphonic acid (22 g, 90 mmol) was heated to 250 °C in a short-path distillation apparatus under high vacuum (~0.02 mmHg) for 72 h and then allowed to cool to room temperature. From the receiving flask under N_2, silasultone **1** (0.27 g, 1.6 mmol, 2%) was collected as a white solid. Data as reported above.

4.3.8. Sodium 2-(dibutylphenylsilyl)ethanesulfonate (14). An aqueous solution of HCl (20 mL, 12 M, 244 mmol), a solution of vinylsilane **20** (20 g, 81 mmol) in PrOH (50 mL) followed by *t*-butyl benzoic peroxide (1.5 mL, 8 mmol) were added dropwise to a solution of Na_2SO_3 (31 g, 244 mmol) in H_2O (24 mL) over 10 min. The resulting biphasic suspension was heated at reflux. After 120 h, the mixture was allowed to cool to room temperature, washed with Et_2O (3×40 mL), and concentrated to dryness. The resulting salts were extracted with PrOH (5×10 mL) and the resultant liquor was concentrated to dryness to afford sodium sulfonate **14** (4.3 g, 12.2 mmol, 15%) as a white solid: mp 280 °C (decomp.); IR (DRIFTS) ν_{max} 1190 cm^{-1}; ^{1}H NMR (270 MHz; DMSO-d_6) δ 7.49–7.41 (m, 2H, Ar), 7.41–7.31 (m, 3H, Ar), 2.42–2.28 (m, 2H, NaO_3SCH_2–), 1.35–1.18 (m, 8H, alk), 1.18–1.06 (m, 2H, $NaO_3SCH_2CH_2$–), 0.91–0.69 (m, 10H, alk) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 137.3, 134.5, 129.7, 128.5, 47.0 (NaO_3SCH_2–), 26.8, 26.3, 14.3 (H_3C–), 12.2, 8.5 ($NaO_3SCH_2CH_2$–) ppm; MS (FAB^-) m/z 327 $[M-Na]^-$.

4.3.9. Sodium 4-(dimethylphenylsilanyl)butane-1-sulfonate (15). A vigorously stirred biphasic suspension of Na_2SO_3 (6.6 g, 44.9 mmol), chlorobutylsilane **26** (2.4 g, 10.5 mmol) and NaI (0.8 g, 5.2 mmol) in H_2O (25 mL) and EtOH (15 mL) was heated at reflux. After 72 h, the mixture was allowed to cool to room temperature, extracted with Et_2O (3×30 mL) and the aqueous was concentrated to dryness. The resulting salts were extracted with EtOH (5×30 mL) and the resultant liquor was concentrated. The resulting salts were washed with acetone (3×10 mL) and dried under vacuum to afford sodium sulfonate **15** (1.6 g, 5.9 mmol, 56%) as a white solid: mp 186–190 °C (decomp.); IR (DRIFTS) ν_{max} 1193 cm^{-1}; ^{1}H NMR (270 MHz; DMSO-d_6) δ 7.54–7.41 (m, 2H, Ar), 7.41–7.28 (m, 3H, Ar), 2.48–2.35 (m, 2H, NaO_3SCH_2–), 1.68–1.49 (m, 2H, $NaO_3SCH_2CH_2$–), 1.38–1.20 (m, 2H, –CH_2CH_2Si), 0.76–0.61 (m, 2H, –CH_2Si), 0.22 (s, 6H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 139.4, 133.9, 129.4, 128.3, 51.7 (NaO_3SCH_2–), 29.4 ($NaO_3SCH_2CH_2$–), 23.5 (–CH_2CH_2Si), 15.6 (–CH_2Si), −2.4 (H_3C–Si) ppm; MS (FAB^-) m/z 271 $[M-Na]^-$.

4.3.10. Sodium 4-(dibutylphenylsilanyl)butane-1-sulfonate (16). A biphasic suspension of Na_2SO_3 (0.7 g, 5.6 mmol), (4-chlorobutyl)silane **27** (0.32 g, 1 mmol) in H_2O (1.5 mL) and EtOH (1.5 mL) was heated at 150 °C at 11,250 mmHg for 60 min using a microwave reactor. After cooling, the biphasic suspension was washed with Et_2O (3×5 mL) and the aqueous layer was concentrated to dryness. The resulting salts were extracted with EtOH (3×10 mL) and PrOH (3×10 mL) and the resultant combined liquors were concentrated to dryness to afford sodium sulfonate **16** (0.16 g, 0.42 mmol, 42%) as a white solid: mp 240–245 °C (decomp); IR (DRIFTS) ν_{max} 1190 cm^{-1}; ^{1}H NMR (270 MHz; DMSO-d_6) δ 7.48–7.39 (m, 2H, Ar), 7.37–7.27 (m, 3H, Ar), 2.52–2.39 (m, 2H, NaO_3SCH_2–), 1.71–1.53 (m, 2H, $NaO_3SCH_2CH_2$–), 1.39–1.12 (m, 10H, alk and $NaO_3SCH_2CH_2CH_2$–), 0.90–0.65 (m, 12H, alk and $NaO_3SCH_2CH_2CH_2CH_2$–) ppm; ^{13}C NMR (68 MHz; DMSO-d_6)

δ 137.8, 134.4, 129.5, 128.4, 51.9 (NaO_3SCH_2–), 29.7 ($NaO_3SCH_2CH_2$–), 26.8, 26.3, 23.6 ($NaO_3SCH_2CH_2CH_2$–), 14.3 (H_3C–), 12.6 ($NaO_3SCH_2CH_2CH_2CH_2$–), 12.3 ppm; MS (FAB$^-$) *m/z* 355 $[M-Na]^-$.

4.3.11. Disodium 4,4,6,6-tetramethyl-5-oxa-4,6-disilanonane-1,9-disulfonate (17). A vigorously stirred biphasic suspension of Na_2SO_3 (25.2 g, 200 mmol), (3-chloropropyl)methoxydimethylsilane **28** (6.68 g, 40.0 mmol) in H_2O (135 mL) was heated at reflux. After 96 h, the mixture was allowed to cool to room temperature, extracted with Et_2O (3×100 mL) and the aqueous was concentrated to dryness under vacuum. The resulting salts were extracted with EtOH (5×100 mL) and the resultant liquor was concentrated to dryness under vacuum to afford disodium disulfonate **17** (5.83 g, 13.8 mmol, 69%) as a white solid: mp>350 °C; IR (DRIFTS) ν_{max} 1213, 1184 cm^{-1}; ^1H NMR (270 MHz; D_2O) δ 3.11–2.96 (m, 4H, NaO_3SCH_2–), 2.00–1.84 (m, 4H, –CH_2–), 0.88–0.74 (m, 4H, –CH_2Si), 0.26 (s, 12H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; D_2O) δ 54.4 (NaO_3SCH_2–), 18.6 (–CH_2–), 16.3 (–CH_2Si), −1.00 (H_3C–Si) ppm; ^1H NMR (270 MHz; DMSO-d_6) δ 2.47–2.41 (m, 4H), 1.70–1.55 (m, 4H), 0.51–0.44 (m, 4H), −0.02 (s, 12H) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 55.4, 19.5, 18.0, 1.0 ppm; MS (FAB$^-$) *m/z* 399 $[M-Na]^-$, 319 $[M-SO_3Na]^-$.

4.3.12. Dibutylsilacyclobutane (18).[3] To a stirred suspension of Mg (1.54 g, 63.3 mmol) in Et_2O (20 mL) at room temperature was added dropwise a solution of 4-bromobutane (6.8 mL, 63.3 mmol) in Et_2O (10 mL) over 30 min so as to maintain a gentle reflux. After a further 3 h at room temperature, the solution of Grignard reagent was decanted from the remaining Mg and added dropwise to a solution of dichlorocyclobutasilane[10] (2.5 mL, 21.1 mmol) in Et_2O (18 mL) at room temperature over 30 min. The resulting mixture was stirred at room temperature for 48 h, aqueous NH_4Cl solution (40 mL) was added, the layers were separated and the aqueous layer was extracted with Et_2O (3×40 mL). The combined organics were dried over $MgSO_4$, concentrated and distilled under reduced pressure to afford silane **18** (3.4 g, 18.3 mmol, 87%) as a colourless oil: bp 104–108 °C/4 mmHg (lit.[1e] 63 °C/0.3 mmHg); IR (neat) ν_{max} 2929, 2872, 2858, 2798 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) δ 2.05 (quintuplet, 2H, ^3J=8.3 Hz, $Si(CH_2)_2CH_2$), 1.50–1.22 (m, 8H, –$CH_2CH_2CH_3$), 0.95 (t, 4H, ^3J=8.3 Hz, $Si(CH_2)_2CH_2$), 0.90 (t, 6H, ^3J=6.9 Hz, –CH_3), 0.80–0.61 (m, 4H, –$CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 26.5, 26.1, 18.5 ($Si(CH_2)_2CH_2$), 14.9 ($Si(CH_2)_2CH_2$), 13.9 (–CH_3), 12.2 ppm; MS (CI$^+$) *m/z* 202 $[M+NH_4]^+$.

4.3.13. Dimethylphenylvinylsilane (19). To a suspension of Mg (4.0 g, 165 mmol) and a crystal of iodine in Et_2O (20 mL) at room temperature, bromobenzene (1.2 mL, 11.5 mmol) was added dropwise over 20 min until decolouration was observed. The remaining bromobenzene (4.6 mL, 43.5 mmol) was added dropwise over 1 h to maintain a gentle reflux. After a further 1 h at room temperature, the solution of Grignard reagent was decanted from the remaining Mg and added dropwise over 1 h to a solution of chlorodimethylvinylsilane (7.1 mL, 50 mmol) in Et_2O (40 mL) at room temperature. After a further 16 h, aqueous NH_4Cl solution (40 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The organics were combined, dried over $MgSO_4$, concentrated and distilled under reduced pressure to give silane **19** (6.1 g, 2.3 mmol, 75%) as a colourless oil: bp 90–93 °C/40 mmHg (lit.[12] 82 °C/20 mmHg); IR (neat) ν_{max} 1592, 1249 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) δ 7.68–7.55 (m, 2H, Ar), 7.50–7.37 (m, 3H, Ar), 6.60 (dd, 1H, ^3J=14.5, 20.0 Hz, Si–C*H*=$CH_{cis}H_{trans}$), 6.13 (dd, 1H, ^2J=3.9 Hz, ^3J=14.5 Hz, Si–CH=$CH_{cis}H_{trans}$), 5.83 (dd, 1H, ^2J=3.9 Hz, ^3J=20.0 Hz, Si–CH=$CH_{cis}H_{trans}$), 0.43 (s, 6H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 138.6, 138.1, 134.0, 133.0, 129.1, 127.9, −2.8 (H_3C–Si) ppm; ^1H NMR (270 MHz; DMSO-d_6) δ 7.54–7.47 (m, 2H), 7.38–7.31 (m, 3H), 6.29 (dd, 1H, ^3J=14.5, 20.0 Hz), 6.04 (dd, 1H, ^2J=3.9 Hz, ^3J=14.5 Hz), 5.74 (dd, 1H, ^2J=3.9 Hz, ^3J=20.0 Hz), 0.32 (s, 6H); ^{13}C NMR (68 MHz; DMSO-d_6) δ 138.4, 138.2, 134.1, 133.4, 129.6, 128.3, -2.5 ppm; MS (CI$^+$) *m/z* 180 $[M+NH_4]^+$, 163 $[M+H]^+$.

4.3.14. Dibutylphenylvinylsilane (20). To a stirred suspension of Mg (7.3 g, 300 mmol) in Et_2O (60 mL) at room temperature, a solution of 4-bromobutane (16.1 mL, 150 mmol) in Et_2O (16 mL) was added dropwise over 1.5 h to maintain a gentle reflux. After a further 3 h at room temperature, the solution of Grignard reagent was decanted from the remaining Mg and added dropwise over 30 min to a solution of dichlorophenylvinylsilane[4] (10.2 mL, 50 mmol) in Et_2O (20 mL) at room temperature. After 48 h at room temperature, a saturated aqueous NH_4Cl solution (100 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3×100 mL). The organics were combined, dried over $MgSO_4$, concentrated and the residual oil was distilled under vacuum to afford silane **20** (10.5 g, 42 mmol, 85%) as a colourless oil: bp 120–125 °C/4 mmHg; IR (neat) ν_{max} 1593 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) δ 7.75–7.51 (m, 2H, Ar), 7.51–7.35 (m, 3H, Ar), 6.37 (dd, 1H, ^3J=14.8, 19.9 Hz, Si–C*H*=$CH_{cis}H_{trans}$), 6.19 (dd, 1H, ^2J=4.4 Hz, ^3J=14.8 Hz, Si–CH=$CH_{cis}H_{trans}$), 5.83 (dd, 1H, ^2J=4.4 Hz, ^3J=19.9 Hz, Si–CH=$CH_{cis}H_{trans}$), 1.53–1.28 (m, 8H, alk), 1.10–0.81 (m, 10H, alk) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 136.0, 134.4, 133.7, 133.7, 128.9, 127.7, 26.7, 26.0, 13.7 (H_3C–), 12.2 ppm; MS (EI$^+$) *m/z* 246 $[M]^{+\cdot}$, 189 $[M-C_4H_9]^{+\cdot}$; HRMS (EI$^+$) *m/z* calculated for $C_{16}H_{26}Si$ $[M]^{+\cdot}$ 246.1804, found 246.1792.

4.3.15. Dibutylmethoxyvinylsilane (22). To a stirred suspension of Mg (5.8 g, 240 mmol) in Et_2O (50 mL) at room temperature, a solution of 4-bromobutane (19.8 mL, 184 mmol) in Et_2O (25 mL) was added dropwise over 1.5 h. After a further 3 h at room temperature, the solution of Grignard reagent was decanted from the remaining Mg and added dropwise over 30 min to a solution of trimethoxyvinylsilane (12.2 mL, 80 mmol) in Et_2O (20 mL) at room temperature. The resulting beige suspension was stirred for a further 18 h at room temperature. The salts were filtered off and washed with petroleum ether (3×20 mL), the filtrate concentrated, petroleum ether (60 mL) was added and the resulting salts were filtered off and washed repeatedly with petroleum ether (3×20 mL). The combined filtrates were concentrated and distilled under reduced pressure to afford methoxysilane **22** (2.5 g, 12.2 mmol, 72%) as a colourless oil: bp 80–82 °C/4 mmHg; IR (neat) ν_{max} 1593 cm^{-1}; ^1H

NMR (270 MHz; $CDCl_3$) δ 6.06 (m, 1H), 6.04 (m, 1H), 5.77 (m, 1H), 3.44 (s, 3H, H_3C–O), 1.41–1.20 (m, 8H, alk), 0.96–0.76 (m, 6H, alk), 0.76–0.58 (m, 4H, alk) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 135.3, 133.9, 50.8 (H_3C–O), 26.5, 25.2, 13.8, 12.8 ppm; MS (CI^+) *m/z* 218 $[M+NH_4]^+$, 201 $[M+H]^+$, 186 $[M-MeOH+NH_4]^+$; HRMS (CI^+) *m/z* calculated for $C_{11}H_{28}NOSi$ $[M+NH_4]^+$ 218.1940, found 218.1942.

4.3.16. [4-(Dibutylvinylsilyl)benzyl]dimethylamine (23). To a suspension of Mg (2.3 g, 96.0 mmol) in THF (60 mL) under reflux, (4-bromobenzyl)dimethylamine (**21**)[6] (10.3 g, 48.0 mmol) was added dropwise over 2 h. After a further 30 min under reflux, methoxysilane **22** (4.8 g, 24.0 mmol) was added dropwise over 1 h. After a further 72 h at reflux, the reaction mixture was allowed to cool to room temperature and saturated aqueous NH_4Cl solution (60 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3×60 mL). The organics were combined, dried over $MgSO_4$, concentrated, and the volatiles were removed under reduced pressure (4 mmHg) to leave amine **23** (5.9 g, 19.4 mmol, 81%) as a yellow oil: IR (neat) ν_{max} 1601 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) δ 7.47 (d, 2H, ^3J=6.8 Hz, Ar), 7.27 (d, 2H, ^3J=6.8 Hz, Ar), 6.27 (dd, 1H, ^3J=10.6, 19.8 Hz, Si–C*H*=CH$_{cis}$H$_{trans}$), 6.12 (dd, 1H, ^2J=4.3 Hz, ^3J=10.6 Hz, Si–CH=CH$_{cis}$*H*$_{trans}$), 5.76 (dd, 1H, ^2J=4.3 Hz, ^3J=19.8 Hz, Si–CH=C*H*$_{cis}$H$_{trans}$), 3.41 (s, 2H, ArC*H*$_2$–), 2.22 (s, 6H, –N(C*H*$_3$)$_2$), 1.42–1.20 (m, 8H, alk), 0.95–0.78 (m, 10H, alk) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 139.5, 136.2, 135.3, 134.5, 133.7, 128.6, 64.5 (Ar*C*H$_2$–), 45.5 (–N(*C*H$_3$)$_2$), 26.7, 26.0, 13.8, 12.3 ppm; MS (CI^+) *m/z* 304 $[M+H]^+$; HRMS (CI^+) *m/z* calculated for $C_{19}H_{34}NSi$ $[M+H]^+$ 304.2461, found 304.2470.

4.3.17. [4-(Dibutylvinylsilyl)benzyl]trimethylammonium iodide (24). To a solution of amine **23** (5.8 g, 19.1 mmol) in EtOH (40 mL) at 0 °C, MeI (1.3 mL, 20.0 mmol) was added dropwise over 30 min. The solution was allowed to warm to room temperature and stirred for 48 h. To the resulting mixture was added Et_2O (60 mL) and the precipitate obtained was filtered off and washed with Et_2O (2× 30 mL). The residue was dried under vacuum for 4 h to give ammonium iodide **24** (6.7 g, 15.0 mmol, 78%) as a white solid: mp 195–196 °C (decomp.); IR (DRIFTS) ν_{max} 1591 cm^{-1}; ^1H NMR (270 MHz; DMSO-d_6) δ 7.61 (d, 2H, ^3J=7.8 Hz, Ar), 7.55 (d, 2H, ^3J=7.8 Hz, Ar), 6.25 (dd, 1H, ^3J=10.6, 19.8 Hz, Si–C*H*=CH$_{cis}$H$_{trans}$), 6.12 (dd, 1H, ^2J=4.4 Hz, ^3J=10.6 Hz, Si–CH=CH$_{cis}$*H*$_{trans}$), 5.76 (dd, 1H, ^2J=4.4 Hz, ^3J=19.8 Hz, Si–CH=C*H*$_{cis}$H$_{trans}$), 4.57 (s, 2H, ArC*H*$_2$–), 3.05 (s, 9H, –N^+(C*H*$_3$)$_3$), 1.40–1.13 (m, 8H, alk), 0.94–0.70 (m, 10H, alk) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 139.5, 135.8, 135.1, 135.1, 132.7, 129.6, 68.1 (Ar*C*H$_2$–), 52.4 (–N^+(*C*H$_3$)$_3$), 26.5, 26.0, 14.2, 11.9 ppm; MS (FAB^+) *m/z* 318 $[M-I]^+$; HRMS (FAB^+) *m/z* calculated for $C_{20}H_{36}NSi$ $[M-I]^+$ 318.2617, found 318.2633.

4.3.18. Sodium {2-[dibutyl-(*p*-trimethylammonium iodide)benzyl]silyl}ethane sulfonate (25). To a solution of Na_2SO_3 (6.1 g, 48.7 mmol) in H_2O (9 mL), an aqueous solution of HCl (4.1 mL, 12 M, 48.7 mmol) was added dropwise over 10 min. A solution of vinylsilane **24** (6.6 g, 14.8 mmol) in MeOH (9 mL) was added dropwise over 5 min followed by *t*-butylbenzoic peroxide (250 μL, 0.4 mmol). The resulting mixture was heated at reflux. After 72 h, the mixture was allowed to cool to room temperature, washed with Et_2O, and concentrated to dryness. The resulting salts were extracted with EtOH (5×20 mL) and the resultant liquor was concentrated to dryness to afford sodium sulfonate **25** (4.8 g, 8.9 mmol, 60%) as a white solid: mp >350 °C; IR (DRIFTS) υ_{max} 1193 cm^{-1}; ^1H NMR (270 MHz; DMSO-d_6) δ 7.72–7.50 (m, 4H, Ar), 4.56 (s, 2H, ArC*H*$_2$–), 3.03 (s, 9H, –N^+(C*H*$_3$)$_3$), 2.43–2.30 (m, 2H, NaO_3SCH_2–), 1.41–1.21 (m, 8H, alk), 1.22–1.13 (m, 2H, $NaO_3SCH_2CH_2$–), 0.93–0.69 (m, 10H, alk) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 139.9, 134.8, 132.7, 129.4, 68.1 (Ar*C*H$_2$–), 52.4 (–N^+(*C*H$_3$)$_3$), 46.8 (NaO_3SCH_2–), 26.5, 26.0, 14.1 (H_3CCH_2–), 11.8, 8.1 ($NaO_3SCH_2CH_2$–) ppm; MS (FAB^+) *m/z* 422 $[M-I]^+$; HRMS (FAB^+) *m/z* calculated for $C_{20}H_{37}NO_3NaSiS$ $[M-I]^+$ 422.2179, found 422.2161.

4.3.19. Dimethyl(4-chlorobutyl)phenylsilane (26). To a solution of *t*-BuLi (39.5 mL, 1.55 M in pentane, 60.8 mmol) in Et_2O (20 mL) at −78 °C, 1-chloro-4-iodobutane[11] (3.8 mL, 30.4 mmol) was added dropwise over 5 min, and the solution was stirred for a further 1 h. A solution of chlorodimethylphenylsilane (4.2 mL, 25.3 mmol) in Et_2O (20 mL) was added dropwise over a 10 min period. The resulting solution was allowed to warm to room temperature and stirred for 16 h. Aqueous NH_4Cl solution (40 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3×40 mL) and the combined organics were washed with brine (60 mL), dried over $MgSO_4$, concentrated and distilled to afford (4-chlorobutyl)silane **26** (4.9 g, 21.5 mmol, 85%) as a colourless oil: bp 138–140 °C/4 mmHg (lit.[13] bp 87–89 °C/1 mmHg); ^1H NMR (270 MHz; $CDCl_3$) δ 7.63–7.47 (m, 2H, Ar), 7.46–7.32 (m, 3H, Ar), 3.54 (t, 2H, ^3J=6.7 Hz, ClC*H*$_2$–), 1.81 (quintuplet, 2H, ^3J=6.7 Hz, $ClCH_2CH_2$–), 1.58–1.40 (m, 2H, –C*H*$_2$-CH_2Si), 0.86–0.72 (m, 2H, –C*H*$_2$Si), 0.31 (s, 6H, H_3C–Si) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 139.2, 133.6, 129.0, 127.9, 44.7, 36.2, 21.3, 15.1, −3.0 ppm; ^1H NMR (270 MHz; DMSO-d_6) δ 7.57–7.40 (m, 2H), 7.40–7.24 (m, 3H), 3.55 (t, 2H, ^3J=6.6 Hz), 1.68 (quintuplet, 2H, ^3J=6.6 Hz), 1.51–1.24 (m, 2H), 0.78–0.62 (m, 2H), 0.21 (s, 6H) ppm; ^{13}C NMR (68 MHz; DMSO-d_6) δ 139.1, 133.8, 129.4, 128.3, 45.4, 36.1, 21.2, 14.8, −2.5 ppm; MS (CI^+) *m/z* 246 and 244 $[M+NH_4]^+$; MS (EI^+) *m/z* 213 and 211 $[M-CH_3]^{+\cdot}$, 135 $[M-C_4H_8Cl]^{+\cdot}$, 172 and 170 $[M-C_4H_8]^{+\cdot}$, 157 and 155 $[M-C_5H_{11}]^{+\cdot}$.

4.3.20. Dibutyl(4-chlorobutyl)phenylsilane (27). To a solution of *t*-BuLi (43.8 mL, 1.60 M in pentane, 70.0 mmol) in Et_2O (20 mL) at −78 °C, 1-chloro-4-iodobutane[11] (4.25 mL, 35.0 mmol) was added dropwise over 5 min. After a further 1 h, silylsulfonate **29** (11.7 g, 31.8 mmol) was added dropwise over 10 min. The solution was allowed to warm to −20 °C and *N*′,*N*′,*N*,*N*-tetramethylethane-1,2-diamine (10.4 mL, 70.0 mmol) was added dropwise over 5 min. The solution was allowed to warm to room temperature and stirred for a further 32 h. Aqueous NH_4Cl solution (60 mL) was added, the layers were separated and the aqueous layer was extracted with Et_2O (3×60 mL). The combined organics were washed with an aqueous HCl solution (3×150 mL, 2 M), brine (150 mL),

dried over $MgSO_4$ and concentrated to afford (4-chlorobutyl)silane **27** (9.3 g, 30 mmol, 94%) as a light yellow oil: IR (neat) ν_{max} 3068, 3049, 2956, 2924, 2858 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) δ 7.52–7.44 (m, 2H, Ar), 7.40–7.31 (m, 3H, Ar), 3.52 (t, 2H, $^3J=7.0$ Hz, $ClCH_2$–), 1.79 (quintuplet, 2H, $^3J=7.0$ Hz, $ClCH_2CH_2$–), 1.54–1.40 (m, 2H, $ClCH_2CH_2CH_2$–), 1.40–1.15 (m, 8H, alk), 0.99–0.72 (m, 12H, alk and $ClCH_2CH_2CH_2CH_2$–) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 137.7, 134.1, 128.8, 127.8, 44.6 ($ClCH_2$–), 36.4 ($ClCH_2CH_2$–), 26.8, 26.1, 21.2 ($ClCH_2CH_2CH_2$–), 13.8, 12.1, 11.8 ($ClCH_2CH_2CH_2CH_2$–) ppm; MS (CI^+) *m/z* 330 and 328 $[M+NH_4]^+$; HRMS (CI^+) *m/z* calculated for $C_{18}H_{35}NSi^{35}Cl$ $[M+NH_4]^+$ 328.2227, found 328.2226; HRMS (CI^+) *m/z* calculated for $C_{18}H_{35}NSi^{37}Cl$ $[M+NH_4]^+$ 330.2198, found 330.2211.

4.3.21. Dibutylphenylsilyl trifluoromethanesulfonate (29). To stirred neat dibutyldiphenylsilane[8] (10.9 mL, 35.0 mmol) at −20 °C, trifluoromethylsulphonic acid (2.81 mL, 31.8 mmol) was added dropwise over 10 min. The resulting mixture was allowed to warm to room temperature and stirred for a further 4 h to afford silylsulfonate **29** (11.7 g, 31.8 mmol, 100%) as a light orange oil: ^1H NMR (270 MHz; $CDCl_3$) δ 7.76–7.66 (m, 2H, Ar), 7.66–7.45 (m, 3H, Ar), 1.63–1.37 (m, 8H, alk), 1.10–0.98 (m, 10H, alk) ppm; ^{13}C NMR (68 MHz; $CDCl_3$) δ 135.0, 133.8, 131.6, 128.4, 118.6 (q, $^1J_{CF}=318$ Hz, CF_3), 26.2, 24.4, 13.5, 13.3 ppm; MS (EI^+) *m/z* 368 $[M]^{+\cdot}$, 311 $[M-C_4H_9]^{+\cdot}$, 181 $[M-C_4H_9\text{-}F_3CSO_3+F]^{+\cdot}$, HRMS ($EI^+$) calculated for $C_{15}H_{23}O_3F_3SSi$ $[M]^{+\cdot}$ 368.1089, found 368.1095.

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References and notes

1. See, for example, trimethylsilyl trifluoromethanesulphonate Sweeney, J.; Perkins, G. In Paquette, L. A., Ed.; Encyclopaedia of reagents for organic synthesis; Wiley: New York, 1995; Vol. 7, pp 5315–5319.
2. (a) Dubac, J.; Mazerolles, P. *Bull. Soc. Chim. Fr.* **1969**, 3608–3609. (b) Dubac, J.; Mazerolles, P. *J. Organomet. Chem.* **1969**, *20*, P5–P6. (c) Dubac, J.; Mazerolles, P.; Joly, M. *J. Organomet. Chem.* **1970**, *22*, C7–C8. (d) Dubac, J.; Mazerolles, P.; Lesbre, M.; Joly, M. *J. Organomet. Chem.* **1970**, *25*, 367–384. (e) Dubac, J.; Mazerolles, P.; Joly, M. *J. Organomet. Chem.* **1978**, *153*, 289–298. (f) Grignon-Dubois, M.; Dunogues, J.; Duffaut, N.; Calas, R. *J. Organomet. Chem.* **1980**, *188*, 311–319.
3. (a) Matsumoto, K.; Mizuno, U.; Matsuoka, H.; Yamaoka, H. *Macromolecules* **2002**, *35*, 555–565. (b) Matsumoto, K.; Aoki, Y.; Oshima, K.; Utimoto, K.; Rahman, N. A. *Tetrahedron* **1993**, *49*, 8487–8502.
4. Scott, R. E.; Frisch, K. C. *J. Am. Chem. Soc.* **1951**, *73*, 2599–2600.
5. Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099–2102.
6. Bhattacharyya, S. *Synth. Commun.* **2000**, *30*, 2001–2008.
7. Negishi, E.-i.; Swanson, D.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406–5409.
8. Topchiev, A. V.; Nametkin, N. S.; Gu, C.-L.; Leonova, N. A. *Dolk. Akad. Nauk. SSSR* **1958**, *118*, 731–734.
9. Matyjaszewski, K.; Chen, Y. L. *J. Organomet. Chem.* **1988**, *340*, 7–12.
10. Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026–7043.
11. Hahn, R. C. *J. Org. Chem.* **1988**, *53*, 1331–1333.
12. Aldrich Catalogue Handbook of Fine Chemicals.
13. Wilt, J. W.; Dockus, C. F. *J. Am. Chem. Soc.* **1970**, *92*, 5813–5814.

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A borderline case between *meso* and stable C_1: an axially chiral, yet configurationally semi-stable biphenyl with two oppositely configured [10]paracyclophane portions

Gerhard Bringmann,[a,*] Tobias A. M. Gulder,[a] Katja Maksimenka,[a] Dirk Kuckling[b,†] and Werner Tochtermann[b,*]

[a]*Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany*
[b]*Institut für Organische Chemie, Universität Kiel, Olshausenstraße 40, D-24098 Kiel, Germany*

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Abstract—The synthesis of the bi[10]paracyclophanes **2** and **4** from the *meso*-configured bioxepine **3** is described. These compounds are stereochemically remarkable: the biaryl axis that connects the constitutionally identical, but oppositely configured planar-chiral paracyclophane portions, is configurationally semi-stable. Thus, **2** is an unprecedented borderline case of a (planar-chiral)–(axially chiral)–(planar-chiral) molecule that is right in between a *meso*-compound (as a macroscopical result of the—albeit slow—rotation about the central C,C-bond) and C_1-symmetry (with respect to the existence of separable—even though configurationally unstable—discrete atropo-enantiomers). Despite their restricted configurational stability, these atropo-enantiomers were resolved on a chiral phase at 5 °C and were stereochemically assigned by LC–CD coupling, in combination with quantum chemical CD calculations.

1. Introduction

meso-Compounds are interesting from both, stereochemical[1,2] and synthetic,[3] points of view. They are constitutionally symmetric molecules with pairwise stereogenic elements, but of opposite configurations. In most cases they possess a conformation with a plane or a center of symmetry, however, examples containing only asymmetric (C_1) conformations have also been discussed.[4] *meso*-Compounds are optically inactive. This characteristic property is often a result of rapidly interconverting enantiomeric conformers in mobile systems.[1–4] For example, it has been shown that *meso*-tartaric acid prefers chiral conformations in solution[5] and in the crystalline state,[6] which equilibrate rapidly in solution, because of their low rotational barriers around the central C,C-bond.

In a previous study,[7,8] we reported on the synthesis of the bi[10]paracyclophane (−)-**1** in enantiomerically pure form. This constitutionally symmetric compound is optically active because of hindered rotation around the central biaryl axis. Therefore, (−)-**1** has three stereogenic elements, two chiral planes and one chiral axis. Its absolute (p*P*,a*P*,p*M*)-configuration was determined by quantum chemical calculation of the circular dichroism (CD) spectrum and comparison with the experimental one.[7,8] According to textbook definitions,[1,2] (−)-**1** is not a *meso*-compound, since it is chiral, configuratively stable at the chiral axis, and non-racemic and thus, optically active. With these results in mind, we envisaged a more mobile molecule with a structure similar to **1**, but with dynamic and thus, chiroptical properties on the border-line between an optically inactive *meso*-compound and a chiral compound. In this paper, we report on the synthesis, the intramolecular mobility and the chiroptical behavior of the title compound **2**, which consists of two atropo-enantiomers, **2a** and **2b**, slowly interconverting at room temperature (Scheme 1).

2. Results and discussion

2.1. Synthesis of 2

In order to obtain an analog of (−)-**1** that is conformationally more mobile, it was obvious to replace the two methoxy

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* Corresponding authors. Tel.: +49 931 888 5323; fax: +49 931 888 4755 (G.B.); fax: +49 6398 993172 (W.T.);
e-mail: bringman@chemie.uni-wuerzburg.de
† Present address: Institut für Makromolekulare Chemie und Textilchemie, Technische Universität Dresden, D-01062 Dresden, Germany

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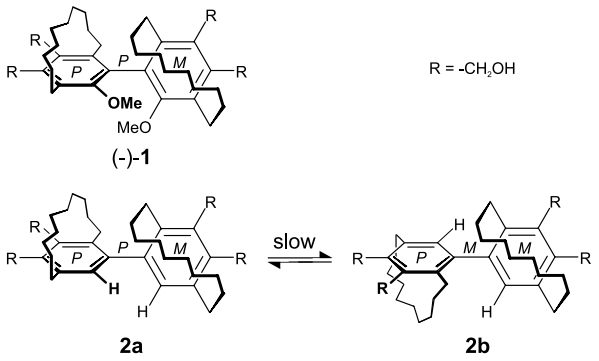
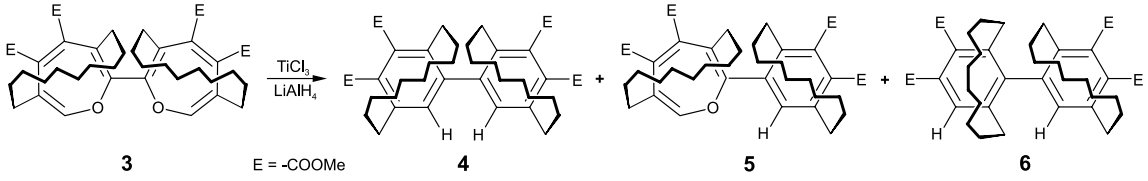


Scheme 1. The optically active bi[10]paracyclophane (−)-**1**, and its configurationally semi-stable analog **2a/b**.

groups in the *ortho*-positions of the biphenyl system of (−)-**1** by hydrogen atoms,[2] making **2** a rewarding target molecule. This new biparacyclophane system was prepared by deoxygenation of the earlier described *meso*-configured bi[10]oxepine **3**.[7,8]

Our previous studies in the paracyclophane field[9] had shown that oxepines that exist predominantly as their seven-membered ring valence tautomer[10] can be deoxygenated by a modified McMurry reagent.[11] At first, titanium trichloride was exposed to dry air until the color had changed from violet to yellow, then tetrahydrofuran, lithium aluminum hydride, and finally, **3** in the same solvent were added. After heating for 4 h, the run was quenched and the resulting mixture was subjected to column chromatography. This procedure led to the formation of three different compounds, the desired bi[10]paracyclophane **4** (32%), the mono-deoxygenated oxepine **5** (24%), and the metaparacyclophane **6** (16%), which were characterized by their analytical and spectroscopic data (for details, see Section 4) (Scheme 2).



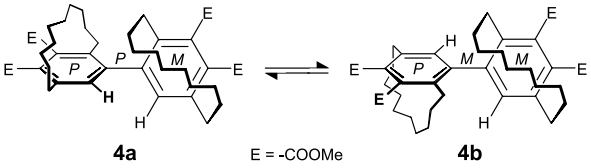
Scheme 2. Synthesis of the biparacyclophanes **4**, **5**, and **6**.

An assignment of the NMR signals of **5** was possible by comparison with those of **3** and **4**. The migration of one decamethylene chain in **6** to give a metaparacyclophane was deduced from differences between **4** and **6**. Thus, the aryl proton of **6** in *ortho*-position next to a methoxycarbonyl group showed a chemical shift of $\delta=7.65$ ppm, which is more downfield than the corresponding signals of **4** ($\delta=$ 6.95 and 7.45 ppm). Moreover, selective $^{1}H,^{13}C$-decoupling experiments hinted at one 2,3- and one 3,4-position of the ester groups relative to the aryl protons. In earlier experiments, we had observed similar isomerizations of a [6]paracyclophane with the same reagent.[12] Obviously the titanium species used here, can react as Lewis acids.

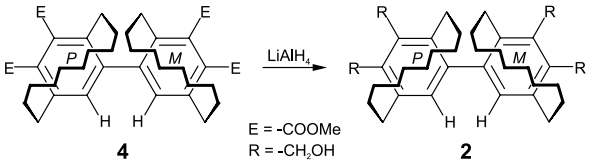
The ^{1}H NMR spectra of **4** with two singlets at $\delta=6.95$ and 7.45 ppm for the aryl protons, eight ddd-signals for the benzylic protons in the decamethylene chains, and the ^{13}C NMR spectra with the (nearly) full set of 40 carbon atoms provided evidence of an axially chiral conformation in the molecule. Thus, **4** prepared from the *meso*-configured oxepine **3** is racemic at ambient temperature, so that three elements of chirality have to be considered: two chiral planes with (p*M*)- and (p*P*)-configuration and one chiral axis. With the aim to get insight into the intramolecular mobility of **4** and hence into the enantiomerization **4a** ⇄ **4b**, 80 MHz ^{1}H NMR spectra in $C_2D_2C1_4$ were taken at higher temperatures (Scheme 3).

The sharp singlets of the two aryl protons of **4** were broadened at higher temperatures and showed coalescence at 143 °C. With $\nu_a-\nu_b=38.06$ Hz at 30 °C and $T_c=416$ K, a rate constant of k (416 K) = 84.5 s^{-1} and a free activation enthalpy of $\Delta G^{\neq}$ (416 K) = 87 kJ/mol were calculated.[13] Provided that the entropy of activation is near zero, a half-life time of ca. 3 min at 25 °C was estimated. These results indicated that a resolution of the enantiomeric conformations of **4** and the observation of their chiroptical properties should be possible at lower temperatures.

For this purpose (and because of its easier enantiomeric resolution, see below), we chose the tetrakis(hydroxymethyl) derivative **2** in consideration of its structural similarity (and, thus, better chiroptical comparability) with (−)-**1**, for which we had previously assigned the absolute configuration, by a combination of experimental and computational CD investigations.[7,8] This tetraol **2** was obtained by reduction of **4** with lithium aluminum hydride in 64% yield. According to its NMR spectra, **2** also occupies non-symmetric conformations, so that two possible enantiomers, **2a** and **2b**, had to be separated. The compound



Scheme 3. Enantiomerization **4a** ⇄ **4b** by rotation around the central biaryl axis.



Scheme 4. Synthesis of the target molecule **2**.

showed two different aryl protons at $\delta = 6.57$ and 7.20 ppm, four different hydroxyl protons at $\delta = 5.00$, 5.04, 5.10, and 5.17 ppm (in DMSO-d_6) and the (nearly) full set of 36 carbon atoms (Scheme 4).

2.2. Stereochemical analysis

For the stereochemical analysis of bi[10]paracyclophanes of the shown type, a method for the enantiomeric resolution on a chiral reversed phase was developed, starting with a racemic mixture of **1**,[8] since, this compound was configurationally stable and thus, more likely to be separable. Moreover, its (p*P*,a*P*,p*M*)-enantiomer, (−)-**1**, had previously been prepared in an enantiomerically pure form[7,8] and had been stereochemically assigned by quantum chemical CD calculations.[8] The best results were obtained using a Chiralcel OD-RH column (Daicel) at slightly elevated temperature (30 °C, Fig. 1a). That the two observed peaks indeed corresponded to the expected atropo-enantiomers of **1** was verified by their online circular dichroism (CD) analysis. This HPLC–CD coupling, which had previously been established[25] and introduced into phytochemical analysis,[14–17] resulted in almost opposite CD spectra for the two peaks, evidencing the existence of enantiomers.

The above developed separation method was then applied to the analysis of racemic **2**. Apparently due to the low rotational barrier at the central axis of **2**, the separation was most unsatisfactory at room temperature, making it necessary to perform the resolution at lower temperature (5 °C, Fig. 1b). Despite the structural similarity of **1** and **2**, their chromatographic behaviors were inverse, the enantiomer with the negative cotton effect now being the faster one, although, the CD spectra of **2** as such were very similar to those of **1**. This, in analogy to the axial configuration already determined for (−)-**1**,[8] permitted to assign the (p*P*,a*P*,p*M*)-configuration to the slower enantiomer of **2** (peak **B**), which has a positive cotton effect, and the (p*P*,a*M*,p*M*)-configuration to the faster one (peak **A**).

For the determination of the half-life ($t_{1/2}$) of the racemization process at the biaryl axis of **2**, the decrease of the CD curve of peak **A** directly after separation was monitored. Because of the relatively unstable axial configuration and therefore, fast vanishing of the CD effect, the time for scanning the CD spectrum had to be reduced dramatically. This was achieved by minimizing the spectral width down to 30 nm (from 200 to 230 nm). On the basis of these experiments, a $t_{1/2}$ of ca. 70 s at room temperature was estimated.

For a further robust confirmation of the stereochemical assignment, quantum chemical CD calculations of the two atropo-enantiomers of **2** were performed.[18,19] Since the CD curve of a compound strongly depends on the molecular geometry, the experimental CD spectrum has to be considered as the averaged overall CD behavior of all relevant conformational species. To obtain these minimum geometries, bi[10]paracyclophane (**2**) was submitted to a conformational analysis using the semiempirical AM1[20] method, arbitrarily starting with the (p*P*,a*P*,p*M*)-enantiomer.

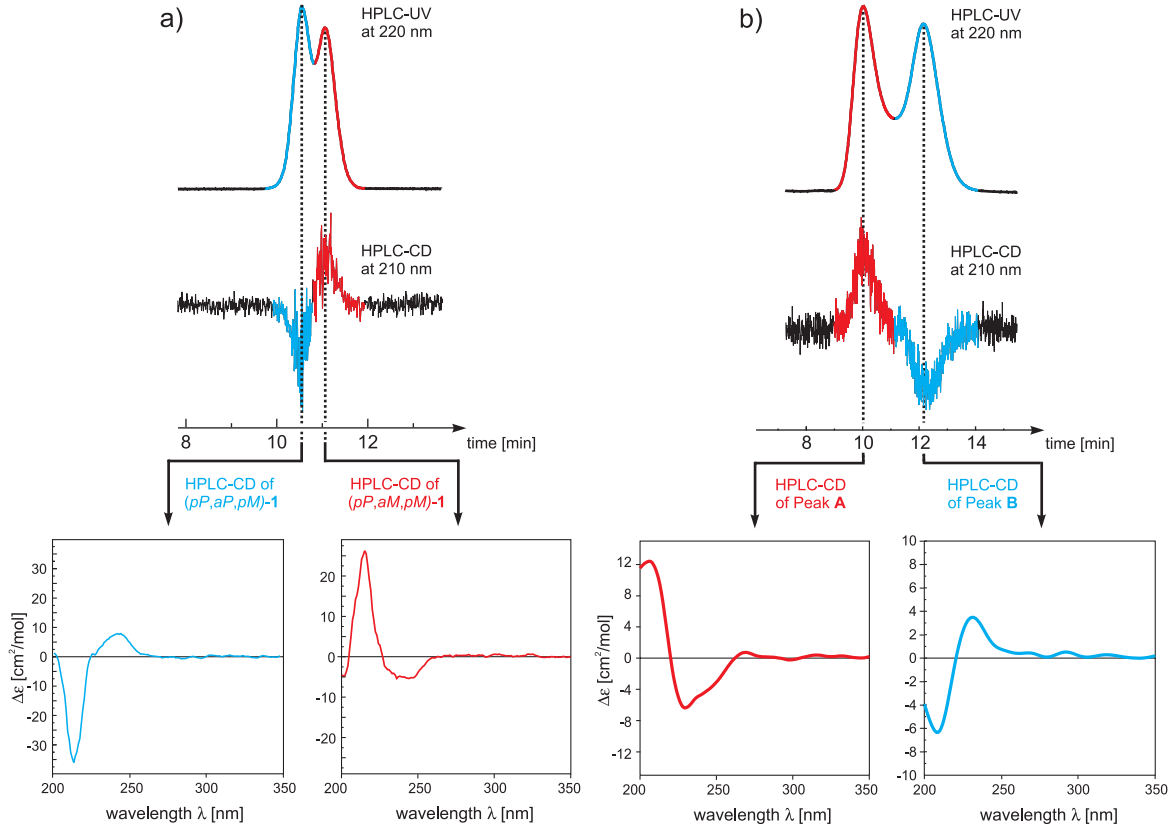


Figure 1. Resolution of enantiomeric mixtures of **1** (a) and **2** (b) by HPLC on a Chiralcel OD-RH reversed phase column; the respective atropo-enantiomers with (p*P*,a*P*,p*M*)-configuration are shown in blue, the (p*P*,a*M*,p*M*)-enantiomers in red.

Expectedly, **2** was found to possess a rotationally more flexible biaryl axis in comparison to **1**, and thus, the dihedral angle at the axis varied from 94 to 104° (in **1**: from 88 to 94°). Assuming that the highly flexible alkylidene bridges do not have a significant influence on the overall CD spectrum, the conformational analysis was concentrated on the hydroxymethyl substituents, which revealed strong hydrogen bondings (d_{H-O} ca. 2.15 Å) to each other (Fig. 2). The oxygen atoms were preferably located above or below the plane of the corresponding phenyl ring.

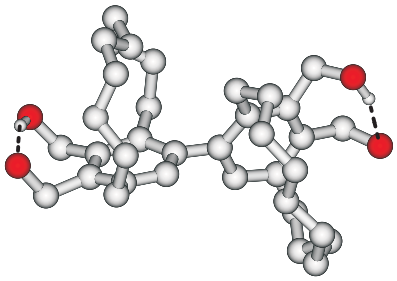


Figure 2. Hydrogen bonds in the global minimum conformer.

In the conformational analysis 240 structures were found within an energetic cut-off of 3 kcal/mol. For these compounds, the single CD curves were computed by using the semiempirical CNDO-S[21] method. The CD spectra thus obtained were then added up according to the respective energies by following the Boltzmann statistics, to give the overall theoretical CD curve predicted for of (p*P*,a*P*,p*M*)-**2**. Reflection of the spectrum at the zero line produced the calculated CD curve for the (p*P*,a*M*,p*M*)-enantiomer of **2**. The comparison of these predicted CD spectra with the measured ones allowed us to attribute the absolute configuration of the two atropo-enantiomers. As can be seen in Figure 3, the experimental CD curve of the more rapidly eluting peak **A** shows a good agreement with the spectrum calculated for the (p*P*,a*M*,p*M*)-enantiomer of **2**, while that one of the slower peak **2** matches well with the CD spectrum predicted for p*P*,a*P*,p*M*, thus, permitting assignment of the peak **A** to correspond to (p*P*,a*M*,p*M*)-**2** and peak **B** to (p*P*,a*P*,p*M*)-**2** (Fig. 3).

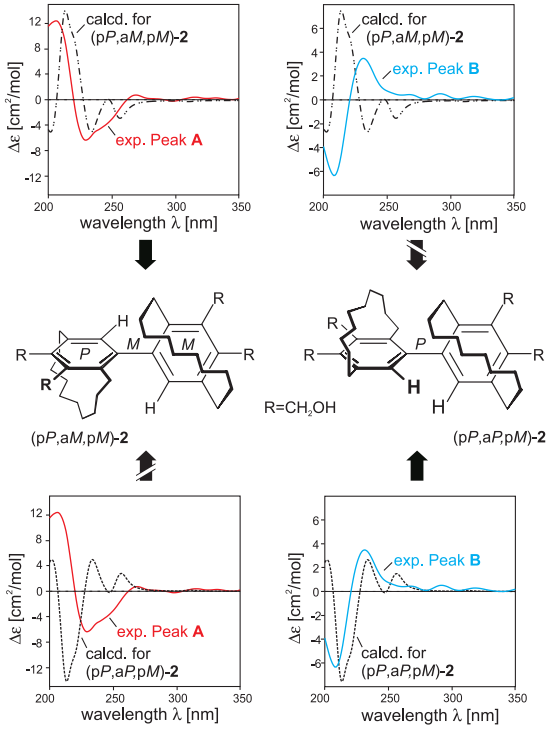


Figure 3. Assignment of the absolute configuration of the two atropo-enantiomers of **2** by comparison of the calculated CD spectra with the experimental curves.

3. Conclusion

In this paper, we describe the synthesis of novel bridged bi[10]paracylophanes **2** having, macroscopically, structural properties right in between *meso* and C_1. These biphenylic molecules consist of two planar-chiral units of identical constitution but of opposite configuration. The linking axis, however, has an only medium-sized rotational barrier, which thus, leads to the occurrence of configuratively semi-stable, slowly interconverting ($t_{1/2}$ ca. 70 s)—and, thus, just separable enantiomers. The online HPLC–CD analysis clearly proved these isomers to be enantiomers and, combined with quantum chemical CD calculations, provided a method for their full stereochemical assignment.

4. Experimental

4.1. General aspects

IR: Perkin-Elmer FTIR 1600. UV: Zeiss DMR 10. $^1H/^{13}C$ NMR: Bruker WP 80, AC 200 P, AM 300; TMS int. standard. Assignments marked with *, **, etc. may be exchanged. MS: Finnigan MAT 8230; direct inlet (El: 70 eV; Cl isobutane). Column Chromatography (CC): Baker Silica gel 40–60 µm. TLC: Macherey-Nagel SIL G/UV$_{254}$. CD: Jasco J-715. Melting points (uncorrected): Büchi 510. Elemental Analyses: Mikroanalytisches Laboratorium Ilse Beetz; D-96301 Kronach. All solvents and reagents were purified and dried according to common procedures. Reactions with hydrides were performed under an argon or nitrogen atmosphere.

4.2. Synthesis of bi[10]paracyclophanes

4.2.1. Tetramethyl(p*M*,p*P*)-2,5; 2′,5′-didecano-biphenyl-3,3′,4,4′-tetracarboxylate (4), dimethyl(p*M,p*M*′*)-3,6-decano-2-(2′,5′-decano-3′,4′-dimethoxycarbonyl-phenyl)-oxepine-4,5-dicarboxylate (5), and tetramethyl-(p*M**,p*P*′*)-2,5;2′,6′-didecano-biphenyl-3,3′,4,4′-tetra-carboxylate (6).** Titanium trichloride (1.3 g, 8.4 mmol) was exposed to dry air in a flask for 16 h. The color changed from violet to yellow. Tetrahydrofuran (20 mL) was added and the yellow suspension was stirred at room temperature for 30 min. After cooling with ice, lithium aluminum hydride (100 mg, 2.63 mmol) was added. The reaction mixture became black and hydrogen was evolved. The suspension was stirred for 15 min and a solution of **3** (298 mg, 0.43 mmol)[7,8] in 11 mL tetrahydrofuran was added dropwise. After heating under reflux for 4 h the reaction was quenched with 20 mL water under ice-cooling and diethyl ether was added. Column chromatography of the

residue of the organic layer after usual work-up on silica gel with diethyl ether/pentane (1:1) provided at first, (R_F=0.36) **6** (45 mg, 16%), then (R_F=0.31) **4** (91 mg, 32%), and finally, (R_F=0.29) **5** (71 mg, 24%).

Compound **4**. Pale yellow non-crystalline solid. IR (KBr): ν=2920, 2855 (CH_2); 1732 (C=O); 1580 (–C=C) cm^{-1}. UV (C_2H_5OH): λ_{max} (log ε)=219 (4.72), 296 (3.67) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.46–0.69 (m, 6H, CH_2), 0.73–1.98 (m, 26H, CH_2), 2.15 (ddd, ^2J=13.9 Hz, ^3J=8.0, 5.0 Hz, 1H, CH_2), 2.50 (ddd, ^2J=13.4 Hz, ^3J=8.0, 5.1 Hz, 1H, CH_2), 2.64 (ddd, ^2J=13.2 Hz, ^3J=6.6, 5.0 Hz, 1H, CH_2), 2.78 (ddd, ^2J=13.9 Hz, ^3J=7.3, 4.9 Hz, 1H, CH_2), 2.85 (ddd, ^2J=13.9 Hz, ^3J=11.2, 5.6 Hz, 1H, CH_2), 2.99 (ddd, ^2J=13.2 Hz, ^3J=7.1, 4.9 Hz, 1H, CH_2), 3.15 (ddd, ^2J=13.4 Hz, ^3J=8.8, 4.7 Hz, 1H, CH_2), 3.22 (ddd, ^2J=13.9 Hz, ^3J=5.6, 4.2 Hz, 1H, CH_2), 3.86 (s, 3H, OCH_3), 3.88 (s, 9H, 3 OCH_3), 6.95 (s, 1H, aryl-H), 7.45 (s, 1H, aryl-H) ppm. ^1H NMR ($C_2D_2Cl_4$, 80 MHz, 30 °C): δ=0.2–3.4 (m, CH_2), 3.9 (s, OCH_3), 7.0 (s, aryl-H), 7.5 (s, aryl-H) ppm. ^1H NMR ($C_2D_2Cl_4$, 80 MHz, 143 °C): δ=0.5–3.4 (m, CH_2), 3.9 (s, OCH_3), 4.0 (s, OCH_3), 7.2 (s, broad, aryl-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.36 (t, CH_2), 25.51 (t, CH_2), 25.87 (t, CH_2), 25.98 (t, CH_2), 27.03 (t, CH_2), 27.24 (t, CH_2), 27.26 (t, CH_2), 27.79 (t, CH_2), 27.87 (t, CH_2), 28.27 (t, $2CH_2$), 28.33 (t, CH_2), 28.45 (t, CH_2), 28.88 (t, CH_2), 28.91 (t, CH_2), 29.56 (t, CH_2), 29.84 (t, $2CH_2$), 32.83 (t, $2CH_2$), 52.34 (q, $2OCH_3$), 52.41 (q, $2OCH_3$), 131.34* (s, C-2′), 132.26* (s, C-2), 133.22* (s, C-5′), 133.44** (d, C-6′), 134.18* (s, C-5), 135.05** (d, C-6), 137.64*** (s, C-4), 138.54*** (s, C-4), 138.81*** (s, C-3′), 139.08*** (s, C-3), 142.62**** (s, C-1′), 143.47**** (s, C-1), 168.25 (s, *C*$OOCH_3$), 168.32 (s, *C*$OOCH_3$), 168.78 (s, *C*$OOCH_3$), 168.85 (s, *C*$OOCH_3$) ppm. MS (EI): *m/z* (%)=662 (M^+, 5). Calcd for: $C_{40}H_{54}O_8$ (662.89): C, 72.48; H 8.21. Found: C, 72.19; H 8.31.

Compound **5**. Mp 169–170 °C (diethyl ether/pentane). IR (KBr): ν=2925, 2855 (CH_2); 1733, 1729 (C=O); 1260 (=C–O) cm^{-1}. UV (C_2H_5OH): λ_{max} (log ε)=212 (4.53), 300 (3.71) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.39–0.68 (m, 4H, CH_2), 0.77–1.85 (m, 27H, CH_2), 1.98–2.11 (m, 1H, CH_2), 2.20–2.60 (m, 4H, CH_2), 2.92–3.15 (m, 4H, CH_2), 3.80 (s, 6H, OCH_3), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.15 (d, ^4J=0.7 Hz, 1H, oxepine-H), 7.31 (s, 1H, aryl-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.49 (t, CH_2), 25.77 (t, CH_2), 26.53 (t, $2CH_2$), 26.78 (t, CH_2), 26.95 (t, $2CH_2$), 27.14 (t, CH_2), 27.29 (t, CH_2), 27.74 (t, $2CH_2$), 28.51 (t, $2CH_2$), 28.62 (t, $2CH_2$), 28.77 (t, CH_2), 29.50 (t, $2CH_2$), 30.76 (t, CH_2), 33.03 (t, CH_2), 52.36 (q, $2OCH_3$), 52.43 (q, $2OCH_3$), 127.69 (s, 2oxepine-C), 132.35 (s, aryl-C), 133.38 (s, aryl-C), 133.91 (d, C-6′), 134.13 (s, oxepine-C), 135.26 (s, aryl-C), 135.41 (s, oxepine-C′), 137.74 (s, aryl-C), 138.91 (s, oxepine-C), 143.48 (s, aryl-C), 146.46 (d, C-7), 166.91 (s, *C*$OOCH_3$), 167.13 (s, *C*$OOCH_3$), 168.04 (s, *C*$OOCH_3$), 168.49 (s, *C*$OOCH_3$) ppm. MS (EI): *m/z* (%)=678 (M^+, 15). Calcd for: $C_{40}H_{54}O_9$ (678.89): C, 70.77; H, 8.02. Found: C, 70.72; H, 7.96.

Compound **6**. Mp 137–138 °C (diethyl ether/pentane). IR (KBr): ν=2925, 2855 (CH_2); 1727 (C=O); 1585 (–C=C) cm^{-1}. UV (C_2H_5OH): λ_{max} (log ε)=216 (4.67), 297 (3.67) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.29–1.88 (m, 32H, CH_2), 2.32–2.60 (m, 2H, CH_2), 2.65–3.13 (m, 6H, CH_2), 3.53 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 7.17 (s, 1H, H-6), 7.65 (s, 1H, H-5′) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=22.94 (t, CH_2), 22.98 (t, CH_2), 24.91 (t, CH_2), 25.54 (t, CH_2), 26.98 (t, CH_2), 27.26 (t, CH_2), 27.42 (t, CH_2), 27.66 (t, CH_2), 27.86 (t, CH_2), 28.28 (t, CH_2), 28.30 (t, $2CH_2$), 28.40 (t, CH_2), 28.43 (t, CH_2), 28.51 (t, CH_2), 29.09 (t, CH_2), 29.29 (t, CH_2), 29.46 (t, CH_2), 30.32 (t, CH_2), 32.96 (t, CH_2), 51.86 (q, OCH_3), 52.19 (q, OCH_3), 52.21(q, OCH_3), 52.25 (q, OCH_3), 129.35 (d, C-5′), 131.44 (s, aryl-C), 132.51 (s, aryl-C), 133.80 (s, aryl-C), 134.35 (d, C-6), 136.03 (s, aryl-C), 137.73 (s, aryl-C), 138.04 (s, aryl-C), 139.01 (s, aryl-C), 139.23 (s, aryl-C), 141.80* (s, C-1), 142.72* (s, C-1′), 168.12 (s, *C*$OOCH_3$ at C-4), 168.45 (s, *C*$OOCH_3$ at C-4′), 168.74 (s, *C*$OOCH_3$ at C-3), 169.17 (s, *C*$OOCH_3$ at C-3′) ppm. MS (CI): *m/z* (%)=663 (M^++H, 11) 631 (100). Calcd for: $C_{40}H_{54}O_8$ (662.89): C, 72.48; H, 8.21. Found: C, 72.54; H, 8.30.

4.2.2. (p*M*,p*P*)-2,5; 2′,5′-Didecano-3,3′,4,4′-tetrakis-(hydroxymethyl)-biphenyl (2). A solution of **4** (138 mg, 0.21 mmol) in 10 mL diethyl ether was added dropwise to lithium aluminum hydride (52 mg, 1.37 mmol) in diethyl ether (20 mL). After heating under reflux for 1 h the reaction was quenched with ice-cold water (30 mL) and then with 2 N sulfuric acid. Usual work-up, concentration of the organic layer in vacuo, and addition of pentane provided colorless crystalline **2** (73 mg, 64%), mp 215 °C (dec) (diethyl ether/pentane). IR (KBr): ν=3330 (broad, OH), 2920, 2855, (CH_2); 1581 (–C=C); 1005 (C–O) cm^{-1}. UV (C_2H_5OH): λ_{max} (log ε)=215 (4.77), 290 (3.21) nm. ^1H NMR (DMSO-d_6, 300 MHz): δ=0.19–1.88 (m, 32H, CH_2), 1.96–2.11 (m, 1H, CH_2), 2.20–2.47 (m, 2H, CH_2), 2.62–2.77 (m, 1H, CH_2), 2.88–3.06 (m, 2H, CH_2), 3.07–3.27 (m, 2H, CH_2), 4.58–4.82 (m, 8H, CH_2O), 5.00 (t, ^3J=5.0 Hz, exchangeable, 1H, OH), 5.04 (t, ^3J=4.8 Hz, exchangeable, 1H, OH), 5.10 (t, ^3J=5.0 Hz, exchangeable, 1H, OH), 5.17 (t, ^3J=4.8 Hz, exchangeable, 1H, OH), 6.57 (s, 1H, aryl-H), 7.20 (s, 1H, aryl-H) ppm. ^{13}C NMR (DMSO-d_6, 150 MHz): δ=24.89 (t, CH_2), 25.04 (t, CH_2), 25.17 (t, CH_2), 25.99 (t, CH_2), 26.62 (t, CH_2), 26.74 (t, CH_2), 26.92 (t, CH_2), 27.48 (t, CH_2), 27.84 (t, CH_2), 27.93 (t, CH_2), 28.09 (t, CH_2), 28.14 (t, $2CH_2$), 28.42 (t, CH_2), 28.73 (t, CH_2), 28.92 (t, $2CH_2$), 29.41 (t, CH_2), 32.81 (t, $2CH_2$), 57.74 (t, $2CH_2O$), 58.41 (t, CH_2O), 58.62 (t, CH_2O), 130.93* (d, C-6), 132.28*(d, C-6′), 136.41 (s, aryl-C), 137.15 (s, aryl-C), 137.75 (s, aryl-C), 137.94 (s, aryl-C), 138.06 (s, aryl-C), 138.70 (s, aryl-C), 139.79 (s, aryl-C), 140.34 (s, aryl-C), 140.73 (s, aryl-C), 141.62 (s, aryl-C) ppm. MS (EI): *m/z* (%)=550 (M^+, 52), 532 (M^+-H_2O, 17), 514 (M^+-2H_2O, 35), 99 (100); HRMS (EI): Calcd for $C_{36}H_{54}O_4$ 550.40221. Found 540.40225.

4.3. Stereochemical analysis

The analytical enantiomeric resolution of *rac*-**1**[8] and *rac*-**2** were performed on a Waters 600 E multisolvent delivery system, Merck-Hitachi L-4000 UV detector, Varian 4290 integrator equipped with a Daicel Chiralcel OD-RH column (4.6×250 mm, 5 μm) and with a solvent mixture of acetonitrile/water=68:32 using a constant flow of 0.8 mL/min. The resolution of **1** was carried out at 30 °C while the

enantiomeric separation of **2** required cooling of the column to 5 °C. The chromatographic system was tempered in a Jetstream 2 column oven (Thermotechnic-Products GmbH). In order to overcome the problem of the fast decrease of the CD curve during the online CD measurements of **2**, the scanning speed had to be enhanced to 1000 nm/min (from 500 nm/min) and the band width had to be raised to 2 nm (from 0.5 nm).

4.4. Computational

The conformational analysis was performed on a Linux AMD MP 2800+ workstation.

For the AM1[20] calculations the Gaussian 98[22] was used, starting from geometries preoptimized by the TRIPOS[23] force field. The wave functions for the calculation of the rotational strengths for the electronic transitions from the ground state to the excited states were obtained by CNDO/S-CI[21] calculations. These calculations were carried out on Linux Pentium III workstations by the use of the BDZDO/MCDSPD program package.[24] For a better comparison of the theoretical spectra with the experimental ones, the calculated rotational strengths were transformed into $\Delta\varepsilon$ values, superimposed with a Gaussian band shape function having a full width at half height of 6 nm, and then scaled to match the experimental spectra.

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References and notes

1. Mislow, K. *Introduction to Stereochemistry*; W.A. Benjamin: New York, 1966.
2. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994. For recent enantiomer resolutions of *meso*-type compounds see also: Oki, M.; Toyota, S. *Eur. J. Org. Chem.* **2004**, 255–267.
3. Hoffmann, R. W. *Angew. Chem.* **2003**, *115*, 1128–1142. *Angew. Chem., Int. Ed.* **2003**, *42*, 1096–1109.
4. See Ref. 1, p 93.
5. Ascenso, J.; Gil, V. M. S. *Can. J. Chem.* **1980**, *58*, 1379–1379.
6. Bootsma, G. A.; Schoone, J. C. *Acta Crystallogr.* **1967**, *22*, 522–532.
7. Tochtermann, W.; Kuckling, D.; Meints, Ch.; Kraus, J.; Bringmann, G. *Tetrahedron: Asymmetry* **1999**, *10*, 21–24.
8. Tochtermann, W.; Kuckling, D.; Meints, Ch.; Kraus, J.; Bringmann, G. *Tetrahedron* **2003**, *59*, 7791–7801.
9. (a) Liebe, J.; Wolff, Ch.; Krieger, C.; Weiss, J.; Tochtermann, W. *Chem. Ber.* **1985**, *118*, 4144–4178. (b) Hunger, J.; Wolff, Ch.; Tochtermann, W.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Chem. Ber.* **1986**, *119*, 2698–2722.
10. Review: von Angerer, S.; Tochtermann, W., 4th ed. In *Methods in Organic Chemistry (Houben-Weyl)*; Thieme: Stuttgart, *Vol. D9d* 1998, pp 1–64.
11. McMurry, J. E. *Acc. Chem. Res.* **1974**, *7*, 281–286.
12. Mauritz-Boeck, I. Dissertation, Universität Kiel, 1984.
13. Hesse, M.; Meier, H.; Zeeh, B. *Spektroskopische Methoden in der Organischen Chemie*, 5th ed.; Thieme: Stuttgart, 1995; p 99.
14. Bringmann, G.; Messer, K.; Wohlfarth, M.; Kraus, J.; Dumbuya, K.; Rückert, M. *Anal. Chem.* **1999**, *71*, 2678–2686.
15. Bringmann, G.; Lang, G. In *Marine Molecular Biotechnology*; Müller, W. E. G., Ed.; Springer: Berlin, 2003; pp 89–116.
16. Bringmann, G.; Tasler, S.; Endress, H.; Kraus, J.; Messer, K.; Wohlfarth, M.; Lobin, W. J. *J. Am. Chem. Soc.* **2001**, *123*, 2703–2711.
17. Bringmann, G.; Mühlbacher, J.; Reichert, M.; Dreyer, M.; Kolz, J.; Speicher, A. *J. Am. Chem. Soc.* **2004**, *126*, 9283–9290.
18. Bringmann, G.; Busemann, S. In Schreier, P., Herderich, M., Humpf, H. U., Schwab, W., Eds.; Natural product analysis; Vieweg: Wiesbaden, 1998; pp 195–212.
19. Bringmann, G.; Menche, D.; Kraus, J.; Mühlbacher, J.; Peters, K.; Peters, E.-M.; Brun, R.; Bezabih, M.; Abegaz, B. M. *J. Org. Chem.* **2002**, *67*, 5595–5610.
20. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E.; Steward, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
21. Del Bene, J.; Jaffé, H. H. *J. Chem. Phys.* **1968**, *48*, 1807–1813.
22. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian* 98, Revision A.7; Gaussian, Inc.: Pittsburgh PA, 1998.
23. *SYBYL*: Tripos Associates, 1699 Hanley Road, Suite 303, St. Louis, MO 63144.
24. Downing, J. W. *Program Package BDZDO/MCDSPD*; Department of Chemistry and Biochemistry, University of Colorado: Boulder, USA; modified by Fleischhauer, J.; Schleker, W.; Kramer, B.; ported to Linux by Gulden, K.-P.
25. Mannschreck, A. *Chirality* **1992**, *4*, 163–169.

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Microwave-assisted conversion of *N*-substituted oxazolidin-2,4-diones into α-hydroxyamides

Thomas Kurz* and Khalid Widyan

Institute of Pharmacy, University of Hamburg, Bundesstrasse 45, 20146 Hamburg, Germany

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Abstract—*N*-Substituted oxazolidin-2,4-diones have been synthesized in a novel one-pot reaction by reacting cyanohydrins stepwise with 1,1′-carbonyldiimidazole and primary amines followed by acidic hydrolysis of the intermediate 4-imino-oxazolidin-2-ones. Their microwave-assisted conversion into α-hydroxyamides was accomplished by treatment with catalytic amounts of sodium methoxide in methanol.

1. Introduction

The α-hydroxyamide moiety is a well known pharmacophore that is present in various biologically active compounds. α-Hydroxyamides have, for example, been identified as inhibitors of methionine aminopeptidase-2 and as HIV protease inhibitors.[1,2] Mycalamides are a class of α-hydroxyamides which exhibit potent antitumour activity.[3] α-Hydroxyamides are as well valuable intermediates in the synthesis of natural products and various biologically active compounds.[4–6] Known methods for their preparation can be divided into four main categories: reactions of carboxylic acids and activated acid derivatives with amines, reduction of α-ketoamides, micellaneous methods and the synthesis of α-hydroxyamides via cyclic precursors.

The conversion of α-hydroxyacids into α-hydroxyamides has been accomplished in moderate to high yields at high temperature, high pressure, Lewis acid catalyzed, by treatment of α-hydroxyacids with *N*-sulfinylanilines and by aminolysis of *O*-TMS-protected acid chlorides.[7–12] Reactions of α-hydroxyesters with amines usually require long reaction times, forcing or enzyme catalyzed reaction conditions.[13] The reduction of α-ketoamides has for instance been accomplished with sodium borohydride, $LiBEt_3H$, $KBEt_3H$, with magnesium- and titanium-based reagents and by catalytic hydrogenation in the presence of palladium on charcoal.[14–17] A novel method for the synthesis of α-hydroxyamides represents the reaction of 2,3-epoxyamides with samarium diiodide.[18] Katritzky reported the synthesis of α-hydroxyamides by treatment of mandelic acid with *N*-(1-methanesulfonyl)benzotriazole and primary amines.[19]

1,3-Dioxolane-2,4-diones, acetonides of α-hydroxycarboxylic acids and oxazolidin-2,4-diones have been used as cyclic precursors in the preparation of α-hydroxyamides.[20–22] Commonly the alkaline hydrolysis of oxazolidin-2,4-diones leads to a mixture of α-carbamoyloxyacid and α-hydroxyamide.[22] Tamariz described the synthesis of two α-hydroxycarboxamides in 34 and 35% yield by alkaline hydrolysis of the corresponding oxazolidin-2,4-diones.[23] Furthermore, Miethchen reported the conversion of a 5,5-disubstituted 3-cyclohexyloxazolidin-2,4-dione into the corresponding α-hydroxy *N*-cyclohexylcarboxamide by refluxing the oxazolidin-2,4-dione in methanol in the presence of an excess of sodium methoxide for 7 h in 97% yield.[24]

Given the importance of the α-hydroxyamide functionality in organic and medicinal chemistry, development of new methods for the efficient synthesis of α-hydroxyamides is still an important challenge. Our group reported the sodium methoxide catalyzed decarbonylation of *O*-substituted 3-hydroxyoxazolidin-2,4-diones, *N*-substituted 3-amino-oxazolidin-2,4-diones and *O*-substituted 3-hydroxy-4-imino oxazolidin-2-ones as novel methods for the synthesis of *O*-substituted α-hydroxyhydroxamic acids, *N*′,*N*′-disubstituted α-hydroxyhydrazides and *O*-substituted α-hydroxyamidoximes.[25] We now report the microwave-assisted conversion of *N*-substituted oxazolidin-2,4-diones into α-hydroxyamides. A comparison of the microwave-

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* Corresponding author. Tel./fax: +49 40 42838 3467;
e-mail: kurz@chemie.uni-hamburg.de

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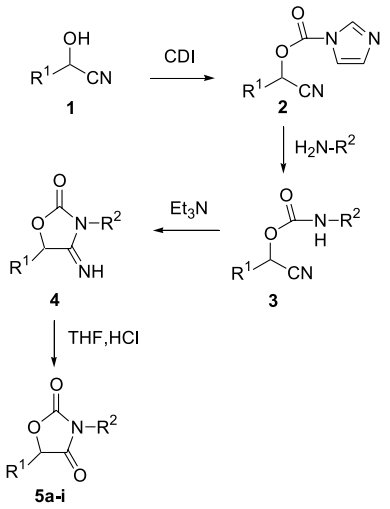
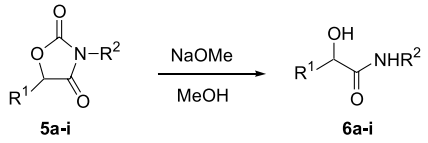


Scheme 1. Synthesis of oxazolidin-2,4-diones (**5a–i**).

Table 1. Synthesis of oxazolidin-2,4-diones (**5a–i**)

5	R^1	R^2	Yield (%)
a	C_6H_5	*m*-FC_6H_4	70
b	1-Naphthyl	*m*-FC_6H_4	70
c	Cyclopropyl	*p*-NCC_6H_4	75
d	2-Thienyl	*p*-$F_3CC_6H_4$	55
e	2-Furyl	*p*-BrC_6H_4	53
f	C_6H_{11}	*p*-ClC_6H_4	68
g	1-Naphthyl	Cyclopropyl	65
h	*p*-MeC_6H_4	*p*-$FC_6H_4CH_2$	67
i	*p*-MeC_6H_4	CH_3	63



Scheme 2. Synthesis of α-hydroxyamides (**6a–i**).

chemistry to the conventional and sealed tube decarbonylation is exemplarily described.

2. Results and discussion

2.1. Synthesis of *N*-substituted oxazolidin-2,4-diones (5a–i)

N-Substituted oxazolidin-2,4-diones (**5**) have been prepared in a novel one pot reaction starting from cyanohydrins (**1**), 1,1′-carbonyldiimidazole (CDI) and primary amines. Reactions of **1** with CDI in dichloromethane furnished imidazolide intermediates **2**. Their treatment with primary amines gave the open-chained carbamate intermediates **3**. Base catalyzed ring closure of **3** furnished 4-imino oxazolidin-2-ones (**4**), which were subsequently hydrolyzed to afford **5** in 53–75% yield (Scheme 1, Table 1).

Due to the characteristic C=O absorption bands of **2–5** the progression of the reaction was readily monitored by IR spectroscopy. *N*-Substituted oxazolidin-2,4-diones (**5**), which have attracted much attention in medicinal and agricultural chemistry,[26] have, for example, previously been prepared from α-hydroxyesters and isocyanates and by reactions of α-hydroxyamides with chloroformates or dialkyl carbonates.[22,26]

2.2. Synthesis of α-hydroxyamides (6a–i)

Microwave-assisted synthesis of **6a–f** was accomplished in high yields of 80–92% by reacting **5a–f** with sodium methoxide (0.2 equiv) in methanol for 3.5–4.5 min (Scheme 2, Table 2). The corresponding reaction of compound **5a** in a sealed tube at 105 °C afforded compound **6a** in 78% yield after 12 min, while conventional heating at atmospheric pressure provided **6a** in 89% yield after 45 min.

Microwave-assisted synthesis of *N*-cyclopropyl, *N*-(4-fluorobenzyl) and *N*-methyl substituted α-hydroxyamides **6g–i** was achieved in moderate to good yields of 55–82% using longer reaction times and harsher reaction conditions. In contrast to the fast microwave-assisted conversion of **5h** into **6h**, the corresponding reaction in a sealed tube at 105 °C took 9 h to give **6h** in only 31% yield. Refluxing **5h** for 35 h in methanol in the presence of sodium methoxide (0.2 equiv) afforded 39% of **6h** (Table 2).

Table 2. Synthesis of α-hydroxyamides (**6a–i**)

6	R^1	R^2	Hold time microwave (min)	Yield (%)	Time conventional	Yield (%)	Time sealed tube	Yield (%)
a	C_6H_5	*m*-FC_6H_4	4.5	90	45 min	89	12 min	78
b	1-Naphthyl	*m*-FC_6H_4	4.5	91	—	—	—	—
c	Cyclopropyl	*p*-NCC_6H_4	4.5	87	—	—	—	—
d	2-Thienyl	*p*-$F_3CC_6H_4$	3.5	80	—	—	—	—
e	2-Furyl	*p*-BrC_6H_4	4	92	—	—	—	—
f	C_6H_{11}	*p*-ClC_6H_4	4.5	84	—	—	—	—
g	1-Naphthyl	Cyclopropyl	14.5	82	—	—	—	—
h	*p*-MeC_6H_4	*p*-$FC_6H_4CH_2$	20	73	35 h	39	9 h	31
i	*p*-MeC_6H_4	CH_3	90	55	—	—	—	—

Microwave reactions were conducted at 100 °C (**6a–g**) or 150 °C (**6h**,**i**) in the presence of 0.2 equiv of sodium methoxide in methanol using microwave glass pressure tubes.

3. Conclusion

We have developed a convenient two-step synthesis for the preparation of α-hydroxyamides using conventional and microwave-assisted chemistry. The first step is a novel one pot-synthesis of *N*-substituted oxazolidin-2,4-diones. In the second step we have demonstrated that *N*-substituted 3-amino-oxazolidin-2,4-diones are valuable precursors for the microwave-assisted synthesis of α-hydroxyamides in moderate to high yields. In comparison to conventional heating at atmospheric pressure and reactions under pressure, the microwave-assisted conversion of *N*-substituted oxazolidin-2,4-diones into α-hydroxyamides proceeds faster and in higher yields. Compared to Shapiro's and Tamariz's methods, the yields of our method are higher, no α-carbamoyloxyacids have been detected and the use of water as a solvent has been avoided. Starting from cyanohydrins our method allows the introduction of different substituents in the α-position of the title compounds. The method is practical and only catalytic amounts of sodium methoxide are necessary for the decarbonylation. The oxazolidin-2,4-dione ring system represents a protecting group for the secondary alcoholic hydroxyl group and the amide nitrogen.

4. Experimental

Cyanohydrins (**1**) have been prepared according to an established literature procedure and were used immediately after structure conformation by IR spectroscopy.[27] Microwave assisted reactions were carried out using a CEM microwave reactor model Discover. Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analysis was carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ as solvent.

4.1. General procedure for the preparation of substituted 3-amino-oxazolidin-2,4-diones (5a–i)

A solution of cyanohydrin **1** (5 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise over a period of 10 min to a suspension of 1,1′-carbonyldiimidazole (851 mg, 5.25 mmol) in dry CH_2Cl_2 (5 mL) under ice cooling. After stirring at room temperature for 10 min a solution of the appropriate amine (5 mmol) in dry CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred at room temperature for 1 h. Triethylamine (3 mL) was added and the reaction mixture was stirred until two sharp bands in the IR spectra appeared at 1780–1800 and 1680–1700 cm^{-1}. The solvent was removed under reduced pressure and the residue was dissolved in THF (10 mL). Hydrochloric acid (10 mL, 20%) was added under ice cooling and the reaction mixture was stirred for 50 min. The reaction mixture was extracted thrice with EtOAc (15 mL) and the combined extracts were dried over $MgSO_4$. Removal of the solvent afforded **5a–i** as solids, analytically pure products were obtained after recrystallization from the indicated solvent or purification by column chromatography.

4.1.1. 3-(3-Fluorophenyl)-5-phenyloxazolidin-2,4-dione (5a). Colorless solid (70%). Mp 140 °C (EtOAc–hexane); IR (KBr) ν=1820, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 5.91 (s, 1H), 7.12–7.17 (m, 1H), 7.25–7.33 (m, 2H), 7.44–7.61 (m, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 80.3, 113.4, 116.4, 116.6, 121.3, 121.4, 126.4, 129.7, 130.4, 130.9, 131.1, 131.6, 161.8, 164.3. Anal. Calcd for $C_{15}H_{10}FNO_3$: C, 66.42; H, 3.72; N, 5.16. Found: C, 66.28; H, 3.70; N, 5.18.

4.1.2. 3-(3-Fluorophenyl)-5-(1-naphthyl)oxazolidin-2,4-dione (5b). Colorless solid (70%). Mp 204 °C (THF–Et_2O); IR (KBr) ν=1811, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 6.69 (s, 1H), 7.16 (t, J=7.12 Hz, 1H), 7.31–7.38 (m, 2H), 7.46–7.68 (m, 5H), 7.96 (t, J=8.90 Hz, 2H), 8.10 (d, J=7.89 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 78.6, 113.4, 113.7, 116.4, 116.6, 121.4, 123.5, 124.7, 125.6, 127.1, 127.9, 129.5, 130.9, 131.1, 131.5, 153.5, 167.9. Anal. Calcd for $C_{19}H_{12}FNO_3$: C, 71.03; H, 3.76; N, 4.36. Found: C, 70.93; H, 3.75; N, 4.43.

4.1.3. 3-(4-Cyanophenyl)-5-cyclopropyloxazolidin-2,4-dione (5c). Colorless solid (75%). Mp 163 °C (THF–Et_2O); IR (KBr) ν=2222, 1805, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 0.64–0.89 (m, 4H), 1.32–1.40 (m, 1H), 4.61 (d, J=7.12 Hz, 1H), 7.70 (d, J=8.65 Hz, 2H), 7.80 (d, J=8.65 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 0.3, 9.7, 79.9, 110.5, 115.9, 123.6, 131.2, 132.9, 150.9, 171.5. Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.19; H, 4.20; N, 11.55.

4.1.4. 5-(2-Thienyl)-3-(4-trifluoromethylphenyl)oxazolidin-2,4-dione (5d). Colorless solid (55%). Mp 190 °C (Et_2O–hexane); IR (KBr) ν=1807, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 6.10 (s, 1H), 7.10 (m, 1H), 7.32 (d, J=3.56 Hz, 1H), 7.50 (d, J=6.36 Hz, 1H), 7.68 (d, J=8.65 Hz, 2H), 7.79 (d, J=8.65 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 77.1, 126.0, 126.9, 127.0, 127.1, 128.0, 128.6, 128.8, 132.7, 153.0, 168.9. Anal. Calcd for $C_{14}H_8F_3NO_3S$: C, 51.38; H, 2.46; N, 4.28; S, 9.80. Found: C, 51.21; H, 2.59; N, 4.20; S, 10.00.

4.1.5. 3-(4-Bromophenyl)-5-(2-furyl)oxazolidin-2,4-dione (5e). Brown solid (53%) after column chromatography EtOAc–hexane. Mp 144 °C; IR (KBr) ν=1825, 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 5.91 (s, 1H), 6.47 (dd, J=3.31, 1.78 Hz, 1H), 6.70 (d, J=3.65 Hz, 1H), 7.40 (d, J=8.90 Hz, 2H), 7.53 (m, 1H), 7.65 (d, J=8.90 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 74.5, 111.5, 114.4, 123.4, 127.5, 130.2, 133.1, 143.9, 145.7, 153.4, 167.9. Anal. Calcd for $C_{13}H_8BrNO_4$: C, 48.47; H, 2.50; N, 4.35. Found: C, 48.28; H, 2.59; N, 4.30.

4.1.6. 3-(4-Chlorophenyl)-5-cyclohexyloxazolidin-2,4-dione (5f). Colorless solid (68%). Mp 163 °C (THF–Et_2O); IR (KBr) ν=1805, 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.14–1.40 (m, 5H), 1.64–1.90 (m, 5H), 2.04–2.14 (m, 1H), 4.77 (d, J=3.81 Hz, 1H), 7.38 (d, J=8.90 Hz, 2H), 7.46 (d, J=8.90 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 25.9, 26.0, 26.1, 26.2, 28.7, 40.3, 83.7, 127.1, 129.7, 130.0, 135.1, 154.4, 171.5. Anal. Calcd for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.13; H, 5.59; N, 4.74.

4.1.7. 3-Cyclopropyl-5-(1-naphthyl)oxazolidin-2,4-dione (5g). Colorless solid (65%). Mp 139 °C (THF–Et_2O). IR (KBr) ν=1811, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.02–1.11 (m, 4H), 2.77–2.83 (m, 1H), 6.43 (s, 1H), 7.44–7.50 (m, 2H), 7.54–7.63 (m, 2H), 7.89–7.93 (m, 2H), 8.03 (d, J=8.65 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 5.4, 5.5, 23.5, 77.9, 123.6, 124.4, 125.5, 126.9, 127.6, 127.9, 129.4, 131.1, 131.3, 134.4, 155.6, 171.9. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.81; H, 5.01; N, 5.26.

4.1.8. 3-(4-Fluorobenzyl)-5-(4-methylphenyl)oxazolidin-2,4-dione (5h). Colorless solid (67%). Mp 130 °C (THF–Et_2O); IR (KBr) ν=1809, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 2.36 (s, 3H), 4.68 (s, 2H), 5.68 (s, 1H), 7.02 (t, J=8.65 Hz, 2H), 7.19–7.23 (m, 4H), 7.40 (d, J=8.14 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.7, 43.7, 80.9, 116.2, 116.4, 126.5, 128.8, 130.3, 130.9, 131.2, 131.3, 140.5, 164.4, 171.5. Anal. Calcd for $C_{17}H_{14}FNO_3$: C, 68.22; H, 4.71; N, 4.68. Found: C, 68.29; H, 4.93; N, 4.80.

4.1.9. 3-Methyl-5-(4-methylphenyl)oxazolidin-2,4-dione (5i). Colorless solid (63%). Mp 111 °C (THF–Et_2O); IR (KBr) ν=1805, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 2.37 (s, 3H), 3.13 (s, 3H), 5.71 (s, 1H), 7.20 (d, J=8.13 Hz, 2H), 7.30 (d, J=8.13 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.7, 26.6, 80.9, 126.4, 128.9, 130.2, 140.4, 155.8, 171.8. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.25; H, 5.43; N, 6.80.

4.2. Microwave-assisted synthesis of 6a–i

Compound **5a–i** (0.5 mmol) and sodium methoxide (0.1 mmol) were weighed in a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar. Methanol (5 mL) was added, the tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation for the indicated time (Table 2) using parameters A and B. The reaction mixture was allowed to cool to room temperature and transferred to a round bottom flask. The solvent was evaporated, water (0.5 mL) was added and the mixture was treated thrice with dichloromethane (15 mL). The combined extracts were dried over $MgSO_4$ and the solution was concentrated to 0.5 mL. Addition of Et_2O and hexane provided **6a–i** as solid compounds.

Parameters A. For compounds **6a–g**: Discover mode; power: 200 W; ramp time: 30 s; hold time: as indicated in Table 2; temperature: 100 °C; pressure: 12 bar; PowerMax-cooling.

Parameters B. For compound **6h,i**: Discover mode, power: 250 W; ramp time: 30 s; hold time: as indicated in Table 2; temperature: 150 °C; pressure: 15 bar, PowerMax-cooling.

Synthesis of **6a,h** *in a sealed tube*. Sodium methoxide (0.1 mmol) was added to a stirred solution of **5a,h** (0.5 mmol) in methanol (5 mL). After being refluxed at 105 °C in a sealed tube for the indicated time (Table 2), the solvent was evaporated, water (0.5 mL) was added and the mixture was extracted thrice with dichloromethane (15 mL). The combined extracts were dried over $MgSO_4$ and the solution was concentrated to 0.5 mL. Addition of Et_2O and hexane provided **6a,h** as solid compounds.

Conventional method for the synthesis of **6a,h**. Sodium methoxide (0.1 mmol) was added to a stirred solution of **5a,h** (0.5 mmol) in methanol (5 mL). After being refluxed for the indicated time (Table 2), the solvent was evaporated, water (0.5 mL) was added and the mixture was extracted thrice with dichloromethane (15 mL). The combined extracts were dried over $MgSO_4$ and the solution was concentrated to 0.5 mL. Addition of Et_2O and hexane provided **6a,h** as solid compounds.

4.2.1. *N*-(3-Fluorophenyl)-2-hydroxy-2-phenylacetamide (6a). *Parameter A*. Colorless solid (90%). Mp 163 °C (Et_2O–hexane); IR (KBr) ν=3302, 3229, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 3.50 (s, 1H), 5.87 (s, 1H), 7.12–7.17 (m, 1H), 7.25–7.33 (m, 2H), 7.44–7.61 (m, 6H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 80.3, 113.4, 116.4, 116.6, 121.3, 121.4, 126.4, 129.7, 130.3, 130.9, 131.1, 131.7, 170.1. Anal. Calcd for $C_{14}H_{12}FNO_2$: C, 68.56, H, 4.93; N, 5.71. Found: C, 68.43; H, 5.01; N, 5.56.

4.2.2. *N*-(3-Fluorophenyl)-2-hydroxy-2-(1-naphthyl)-acetamide (6b). *Parameter A*. Colorless solid (91%). Mp 175 °C (Et_2O–hexane); IR (KBr) ν=3302, 3229, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 3.51 (s, 1H), 5.83 (s, 1H), 6.81 (t, J=8.41 Hz, 1H), 7.11 (d, J=9.16 Hz, 1H), 7.20–7.27 (m, 1H), 7.46–7.62 (m, 5H), 7.89–7.92 (m, 2H), 8.12 (s, 1H), 8.19 (d, J=8.41 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 80.3, 113.4, 113.6, 116.4, 116.6, 121.4, 126.4, 129.7, 130.5, 130.9, 131.1, 131.6, 132.4, 132.5, 153.8, 161.8, 164.3, 170.0. Anal. Calcd for $C_{18}H_{14}FNO_2$: C, 73.21; H, 4.78; N, 4.74. Found: C, 73.21; H, 4.79; N, 4.86.

4.2.3. *N*-(4-Cyanophenyl)-2-cyclopropyl-2-hydroxy-acetamide (6c). *Parameter A*. Colorless solid (87%). Mp 120 °C (Et_2O–hexane); IR (KBr) ν=3462, 3317, 2218, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 0.69–0.78 (m, 4H), 1.20–1.28 (m, 1H), 2.80 (s, 1H), 3.72 (d, J=7.89 Hz, 1H), 7.63 (d, J=8.65 Hz, 2H), 7.75 (d, J=8.65 Hz, 2H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 2.6, 3.4, 16.3, 76.0, 107.7, 119.2, 120.0, 133.8, 141.8, 171.8. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.43; H, 5.72; N, 12.89.

4.2.4. 2-Hydroxy-2-(2-thienyl)-*N*-(4-trifluoromethyl-phenyl)acetamide (6d). *Parameter A*. Colorless solid (80%). Mp 196 °C (Et_2O–hexane); IR (KBr) ν=3292, 3111, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 3.35 (s, 1H), 5.63 (s, 1H), 7.04 (t, J=3.56 Hz, 1H), 7.23 (d, J=3.31 Hz, 1H), 736 (d, J=5.09 Hz, 1H), 7.60 (d, J=8.65 Hz, 2H), 7.70 (d, J=8.65 Hz, 2H), 8.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 71.3, 119.9, 126.8, 127.1, 127.6, 130.7, 137.1, 138.4, 140.7, 172.1. Anal. Calcd for $C_{13}H_{10}F_3NO_2S$: C, 51.83; H, 3.35; N, 4.65; S, 10.64. Found: C, 51.75; H, 3.21; N, 4.50; S, 10.49.

4.2.5. *N*-(4-Bromophenyl)-2-(2-furyl)-2-hydroxyacetamide (6e). *Parameter A*. Colorless solid (92%). Mp 162 °C (Et_2O–hexane); IR (KBr) ν=3281, 3163, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 3.34 (s, 1H), 5.29 (s, 1H), 6.40 (dd, J=3.31, 1.78 Hz, 1H), 6.55 (d,

J=3.31 Hz, 1H), 7.44–7.49 (m, 5H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 68.8, 109.7, 111.3, 117.9, 121.9, 132.5, 140.0, 174.6. Anal. Calcd for $C_{12}H_{10}BrNO_3$: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.52; H, 3.51; N, 4.75.

4.2.6. *N*-(4-Chlorophenyl)-2-cyclohexyl-2-hydroxyacetamide (6f). *Parameter A*. Colorless solid (84%). Mp 145 °C (Et_2O–hexane); IR (KBr) ν=3315, 3111, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.10–1.33 (m, 5H), 1.65–1.81 (m, 5H), 1.91–1.97 (m, 1H), 2.37 (s, 1H), 4.09 (d, J=3.31 Hz, 1H), 7.29 (d, J=8.90 Hz, 2H), 7.57 (d, J=8.90 Hz, 2H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 26.2, 26.3, 26.4, 26.7, 30.0, 42.1, 77.1, 121.4, 129.5, 129.9, 136.2, 171.6. Anal. Calcd for $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.60; H, 6.89; N, 5.17.

4.2.7. *N*-Cyclopropyl-2-hydroxy-2-(1-naphthyl)acetamide (6g). *Parameter A*. Colorless solid (82%). Mp 103 °C (Et_2O–hexane); IR (KBr) ν=3315, 3111, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 0.31–0.72 (m, 4H), 2.68–2.70 (m, 1H), 3.46 (s, 1H), 5.49 (s, 1H), 6.05 (s, 1H), 7.43–7.62 (m, 4H), 7.86 (t, J=8.64 Hz, 2H), 8.06 (d, J=6.11 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 6.8, 7.1, 23.1, 73.3, 124.2, 125.7, 126.5, 127.2, 127.4, 129.3, 130.1, 131.5, 134.7, 134.9, 174.6. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.60; H 6.15; N, 5.90.

4.2.8. *N*-(4-Fluorobenzyl)-2-hydroxy-2-(4-methylphenyl)acetamide (6h). *Parameter B*. Colorless solid (73%). Mp 125 °C (Et_2O–hexane); IR (KBr) ν=3134, 3132, 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.34 (s, 3H), 3.44 (s, 1H), 4.38 (m, 2H), 5.01 (s, 1H), 6.65 (s, 1H), 6.97 (t, J=8.65 Hz, 2H), 7.13–7.17 (m, 4H), 7.26 (d, J=8.14 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.6, 43.2, 74.5, 115.9, 116.1, 127.2, 129.7, 129.8, 130.0, 134.0, 136.8, 139.1, 163.8, 172.7. Anal. Calcd for $C_{16}H_{16}FNO_2$: C, 70.32; H, 5.90; N, 5.12. Found: C, 70.19; H, 5.77; N, 5.10.

4.2.9. 2-Hydroxy-*N*-methyl-2-(4-methylphenyl)acetamide (6i). *Parameter B*. Colorless solid (55%). Mp 96 °C (Et_2O–hexane); IR (KBr) ν=3337, 3198, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.34 (s, 3H), 2.80 (d, J=4.80 Hz, 3H), 3.45 (s, 1H), 4.97 (s, 1H), 6.21 (s, 1H), 7.17 (d, J=8.13 Hz, 2H), 7.26 (d, J=8.13 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.6, 26.7, 74.4, 127.2, 129.90, 129.93, 136.9, 138.9, 173.5. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.13; H, 7.20; N, 7.85.

References and notes

1. Ahmad, A.; Ashfaq, A.; Alam, M.; Bisacchi, G. S.; Chen, P.; Cheng, P. T. W.; Greytok, J. A.; Hermsmeier, M. A.; Lin, P. F.; Lis, K. A.; Merchant, Z.; Mitt, T.; Skoog, M.; Spergel, S. H.; Tino, J. A.; Vite, G. D.; Colonno, R. J.; Zahler, R.; Barrish, J. C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1729.
2. Sheppard, J. W.; Wang, J.; Kawai, M.; BaMaung, N. Y.; Craig, R. A.; Erickson, A.; Lynch, L.; Patel, J.; Yang, F.; Searle, X. B.; Lou, P.; Park, C.; Kim, K. H.; Henkin, J.; Lesniewski, R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 865.
3. Thompson, A. M.; Blunt, J. W.; Munro, M. H. G.; Perry, N. B.; Pannell, L. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1335 and references therein.
4. Menendez, J. C.; Villacampa, M.; Sollhuber, M. M. *Heterocycles* **1991**, *32*, 469.
5. Lai, J. Y.; Shi, X. X.; Gong, Y. S.; Dai, L. X. *J. Org. Chem.* **1993**, *58*, 4775.
6. Wipf, P.; Kim, H. *J. Org. Chem.* **1993**, *58*, 5592.
7. Khalaj, A.; Nahid, E. *Synthesis* **1985**, 1153.
8. Matsumoto, K.; Hashimoto, S.; Otani, S. *Angew. Chem.* **1986**, *98*, 569.
9. Solladie-Cavallo, A.; Benchegroin, M. *J. Org. Chem.* **1992**, *57*, 5831.
10. Kiely, D. E.; Naiva, J. L. *Tetrahedron Lett.* **1991**, *32*, 3859.
11. Kelly, S. E.; LaCour, T. G. *Synth. Commun.* **1992**, *22*(6), 859.
12. Shin, J. M.; Kim, Y. H. *Tetrahedron Lett.* **1986**, *27*, 1921.
13. Adamczyk, M.; Grote, J.; Rege, S. *Tetrahedron: Asymmetry* **1997**, *8*, 2509.
14. (a) Soai, K.; Komiya, K.; Shigematsu, Y.; Hasegawa, H.; Ookawa, A. *J. Chem. Soc., Chem. Commun.* **1982**, 1282. (b) Soai, K.; Hasegawa, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 769. (c) Solodin, I.; Goldberg, Y.; Zelcans, G.; Lukevics, E. *J. Chem. Soc., Chem. Commun.* **1990**, 1321.
15. Kawanami, Y.; Fujita, I.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Chem. Lett.* **1987**, 2021.
16. Fujisawa, T.; Ukaji, Y.; Funabora, M.; Yamashita, M.; Sato, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1984.
17. Harada, K.; Munegumi, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3203.
18. Concellón, J. M.; Bardales, E. *Org. Lett.* **2003**, *25*, 4783.
19. Katritzky, A. R.; He, H. Y.; Susuki, K. *J. Org. Chem.* **2000**, *65*, 8210.
20. Toyooka, K.; Yoshiyuki, T.; Kubota, S. *Heterocycles* **1989**, *29*, 965.
21. Khalaj, A.; Nahid, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1153.
22. (a) Clark-Lewis, J. W. *Chem. Rev.* **1958**, *58*, 63. (b) Shapiro, S. L.; Rose, I. M.; Testa, F. C.; Roskin, E.; Freedmann, L. *J. Am. Chem. Soc.* **1959**, *81*, 6498.
23. Benavides, A.; Martínez, R.; Jiménez- Vázquez, H. A.; Delgado, F.; Tamariz, J. *Heterocycles* **2001**, *55*, 469.
24. Frank, M.; Miethchen, R. *Carbohydr. Res.* **1998**, *313*, 49.
25. (a) Kurz, T.; Widyan, K. *Org. Biomol. Chem.* **2004**, *2*, 2023. (b) Kurz, T.; Widyan, K. *Org. Lett.* **2004**, *6*, 4403. (c) Kurz, T.; Widyan, K. *J. Org. Chem.* **2005**, *70*, 3108.
26. (a) Tomlin, C. D. S. *The Pesticide Manual*, 12th ed. British Crop Protection Council: Farnham, Surrey, 2000; p. 375. (b) Tomlin, C. D. S. *The Pesticide Manual*, 12th ed. British Crop Protection Council: Farnham, Surrey, 2000; p. 956. (c) Thueson, D.O.; Withrow, C. D.; Giam, C. S.; Woodbury, D. M. *Epilepsia* **1974**, *15*, 563.
27. Gassman, P. G.; Talley, J. J. *Tetrahedron Lett.* **1978**, *40*, 3773.

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The first sorbicillinoid alkaloids, the antileukemic sorbicillactones A and B, from a sponge-derived *Penicillium chrysogenum* strain ☆

Gerhard Bringmann,[a,*] Gerhard Lang,[a] Tobias A. M. Gulder,[a] Hideyuki Tsuruta,[a] Jörg Mühlbacher,[a,†] Katja Maksimenka,[a] Stefan Steffens,[b] Karsten Schaumann,[b] Rüdiger Stöhr,[c] Jutta Wiese,[c] Johannes F. Imhoff,[c] Sanja Perović-Ottstadt,[d] Olexandra Boreiko[d] and Werner E. G. Müller[d]

[a]*Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany*
[b]*Alfred-Wegener-Institut für Polar- und Meeresforschung, Am Handelshafen 12, D-27570 Bremerhaven, Germany*
[c]*Leibniz-Institut für Meereswissenschaften, Düsternbrooker Weg 20, D-24105 Kiel, Germany*
[d]*Institut für Physiologische Chemie, Abteilung Angewandte Molekularbiologie, Universität Mainz, Duesbergweg 6, D-55099 Mainz, Germany*

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Abstract—The saltwater culture of a *Penicillium chrysogenum* strain isolated from the Mediterranean sponge *Ircinia fasciculata* yielded three new sorbicillin-derived compounds (**1**–**3**), whose structures were elucidated mainly by 2D NMR and mass spectrometry. Among them, sorbicillactones A (**1**) and B (**2**) are the first sorbicillinoid natural products that contain nitrogen. Compound **1** is anti-HIV active and it exhibits a strong cytotoxic activity against L5178y leukemic cells, combined with a relatively low toxicity to cervical carcinoma HeLa S3 cells and pheochromocytoma PC 12 cells. The absolute configurations of **1** and **2** were elucidated by quantum chemical calculation of circular dichroism (CD) spectra. Another compound isolated, sorbivinetone (**3**), might be an artifact derived from sorbicillinol (**4**) by Diels–Alder reaction with ethyl vinyl ether. Furthermore, the known sorbicillinoid fungal metabolites oxosorbicillinol (**5**), sorbicillin (**6**), and bisvertinolone (**7**) were identified, as well as the alkaloids meleagrine and roquefortine C. The biosynthetic origin of sorbicillactone A (**1**) from acetate, alanine, and methionine was investigated by feeding experiments with ^{13}C-labeled precursors.

1. Introduction

Penicillium chrysogenum, which is one of the most widespread fungal species,[2] is known to produce a great variety of natural products.[2] Apart from the penicillins, the metabolites encountered most frequently in this species are the roquefortines[3] and related compounds.[2] These are prenylated diketopiperazine alkaloids with antibiotic and neurotropic properties derived from tryptophan and histidine.[3] The majority of strains also sequester yellow pigments into the growth medium, two of which have previously been isolated and shown to be sorbicillin (**6**, Fig. 1)[4] and the bisorbicillinoid trichodimerol.[5] The typical carbon skeleton of sorbicillin is found in a wide variety of fungal metabolites, which accordingly are called sorbicillinoid or, in the case of dimers, bisorbicillinoid natural products. They are not only produced in *P. chrysogenum*, but also in fungi of the genera *Trichoderma*,[5] *Verticillium*,[6] and *Acremonium*.[7] Starting from sorbicillinol (**4**), an oxidatively dearomatized derivative of sorbicillin, there are three major biosynthetic routes that lead to the different classes of sorbicillinoid compounds. Further oxidation of **6** yields simple compounds, for example, oxosorbicillinol (**5**)[8] and epoxysorbicillinol,[9] which are, in contrast to sorbicillinol itself,[10] stable enough to be isolated. The majority of the known sorbicillinoid natural products, however, belong to the class of bisorbicillinoids. These are compounds formed from two molecules of sorbicillinol or other oxidatively activated sorbicillin species either by [4+2] cycloaddition or by Michael addition→ketalization sequences, thus, leading to highly complex structures, which are sometimes

☆ See Ref. 1.

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* Corresponding author. Tel.: +49 931 888 5323; fax: +49 931 888 4755; e-mail: bringman@chemie.uni-wuerzburg.de
† Present address: Novartis Institutes for BioMedical Research, CH-4002 Basel, Switzerland.

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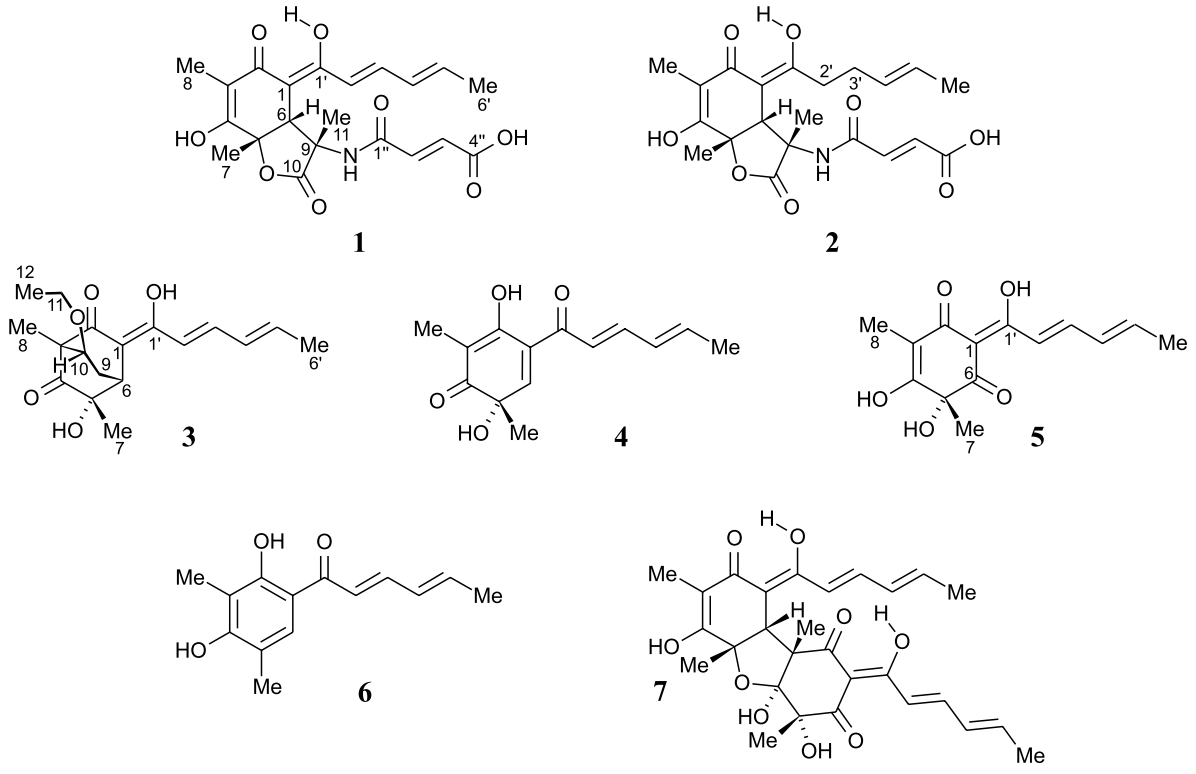


Figure 1. Structures of the isolated metabolites.

further modified by rearrangement reactions.[11] Prominent examples of this fascinating class of compounds are bisorbicillinol[12] and trichodimerol,[5] which have, recently, been prepared in biomimetic syntheses.[13,14] Some of the bisorbicillinoids also show promising biological activities. Bisvertinolone (**7**) inhibits the fungal biosynthesis of β-(1,6)-glucan,[7] trichodimerol suppresses the formation of tumor necrosis factor α (TNF-α),[15] and a number of bisorbicillinoids are known to exhibit antioxidant properties.[12]

In the course of a program aiming at the isolation of novel bioactive natural products from microorganisms derived from marine sponges,[16–18] we have isolated a strain of *P. chrysogenum* from a specimen of the Mediterranean sponge *Ircinia fasciculata*. In this paper, we describe the identification and structural elucidation of three sorbicillinoid compounds (**1**–**3**) belonging to neither of the aforementioned structural classes and their formation under discrete culture conditions, as well as the identification of five known[2,4,7,8] metabolites (meleagrine, roquefortine C, and compounds **5**–**7**). The absolute configurations of **1** and **2** were elucidated by quantum chemical circular dichroism (CD) calculations. The biosynthesis of **1** from acetate, methionine, and alanine, as elucidated by feeding experiments with ^{13}C-labeled precursors, and the strong and selective antileukemic and anti-HIV activities of **1** are described.[19]

2. Results and discussion

2.1. Structural elucidation of metabolites

The fungus was propagated as a 10-L culture in saline medium for 14 days. After this period, mycelium and culture broth were extracted. The combined extracts were then investigated using an array of coupled HPLC techniques, namely HPLC-UV, -MS/MS, -NMR, and -CD.[18] By their UV spectra two types of metabolites could be distinguished, two alkaloids of the roquefortine family and three sorbicillin-related compounds. In HPLC-MS, the latter (**1**, **3**, and **7**) showed pseudomolecular ions $[M+H]^+$ at *m/z* 418, 321, and 513, respectively. Thus, the molecular masses of **1** and **3** were neither in agreement with the bisorbicillinoids nor with the simple oxidized 'monomeric' sorbicillinol species. The sorbicillinoid nature of **1** was evident not only from its UV spectrum, but also from the signals of the sorbyl chain in its HPLC-^{1}H NMR spectrum, that is, one methyl doublet at 1.8 ppm and four olefinic protons between 6.0 and 7.2 ppm. The apparently novel-type structures of **1** and **2** made it rewarding to analyze these natural products more closely, offline. Moreover, compound **1** appeared to be the first nitrogen-containing natural product with a sorbicillinoid structure, as indicated by its odd molecular mass of 417. A further, structurally closely related compound, **2**, almost coeluted with **1**. It possessed a molecular mass of 419, that is, only two units higher than **1**, but differed markedly from the sorbicillinoid compounds by its UV spectrum.

After isolation by preparative HPLC, **1** was obtained as a yellow solid, which had, thus, become amenable for completion of structural elucidation using the standard array of one- and two-dimensional NMR experiments. On the basis of its HRESIMS (*m/z* 418.1515 $[M+H]^+$, 418.1502 calcd for $C_{21}H_{24}NO_8$), the compound was assigned a molecular formula of $C_{21}H_{23}NO_8$. The ^{13}C spectrum showed 21 signals, all of which could be attributed

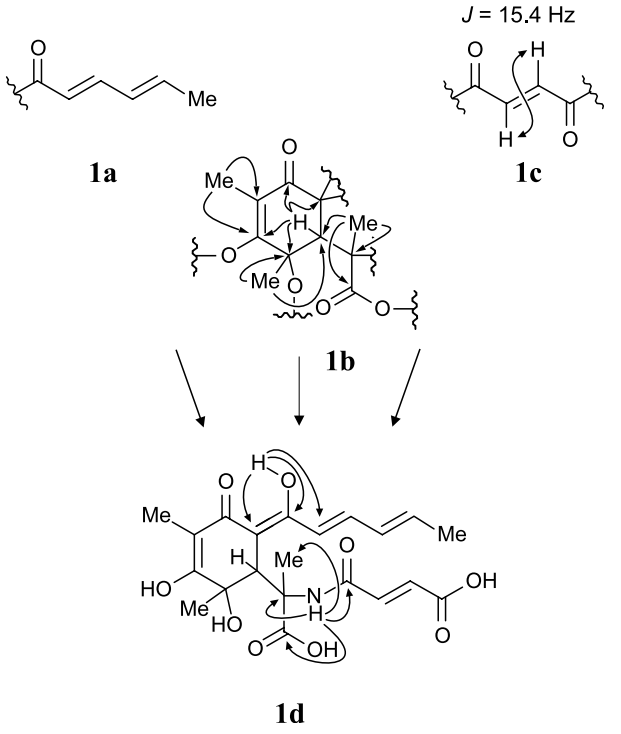
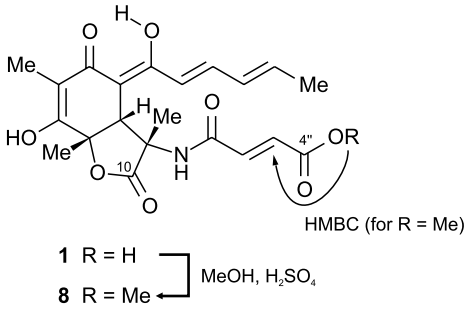


Figure 2. Partial structures **1a–c** assembled to the hypothetical gross structure **1d** by HMBC correlations.

to three substructures identified with the help of COSY, HMQC, and HMBC experiments: the sorbyl residue (**1a**), which had already been identified in the HPLC-NMR experiment, one highly substituted cyclohexenone ring (**1b**), and one fumaryl residue (**1c**), whose *E*-configuration was evident from the large coupling constant of $^{3}J_{HH}=15.4$ Hz (Fig. 2). The highfield chemical shift of the carbonyl carbon in the sorbyl chain (169.7 ppm, Table 1) showed this ketone to be present in its enolic form. Since, all NMR spectra were taken in THF-d_8, the enolic proton of the sorbyl moiety and an amidic NH proton provided sharp signals. The long-range H–C couplings of these two protons allowed us to combine the three substructures **1a–c** to one overall gross structure **1d**.

The observed molecular mass of 417, however, obviously required the formal loss of one molecule of water from **1d**. The only possibility in accordance with the NMR data was a lactone formation between one of the two carboxylic acid groups in **1d** and either the tertiary alcohol at C-5 or the enolic hydroxy group at C-4, but for steric reasons the latter could be excluded. For an unequivocal determination of the position of the lactone ring, the natural product was converted into its methyl ester by treatment with MeOH/H_2SO_4. The reaction yielded one single monomethylated product, **8**. HMBC correlations showed the methyl ester group to be located at C-4″ of the fumaric acid moiety, whose carboxy function was, thus, free in **1**, not participating in the lactone ring. Since, no methylation was observed on the oxygen function at C-10, it was concluded that it was not free, but part of a 5-ring lactone. Consequently, compound **1** had the bicyclic structure depicted in Scheme 1.



Scheme 1. *O*-Methylation of sorbicillactone A (**1**).

The relative configuration of the three stereocenters was obvious from ROEs of 6-H to the methyl groups at C-5 and C-9, indicating a *cis*-array of 6-H to these methyl groups,

Table 1. NMR data for sorbicillactone A (**1**) in THF-d_8

Position	^{13}C (ppm)	^{1}H (ppm)	HMBC	ROESY	COSY [J_{HH} (Hz)]
1	99.6				
2	192.1				
3	110.9				
4	166.5				
5	81.0				
6	53.0	3.43 s	1, 2, 4, 5, 7, 9, 11, 1′	7, 11, 2′	
7	25.0	1.55 s	5, 6	6	
8	7.3	1.54 s	2, 3, 4		
9	60.0				
10	173.0				
11	26.0	1.42 s	6, 9, 10	6, 2′, NH	
1′	169.7				
2′	121.7	6.38 d	1′, 4′	6, 11	3′ (14.7)
3′	139.1	7.19 dd	4′, 5′	5′	2′, 4′ (11.0)
4′	132.0	6.28 ddd	6′		3′, 5′, 6′ (1.3)
5′	136.9	6.08 m	3′, 6′	3′	4′ (14.5), 6′ (6.2)
6′	18.5	1.83 dd	4′, 5′		4′, 5′
1″	162.5				
2″	136.0	6.67 d	1″, 3″, 4″	NH	3″ (15.4)
3″	131.2	6.49 d	1″, 2″, 4″		2″
4″	166.3				
1′-OH		16.60 s	1, 1′, 2′		
NH		7.60 s	9, 10, 11, 1″	11, 2″	

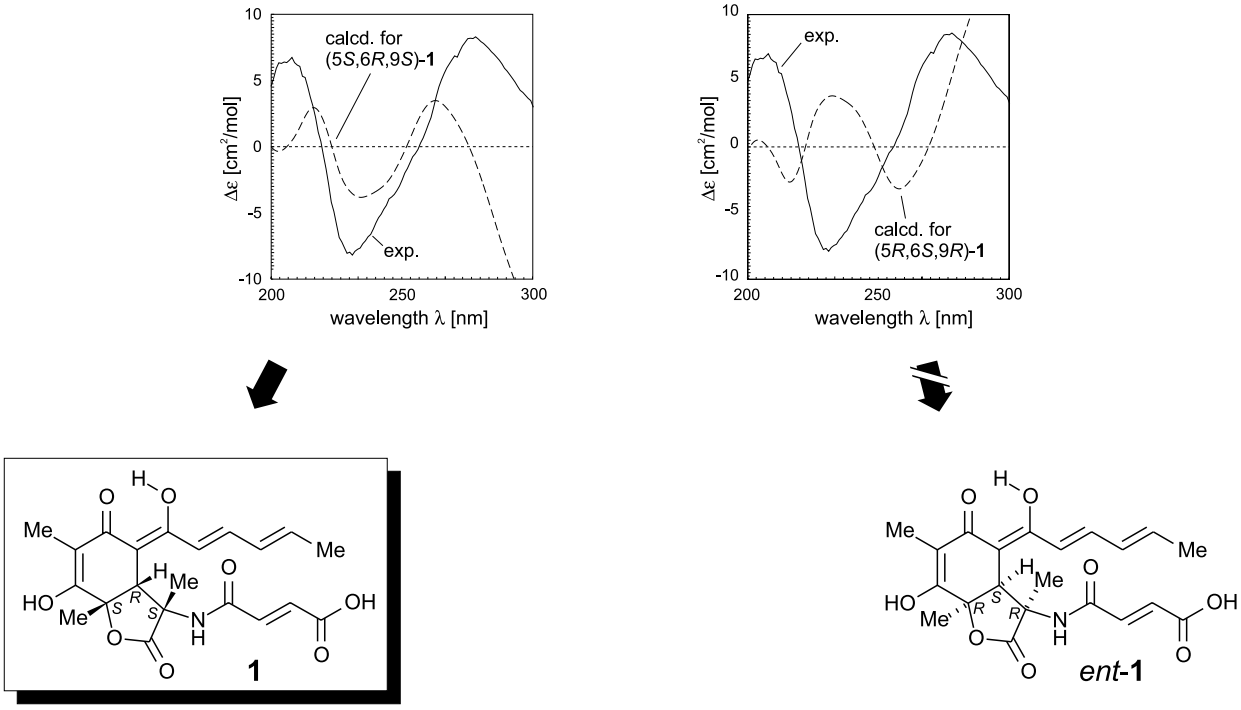


Figure 3. Comparison of the CD spectrum of **1** with the spectra calculated for its two possible enantiomers, (5*S*,6*R*,9*S*)-**1** and (5*R*,6*S*,9*R*)-**1**.

which meant (5*S*,6*R*,9*S*)- or (5*R*,6*S*,9*R*)-configuration for **1**.[20]

For an assignment of the absolute configuration of **1**, CD spectra were calculated for both possible enantiomers, (5*S*,6*R*,9*S*)-**1** and (5*R*,6*S*,9*R*)-**1**, using a molecular dynamics (MD) based approach described in detail earlier.[21] The MD simulation was carried out at a virtual temperature of 500 K by using the TRIPOS force field.[22] During a single molecular dynamics run with a total period of 500 ps, 1000 single structures were collected. The calculations of the CD spectra for these structures and their arithmetical averaging provided the overall theoretical CD spectrum. Its comparison with the experimental data showed a good agreement of the spectrum calculated for (5*S*,6*R*,9*S*)-**1** with the one of the natural product (Fig. 3), and the near-opposite curve of the one computed for (5*R*,6*S*,9*R*)-**1**, assigned the (5*S*,6*R*,9*S*)-configuration to natural sorbicillactone A (**1**).

Since the lactone structure of **1** is unprecedented among all known sorbicillinoid natural products, the compound was named sorbicillactone A. It is, moreover, the first member of this class of natural products to contain nitrogen, that is, the first sorbicillin-derived alkaloid. A compound with the same bicyclic carbon skeleton, but lacking the methyl group at C-9, the nitrogen, and the fumaryl residue on the lactone ring, had previously been obtained as an undesired product in the synthesis of bisorbicillinoids.[14]

Compound **2**, which by HPLC-MS had been shown to differ from **1** by only two mass units, was again isolated by preparative HPLC, yielding a brownish powder. Its NMR spectra closely resembled those of **1** (Table 2). In particular, the ^{1}H and ^{13}C chemical shifts of the bicyclic core and the fumaryl residue were nearly identical to those of **1**, but there were differences in the signals for the sorbyl side chain. The NMR spectra of **2** showed C-2′ and C-3′ to be methylene instead of methine carbons, indicating that the corresponding double bond in the sorbyl chain of **1** was replaced by a single bond in **2**. As a consequence, this 2′,3′-dihydro-derivative **2** of sorbicillactone A (**1**), henceforth, named sorbicillactone B, was only weakly colored. In accordance with the assigned structure, HRESIMS displayed a pseudo-molecular ion $[M+H]^+$ at *m/z* 420.1646 (420.1658 calcd for $C_{21}H_{26}NO_8$). Such 2′,3′-dihydro derivatives are quite common in this class of natural products; besides

Table 2. NMR data for sorbicillactone B (**2**) in THF-d_8

Position	^{13}C (ppm)	^{1}H (ppm)	HMBC	COSY [J_{HH} (Hz)]
1	98.6			
2	191.7			
3	110.2			
4	166.6			
5	81.6			
6	53.9	3.31 s	1, 2, 4, 5, 7, 9, 11, 1′	
7	25.1	1.54 s	4, 5, 6	
8	7.6	1.53 s	2, 3, 4	
9	60.1			
10	172.0			
11	25.9	1.44 s	6, 9, 10	
1′	180.2			
2′	33.7	α 2.37 m	1, 1′, 3′, 4′	
3′	30.6	β 2.53 m	1, 1′, 3′, 4′	2′α,3′
		2.32 m	2′, 4′, 5′	2′,4′
4′	130.9	5.48 m	3′, 6′	3′,5′,6′
5′	126.8	5.48 m	3′, 6′	4′,6′
6′	18.2	1.61 dd	4′, 5′	3′,4′,5′
1″	162.9			
2″	136.4	6.64 d	1″, 4″	3″ (15.5)
3″	131.6	6.49 d	1″, 4″	2″
4″	166.7			
1′-OH		16.98 s		
NH		7.61 s	9, 10, 11, 1″	

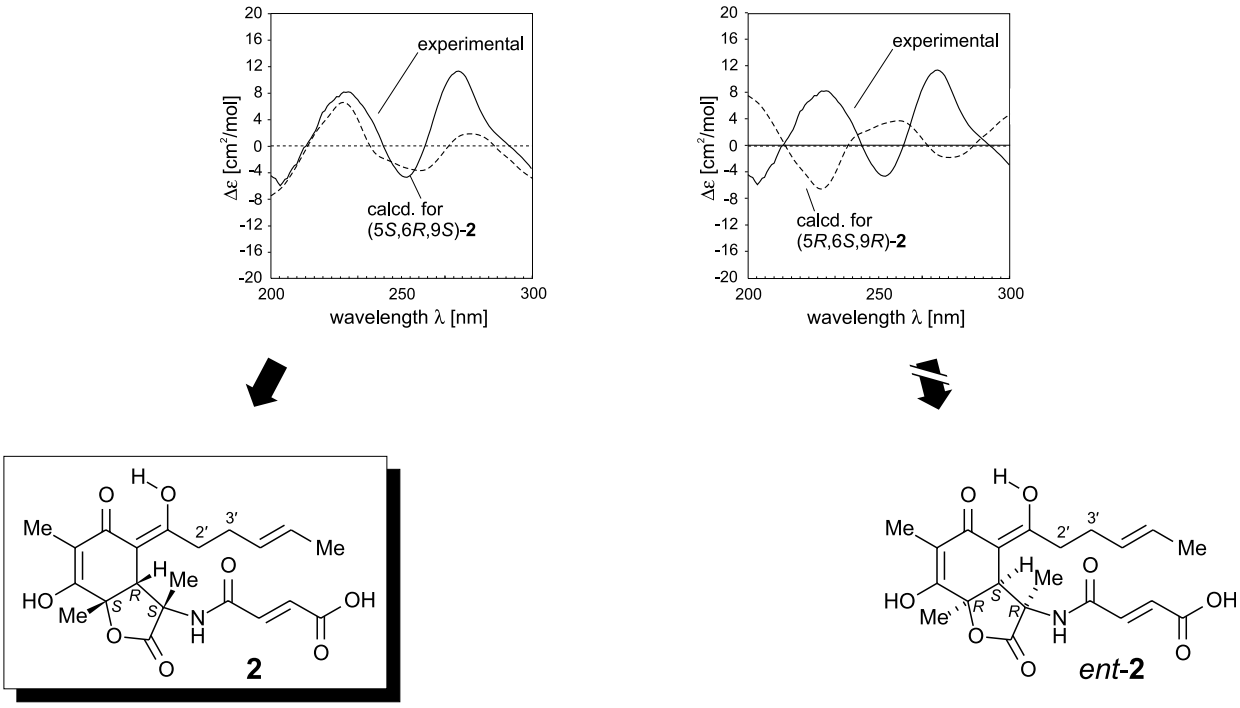


Figure 4. Determination of the absolute configuration of **2** by comparison of the experimental CD spectrum with the spectra calculated for its two possible enantiomers, (5*S*,6*R*,9*S*)-**2** and (5*R*,6*S*,9*R*)-**2**.

2′,3′-dihydrosorbicillin[23] itself, several bisorbicillinoids with this structural element are known, among them, for example, 2′,3′-dihydrobisorbicillinol.[6] As before for **1**, the absolute configuration of sorbicillactone B (**2**) was determined by quantum chemical CD calculations. The theoretical CD spectrum calculated for the (5*S*,6*R*,9*S*)-enantiomer of **2** matched very well the measured CD curve, while the one calculated for (5*R*,6*S*,9*R*)-**2** behaved nearly mirror-image like (Fig. 4). Accordingly, the CD calculations showed identical absolute configurations for **1** and **2**, thus, permitting an additional independent configurational assignment for this novel structural type.

The third compound was determined to have the molecular formula $C_{18}H_{24}O_5$ (*m*/*z* 320.1622, 320.1624 calcd for $C_{18}H_{24}O_5$) by HREIMS. The NMR data (Table 3) suggested the presence of a sorbyl chain in an enolic form as in sorbicillactone A (**1**). This chain was attached to a cyclohexanedione ring substituted with a hydroxy and two methyl groups, resembling the central six-membered ring of **1**. In addition to the resonances of the 14 carbon atoms of these two structural elements, the ^{13}C NMR spectrum showed the signals of four further carbons: one methyl (C-12; 15.4 ppm), two methylene (C-9 and C-11; 31.8 and 66.3 ppm, respectively), and one methine carbon (C-10; 79.9 ppm).

Several HMBC correlations (Fig. 5) allowed us to assign

Table 3. NMR data for sorbivinetone (**3**) in MeOD

Position	^{13}C (ppm)	^{1}H (ppm)	HMBC	NOESY	COSY [J_{HH} (Hz)]
1	112.3				
2	198.3				
3	68.7				
4	210.4				
5	74.9				
6	41.7	3.17 t	1, 2, 4, 5, 7, 9, 10, 1′	7, 2′	9α (2.7), 9β
7	24.0	1.15 s	4, 5, 6	6	
8	9.6	1.22 s	2, 3, 4, 10	10	
9	31.8	α 1.63 m	5, 6, 10		6, 9β (13.8), 10
		β 2.85 ddd	1, 3, 5, 6		6, 9α, 10 (8.4)
10	79.9	3.62 m	2, 3, 4, 6, 8, 11	8	9α, 9β
11	66.3	α 3.35 m	10, 12		11β (9.5), 12
		β 3.58 dq	10, 12		11α, 12 (7.0)
12	15.4	1.11 t	11		11α, 11β
1′	167.3				
2′	119.5	6.38 d	1, 3′	6	3′ (14.9)
3′	142.9	7.27 dd	1′, 4′, 5′	5′	2′, 4′ (11.0)
4′	132.3	6.38 m	1′, 6′		3′, 5′, 6′ (1.5)
5′	139.7	6.20 m	3′, 6′	3′	4′, 6′ (6.9)
6′	18.8	1.88 dd	4′, 5′		4′, 5′

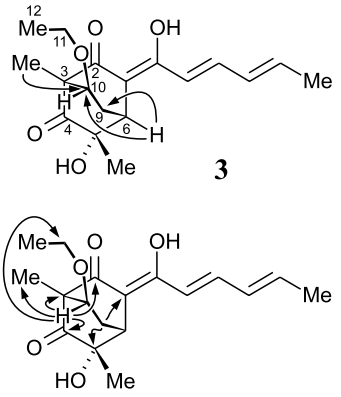
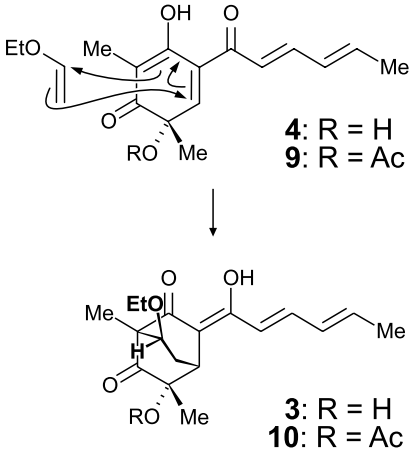


Figure 5. Key HMBC correlations of **3**.

C-9 and C-10 to a C_2-bridge across the cyclohexanedione ring from C-3 to C-6 forming a bicyclo[2.2.2]octanedione system. The orientation of the C_2-bridge was unequivocally determined with the help of the HMBC correlations 10-H↔C-2, 10-H↔C-4, 9-H↔C-1, and 9-H↔C-5, proving C-9 to be attached to C-6 and C-10 to C-3. The remaining two carbons were assigned to an *O*-ethyl group attached to C-10. This position was substantiated by the HMBC correlations 10-H↔C-11 and 11-H↔C-10, and by the chemical shift of C-10 (79.9 ppm), which indicated the presence of an oxygen function at this carbon, finally leading to the constitution **3** of the isolated compound. The relative configuration of the four stereocenters C-3, C-5, C-6, and C-10 remained unclear, because no informative couplings were observed in the NOESY spectrum. The fact that no doubled signals were seen in the ^{13}C NMR spectrum pointed to the presence of only one diastereomer of **3**.

Since *O*-ethyl groups are quite uncommon in natural products,[24] the presence of this group raised the suspicion that **3** might be an artifact of the work-up procedure. In agreement with this assumption, **3** as isolated from the feeding experiments with [$^{13}C_2$]-acetate was labeled in the sorbicillinoid part, but neither in the ethoxy function nor in the two bridging C-atoms. One possible way for the formation of **3** was a [4+2]-cycloaddition of ethyl vinyl ether to sorbicillinol[10] (**4**), a highly reactive precursor of many sorbicillin-derived metabolites, which is known to readily undergo Diels–Alder reactions.[14] To test this hypothesis, *O*-acetylsorbicillinol (**9**) as a more stable analog of **4** (albeit racemic) was prepared following a known synthetic procedure[14] and was reacted with ethyl vinyl ether in dilute aqueous acetonitrilic solution (Scheme 2). The reaction yielded a single product, which was shown to be *O*-acetylsorbivinetone (**10**) by NMR analysis. No signal-doubling was observed in the ^{13}C NMR spectrum, as would have been expected for the presence of a mixture of diastereomers. This reaction, thus, provides a plausible mechanism for the formation of **3**, even if the origin of the ethyl vinyl ether in the fungal culture (or in the solvent used for extraction) remains unclear (possibly from ethyl acetate). Since, the concentration of the artifact **3** probably reflects the concentration of sorbicillinol (**4**) present in the culture before its reaction with ethyl vinyl ether, this derivatization reaction might provide a useful method for trapping and analyzing sorbicillinol (**4**) and related highly unstable fungal metabolites, which can otherwise only be handled in dilute aqueous solution.[10] Because of its formation from ethyl vinyl ether and sorbicillinol, compound **3** was named sorbivinetone.



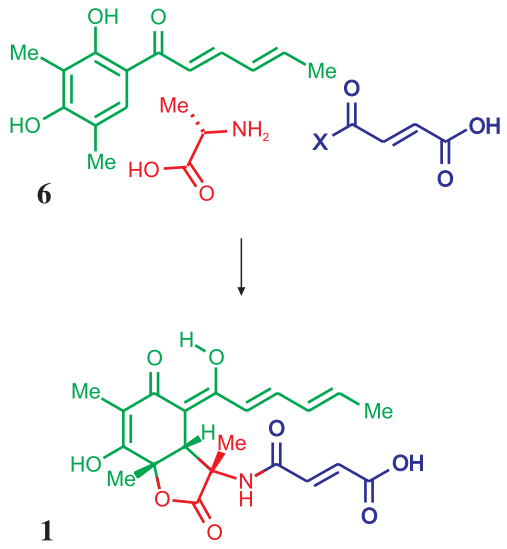
Scheme 2. Formation of **3** and **10** by Diels–Alder reaction.

By its NMR data and molecular mass, compound **7** was identified as the known sorbicillinoid dimer bisvertinolone.[7] The two remaining compounds were shown to be the known alkaloids meleagrine and roquefortine C. The latter was identified—including its absolute configuration—without isolation, merely by its spectral data gained by HPLC-UV, -MS, -NMR, and -CD.

The pattern of metabolites produced by the investigated strain of *P. chrysogenum* strongly depended on the growth conditions. The compounds described above were found in static liquid culture, but an agitated culture produced only two major metabolites. After isolation and spectroscopic analysis, one of these was identified as the known[8] compound oxosorbicillinol (**5**), one of the oxidized monomeric sorbicillinol-derived compounds. In the extract of a fungal culture grown in medium supplied with acetate as an additional carbon source (as a non-isotope preparation of the ensuing biosynthetic experiments, vide infra), sorbicillin (**6**)[4] was found, which is the parent structure of all of the compounds described in this paper (except for the non-sorbicillinoid alkaloids meleagrine and roquefortine C).

2.2. Biosynthesis of sorbicillactone A (1)

The unprecedented molecular framework of **1** made it rewarding to investigate the biosynthetic pathway leading to it. The 'sorbicillinoid' part of the molecule, that is, the six-membered ring and the sorbyl residue, appeared to be derived from a twofold *C*-methylated hexaketide, as recently, demonstrated for sorbicillinol (**4**), sorbicillin (**6**), and some bisorbicillinoids (Scheme 3).[25] The origin of the carbon atoms forming the lactone ring, C-9 and C-10, and its attached methyl carbon C-11 was less clear. The nitrogen at C-9 suggested this C_3 unit to be derived from alanine, but an origin from acetate with subsequent *C*-methylation could not be precluded a priori. To address this problem, feeding experiments were performed with [$^{13}C_2$]-acetate, [$^{13}C_3$]-L-alanine, and [methyl-^{13}C]-L-methionine after optimizing the growth conditions of the fungus for the production of sorbicillactone A (**1**) as the major secondary metabolite.



Scheme 3. Proposed biosynthesis of sorbicillactone A (**1**) from the three key precursors sorbicillin (**6**, Green), L-alanine (Red), and a fumaric acid precursor (Blue).

The ^{13}C NMR spectrum of sorbicillactone A (**1**) isolated from the fungus treated with [$^{13}C_2$]-acetate showed high incorporation of ^{13}C in all positions of the six-membered ring and the sorbyl chain, lower incorporation into the fumaryl residue (see below), but no labeling at all at C-9, C-10, and C-11, nor at the methyl carbons C-7 and C-8. The ^{13}C–^{13}C pairs observed in the INADEQUATE spectrum (Fig. 6A) gave full evidence for the folding mode of the hexaketide chain showing that of the two possible cyclization modes, that is, the question whether C-1 of the polyketide chain becomes C-2 or C-6 in sorbicillactone A (**1**), the latter was found to be true. This incorporation pattern of acetate into the sorbicillinoid part of the molecule was consistent with the one previously found in sorbicillinol (**5**) and sorbicillin (**6**) by Abe et al.[25] The fact that only one of the two possible incorporation patterns of acetate into the six-membered ring was observed also ruled out the possibility of a symmetric cyclic intermediate in the biosynthesis of **1**.

Administration of [$^{13}C_3$]-L-alanine to the fungus again resulted in a labeling of all those carbons that had been ^{13}C-enriched in the acetate experiment above, due to the (expected) partial metabolic transformation of alanine to pyruvate and, finally, to acetyl-CoA. But this time, the C_3 unit comprising C-9, C-10, and C-11 was also labeled, even with significantly higher incorporation of ^{13}C than in the other positions. The INADEQUATE spectrum (Fig. 6B) revealed the same incorporation pattern of C_2 units into the 6-ring and the sorbyl chain as in the acetate-feeding experiment. Additional $^1J_{CC}$-couplings between C-9 and C-10 as well as C-11 and C-10 evidenced incorporation of an alanine building block into this position—intact, without bond rupture. These results clearly indicated the C_3 unit forming the lactone ring to be derived directly from alanine, not from acetate. Again, no incorporation was observed for the methyl carbons C-7 and C-8. For related sorbicillinoid compounds, these had been proposed to originate from *C*-methylation reactions on the hexaketide chain,[25] presumably by methyl transfer from *S*-adenosylmethionine (SAM). This hypothesis was verified by feeding [methyl-^{13}C]-L-methionine to the fungus, leading to a significant increase in relative intensity of the C-7 and C-8 signals of sorbicillactone A, by a factor of 5.5 (Fig. 7).

As compared to the respective other labeled parts of the molecule, the fumaryl residue showed weaker labeling, both, when feeding [$^{13}C_2$]-acetate or [$^{13}C_3$]-L-alanine. Moreover, the labeling pattern of the amidic side chain was found to be non-symmetric, which clearly indicated that this residue was derived, at least partially, from an unsymmetric compound, thus excluding fumaric acid itself as a precursor. Indeed, feeding of [$^{13}C_4$]-fumaric acid did not result in a labeling of the fumaryl residue of sorbicillactone A (**1**), further, supporting the assumption that fumaric acid itself as a symmetric molecule is not the biosynthetic precursor of this side chain.

Based upon these feeding experiments, a biosynthetic route to sorbicillactone A (**1**) can be outlined. A key intermediate of this presumed biosynthesis is a twice *C*-methylated and, thus, branched hexaketide chain **11**, which is reduced at *C*-1, cyclized, and oxidatively dearomatized to give sorbicillinol (**4**). To this highly reactive compound, alanine (possibly activated by Schiff base formation with pyridoxal phosphate) is attached by esterification with the hydroxyl group at C-5 to give the intermediate **12**. After α-deprotonation of the alanine portion, the 5-ring lactone could be closed by intramolecular Michael addition (route A, Scheme 4). Alternatively, the Michael addition could take place first, leading to the intermediate **13**, followed by the ring-closing step now through an S_N1 type substitution (route B). Both routes seem imaginable, but the *cis*-fused annulated ring system can be seen as an argument in favor of route A, which leads to this configuration 'automatically', as a consequence of the intramolecular C,C-bond formation. In the last step of the proposed pathway, the bicyclic amino lactone **14** is converted to sorbicillactone A (**1**) by *N*-acylation with a fumaric acid related, yet unsymmetric precursor.

To exclude the possibility that alanine is already part of the open polyketide chain (route C), attempts were made to detect the highly reactive intermediate sorbicillinol (**4**) in the fungal extract. LC–MS investigations revealed no **4** therein, which, however, is not unexpected considering its high reactivity[11] and its, hence, possibly low concentration. In an alternative approach, ethyl vinyl ether was added to fungal cultures producing sorbicillactone A (**1**) in order to trap the sorbicillinol (**4**) by in vivo cycloaddition and to detect, for example, sorbivinetone (**3**) as a stable product of this reaction. The HPLC of the extract of the cultivation in the presence of ethyl vinyl ether displayed one single additional compound with a UV spectrum similar to that of sorbivinetone (**3**). Surprisingly, this compound was not identical to **3**, but significantly more polar. Isolation and investigation by NMR and mass spectrometry revealed it to have the structure **15**. The compound was named sorbivinetol, due to the presence of the secondary hydroxy group at C-4 instead of a carbonyl group as in sorbivinetone (**3**).

One possible explanation for the presence of sorbivinetol (**15**) at the expense of sorbivinetone (**3**) in the fungal culture

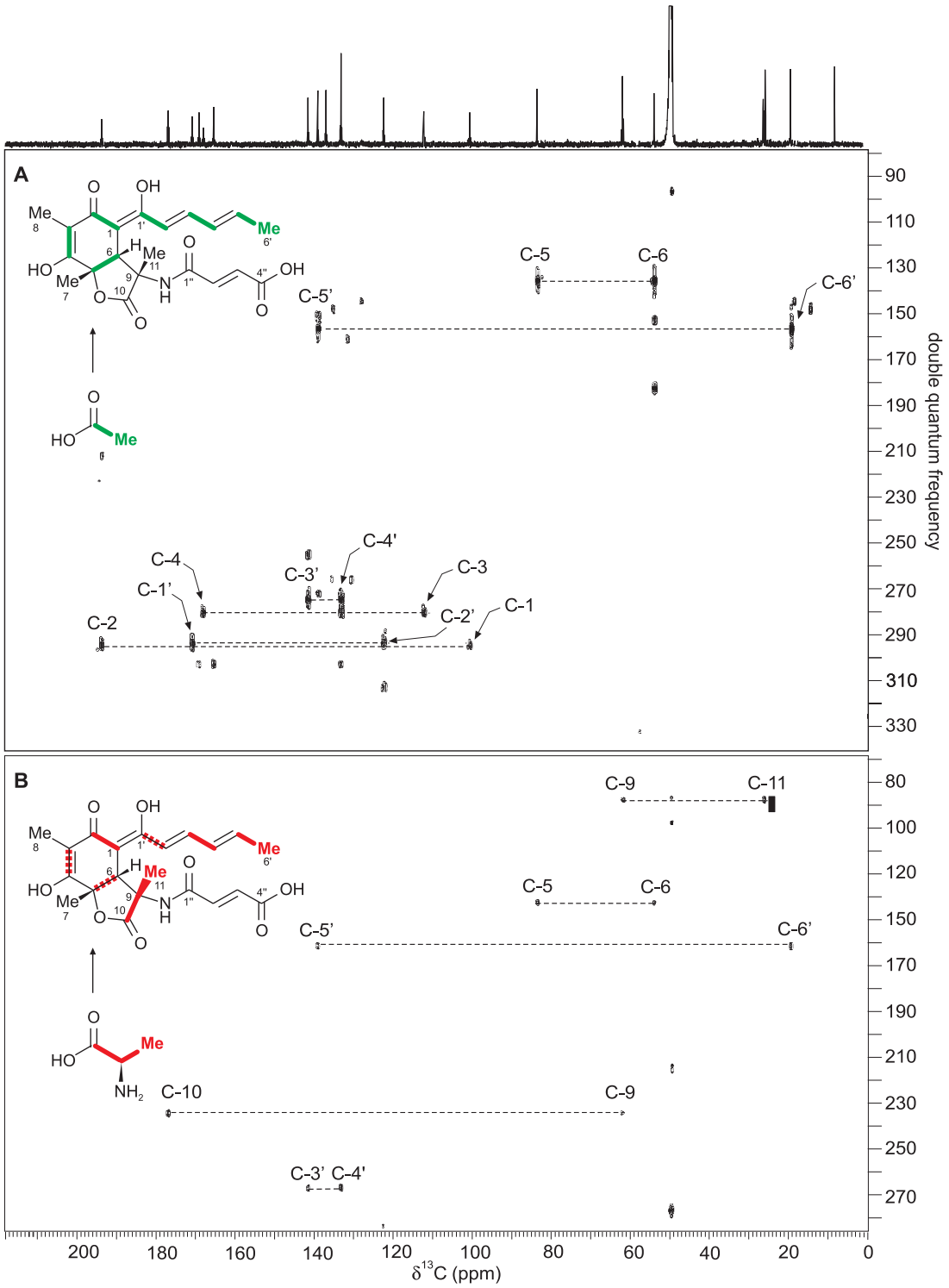


Figure 6. INADEQUATE spectra of sorbicillactone A (**1**) after feeding [$^{13}C_2$]-acetate (A) and [$^{13}C_3$]-L-alanine (B) to *P. chrysogenum* cultures; interactions of dotted bondings not visible in the INADEQUATE spectrum; ^{13}C NMR spectrum of **1** with its natural ^{13}C content is shown above A.

treated with ethyl vinyl ether was the quenching of sorbicillinol (**4**) with ethyl vinyl ether with formation of sorbivinetone (**3**, Scheme 5, pathway A), already at an earlier stage than a trapping during workup observed above, so that the adduct **3** formed in cultures of the living fungus had the possibility of subsequently being enzymatically reduced to sorbivinetol (**15**). This seems more reasonable than the direct formation of **15** by reaction of ethyl vinyl ether with the hypothetical intermediate **16** (pathway B), a reduced form of sorbicillinol (**4**), which should not be as reactive as the electron-poorer dienone **3**, which constitutes an ideal diene for Diels–Alder additions with inverse electron demand.

The feeding experiments clearly demonstrated the carbon skeleton of sorbicillactone A (**1**) to be derived from a

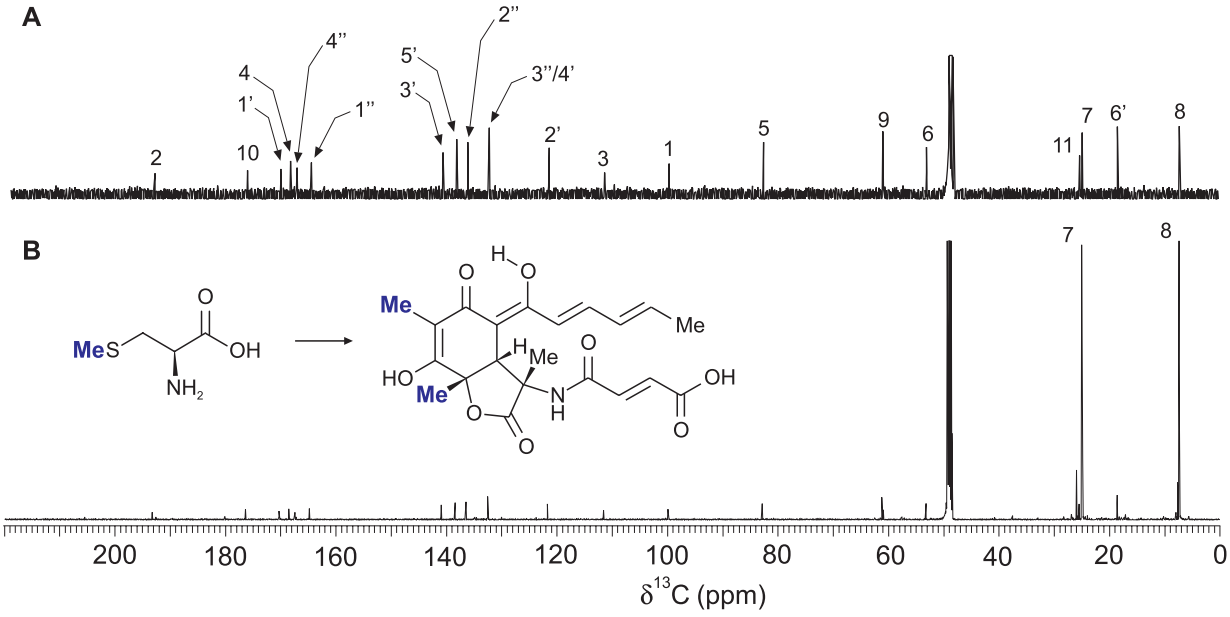
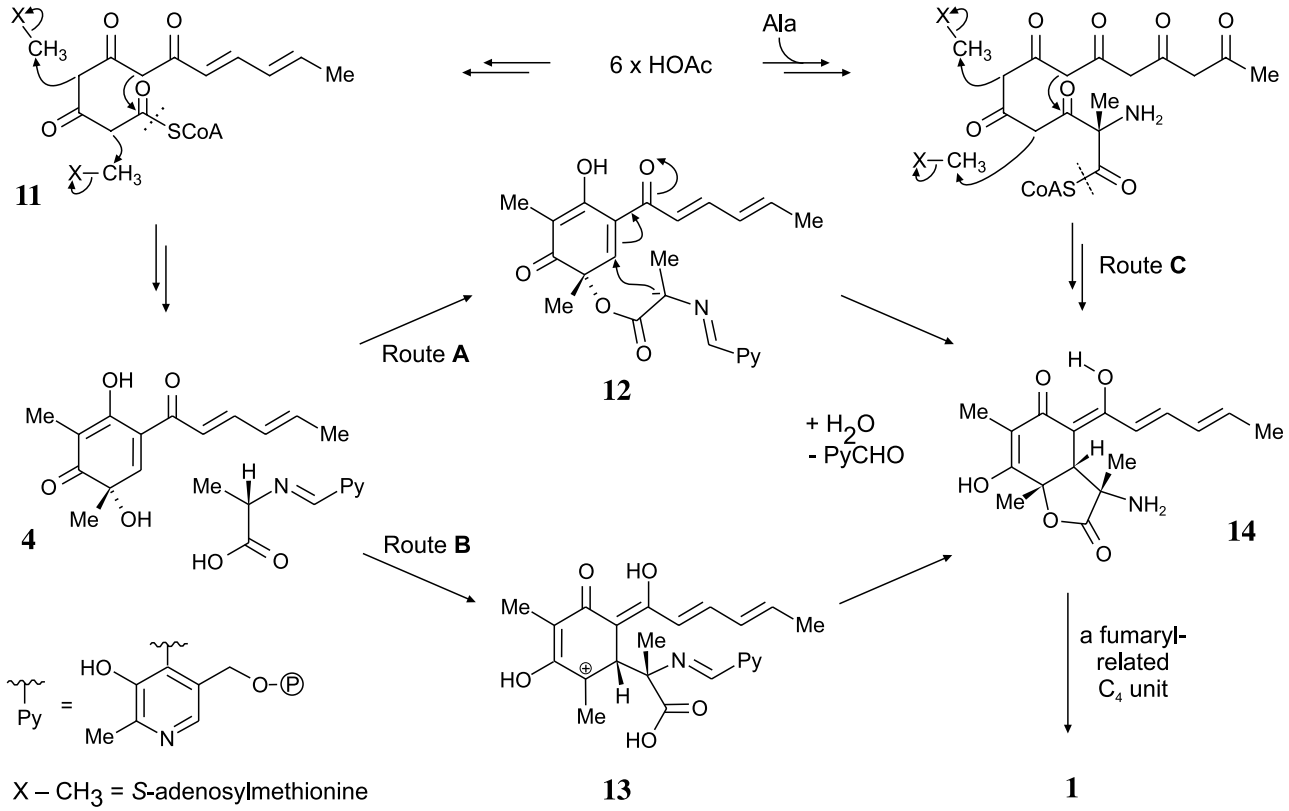


Figure 7. ^{13}C NMR spectra of sorbicillactone A (**1**) with its natural ^{13}C content (A) and after feeding [methyl-^{13}C]-L-methionine (B).

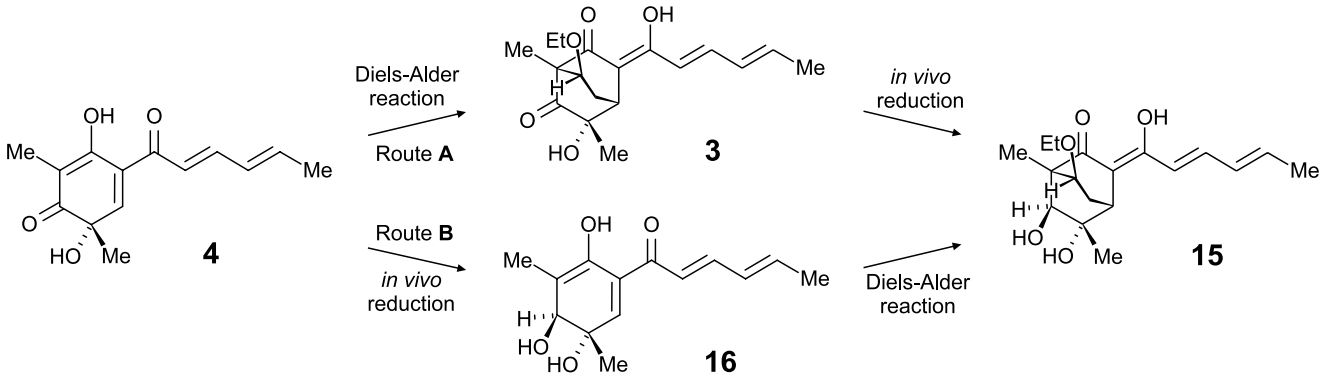
'sorbicillinol unit' formed from acetate and *S*-adenosylmethionine, the amino acid alanine, and a biosynthetic equivalent of fumaric acid. Consequently, this fungal metabolite does not only possess a unique structure, but is also the first member of a novel class of amino acid derived sorbicillinoid natural products, the 'sorbicillinoid alkaloids'. All other sorbicillinoid and bisorbicillinoid metabolites as yet known are derived from one or two sorbicillinol molecules with no other precursors involved in their biosynthesis.

2.3. Biological properties

2.3.1. Antileukemic activities. All new compounds isolated were tested for their cytotostatic/cytotoxic activity against several tumor cell lines, namely murine leukemic



Scheme 4. Possible biosynthetic routes to sorbicillactone A (**1**).



Scheme 5. Formation of sorbivinetol (**15**).

lymphoblasts L5178y, rat adrenal pheochromocytoma PC12 cells, human T lymphocytes H9 cells, and human cervix carcinoma HeLa S3 cells. Sorbicillactone A (**1**) displayed a notable selective activity against L5178y cells with an IC_{50} of 2.2 μg/mL, for the other cell lines tested the IC_{50} was >10 μg/mL.[26,27] The structurally related sorbicillactone B (**2**) exhibited a significantly lower activity than **1**, with IC_{50} values of >10 μg/mL for L5178y, PC12, and HeLa cells. Sorbivinetone (**3**), by contrast, caused only a low inhibitory activity on L5178y cells (IC_{50} value >10 μg/mL). Interestingly, the synthetic compound *O*-acetylsorbivinetone (**10**) displayed a much stronger activity than **3**. Its IC_{50} concentrations against L5178y, PC12, and HeLa S3 cells were found to be 0.62, 9.2, and 3.6 μg/mL, respectively.[28] When comparing the bioactivities of **3** and **10**, it is important to take into consideration the racemic nature of the latter. Sorbivinetol (**15**) was cytotoxic for the L5178y cells (IC_{50} 20 μg/mL). The IC_{50} values for PC12 and HeLa cells were >30 μg/mL.

2.3.2. Anti-HIV activity of sorbicillactone A (1). Besides its cytotoxicity, sorbicillactone A (**1**) also showed a high anti-HIV activity. In the concentration range between 0.3 and 3.0 μg/mL, sorbicillactone A protected human T lymphocytes (H9 cells) against the cytopathic effect of HIV-1 and inhibited the expression of viral proteins.[26,27]

2.3.3. Effect of 1 on $[Ca^{2+}]_i$ in primary neurons. The addition of 10 μg/mL of sorbicillactone A (**1**) induced no changes of $[Ca^{2+}]_i$ in primary neurons (data not shown). The incubation of neurons with 200 μM L-glutamic acid (L-Glu) and 2.5 mM Ca^{2+} (Fig. 8) resulted in a strong increase of $[Ca^{2+}]_i$ after 10 min with ratio values (340/380 nm) from 0.83 ± 0.01 to 2.54 ± 0.08 (307%). This control value (Δ ratio 1.715) was set as 100%. Pre-incubation of neurons with 10 μg/mL of sorbicillactone A (**1**) resulted in a significant decrease of the $[Ca^{2+}]_i$ level (by approximately 50%) after incubation of neurons with 200 μM L-Glu and 2.5 mM $CaCl_2$ ($p<0.001$).

Addition of 200 μM of serotonin (5-HT) and 2.5 mM Ca^{2+} to the primary neurons (Fig. 9) also induced an increase in $[Ca^{2+}]_i$ after 10 min. The ratio value significantly increased from 0.81 ± 0.10 to 1.78 ± 0.11 (220%). The decrease in the intracellular calcium concentration after pre-incubation of neurons with 10 μg/mL of sorbicillactone A (**1**) and following incubation with 200 μM of 5-HT and 2.5 mM Ca^{2+} was significant ($p<0.001$) and reached values found in untreated cells.

L-Glutamic acid and serotonin are important neurotransmitters that play crucial roles in many neurological diseases. On the basis of the results obtained, sorbicillactone A (**1**) can be

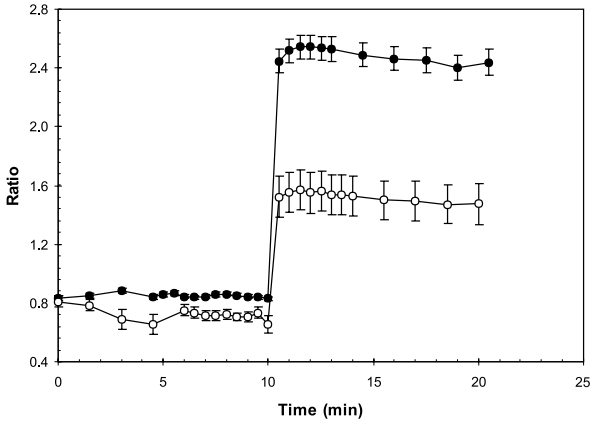


Figure 8. Change of the $[Ca^{2+}]_i$ level after incubation of neuronal cells with 200 μM of L-glutamic acid (L-Glu) and 2.5 mM Ca^{2+} without [(●); control; 10 min], and after pre-incubation (5 min) of neurons with 10 (○) μg/mL of sorbicillactone A (**1**). The results are expressed as mean values ± SE (control $n=72$, L-glu $n=19$). The fluorescence ratio of the Ca^{2+} indicator dye fura-2 at 340 and 380 nm is indicated.

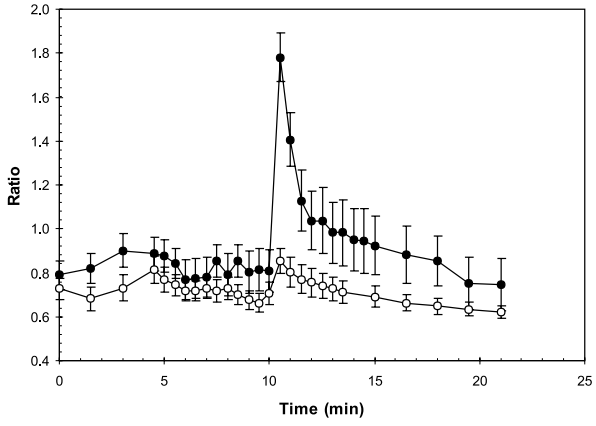


Figure 9. Change of the $[Ca^{2+}]_i$ level after stimulation of neuronal cells with 200 μM of serotonin (5-HT) and 2.5 mM Ca^{2+} without [(●); control; 10 min], and after pre-incubation (5 min) of neurons with 10 (○) μg/mL of sorbicillactone A (**1**). The results are expressed as mean values ± SE (control $n=14$, 5-HT $n=21$). The fluorescence ratio of the Ca^{2+} indicator dye fura-2 at 340 and 380 nm is indicated.

considered as a promising neuroprotective compound also for in vivo models.

3. Conclusions

The sorbicillactones A (**1**) and B (**2**) are the first members of a novel class of secondary metabolites, the sorbicillin derived alkaloids. These unique structures originate via a likewise unprecedented biosynthetic pathway investigated by feeding experiments with ^{13}C-labeled precursors. Furthermore, sorbicillactone A (**1**) shows selective anti-leukemic activities and furthermore antiviral and neuroprotective properties. It could, therefore, be a potential new lead structure in medicinal chemistry.

4. Experimental

4.1. General experimental procedure

Melting points are uncorrected. NMR spectra were recorded on 600 and 400 MHz spectrometers. For calibration of ^{13}C and ^{1}H chemical shifts the carbon signals and the residual proton signals, respectively, of the solvents were used (CH_3OD: δ_H 3.31 and δ_C 49.15; THF-d_8: δ_H 3.58 and δ_C 67.57). Proton-detected, heteronuclear correlations were measured using HMQC (optimized for $^{1}J_{HC}=145$ Hz) and HMBC (optimized for $^{n}J_{HC}=7$ Hz or $^{n}J_{HC}=3.5$ Hz) pulse sequences. ROESY and INADEQUATE experiments were performed using pulse sequences from the standard Bruker library. For HPLC NMR, a 60 μL *z*-gradient flow probe (Bruker) was used in a 14.1 T magnet (600 MHz, Bruker); for solvent suppression the WET pulse sequence was applied.[29] In high-performance liquid chromatography (HPLC) separations, Symmetry C_{18} columns were used (Waters, 2.1×150 mm or 19×300 mm); the eluents were water and acetonitrile with 0.05% TFA each. All solvents used were analytical grade or distilled prior to use.

4.2. Computational methods

The MD simulations of **1** were performed on an SGI Octane (R 10000) workstation using the TRIPOS[22] force field as implemented in the molecular modeling package Sybyl 6.4,[22] using a time step of 0.5 fs. In the case of **2** the MD calculations were performed on a Linux AMD MP 2400+ workstation by using the program package Sybyl 6.9. The molecules were weakly coupled to a thermal bath at $T=$ 500 K in the case of **1**, and 600 K in the case of **2**. The wave functions for the calculation of the rotational strengths for the electronic transitions from the ground state to excited states were obtained by CNDO/S-CI[30,31] calculations, in which the CI expansion takes into account the ground state and all n and π orbitals. These calculations were carried out on iPII-, iPIII-Linux, and Linux AMD MP 2400+ workstations using the BDZDO/MCDSPD[32] program package. For a better comparison of the theoretical CD spectrum with the experimental one, a Gaussian band shape function was generated over the calculated rotational strength values.

4.3. Organism

The fungus was isolated from the interior of a specimen of the Mediterranean sponge *I. fasciculata*, collected by scuba diving from a depth of 17.5 m in the Bight of Fetovaia (Elba, Italy). By morphological criteria and 18S rDNA sequence data, the fungus was identified as a strain of *P. chrysogenum*. This strain was deposited at DSMZ under DSM 16137.

4.4. Fermentation

For chemical investigations, the fungus was grown as a static culture in 30 1-L Erlenmeyer flasks containing 300 mL of liquid saline Wickerham Medium (WS: 3 g yeast extract, 3 g malt extract, 5 g peptone, 10 g glucose dissolved in 1 L sea water, pH adjusted to 7.3)[33] and incubated at 30 °C in the dark. After a growth period of 14 days, 30 mL of ethyl acetate were added to each flask, and the mixture was kept at −80 °C until extraction.

4.5. Biosynthetic investigations

For the feeding experiments, the fungus was grown on WS liquid medium (pH 6) prepared with 0.5% aqueous NaCl solution instead of seawater at 30 °C. After formation of a stable surface mycelium, the medium was substituted. The fresh medium contained a reduced glucose concentration of 4 g/L, the ^{13}C-labeled compound (sodium [$^{13}C_2$]-acetate, [$^{13}C_3$]-L-alanine, [methyl-^{13}C]-L-methionine, or [$^{13}C_4$]-fumaric acid) at a concentration of 0.2 mg/mL, and the respective unlabeled compound (0.8 mg/mL) after optimization of the feeding concentrations. After incubation of the cultures with the labeled substrates for 6 days, 50 mL of ethyl acetate were added per 100 mL culture medium. In Diels–Alder trapping experiments, 50 μL of ethyl vinyl ether were added to 100 mL of culture on 4 consecutive days (days 4 to 7), and growth was stopped by addition of 50 mL ethyl acetate on day 8.

4.6. Extraction and isolation

The mycelium and the culture broth of static cultures were separately extracted with dichloromethane–methanol (1:1) and ethyl acetate, respectively. The combined extracts were then partitioned between methanol–water (4:1) and petroleum ether. After evaporation of the solvents, the MeOH/H_2O fraction of a 10-L static culture was separated by preparative HPLC, using a linear solvent gradient from 15 to 100% acetonitrile in 25 min (flow rate 11 mL/min), to give meleagrine (234 mg, t_R 8.0 min), a mixture of sorbicillactones A and B (**1** and **2**, t_R 12.7 and 13.2 min), sorbivinetone (**3**, 5.1 mg, t_R 20.0 min), and bisvertinolone (**7**, 9.8 mg, t_R 22.1 min). The mixture of **1** and **2** was resolved by preparative HPLC under isocratic conditions (35% acetonitrile; flow 12 mL/min) yielding 6.0 mg of sorbicillactone A (**1**) and 2.6 mg of sorbicillactone B (**2**).

Agitated cultures were extracted using the procedure described above. The combined extracts of mycelium and culture broth were desalted by partitioning between water and ethyl acetate. Preparative HPLC of the extract from a 750 mL culture (linear gradient from 20 to 80% acetonitrile

in 35 min; flow rate 12 mL/min) yielded oxosorbicillinol (**5**, 6.1 mg, t_R 29 min).

The filtrate of the fungal cultures fed with ^{13}C-labeled precursors was extracted with XAD-16 resin, which then was washed with water. The adsorbed metabolites were subsequently eluted with methanol. The methanol was evaporated from the solvent mixture, and the residual aqueous phase (pH 7) was extracted with ethyl acetate. This extract was discarded. After acidification to pH 2 with phosphoric acid, the aqueous phase was exhaustively extracted with ethyl acetate. Separation of the ethyl acetate extracts by preparative HPLC (linear gradient from 30 to 70% acetonitrile in 30 min; flow rate 12 mL/min) gave 2.7, 4.8, and 6.8 mg of sorbicillactone A (**1**; t_R 17.1 min) from the cultures fed with [$^{13}C_2$]-acetate (100 mL culture), [$^{13}C_3$]-L-alanine (200 mL culture) and [methyl-^{13}C]-L-methionine (200 mL culture), respectively. The fungus grown in the presence of ethyl vinyl ether (300 mL culture) was extracted and separated in the same manner, to give 2.6 mg of sorbivinetol (**15**, t_R 21 min).

4.6.1. Sorbicillactone A (1). Yellow crystalline needles (MeOH/H_2O); mp 205 °C (dec); $[\alpha]_D^{20}$ −939° (*c* 0.2, MeOH); CD (*c* 0.2, MeOH) $\Delta\varepsilon_{208}$ +16.7, $\Delta\varepsilon_{231}$ −21.2, $\Delta\varepsilon_{277}$ +21.0, $\Delta\varepsilon_{372}$ −20.9; IR (KBr) ν_{max} 3257, 3089, 2980, 2937, 1771, 1616, 1555, 1446, 1410, 1348, 1264, 1204, 1067, 993, 944 cm^{-1}; NMR data, see Table 1; HRESIMS 418.1515 ([M+H]$^+$, 418.1502 calcd for $C_{21}H_{24}NO_8$).

4.6.2. Sorbicillactone B (2). Light-brown amorphous solid (MeOH/H_2O); mp 109–115 °C; $[\alpha]_D^{20}$ −327° (*c* 0.2, MeOH); CD (*c* 0.2, MeOH) $\Delta\varepsilon_{194}$ −6.0, $\Delta\varepsilon_{223}$ +8.2, $\Delta\varepsilon_{248}$ −4.7, $\Delta\varepsilon_{270}$ +11.3, $\Delta\varepsilon_{331}$ −13.3; IR (KBr) ν_{max} 3291, 3065, 2982, 2931, 1772, 1717, 1672, 1557, 1450, 1384, 1347, 1223, 1108, 1065, 969 cm^{-1}; NMR data, see Table 2; HRESIMS 420.1646 ([M+H]$^+$, 420.1658 calcd for $C_{21}H_{26}NO_8$).

4.6.3. Sorbivinetone (3). Light-brown amorphous solid (MeOH/H_2O); mp 100–118 °C; $[\alpha]_D^{20}$ +219° (*c* 0.1, MeOH); CD (*c* 0.1, MeOH) $\Delta\varepsilon_{223}$ −2.5, $\Delta\varepsilon_{246}$ +1.8, $\Delta\varepsilon_{310}$ +9.7, $\Delta\varepsilon_{353}$ +8.1; IR (KBr) ν_{max} 3425, 2966, 2926, 2860, 1728, 1629, 1451, 1380, 1092, 1026, 998 cm^{-1}; NMR data, see Table 3; EIMS (70 eV) *m/z* (rel int.) 320 [M]$^+$(30), 274 (81), 245 (48), 231 (28), 217 (18), 205 (31), 203 (24), 191 (33), 181 (35), 180 (23), 167 (24), 151 (45), 137 (22), 95 (100); HREIMS 320.1622 (320.1624 calcd for $C_{18}H_{24}O_5$).

4.6.4. Sorbivinetol (15). Yellow amorphous solid (MeOH/H_2O); mp 78–81 °C; IR (KBr) ν_{max} 3422, 2980, 2940, 2870, 1726, 1700, 1680, 1451, 1399, 1380, 1345, 1299, 1240, 1205, 1180, 1115, 1100, 1060, 1020, 998, 950, 900, 880 cm^{-1}; ^1H NMR (400 MHz, MeOH-d_4) δ 1.10 (3H, t, *J*=7.0 Hz, 12-H), 1.13 (3H, s, 7-H), 1.19 (3H, s, 8-H), 1.28, (1H, m, 9α-H), 1.68 (3H, d, *J*=6.8 Hz, 6′-H), 2.70 (1H, ddd, *J*=8.6, 13.1 Hz, 9β-H), 2.78 (1H, t, *J*=2.7 Hz, 6-H), 3.32 (1H, m, 11α-H), 3.40 (1H, s, 3-H), 3.56 (1H, m, 10-H), 3.56 (1H, m, 11β-H), 6.12 (1H, m, 5′-H), 6.30 (1H, d, *J*=14.9 Hz, 2′-H), 6.33 (1H, m, 4′-H), 7.18 (1H, dd, *J*=10.9, 14.9 Hz, 3′-H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 206.0 (C-2), 165.6 (C-1′), 141.3 (C-3′), 138.5 (C-5′), 132.5 (C-4′), 120.1 (C-2′), 112.2 (C-1), 82.5 (C-4), 79.8 (C-10), 76.9 (C-5), 65.8 (C-11), 57.4 (C-3), 42.9 (C-6), 32.1 (C-9), 24.5 (C-7), 18.9 (C-6′), 15.7 (C-12), 13.7 (C-8); EIMS (70 eV) *m/z* (rel int.) 322 [M]$^+$(18), 258.1 (10), 217.1 (13), 215.1 (17), 205.1 (15) 203.1 (42), 189.1 (13), 149.1 (11), 135.1 (20), 109.1 (10), 105.1 (14), 97.7 (15), 95.1 (100), 91.1 (13), 85.2 (17), 83.1 (15), 81.1 (12), 77.1 (11), 71.1 (15), 69.1 (30), 67.1 (35), 57.1 (36), 55.1 (28), 44 (44), 43.1 (23), 43.0 (35), 41.1 (36); HREIMS 322.1783 (322.1782 calcd for $C_{18}H_{24}O_5$).

4.6.5. Sorbicillactone A methyl ester (8). A mixture of 5 mL methanol, 0.2 mL concn H_2SO_4, and 30 mg of sorbicillactone A (**1**) was stirred for 6 h at room temperature, poured into 100 mL water, and extracted twice with 100 mL ethyl acetate. The solvent of the organic layer was evaporated. The residue was subjected to preparative HPLC (linear gradient from 30 to 70% acetonitrile; flow rate 12 mL/min) to afford 18.6 mg of sorbicillactone A methyl ester (**8**, t_R 21 min).

Compound **8**. Yellow solid; mp 166–170 °C; $[\alpha]_D^{20}$ −558° (*c* 0.2, MeOH); CD (*c* 0.2, MeOH) $\Delta\varepsilon_{208}$ +11.1, $\Delta\varepsilon_{231}$ −12.6, $\Delta\varepsilon_{278}$ +12.5, $\Delta\varepsilon_{370}$ −13.0; IR (KBr) ν_{max} 3333, 2931, 1783, 1730, 1681, 1612, 1552, 1442, 1415, 1384, 1350, 1310, 1198, 1176, 1065 cm^{-1}; ^1H NMR (400 MHz, THF-d_8) δ 16.6 (1H, br s, 1′-OH), 7.66 (1H, s, NH), 7.20 (1H, dd, *J*=11.0, 14.7 Hz, 3′-H), 6.71 (1H, d, *J*=15.4 Hz, 2″-H), 6.52 (1H, d, *J*=15.4 Hz, 3″-H), 6.39 (1H, d, *J*=14.7 Hz, 2′-H), 6.28 (1H, m, 4′-H), 6.09 (1H, m, 5′-H), 3.69 (3H, s, COOCH_3), 3.47 (1H, s, 6-H), 1.82 (3H, dd, *J*=1.3, 6.2 Hz, 6′-H), 1.55 (3H, s, 7-H), 1.52 (3H, s, 8-H), 1.42 (3H, s, 11-H); ^{13}C NMR (100 MHz, THF-d_8) δ 192.0 (C-2), 173.0 (C-10), 169.7 (C-1′), 166.7 (C-4), 165.9 (C-4″), 162.3 (C-1″), 139.1 (C-3′), 137.0 (C-5′), 136.3 (C-2″), 131.9 (C-4′), 130.3 (C-3″), 121.7 (C-2′), 110.8 (C-3), 99.5 (C-1), 81.1 (C-5), 60.0 (C-9), 53.2 (C-6), 51.8 (COO*C*H_3), ~26.0 (C-11), ~25.5 (C-7), 18.6 (C-6′), 7.3 (C-8); ESIMS (positive) *m/z* 432 [M+H]$^+$.

4.6.6. *O*-Acetylsorbivinetone (10). Eight milligrams of racemic *O*-acetylsorbicillinol (**9**) synthesized following a known procedure[14] were purified using preparative HPLC. Since, **9** was rather unstable, it was not isolated by evaporation of the solvents of the respective HPLC fractions (11 mL), but was immediately reacted further, by addition of 100 μL of ethyl vinyl ether to the respective fractions. After 24 h the solvent was evaporated to yield 3.2 mg of *O*-acetylsorbivinetone (**10**).

Compound **10**. Yellow oil; IR (KBr) ν_{max} 3451, 2983, 2939, 2876, 1738, 1619, 1571, 1450, 1373, 1243, 1094, 1023 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 7.32 (1H, dd, *J*=11.0, 15.0 Hz, 3′-H), 6.40 (1H, m, 4′-H), 6.38 (1H, d, *J*=15 Hz, 2′-H), 3.91 (1H, t, *J*=2.8 Hz, 6-H), 3.75 (1H, dd, *J*=2.5, 8.2 Hz, 10-H), 3.58 (1H, m, 11-H_β), 3.36 (1H, m, 11-H_α), 2.48 (1H, ddd, *J*=2.7, 8.2, 14.3 Hz, 9-H_β), 2.07 (3H, s, OCOCH_3), 1.89 (3H, d, *J*=6.8 Hz, 6′-H), 1.72 (1H, dd, *J*=2.9, 14.3 Hz, 9-H_α), 1.36 (3H, s, 7-H), 1.26 (3H, s, 8-H), 1.09 (3H, t, *J*=7.0 Hz, 12-H); ^{13}C NMR (100 MHz, MeOD) δ 204.0 (C-4), 197.2 (C-2), 171.5 (O*C*OCH$_3$), 168.3 (C-1′), 143.8 (C-3′), 140.7 (C-5′), 132.4 (C-4′), 119.3 (C-2′), 111.3

(C-1), 82.5 (C-5), 79.3 (C-10), 68.7 (C-3), 66.4 (C-11), 39.0 (C-6), 32.2 (C-9), 21.8 (C-7), 21.4 ($OCOCH_3$), 19.0 (C-6′), 15.6 (C-12), 9.9 (C-8); EIMS (70 eV) *m/z* (rel int.) 362 $[M]^+$(21), 320 (20), 294 (29), 274 (25), 245 (18), 207 (53), 205 (30), 191 (18), 179 (159; 95 (69), 43 (100); HREIMS 362.1731 (362.1729 calcd for $C_{20}H_{26}O_6$).

4.7. Biological activities

4.7.1. Cell lines. L5178y (ATCC CRL-1722) and H9 cells (ATCC HTB-176) were grown in RPMI1640 supplemented with 10 mM Hepes, 10% fetal calf serum (FCS) (PAA, Cölbe, Germany) and 0.1% gentamycin. PC12 cells (ATCC CRL-1573) were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% horse serum, 5% FCS, and 0.1% gentamycin. HeLa S3 cells (ATCC CCL-2.2) were cultured in DMEM supplemented with 10% FCS. All cells were routinely passaged once or twice weekly.

4.7.2. MTT assay. The cell viability was determined using the MTT assay.[34] The evaluation was performed in 96-well plates at 595 nm using an ELISA plate reader.

4.7.3. Calcium measurement on primary neurons. The primary cortical cell culture was prepared from 17 to 18 days old rat embryos following the modified procedure.[35,36] The same materials were used as published before.[37] Sorbicillactone A (**1**) was dissolved in 100% (v/v) DMSO (Stock solution 10 mg/mL) and stored at −20 °C. In the pre-incubation period I (0–5 min) the base line of the calcium level in the neurons was determined. During the pre-incubation period II (5 to 10 min) neurons were pre-incubated with 0.1% (v/v) DMSO (control) or 10 μg/mL of **1**. After pre-incubation period II, at time 10 min, 200 μM L-glutamic acid (L-Glu) or 200 μM serotoin (5-HT) and 2.5 mM $CaCl_2$ were added to the neurons. In all sets of experiments Locke's solution (154 mM NaCl; 5.6 mM KCl; 3.6 mM $NaHCO_3$; 5.6 mM glucose and 10 mM Hepes; pH 7.4; without Ca^{2+} and Mg^{2+}) was used as a buffer. The calcium level was monitored for at least 20 min.

Acknowledgements

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References and notes

1. Part 7 in the series Novel Marine Natural Products, for part 6 see Ref. 17.
2. Kozlovskii, A. G.; Vinokurova, N. G.; Ozerskaya, S. M. *Microbiology* **1998**, *67*, 397–400.
3. Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. *Top. Curr. Chem.* **2000**, *209*, 97–173.
4. Cram, D. J.; Tishler, M. *J. Am. Chem. Soc.* **1948**, *70*, 4238–4239.
5. Andrade, R.; Ayer, W. A.; Mebe, P. P. *Can. J. Chem.* **1992**, *70*, 2526–2535.
6. Trifonov, L. S.; Hilpert, H.; Floersheim, P.; Dreiding, A. S.; Rast, D. M.; Skrivanova, R.; Hoesch, L. *Tetrahedron* **1986**, *42*, 3157–3179.
7. Kontani, M.; Sakagami, Y.; Marumo, S. *Tetrahedron Lett.* **1994**, *35*, 2577–2580.
8. Abe, N.; Yamamoto, K.; Hirota, A. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 620–622.
9. Sperry, S.; Samuels, G. J.; Crews, P. *J. Org. Chem.* **1998**, *63*, 10011–10014.
10. Abe, N.; Sugimoto, O.; Tanji, K.; Hirota, A. *J. Am. Chem. Soc.* **2000**, *122*, 12606–12607.
11. Nicolaou, K. C.; Jautelat, R.; Vassilikogiannakis, G.; Baran, P. S.; Simonsen, K. B. *Chem. Eur. J.* **1999**, *5*, 3651–3665.
12. Abe, N.; Murata, T.; Hirota, A. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 661–666.
13. Barnes-Seeman, D.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1503–1504.
14. Nicolaou, K. C.; Vassilikogiannakis, G.; Simonsen, K. B.; Baran, P. S.; Zhong, Y.-L.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 3071–3079.
15. Warr, G. A.; Veitch, J. A.; Walsh, A. W.; Hesler, G. A.; Pirnik, D. M.; Leet, J. E.; Lin, P.-F.M; Medina, I. A.; McBrien, K. D.; Forenza, S.; Clark, J. M.; Lam, K. S. *J. Antibiot.* **1996**, *49*, 234–240.
16. Bringmann, G.; Lang, G.; Steffens, S.; Günther, E.; Schaumann, K. *Phytochemistry* **2003**, *63*, 437–443.
17. Bringmann, G.; Lang, G.; Steffens, S.; Schaumann, K. *J. Nat. Prod.* **2004**, *67*, 311–315.
18. Bringmann, G.; Lang, G. In *Marine Molecular Biotechnology*; Müller, W. E. G., Ed.; Sponges (porifera); Springer: Berlin, 2003; Vol. 1, pp 89–116.
19. Part of this work has been published in preliminary form.[26]
20. Both, the constitution and the relative configuration of **1** were verified by a single-crystal X-ray analysis.
21. Bringmann, G.; Mühlbacher, J.; Repges, C.; Fleischhauer, J. *J. Comput. Chem.* **2001**, *22*, 1273–1278.
22. *SYBYL*: Tripos Associates, 169 Kanley Road, Suite 303, St. Louis, MO 63144.
23. Trifonov, L. S.; Bieri, J. H.; Prewo, R.; Dreiding, A. S.; Hösch, L.; Rast, D. M. *Tetrahedron* **1983**, *39*, 4243–4256.
24. Laatsch, H., *Antibase 2000, a Natural Products Database for Rapid Structure Determination, Chemical Concepts*; Wiley: Weinheim; 2000.
25. Abe, N.; Arakawa, T.; Yamamoto, K.; Hirota, A. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 2090–2099.
26. Bringmann, G.; Lang, G.; Mühlbacher, J.; Schaumann, K.; Steffens, S.; Rytik, P. G.; Hentschel, U.; Morschhäuser, J.; Brun, R. In *Marine Molecular Biotechnology*; Müller, W. E. G., Ed.; Sponges (porifera); Springer: Berlin, 2003; Vol. 1, pp 231–253.
27. Bringmann, G.; Lang, G.; Mühlbacher, J.; Schaumann, K.;

Steffens, S.; Müller, W. E. G. German Patent Application DE 102 38 257.3, filed 21.08.2002; PCT/EP2003/007805 (17.7.2003); International Patent Number WO 2004/026854 A1 (1.4.2004).
28. Bringmann, G.; Lang, G.; Gulder, T.; Schaumann, K.; Steffens, S.; Imhoff, J. F.; Müller, W. E. G.; Perović, S. German Patent Application DE 10 2004 005 106.2, filed 02.02.2004; PCT/EP2003/007805 (07.17.2003); International Patent Number WO 2004/026854 A1, (04.01.2004).
29. Ogg, R. J.; Kingsley, P. B.; Taylor, J. S. *J. Magn. Reson., Ser. B* **1994**, *104*, 1–10.
30. Del Bene, J.; Jaffe, H. H. *J. Chem. Phys.* **1968**, *48*, 1807–1813.
31. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E.; Steward, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
32. Downing, J. W. *Program Package BDZDO/MCDSPD*; Department of Chemistry and Biochemistry, University of Colorado: Boulder, USA; modified by Fleischhauer, J.; Schleker, W.; Kramer, B.; ported to Linux by Gulden, K. -P.
33. Wickerham, L. J. *US Dept. Agric. Wash. D.C., Technol. Bull.* **1951**, *1029*, 1–56.
34. Scudiero, D. A.; Shoemaker, R. H.; Paull, K. D.; Monks, A.; Tierney, S.; Nofziger, T. H.; Currens, M. J.; Seniff, D.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 4827–4833.
35. Freshney, R. I. Culture of Specific Cell Types. In *Culture of Animal Cells. A Manual of Basic Technique*; A.R. Liss: New York, 1987; pp 257–288.
36. Perović, S.; Schleger, C.; Pergande, G.; Iskric, S.; Ushijima, H.; Rytik, P.; Müller, W. E. G. *Eur. J. Pharmacol. (Mol. Pharmacol. Sec.)* **1994**, *288*, 27–33.
37. Perović, S.; Böhm, M.; Meesters, E.; Meinhardt, A.; Pergande, G.; Müller, W. E. G. *Mech. Ageing Dev.* **1998**, *101*, 1–19.

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Daminin, a bioactive pyrrole alkaloid from the Mediterranean sponge *Axinella damicornis*

Anna Aiello,[a] Monica D'Esposito,[a] Ernesto Fattorusso,[a,*] Marialuisa Menna,[a] Werner E. G. Müller,[b,*] Sanja Perović-Ottstadt,[b] Hideyuki Tsuruta,[c] Tobias A. M. Gulder[c] and Gerhard Bringmann[c,*]

[a]*Dipartimento di Chimica delle Sostanze Naturali, Università di Napoli 'Federico II', via D. Montesano 49, I-80131 Napoli, Italy*
[b]*Institut für Physiologische Chemie, Abt. Angewandte Molekularbiologie, Duesbergweg 6, D-55099 Mainz, Germany*
[c]*Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97070 Würzburg, Germany*

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Abstract—The isolation and characterization of the known pyrrole alkaloid agelongine (**6**) and of the new natural product daminin (**7**), the bromine-free analogue of **6**, from a specimen of the marine sponge *Axinella damicornis* is described. Compound **7** showed significant neuroprotective properties. Moreover, for the supply of sufficient material for future medicinal investigations, a short total synthesis of **7** was developed.

1. Introduction

Marine sponges are rich sources of pyrrole alkaloids.[1] These secondary metabolites are of interest because of their structural variety and pharmacological activities. Most of them are characterized by the presence of a short linear aliphatic segment connecting a pyrrole-2-carboxylic acid moiety equipped with different bromine substitution patterns, with a heterocyclic ring, frequently an amino-imidazole unit (Fig. 1). The first member of this group to be discovered, initially in *Agelas oroides* in 1971 and then in various other sponges, was the dibrominated compound oroidin (**1**).[2] This alkaloid **1** shows antimicrobial activity and interacts with muscarinic acetylcholine receptors (mAChR) in rat brain membranes.[3] In the meantime, numerous similar alkaloids have been isolated from Agelasidae, Hymeniacidonidae, and Axinellidae species,[4–9] with diverse structures and interesting biological properties ranging from antiserotonergic and antihistaminic activities to inhibitory effects against EGF receptor kinase.[3,10–14]

More recently, manzacidins A–D (**2**–**5**), from a *Hymeniacidon* sp.[15] and agelongine (**6**), from the sponge *Agelas longissima*,[16] have extended the structural variety of the so far known pyrrole alkaloids in having a 3,4,5,6-tetrahydropyrimidine and a pyridinium ring, respectively, instead of the commonly found imidazole nucleus, and an ester linkage that replaces the usual amidic bond in the central segment. Agelongine (**6**) exhibits antiserotonergic activity on rat stomach fundus strip.

During our search for bioactive substances from Mediterranean sponges in the frame of the NOMATEC (BIOTECmarin) project, which aims at the sustainable development of the Mediterranean resources, we have now chemically investigated the organic extract of a specimen of *Axinella damicornis*. This study led to the renewed isolation of agelongine (**6**), together with the identification of a new alkaloid, daminin (**7**), the first naturally occurring agelongine analogue. In vitro tests on rat cortical cell cultures showed that daminin (**7**) might represent a new therapeutic tool for the treatment of CNS diseases such as Parkinson's and Alzheimer's diseases.[17]

2. Results and discussions

2.1. Isolation and structural elucidation of daminin (7)

Specimens of the sponge *Axinella damicornis* collected in the Bay of Calvi (Corsica) were extracted with methanol

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* Corresponding authors. Tel.: +39 81 678503 (E.F.); tel.: +49 61 31 3925910; fax: +49 61 31 3925243 (W.M.); tel.: +49 931 888 5323; fax: +49 931 888 4755 (G.B.); e-mail addresses: fattoru@unima.it; wmueller@uni-mainz.de; bringman@chemie.uni-wuerzburg.de

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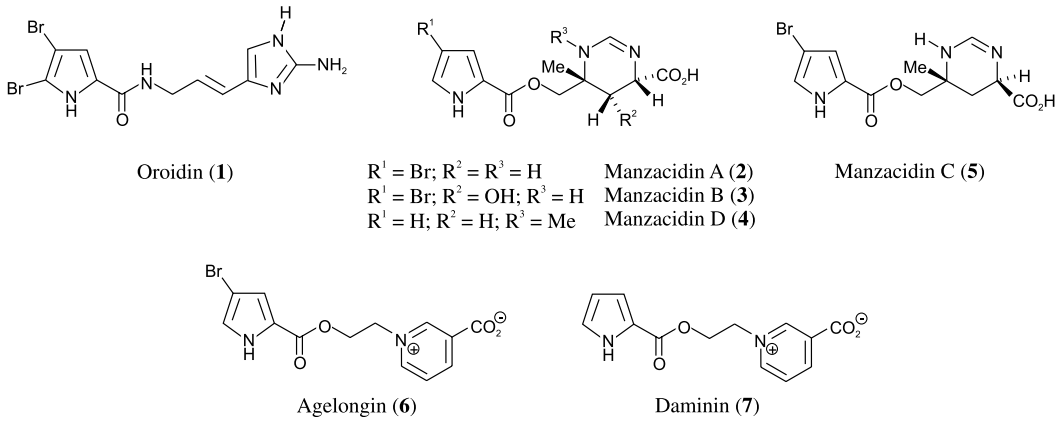

Figure 1. Structures of known pyrrole alkaloids (**1**–**6**) isolated from marine sponges and of the new natural product daminin (**7**).

and, subsequently, with chloroform. The combined extracts were concentrated in vacuo and partitioned between butanol and water. The butanol soluble material was initially subjected to a medium pressure liquid chromatography (MPLC) using a reversed-phase C-18 column. Further separation of the alkaloid-containing fractions was achieved by repeated preparative high performance liquid chromatography (HPLC) on an RP-18 column, thus giving the known agelongine (**6**, 3 mg) and the new compound daminin (**7**, 4 mg), both in a pure form. Compound **6** was identified by comparison of its spectral properties with those reported for agelongine (**6**) isolated from the sponge *Agelas longissima*.[16]

The ESI (positive ions) mass spectrum of daminin (**7**, Fig. 2) exhibited pseudomolecular ion peaks at *m/z* 261 $[M+H]^+$ and 283 $[M+Na]^+$. The molecular formula $C_{13}H_{12}N_2O_4$ was deduced from the HRFABMS (positive ions) of this compound, measured on the peak at *m/z* 261.0890 $[M+H]^+$ (calculated value: *m/z* 261.0875).

The presence of an aromatic ester function and a carboxylate group was suggested by IR absorptions at ν_{max} 1710 and 1646 cm^{-1}, respectively, which was confirmed by the carbonyl resonances in the ^{13}C NMR spectrum of **7** (DMSO-d_6) at δ 161.6 and 159.0 (Table 1).

The ^{13}C NMR spectrum also contained seven sp^2 methines and two sp^2 unprotonated carbons, which indicated the presence of aromatic rings, and furthermore two sp^3 methylene signals. The ^1H NMR spectrum (DMSO-d_6) exhibited ten well separated signals. The lowfield region of the spectrum contained seven signals of aromatic protons and one signal exchangeable with D_2O, while two mutually coupled methylene signals were visible in the central region of the spectrum (see Table 1). Analysis of the NMR spectra, including 2D COSY, ROESY, HSQC, and HMBC, clearly showed **7** to be a close structural analogue of agelongine (**6**). In fact, the spectral data obtained for **7** revealed it to contain the same pyridinium-β-carboxylate moiety as agelongine (**6**) linked through an ethylenoxy bridge to a pyrrole-2-carboxylic acid connected via an ester bond. The carboxylate portion of the ester corresponds to the chemical structure of the known betaine alkaloid pyridinebetaine A.[18] The latter heterocyclic moiety, however, was found to lack a bromine substituent, as clearly indicated by NMR signals of a complete set of three neighboring aromatic protons [δ_H 6.78 (t, J=0.9; 1.9 Hz), H-3; 6.16 (d, J=1.9 Hz), H-4; 7.05 (d, J=0.9 Hz), H-5; δ_C 120.7, C-2; 115.7, C-3; 109.5, C-4; 124.6, C-5], as well as by mass data (see Section 4). Thus, daminin (**7**) was concluded to be the non-brominated parent compound of agelongine (**6**). The NMR analysis also allowed us to assign all of the resonances present in ^{13}C and

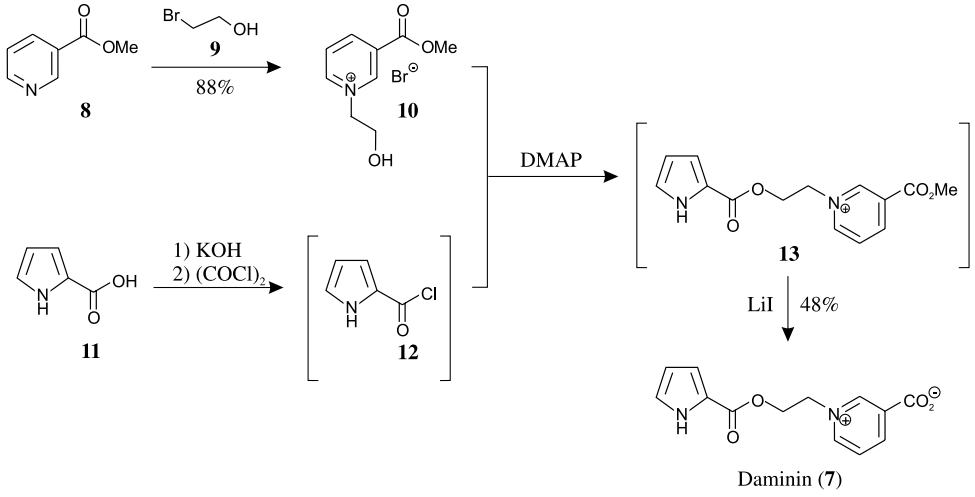

Figure 2. Synthesis of daminin (**7**) from the building blocks **8** and **1**.

Table 1. ^{1}H and ^{13}C NMR data (DMSO-d_6) of compound **7**

No.	δ_H (mult., J Hz)	δ_C	HMBC	COSY
1	12.3 (s)	—		
2	—	120.7		
3	6.78 (t, 0.9, 1.9)	115.7	2	4, 5
4	6.16 (d, 1.9)	109.5	2, 5	3, 5
5	7.05 (d, 0.9)	124.6	2, 3, 4	3, 4
6	—	159.0		
7	4.65 (t, 3.7)	61.8	8	8
8	5.01 (t, 3.7)	58.9	7	7
9	9.4 (s)	145.7	8, 10, 11, 14	11, 13
10	—	140.9		
11	8.78 (d, 7.4)	144.7	13, 14	9, 12
12	8.06 (t, 6.5, 7.4)	126.6	10, 11, 13	11, 13
13	9.04 (d, 6.5)	144.0	11, 12	9, 12
14	—	161.6		

^{1}H NMR spectra, which are reported in Table 1; particularly, the assignments of the pyrrole moiety were in good agreement with those reported for 2-substituted pyrroles.[8,19]

2.2. Synthesis of daminin (7)

A synthetic access (Fig. 2) to the new compound daminin (**7**) was realized by esterification of 1-(2-hydroxyethyl)-3-methoxycarbonyl-pyridinium bromide (**10**) with pyrrole-2-carboxylic acid chloride (**12**). *N*-alkylation of nicotinic acid methyl ester (**8**) using 2-bromoethanol (**9**) delivered the pyridinium salt **10** in 88% yield. The acid chloride **12** was prepared from pyrrole-2-carboxylic acid (**11**) and oxalyl chloride under basic conditions. In situ reaction of **12** with **10** and selective cleavage of the more reactive methyl ester on the electron-poor pyridinium portion of the crude intermediate **13** using lithium iodide gave daminin (**7**) in 48% yield, identical in all chromatographic and spectroscopic respects with the natural product from *A. damicornis*.

2.3. Bioactivities of daminin (7)

2.3.1. Cytostatic/cytotoxic activity of daminin (7). Daminin (**7**) was tested for its cytotostatic/cytotoxic activity against several tumor cell lines, namely murine leukemic lymphoblasts L5178y, rat adrenal pheochromocytoma PC12 cells, and human cervix carcinoma HeLa S3 cells. It displayed no cytotoxic activity against all tested cell lines. In all cases, the IC_{50} was >40 μg/mL.

2.3.2. Influence of L-Glu and $CaCl_2$ on the $[Ca^{2+}]_i$ level in neuronal cells after pre-incubation with daminin (7). Incubation of neurons with 200 μM of L-Glu (glutamic acid) and 2.4 mM $CaCl_2$ resulted in a strong rise in $[Ca^{2+}]_i$. If these components were added 10 min after starting the experiment, the 340/380 nm ratio value increased by 1.537 (305%, Fig. 3). However, if the neurons were pre-incubated for 5 min with 0.5, 1.0 or 3.0 μg/mL of daminin (**7**) a significant decrease of the $[Ca^{2+}]_i$ levels was recorded; after addition of L-Glu and $CaCl_2$ at time 10 min, the $[Ca^{2+}]_i$ level dropped to 58.1% (0.5 μg/mL of **7**), to 65.4% (1 μg/mL of 7) or to 25.1% (3 μg/mL of **7**, Fig. 3). Daminin (**7**) was present from time 5 min up to the end of the experiments (30 min). In the pre-incubation set of experiments neurons were incubated 5–10 min only in the presence of **7** and in the absence of L-Glu/$CaCl_2$. No effect on the $[Ca^{2+}]_i$ was measured (Fig. 3). In a parallel series of experiments it could be shown that daminin (**7**) caused no effect on the $[Ca^{2+}]_i$ level (not presented).

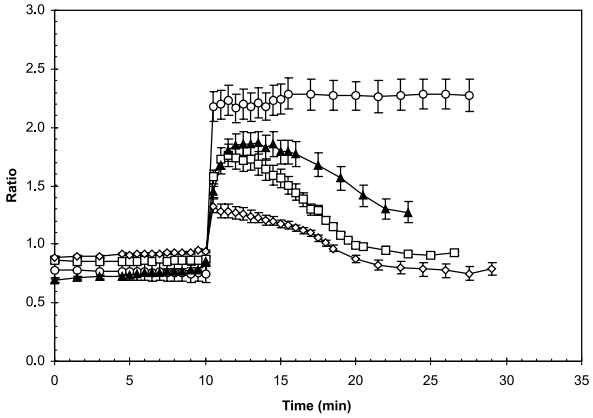

Figure 3. Incubation of the neurons with L-Glu and Ca^{2+} in the absence (○) or in the presence of 0.5 (▲), 1 (□), or 3 (◇) μg/mL of daminin (**7**). Daminin (**7**) was added at time 5 min and remained in the cultures during the entire incubation period. At time 10 min, neurons were stimulated with L-Glu and $CaCl_2$ as described in Experimental. The results are expressed as mean value ($n=35$) plus standard deviation (±SE).

2.3.3. Modulating effect of daminin (7) on the NMDA-caused $[Ca^{2+}]_i$ level. Incubation of neurons with 200 μM of NMDA (*n*-methyl-D-aspartate) and 2.4 mM $CaCl_2$ (here added at time 10 min) resulted in a strong increase in $[Ca^{2+}]_i$; the 340/380 nm ratio value increased by 1.117 (235%). This strong rise was statistically reduced to 63.5% (controls were set to 100) if the cells were pre-incubated with 1 μg/mL of daminin (**7**); Figure 4.

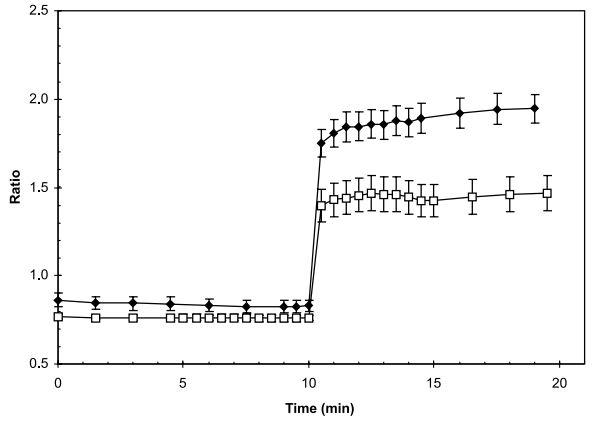

Figure 4. Incubation of the neurons with 200 μM of NMDA and 2.4 mM Ca^{2+} in the absence (◆) or in the presence of 1 (□) μg/mL of **7**. Daminin (**7**) was added at time 5 min and remained in the cultures, while NMDA/Ca^{2+} was added at time 10 min.

3. Conclusion

Daminin (**7**) is one of the relatively few non-brominated pyrrole alkaloids of marine origin. The promising neuroprotective activities of this natural product combined with its very low cytotoxicity and its easy synthetic access presented in this paper make further investigations concerning possible medicinal uses potentially promising.

4. Experimental

4.1. General aspects

ESI mass spectra (positive ions) were performed on an API 2000 mass spectrometer. High resolution FAB mass spectra (glycerol matrix) were taken on a VG Prospec (FISONS) mass spectrometer. NMR experiments were done on a Bruker AMX-500 and AV-400 spectrometers; chemical shifts are referred to the residual solvent signal (DMSO: $\delta_H = 2.49$ ppm, $\delta_C = 39.5$ ppm). Homonuclear (^1H–^1H) and heteronuclear (^1H–^{13}C) connectivities were determined by COSY and HSQC experiments, respectively. Two- and three-bond ^1H–^{13}C connectivities were investigated by HMBC experiments optimized for a $^{2,3}J$ of 10 Hz. Separations by medium-pressure liquid chromatography (MPLC) were performed on a Büchi 861 apparatus with SiO_2 (230–400 mesh) packed columns. High performance liquid chromatography (HPLC) separations were achieved on a Waters 501 apparatus equipped with an RI detector. IR (KBr) spectra were recorded on a Bruker model IFS-48 spectrophotometer.

4.2. Collection, extraction, and isolation

Specimens of the sponge *Axinella damicornis* were collected in November 2001 in the Bay of Calvi (Corsica) and kept frozen until use. For the extraction, the fresh thawed sponge (75.2 g dry weight after extraction) was homogenized and treated at room temperature with methanol (3×600 mL) and, subsequently, with chloroform (3×600 mL). The extracts were concentrated in vacuo and the water-insoluble lipid fraction obtained was treated with BuOH. The BuOH soluble portion was subjected to MPLC on a reversed-phase column eluting with $H_2O \rightarrow MeOH \rightarrow CHCl_3$. Two main alkaloid-containing fractions, eluted with MeOH/H_2O 3:7 (fraction A) and MeOH/H_2O 2:8 (fraction B), were obtained. The more polar fraction A was separated by HPLC on an RP-18 column (Luna, 5 μm, 250×4.6 mm) using MeOH/H_2O 3:7 as the eluent and further purified by HPLC on an C18 column (AQUA, 5 μm, 250×4.6 mm) thus providing **7** (4 mg) in a pure form. Fraction B was separated and purified by consecutive HPLC runs on RP-18 columns (Luna, 5 μm, 250×4.6 mm; Luna, 3 μm, 250×4.6 mm) with MeOH/H_2O 1:1 as the eluent, giving rise to pure **6** (3 mg).

4.2.1. Daminin (7). Amorphous white solid. IR (KBr): ν_{max} 1710, 1646 cm^{-1}. HRFABMS *m/z* $[M+H]^+$ 261.0890 (Calcd for $C_{13}H_{12}N_2O_4$, 261.0875). ^1H (500 MHz, DMSO-d_6) and ^{13}C NMR (125 MHz, DMSO-d_6) data: Table 1.

4.2.2. Agelongine (6). The data fully matched those reported in the literature.[16]

4.3. Total synthesis of daminin (7)

4.3.1. Synthesis of 1-(2-hydroxyethyl)-3-methoxycarbonylpyridinium bromide (10). A solution of 1.00 g (7.29 mmol) nicotinic acid methyl ester (**8**) and 5 mL (70.82 mmol) 2-bromoethanol (**9**) in 7 mL of toluene was stirred at 120 °C for 2.5 h. The solvent was removed under reduced pressure and the residue was washed 3 times with 15 mL diethyl ether. The solid was recrystallized from acetonitrile–diethyl ether (1:2) to give 1.17 g (6.41 mmol, 88%) pure **10** as colorless crystals.

Mp 108–109 °C (acetonitrile–diethyl ether); ^1H NMR (400 MHz, CD_3OD) δ 4.07 (t, $J=5.0$ Hz, 2H), 4.09 (s, 3H), 4.89 (t, $J=5.0$ Hz, 2H), 8.31 (dd, $J=8.2$, 6.1 Hz, 1H), 9.12 (ddd, $J=8.2$, 1.4, 1.4 Hz, 1H), 9.25 (ddd, $J=6.1$, 1.4, 1.4 Hz, 1H), 9.57 (bs, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 57.0, 64.3, 68.2, 132.1, 134.7, 149.6, 150.4, 152.2, 166.1. FABMS *m/z* 182.1 $[M+H\text{-}Br]^+$, 445.1 $[2M+H\text{-}Br]^+$.

4.3.2. Synthesis of daminin (7). A suspension of 230 mg (2.07 mmol) pyrrole-2-carboxylic acid potassium salt (**11**) (Aldrich, Germany) and 0.25 mL (2.98 mmol) oxalyl chloride in 5 mL CH_2Cl_2 was stirred at room temperature under N_2. After 4 h the solvent was removed under reduced pressure and the residue was re-dissolved in 5 mL CH_2Cl_2. 262 mg (1.43 mmol) of **10** were added together with a catalytic amount of 4-*N*,*N*-dimethylaminopyridine and the mixture was stirred over night at room temperature. The solvent was removed under reduced pressure and the remaining solid washed with diethyl ether and then dissolved in 4 mL of pyridine. After addition of 900 mg (6.72 mmol) of lithium iodide, the mixture was stirred at 100 °C for 3 h. The solvent was evaporated and the remaining solid was purified by chromatography on a silica gel column with ethyl acetate–MeOH (2:8) as the eluent. After recrystallization of the crude product from EtOH–diethylether (2:1), 177 mg (0.68 mmol, 48%) of pure daminin (**7**) were obtained.

Mp 193 °C (decomposition); all spectral data identical with those of the natural product **7** (see above).

4.4. Cell lines

L5178y cells (ATTCC CRL-1722) were grown in RPMI1640 supplemented with 10 mM Hepes, 10% (v/v) fetal calf serum (FCS) (PAA, Cölbe, Germany) and 0.1% (w/v) Gentamycin. PC12 cells (ATCC CRL-1573) were kept in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% (v/v) horse serum, 5% (v/v) FCS and 0.1% (w/v) of gentamycin. HeLa S3 cells (ATCC CCL-2.2) were cultured in DMEM supplemented with 10% (v/v) FCS. All cells were routinely passaged once or twice weekly.

4.5. MTT assay

The cell viability was determined using MTT assay.[20] The evaluation was performed in 96-well plates at 595 nm using an ELISA plate reader.

4.6. Calcium measurement on primary neurons

The primary cortical cell culture was prepared from 17 to 18 days old rat embryos following the modified procedure.[21–23] Daminin (**7**) was dissolved in sterile water (stock concentration of 10 mg/mL) and stored at 4 °C. Neurons were exposed to 200 μM of L-glutamic acid (L-Glu) or *N*-methyl-D-aspartic acid (NMDA), both compounds together with

2.4 mM $CaCl_2$, 10 min after the beginning of the recording. The $[Ca^{2+}]_i$ level was measured for 20 (experiment with NMDA) or 30 min (L-Glu). Compound **7** was added to the cultures 5 min prior to the stimulation with L-Glu/$CaCl_2$ or NMDA/$CaCl_2$.

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References and notes

1. Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237–243.
2. Forenza, S.; Minale, L.; Riccio, R.; Fattorusso, E. *J. Chem. Soc., Chem. Commun.* **1971**, 1129–1130.
3. Morales, J. J.; Rodiguez, A. D. *J. Nat. Prod.* **1991**, *54*, 629–631.
4. Kobayaschi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y. *Experientia* **1986**, *42*, 1176–1177.
5. Rosa, R.; Silva, W.; Escalona de Motta, G.; Rodriguez, A. D.; Morales, J. J., '; Ortiz, M. *Experientia* **1992**, *48*, 885–887.
6. Cafieri, F.; Fattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O. *Tetrahedron* **1996**, *52*, 13713–13720.
7. Kobayashi, J.; Inaba, K.; Tsuda, M. *Tetrahedron* **1997**, *53*, 16679–16682.
8. Tsuda, M.; Uemoto, H.; Kobayashi, J. *Tetrahedron Lett.* **1999**, *40*, 5709–5712.
9. Uemoto, H.; Tsuda, M.; Kobayashi, J. *J. Nat. Prod.* **1999**, *62*, 1581–1583.
10. Nakamura, H.; Ohizumi, Y.; Kobayashi, J.; Kasei, M. *Tetrahedron Lett.* **1984**, *25*, 2475–2478.
11. Cafieri, F.; Fattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O. *Tetrahedron Lett.* **1996**, *37*, 3587–3590.
12. Jahn, T.; König, G. M.; Wright, A. D. *Tetrahedron Lett.* **1997**, *38*, 3883–3884.
13. Cafieri, F.; Carnuccio, R.; Fattorusso, E.; Taglialatela-Scafati, O.; Vallefuoco, T. *Bio. Med. Chem. Lett.* **1997**, *7*, 2283–2288.
14. Fattorusso, E.; Taglialatela-Scafati, O. *Tetrahedron Lett.* **2000**, *41*, 9917–9922.
15. Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. *J. Org. Chem.* **1991**, *56*, 4574–4576.
16. Cafieri, F.; Fattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O.; Carnuccio, R. *Biol. Med. Chem. Lett.* **1995**, *5*, 799–804.
17. Perović, S.; Böhm, M.; Meesters, E.; Schröder, H. C.; Pergande, G.; Müller, W. E. G. *Mech. Ageing Develop.* **1998**, *101*, 1–19.
18. Cafieri, F.; Fattorusso, E.; Taglialatela-Scafati, O. *J. Nat. Prod.* **1998**, *61*, 1171–1173.
19. Cheng, Y.; Zhou, J.; Tan, N.; Teng, R.; Lu, Y.; Wang, C.; Zheng, Q. *J. Nat. Prod.* **2002**, *65*, 750–752.
20. Scudiero, D. A.; Shoemaker, R. H.; Paull, K. D.; Monks, A.; Tierney, S.; Nofziger, T. H.; Currens, M. J.; Seniff, D.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 4827–4833.
21. Freshney, R. I. Culture of specific cell types. *In Culture of Animal Cells. A Manual of Basic Technique*; A. R. Liss: New York, 1987; pp 257–288.
22. Perović, S.; Schleger, C.; Pergande, G.; Iskric, S.; Ushijima, H.; Rytik, P.; Müller, W. E. G. *Eur. J. Pharmacol. (Mol. Pharmacol. Sec.)* **1994**, *288*, 27–33.
23. Perović, S.; Böhm, M.; Meesters, E.; Meinhardt, A.; Pergande, G.; Müller, W. E. G. *Mech. Ageing Dev.* **1998**, *101*, 1–19.

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A convenient and efficient synthesis of (*S*)-lysine and (*S*)-arginine homologues via olefin cross-metathesis

Timothy P. Boyle,[a] John B. Bremner,[a,*] Jonathan A. Coates,[b] Paul A. Keller[a,*] and Stephen G. Pyne[a,*]

[a]*Department of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia*
[b]*Avexa Ltd, 576 Swan St, Richmond, Vic. 3121, Australia*

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Abstract—A convenient five step synthesis of (*S*)-homolysine, incorporating a key olefin cross-metathesis step in the chain extension methodology, has been developed, together with a six step related synthesis of a new homologue of arginine, (*S*)-bishomoarginine.

1. Introduction

Cationic amino acids, such as arginine and lysine, are important constituents of biologically active peptides,[1,2] and play a significant role in the binding of peptide substrates and their molecular targets. Homologues of these cationic amino acids are also valuable tools in the preparation of peptidic enzyme inhibitors and, in particular, for probing enzyme active site pockets in ligand based drug design.[3] For example, (*S*)-homolysine **1** (shown as the di-HCl salt), a nonproteinogenic amino acid, has been used as a lysine replacement residue in vasopressin[4] and in cyclic enkephalin analogues[5] as well as in the design of renin inhibitors.[6] Homoarginine is found in several proteins, including some within the brain,[7] and it has also been shown to inhibit arginine kinases.[8] In this context, extended homologues such as (*S*)-bishomoarginine **2** (shown as the di-HCl salt) would also be of considerable interest. However, no method for the preparation of **2** has been reported. Previous syntheses of its potential precursor homolysine **1**, produce either the racemic form[9] or an enantiomerically enriched form by excessive multistep methods from a chiral cyclic amino acid template,[10,11] or by constructing a chiral aldehyde template from serine and applying Wittig methodology to incorporate the desired sidechain.[12] Homolysine **1** was then finally produced by deprotection protocols in the synthesis. Facile access to both **1** and **2** in high enantiomeric purity would provide increased opportunities for the incorporation of these unnatural amino acids into drug discovery processes, including combinatorially-based and rational drug design programs.

2. Results and discussion

We report here an efficient synthesis of both (*S*)-homolysine **1** and (*S*)-bishomoarginine **2**. Our strategy (Scheme 1) incorporated the stereochemical element using commercially available (*S*)-allylglycine, thus avoiding the use of chiral templates. The reliable olefin cross-metathesis reaction[13] provided the necessary chain elongation and established guanidation methodology[14] was then applied for the required primary amine to guanidine functional group transformation. This strategy of amino acid chain elongation via olefin cross-metathesis could potentially be used to prepare a variety of unnatural amino acids and amino acid homologues rapidly, with the advantage of incorporating the C2-chiral stereocentre from the outset.

Therefore, the protected amine **5** was prepared[15] by treating the bromobutene **3** with di-*tert*-butyliminodicarboxylate and cesium carbonate affording the di-Boc-homoallylic amine **4**, which was then selectively deprotected with 2 equiv of TFA in dilute CH_2Cl_2 to give the *N*-Boc-allylamine **5** in an overall yield of 89% (Scheme 1).

Reaction of **5** with half an equivalent of the protected allylglycine derivative **6**[16] and Grubbs' ruthenium catalyst I in an analogous manner to reported cross-metatheses of allylglycines[17,18] afforded **7** in moderate yield (69%) as a

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* Corresponding authors. Fax: +61 2 4221 4287 (J.B.B.), (P.A.K.), (S.G.P.); e-mail addresses: bremner@uow.edu.au; keller@uow.edu.au; spyne@uow.edu.au

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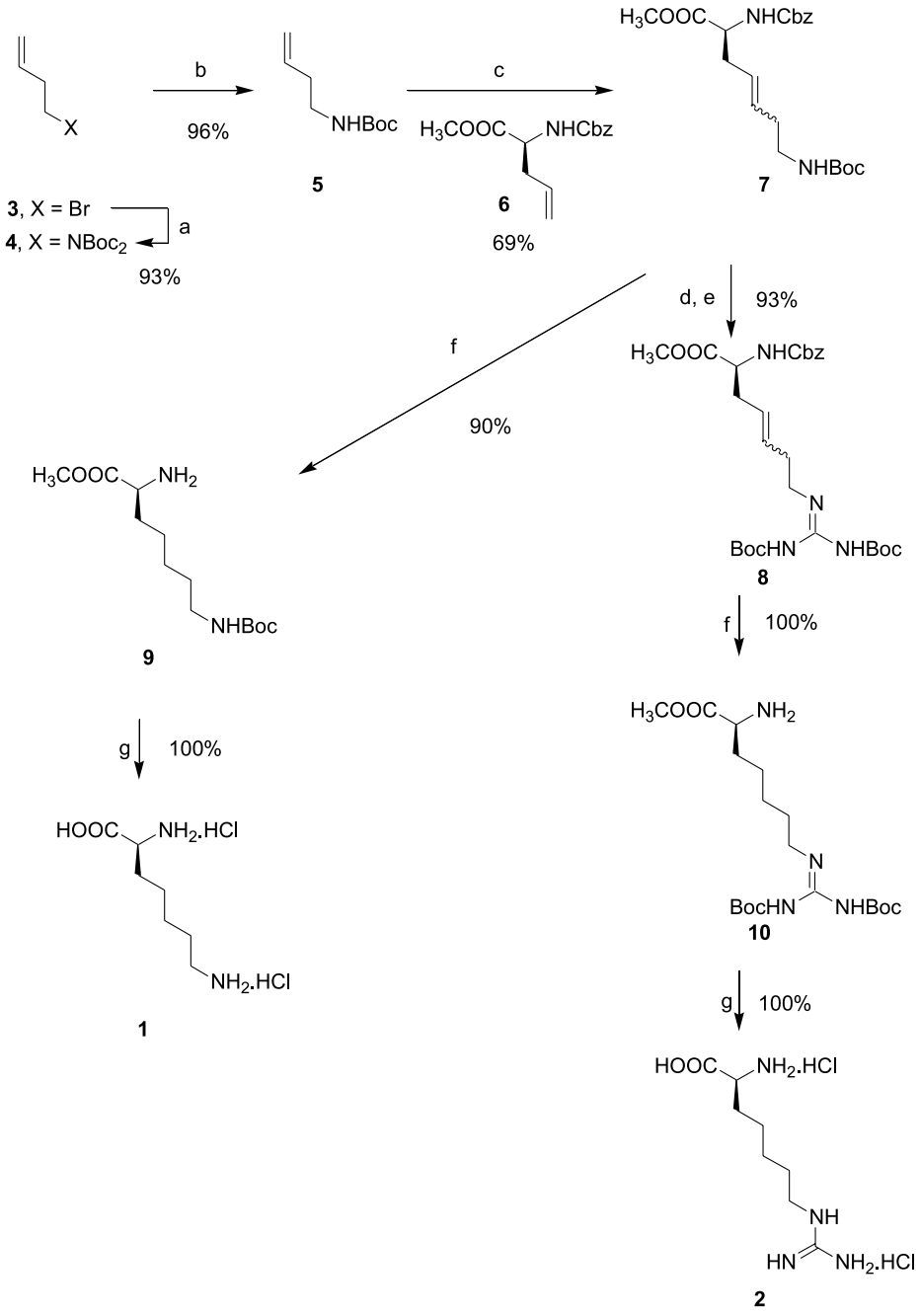
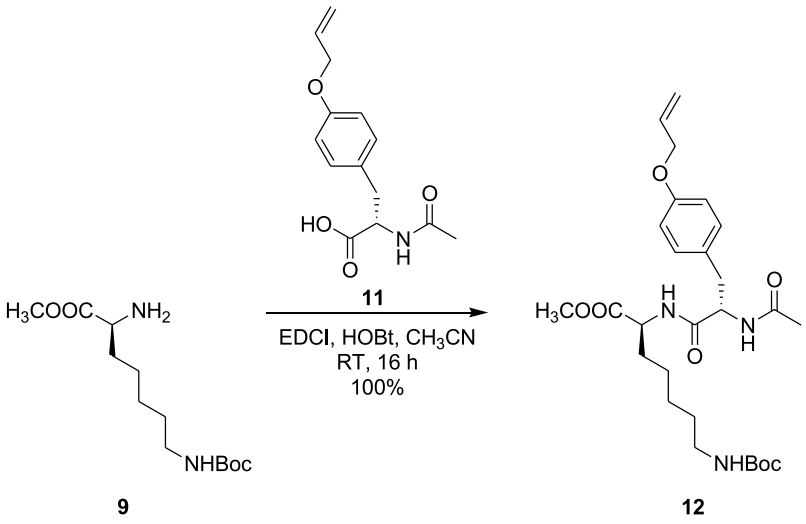


Scheme 1. Synthesis of (*S*)-lysine and (*S*)-arginine homologues. Reagents and conditions: (a) $NH(Boc)_2$, Cs_2CO_3, LiI, 2-butanone, reflux, 48 h, 93%. (b) TFA (2 equiv), DCM, 3 h, RT, and then NaOH, 96%. (c) $RuCl_2(PCy_3)_2(=CHPh)$ 10 mol%, DCM, 16 h, 69%. (d) TFA/DCM (1:1), RT, 3 h. (e) $TfNC(NHBoc)_2$, Et_3N, DCM, RT, 16 h, 93%. (f) Pd/C, H_2, THF, RT, 16 h, 90% (9), 100% (10). (g) 10M HCl, RT, 48 h, 100%.

mixture of *E*/*Z* stereoisomers. It is interesting to note that a homo-dimer of the protected allylglycine **6** was not observed, as sometimes reported for similar cross-metathesis conditions with allylglycine derivatives.[19] Both the *E* and *Z* isomers were evident in the ^1H NMR spectrum from the doubling up of most signals, however the exact ratio could not be determined due to overlapping signals. Preparation of bishomoarginine **2** required removal of the acid labile *N*-Boc protecting group of **7** by treatment with TFA. Subsequent exposure to *N*-triflyl-*N*,*N*-di-*tert*-butoxy-carbonyl-protected guanidine (Aldrich Chemical Co.) and triethylamine then yielded the protected arginine analogue **8** in 93% yield. The alkene group and benzylcarbamate protecting group of **7** and **8** were then removed in one step by hydrogenation over Pd/C to yield the free amino esters **9** and **10**, in 90% and quantitative yields, respectively. Exposure of the amino ester derivatives **9** and **10** to 10 M HCl for 48 h resulted in the free amino acids **1** and **2**, as their corresponding dihydrochloride salts, in quantitative yield.

The specific rotation observed for **1** ($[\alpha]_D^{22}$ +10.9 (*c* 0.1 in 2 N HCl)), was in general accordance with the reported literature values for the enantiomeric hydrochlorides ($[\alpha]_D^{23}$ −10.6 (*c* 1, 1 N HCl) (*R*)-isomer[12] and $[\alpha]_D^{23}$ +14.4 (*c* 0.5, in 1 N HCl) (*S*)-isomer[11]), while the previously unreported **2** had an $[\alpha]_D^{22}$ of −23.3 (*c* 0.03 in 2 M HCl). Further evidence



Scheme 2. Synthesis of the diastereomeric dipeptide **12**.

for the enantiomeric purity of **1** was forthcoming from the peptide coupling reaction of its immediate precursor, **9**, with the known[20] chiral protected tyrosine derivative *O*-allyl-*N*-acetyl-(*S*)-tyrosine **11**[21] (Scheme 2). The dipeptide derivative **12** from this coupling showed a diagnostic sharp singlet peak in the ^{1}H NMR spectrum at δ 3.69, integrating for three protons. Our experience with these types of dipeptides has shown us that this methyl ester peak is indicative in delineating the presence of diastereomers, and in the case of **12**, the dr was calculated to be $>96\%$.[22] Consistent with this NMR analysis, the chiral GC analysis (Chirasil L-Val) of the *N*-pentafluoropropionyl, isopropyl esters of **1** and **2** showed a single peak, whereas the same derivatives of racemic lysine and arginine showed two well resolved peaks (see Section 4 for details).

3. Conclusion

The presented methodology provides a rapid and convenient synthesis of (*S*)-homolysine **1** in five steps in 55% overall yield which is an improvement over the previously reported procedure (nine steps, 22% overall yield) of Beaulieu et al.,[12] and that of Dong[11] (five steps, 51% overall yield). Bishomoarginine **2** was prepared in six steps, in 57% overall yield. The flexibility of the methodology also allows, in principle, for the synthesis of the corresponding (*R*)-amino acids, via the commercially available (*R*)-allylglycine.

4. Experimental

4.1. General

All NMR spectra were determined in $CDCl_3$ solution at 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR) unless otherwise stated. All compounds were determined to be $>95\%$ pure by ^{1}H NMR spectroscopy. Enantiomeric purities of amino acids was made on their *N*-pentafluoropropionyl isopropyl esters by gas chromatography on a fused silica capillary column coated with the stationary phase Chirasil L-Val.[23] Derivatisation of the amino acids was performed according to published procedures.[23]

Derivatisation: One milligram of the amino acids were transferred to 3 mL Pierce reaction-vials using methanol and brought to dryness under a stream of dry nitrogen. Esterification of the amino acids was undertaken by adding 250 μL of 3.5 N isopropanol/HCl and heating for 1 h at 110 °C. The samples were then allowed to cool to ambient temperature and were subsequently dried under a stream of dry nitrogen. Samples were then acylated with 250 μL of CH_2Cl_2 and 50 μL of pentafluoropropionic acid anhydride (PFPA) and heated at 110 °C for 15 min. After cooling, samples were dried completely under a stream of nitrogen.

Gas chromatography. Analysis of the *N*-pentafluoropropionyl-amino acid isopropyl esters were undertaken using a Varian model 3700 gas chromatograph with a flame ionization detector and a coiled, fused silica capillary column (25 m length) coated with the stationary phase Chirasil-L-Val. The temperature program consisted of a single ramp set at the following conditions: (1) initial temperature 50 °C for 2 min; (2) ramp at 4 °C/min to a ceiling at 200 °C and (3) a plateau at 200 °C for 10 min. High purity helium was used as a carrier gas. An authentic sample of D,L-lysine showed two peaks at retention times of 32.19 and 32.33 min, while L-homolysine **1** showed a single peak at a retention time of 33.57 min. An authentic sample of D,L-arginine showed two peaks at retention times of 32.12 and 32.26 min, while L-bishomoarginine **2** showed a single peak at a retention time of 29.30 min.

4.1.1. Di-*tert*-butyl *N*-3-butenyliminodicarboxylate (4). To a solution of di-*tert*-butyl iminodicarboxylate (868 mg, 4 mmol), cesium carbonate (2.61 g, 8 mmol) and lithium iodide (28 mg, 0.2 mmol) in 2-butanone (20 mL) was added 4-bromo-1-butene **3** (812 mg, 6 mmol) and the mixture was heated at reflux for 48 h. The reaction was allowed to cool, quenched with brine (40 mL) and then extracted with diethyl ether (3×20 mL). The combined organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to yield the title compound **4** (1.01 g, 3.7 mmol, 93%) as a light brown oil. ν_{max}(neat) 2974 (s), 1735 (s), 1697 (s), 1129 (s) cm^{-1}. ^{1}H NMR: δ 5.84–5.70 (m, 1H, H3); 5.10–4.99 (m, 2H, H4); 3.62 (dd,

J=6.0, 8.7 Hz, 2H, H1); 2.36–2.29 (m, 2H, H2); 1.51 (s, 18H, 6×CH_3). ^{13}C NMR: δ 152.5, (CO); 135.0, (C3); 116.7, (C4); 82.0, (2×$C(CH_3)_3$); 45.6, (C1); 33.5, (C2); 28.0, (6×CH_3). MS (ES, +ve) m/z 272 (40%) [MH^+], 294 (30%) [MNa^+], 310 (55%) [MK^+]. HRMS (ES) calcd for $C_{14}H_{26}NO_4$ 272.1862, found 272.1848.

4.1.2. *tert*-Butyl *N*-3-butenylcarbamate (5). To a solution of **4** (708 mg, 2.60 mmol) in CH_2Cl_2 (21 mL) was added TFA (593 mg, 5.20 mmol) and the mixture was allowed to stir at rt for 5 min before being quenched with 2 M NaOH (25 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated to yield the title compound **5**[15] (429 mg, 2.50 mmol, 96%) as a light brown oil. ν_{max}(neat) 2979 (s), 1799 (m), 1732 (s), 1697 (s), 1392 (m), 1367 (s), 1130 (s) cm^{-1}. ^{1}H NMR: δ 5.83–5.69 (m, 1H, H3); 5.13–5.05 (m, 2H, H4); 4.59 (br s, 1H, NH); 3.20 (dd, J=6.3, 12.6 Hz, 2H, H1); 2.24 (dd, J=6.9, 12.6 Hz, 2H, H2); 1.44 (s, 9H, 3×CH_3). ^{13}C NMR: δ 155.9, (CO); 135.3, (C3); 117.0, (C4); 82.0, ($C(CH_3)_3$); 39.6, (C1); 34.2, (C2); 28.4, (3×CH_3). MS (ES, +ve) m/z 116 (100%).

4.1.3. Methyl (2*S*)-2-benzyloxycarboxamido-4-pentenoate (6).[16] To a solution of methyl (2*S*)-2-amino-4-pentenoate hydrochloride[24] (422 mg, 2.56 mmol) and $NaHCO_3$ (645 mg, 7.68 mmol) in THF/water (3 mL/3 mL) was added benzyl chloroformate (482 mg, 2.82 mmol) and the mixture was allowed to stir at rt for 16 h. The reaction was quenched with 3% HCl (20 mL) and extracted with CH_2Cl_2 (3×20 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated to give the title known compound **6** (676 mg, 2.56 mmol, 100%) as a colourless oil. Spectral data matched closely with that in the literature[16] $[\alpha]_D^{20}$ +9.1 (c 0.15 in $CHCl_3$). ^{1}H NMR: δ 7.38–7.22 (m, 5H, ArH); 5.75–5.58 (m, 1H, H4); 5.56 (d, J=7.8 Hz, 1H, NH); 5.18–5.08 (m, 4H, $ArCH_2$ and C5); 4.47 (dd, J=6.3, 13.2 Hz, 1H, H2); 3.72 (s, 3H, OCH_3); 2.54 (AB_q, J=6.3, 13.8 Hz, 2H, H3).

4.1.4. Methyl (2*S*,4*E*/*Z*)-2-(benzyloxycarboxamido)-7-(*tert*-butoxycarboxamido)-4-heptenoate (7). To a solution of **5** (220 mg, 1.29 mmol) in CH_2Cl_2 (13 mL) was added, **6** (169 mg, 0.64 mmol) and $RuCl_2(PCy_3)_2$(=CHPh) (53 mg, 0.064 mmol). The mixture was heated at reflux for 16 h before the solvent was removed by rotary evaporation and the crude product purified by flash column chromatography (silica gel, 6:1, hexane/EtOAc) to yield the title compound **7** (180 mg, 0.44 mmol, 69%) as a brown oil. $[\alpha]_D^{24}$ −34.6 (c 0.3 in EtOH). ν_{max}(neat) 2345, 2225, 1684, 1630 cm^{-1}. ^{1}H NMR: δ 7.36–7.28 (m, 5H, ArH); 5.52–5.34 (m, 3H, H4, H5, NH); 5.11/5.10 (s, 2H, H4′); 4.61 (br s, 1H, NH); 4.49–3.90 (m, 1H, H2); 3.75/3.72 (s, 3H, OCH_3); 3.18–3.04 (m, 2H, H7); 2.62–2.40 (m, 2H, H3); 2.26–2.12 (m, 2H, H6); 1.43 (s, 9H, CH_3). ^{13}C NMR: δ 172.1/172.0, (C1); 155.8, (NCO_2′); 155.6, (NCO_2); 131.8, (C4); 130.4, (C5); 129.3, (ArC1′); 128.6/128.4, (ArC2′ and ArC6′); 128.0/126.8, (ArC3′ and ArC5′); 126.0/125.3, (ArC4′); 79.0, ($C(CH_3)_3$); 66.9, ($ArCH_2$); 53.6/53.4, (OCH_3); 52.3/52.2, (C2); 39.9/39.7, (C7); 35.5/35.2, (C3); 33.0/32.9, (C6); 28.3/28.1, (CH_3). MS (ES, +ve) m/z 297 (100%), 407 (20%) [MH^+], 429 (90%) [MNa^+]. HRMS (ES) calcd for $C_{21}H_{31}N_2O_6$ 407.2182, found 407.2171.

4.1.5. Methyl (2*S*,4*E*/*Z*)-2-(benzyloxycarboxamido)-7-(*N*,*N*′-di-*tert*-butoxycarbonyl-guanidino)-4-heptenoate (8). To a solution of **7** (52 mg, 0.128 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL) and the resulting solution was allowed to stir at rt for 3 h before being evaporated to dryness and resuspended in CH_2Cl_2 (2 mL) and triethylamine (0.2 mL). To this solution was added *N*,*N*′-Bis(tert-butoxycarbonyl)*N*″-triflylguanidine methyl propanamide (75 mg, 0.192 mmol) and the resulting mixture was allowed to stir overnight under a nitrogen atmosphere. The mixture was concentrated and the crude product purified by flash column chromatography (silica gel, 5% MeOH/CH_2Cl_2) to yield the title compound **8** (64 mg, 0.12 mmol, 93%) as a light brown/red oil. $[\alpha]_D^{23}$ +13.2 (c 0.05 in EtOH). ν_{max}(neat) 2925, 2851, 2352, 2336, 1866, 1644, 1403 cm^{-1}. ^{1}H NMR: δ 8.28 (br s, 1H, NH); 7.39–7.30 (m, 5H, ArH); 5.68–5.35 (m, 3H, H4, H5, NH); 5.09 (s, 2H, $ArCH_2$); 4.49–4.39 (m, 1H, H2); 3.74/3.72 (s, 3H, OCH_3); 3.49–3.35 (m, 2H, H7); 2.58–2.46 (m, 2H, H3); 1.89–1.82 (m, 2H, H6); 1.48/1.47 (s, 9H, CH_3). ^{13}C NMR: δ 171.59, (C1); 163.4, (CN_3); 156.0, (NCO'); 155.7, (NCO); 131.7, (C4); 130.1, (C5); 128.5, (ArC1′); 128.1, (ArC2′ and ArC6′); 126.6, (ArC3′ and ArC5′); 126.0, (ArC4′); 83.3, ($C(CH_3)_3$); 79.4, ($C'(CH_3)_3$); 67.0/66.9, ($ArCH_2$); 53.4, (OCH_3); 52.4/52.3, (C2); 40.3/40.1, (C7); 35.3/34.5, (C3); 31.8/30.1, (C6); 28.2/28.0, (C(CH_3)$_3$); 26.9/26.8, (C($C'H_3$)$_3$). MS (ES, +ve) m/z 549 (100%) [MH^+]. HRMS (ES) calcd for $C_{27}H_{41}N_4O_8$ 549.2924, found 549.2947.

4.1.6. Methyl (2*S*)-2-amino-7-(*tert*-butoxycarboxamido)-heptanoate (9). To a solution of **7** (25 mg, 0.061 mmol) in THF (4 mL) was added, palladium (10%) on activated carbon (13 mg, 0.006 mmol). The reaction vessel was evacuated, flushed with H_2 and allowed to stir at rt for 16 h. The resulting crude product was filtered through Celite and the solvent evaporated to yield the title compound **9** (15 mg, 0.055 mmol, 90%) as a colourless oil. $[\alpha]_D^{24}$ +9.6 (c 0.1, in EtOH). ν_{max}(neat) 2923, 2310, 2290, 1664, 1526 cm^{-1}. ^{1}H NMR: δ 4.55 (br s, 1H, NH); 3.72 (s, 3H, OCH_3); 3.44 (t, J=6.0 Hz, 1H, H2); 3.10 (dd, J=6.0, 12.6 Hz, 2H, H7); 1.80–1.68 (m, 4H, H3, H4); 1.44 (s, 9H, CH_3); 1.39–1.23 (m, 4H, H5, H6). ^{13}C NMR: δ 176.5, (C1); 155.9, (NCO); 79.9, ($C(CH_3)_3$); 54.2, (OCH_3); 51.8, (C2); 40.3, (C7); 34.7, (C3); 29.9, (C6); 28.3, (CH_3); 26.4, (C4); 25.3, (C5). MS (ES, +ve) m/z 219 (100%); 275 (90%) [MH^+]. HRMS (ES) Calcd for $C_{13}H_{27}N_2O_4$ 275.1971, found 275.1967.

4.1.7. Methyl (2*S*)-2-amino-7-(*N*,*N*-di-*tert*-butoxycarbonyl-guanidino)-heptanoate (10). To a solution of **8** (50 mg, 0.091 mmol) in THF (10 mL) was added, palladium (10%) on activated carbon (19 mg, 0.009 mmol). The reaction vessel was evacuated, flushed with H_2 and the mixture allowed to stir at rt for 16 h. The resulting crude mixture was filtered through Celite and the solvent was evaporated to yield the title compound **10** (28 mg, 0.091 mmol, 100%) as a red oil. $[\alpha]_D^{28}$ −15.3 (c 0.25, in EtOH). ν_{max}(neat) 2934, 2360, 2338, 1746, 1722, 1633, 1371, 1155 cm^{-1}. ^{1}H NMR: δ 8.34 (br s, 1H, NH); 3.79–3.76 (m, 1H, H2); 3.74 (s, 3H, OCH_3); 3.40 (t, J=6.6 Hz, 2H, H7); 1.92–1.82 (m, 4H, H3 and H4); 1.50 (s, 18H, 6×CH_3); 1.42–1.35 (m, 4H, H5 and H6). ^{13}C NMR: δ 171.6, (C1); 163.4, (CN_3); 156.1/153.3, (NCO); 83.1/79.3,

($C(CH_3)_3$); 54.2, (OCH_3); 52.1, (C2); 40.7, (C7); 35.3/34.5, (C3); 28.6/28.2, (CH_3); 28.0, (CH_3) 26.8/26.6, (C4); 26.1/26.0, (C5). MS (ES, +ve) *m/z* 417 (100%) [MH^+]. HRMS (ES) calcd for $C_{19}H_{37}N_4O_6$ 417.2713, found 417.2710.

4.1.8. (2*S*)-2,7-Diaminoheptanoic acid dihydrochloride (1). A solution of **9** (16 mg, 0.058 mmol) in 10 M HCl (3 mL) was allowed to stir at rt for 48 h before evaporation of the solvent and drying of the residue (P_2O_5) to yield the title compound **1** (14 mg, 0.058 mmol, 100%) as a hygroscopic white solid. $[\alpha]_D^{22}$ +10.9 (*c* 0.1 in 2 M HCl) (lit.[11] $[\alpha]_D^{23}$ +14.4, and lit.[12] $[\alpha]_D^{23}$ −10.6 for the opposite (*R*)-enantiomer). ν_{max}(neat) 2927, 2870, 2851, 1734, 1559, 1541, 1457, 1103 cm^{-1}. ^1H NMR (D_2O): δ 3.90 (t, J=6.3 Hz, 1H, H2); 2.83 (t, J=7.5 Hz, 2H, H7); 1.80–1.70 (m, 2H, H3); 1.58–1.48 (m, 2H, H5); 1.32–1.22 (m, 4H, H6 and H4). ^{13}C NMR (D_2O, 125 MHz): δ 172.5, (C1); 53.1, (C2); 39.4, (C7); 29.6, (C3); 26.5, (C6); 25.3, (C4); 23.8, (C5). MS (ES, +ve) *m/z* 161 (100%) [MH^+]. HRMS (ES) calcd for $C_7H_{17}N_2O_2$ 161.1290, found 161.1294.

4.1.9. (2*S*)-2-Amino-7-guanidinoheptanoic acid dihydrochloride (2). A solution of **10** (34 mg, 0.082 mmol) in 10 M HCl (5 mL) was allowed to stir at rt for 48 h before evaporation of the solvent and drying of the residue (P_2O_5) to yield the title compound **2** (23 mg, 0.082 mmol, 100%) as a hygroscopic white solid. $[\alpha]_D^{20}$ −23.3 (*c* 0.03 in HCl). ν_{max}(neat) 2927, 2852, 1752, 1617, 1552, 1140 cm^{-1}. ^1H NMR (D_2O): δ 3.77 (t, J=6.3 Hz, 1H, H2); 3.14 (t, J=6.6 Hz, 2H, H7); 1.90–1.78 (m, 2H, H3); 1.64–1.52 (m, 2H, H5); 1.46–1.30 (m, 4H, H6 and H4). ^{13}C NMR (D_2O): δ 172.6, (C1); 53.1, (C2); 41.1, (C7); 29.8, (C3); 27.6, (C6); 25.5, (C4); 23.9, (C5). MS (ES, +ve) *m/z* 203 (100%) [MH^+]. HRMS (ES) calcd for $C_8H_{19}N_4O_2$ 203.1508, found 203.1500.

4.1.10. Methyl (2*S*,5*S*)-5-(4-allyloxybenzyl)-3,6-diaza-2-(5-[*tert*-butoxycarboxamido]pentyl)-4,7-dioxooctanoate (12). To a solution of *O*-allyl-*N*-acetyl-(*S*)-tyrosine **11**[21] (53 mg, 0.20 mmol) and **9** (65 mg, 0.24 mmol) in CH_3CN (10 mL), was added EDCI (38 mg, 0.20 mmol) and HOBt (30 mg, 0.22 mmol) and the resulting mixture was allowed to stir at rt for 16 h. The reaction was diluted with H_2O (20 mL) and the solid precipitate collected by vacuum filtration, then dissolved in EtOAc (30 mL) and the EtOAc solution was washed with water (3×30 mL). The crude product was purified by column chromatography (silica gel, 5% MeOH/CH_2Cl_2) to afford **12** (103 mg, 0.20 mmol, 100%) as an off-white solid. Mp 96–103 °C. ν_{max}(neat) 2943, 2942, 1832, 1618, 1604, 1565, 1411, 1132 cm^{-1}. ^1H NMR: δ 7.11 (d, J=8.7 Hz, 2H, ArH2″ and ArH6″); 6.82 (d, J=8.7 Hz, 2H, ArH3″ and ArH5″); 6.50 (d, J=7.8 Hz, 1H, NH); 6.03 (m, 1H, H2‴); 5.39 (dd, J=1.8, 17.4 Hz, 1H, $H3_a$‴); 5.26 (dd, J=1.8, 9.3 Hz, 1H, $H3_b$‴); 4.66 (m, 2H, H2 and H5); 4.48 (m, 2H, H1‴); 3.69 (s, 3H, OCH_3); 2.98 (m, 4H, H5′ and $ArCH_2$); 1.96 (s, 3H, H8); 1.75 (m, 2H, H1′); 1.64 (m, 2H, H3′); 1.43 (s, 9H, $C(CH_3)_3$); 1.26 (m, 4H, H2′ and H4′). ^{13}C NMR: δ 172.2, C4; 171.2, C1; 170.2, C7; 157.5, NCO_2; 156.2, ArC4″; 133.2, C2″; 130.2, ArCH2″ and ArCH6; 128.6, ArC1″; 117.5, C3‴; 114.7, ArCH3″ and ArCH5″; 79.0, $C(CH_3)_3$; 68.7, C1‴; 54.5, C2; 54.4, C5; 52.2, C5′; 52.1, OCH_3; 40.0, C4′; 37.2, $ArCH_2$; 31.8, C1′; 28.3, $C(CH_3)_3$; 26.2, C8; 25.9, C3′; 22.9, C2′. Mass Spectrum (ES, +ve) *m/z* 520 (100%) [MH^+]. HRMS calcd for $C_{27}H_{41}N_3O_7$ 542.2842, found 542.2855.

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References and notes

1. Greenstein, J. P.; Winitz, M. In *Chemistry of the Amino Acids*, *Vol. 3*; Wiley: New York, 1961; pp 2463–2498.
2. Vizioli, J.; Salzet, M. *Trends Pharmacol. Sci.* **2002**, *23*, 494–496.
3. Beeson, C.; Dix, T. A. *J. Am. Chem. Soc.* **1993**, *115*, 10275–10281.
4. Bodanszky, M.; Lindeberg, G. *J. Med. Chem.* **1971**, *14*, 1197–1199.
5. Schiller, P. W.; Nguyen, T. M. D.; Maziak, L. A.; Lemieux, C.; Wilkes, B. C. In Peptides (*Proceedings of the 19th European Peptide Symposium*); Theodoropoulos, D., Ed.; W. de Gruyter: Berlin, 1986; Vol. 1987, p 389.
6. Doherty, A. M.; Kaltenbronn, J. S.; Hudspeth, J. P.; Repine, J. T.; Roark, W. H.; Sircar, I.; Tinney, F. J.; Connolly, C. J.; Hodges, J. C. *J. Med. Chem.* **1991**, *34*, 1258–1271.
7. Hiramatsu, M. *Mol. Cell. Biochem.* **2003**, *244*, 57–62.
8. Pereira, C. A.; Alonso, G. D.; Ivaldi, S.; Bouvier, L. A.; Torres, H. N.; Flawia, M. M. *J. Eukaryotic Microbiol.* **2003**, *50*, 132–134.
9. Payne, L. S.; Boger, J. *Synth. Commun.* **1985**, *15*, 1277–1290.
10. Kennedy, K. J.; Lundquist, J. T. I. V.; Simandan, T. L.; Beeson, C. C.; Dix, T. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1937–1940.
11. Dong, Z. *Tetrahedron Lett.* **1992**, *33*, 7725–7726.
12. Beaulieu, P. L.; Schiller, P. W. *Tetrahedron Lett.* **1988**, *29*, 2019–2022.
13. Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7717–7140.
14. Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804–3805.
15. van Benthem, R. A. T. M.; Michels, J. J.; Hiemstra, H.; Speckamp, W. N. *Synlett* **1994**, 368–370.
16. Abbott, S. D.; Lane-Bell, P.; Sidhu, K. P. S.; Vederas, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 6513–6520.
17. Biagini, S. C. G.; Gibson, S. E.; Keen, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2485–2499.
18. Pernerstorfer, J.; Schuster, M.; Blechert, S. *Chem. Commun.* **1997**, 1949–1950.
19. Vernall, A. J.; Abell, A. D. *Aldrichim. Acta* **2003**, *36*, 93–105.
20. Tous, G.; Bush, A.; Tous, A.; Jordan, F. *J. Med. Chem.* **1990**, *33*, 1620–1634.
21. The acid **11** was prepared by base hydrolysis of the ethyl ester derivative.[20] Subsequent reesterification using $SOCl_2$–ethanol yielded the ester, which had a specific rotation close to that of the starting ester of $[\alpha]_D^{22}$ +20.8, hence confirming the enantiomeric integrity of **11**.
22. The ^1H NMR of **12** contains small peaks adjacent to the

methyl ester signal which are assigned as either amide rotamers or a small quantity of a diastereomer. The dr for **12** of $>96\%$ is calculated from the NMR taking into account these peaks.

23. For conditions see: Murray-Wallace, C. V. *The Artefact* **1993**, 19–26.
24. McGrady, K. A. W.; Overberger, C. G. *Polym. J.* **1987**, *19*, 539–555.

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DABCO-catalyzed reactions of hydrazones with activated olefins

Gui-Ling Zhao and Min Shi*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

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Abstract—This paper describes several highly efficient DABCO-catalyzed aza-Michael addition reactions of hydrazones to activated olefins. In most cases, these aza-Michael addition reactions gave the corresponding products in high yields under mild conditions. The plausible reaction mechanism is discussed on the basis of deuterium labeling experiments. Upon treatment with HCl, the corresponding cyclized products can be obtained in high yields from the Michael addition products.

1. Introduction

Great progress has been made in the execution of the Morita–Baylis–Hillman reaction,[1] since Baylis and Hillman first reported the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of strong nucleophilic Lewis base such as 1,4-diazabicyclo[2,2,2]octane (DABCO) in 1972.[2] During our ongoing investigations on the aza-Baylis–Hillman reactions of *N*-tosylated imines (ArCH=NTs) with activated olefins, we found that either 'normal' or 'abnormal' reaction products were formed depending on the employed nucleophilic Lewis base.[3] In this paper, we wish to report DABCO-catalyzed reactions of hydrazones **1** (R–CH=N–NHTs, 4-methylbenzenesulfonic acid *N*-methylidene-hydrazide) and **2** [R–CH=N–NHC(O)Ph, benzoic acid *N*-methylidene-hydrazide] with activated olefins such as methyl vinyl ketone (MVK), methyl acrylate, acrylonitrile and phenyl vinyl ketone (PVK) to give the Michael addition products in good yields. In the present reaction, DABCO served as a Brønsted base or a proton-sponge rather than a nucleophilic Lewis base in Baylis–Hillman reaction.

2. Results and discussion

As initial examination, a variety of organic bases have been examined as catalysts in the reaction of hydrazone **1a** with MVK and the results are summarized in Table 1. As can be seen from Table 1, the reaction proceeded smoothly to give the Michael addition product **3a** in high yields in the presence of nitrogen containing organic bases such as DABCO, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or Et_3N (10 mol%) for 10 h (Table 1, entries 2, 8, 9 and 10). The solvent effects have been examined using DABCO as a promoter. We found that tetrahydrofuran (THF) is the solvent of choice. In the presence of 1.0 mol% of DABCO in THF, the reaction also proceeded efficiently to give the addition product **3a** in >99% yield after 24 h (Table 1, entry 6). DMAP (1.0 mol%) and DBU (1.0 mol%) are not as effective as DABCO (1.0 mol%) under the identical conditions (Table 1, entries 8 and 9). Triphenylphosphine or tributylphosphine did not catalyze this reaction (Table 1, entry 7).[4] It should be noted that using inorganic bases such as K_2CO_3, KOAc and KOBu^t in this reaction under the same conditions, the reaction took place as well, but in low yields even after a prolonged reaction time, which is presumably due to their low solubilities in THF.

Under the optimized reaction conditions, we next examined the reactions of a variety of hydrazones **1** with MVK. The results are summarized in Table 2. The corresponding adducts **3** were obtained in good to high yields in the presence of DABCO (1.0 mol%) (Table 2, entries 1–6). For aromatic substrates **1b–f**, the corresponding adducts **3b–f** were obtained in high yields (Table 2, entries 1–5). When the benzene ring bears a strongly electron-withdrawing group such as *p*-nitrobenzenealdehyde, the reaction proceeds quickly to give the adduct within shorter reaction time (Table 1, entry 5). For aliphatic substrate **1g**, the corresponding adduct **3g** was obtained in good yield (Table 2, entry 6).

Under the same conditions, we further examined the

Keywords: Hydrazones; DABCO; Lewis base; MVK; Methyl acrylate; Acrylonitrile; Phenyl vinyl ketone.
* Corresponding author. Fax: +86 21 64166128;
e-mail: mshi@pub.sioc.ac.cn

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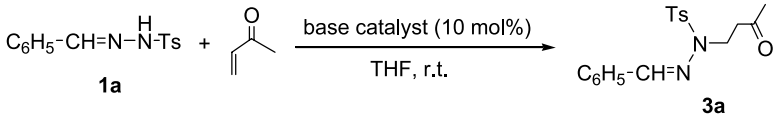
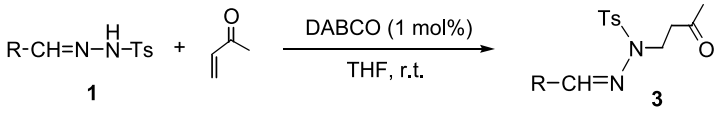
Table 1. Reactions of hydrazone **1a** (1.0 equiv) with MVK (1.2 equiv) in the presence of organic base catalyst (10 mol%) at room temperature



Entry	Base catalyst	Solvent	Time (h)	Yield (%)[a] **3a**
1	—	THF	10	0
2	DABCO	THF	10	>99
3	DABCO	CH_2Cl_2	10	91
4	DABCO	MeCN	10	94
5	DABCO	DMF	10	83
6	DABCO[b]	THF	24	>99
7	PPh_3 or PBu_3	THF	10	0
8	DMAP[c]	THF	10	>99
9	DBU[d]	THF	10	>99
10	Et_3N	THF	10	96

[a] Isolated yields.
[b] DABCO (1.0 mol%) was used.
[c] Using 1.0 mol% of DMAP, **3a** was obtained in 82% yield.
[d] Using 1.0 mol% of DBU, **3a** was obtained in 80% yield.

Table 2. Reactions of hydrazones **1** (1.0 equiv) with MVK (1.2 equiv) in the presence of DABCO (1.0 mol%) at room temperature



Entry	R	Time (h)	Yield (%)[a] **3**
1	*p*-MeC_6H_4 **1b**	36	**3b**, >99
2	*p*-FC_6H_4 **1c**	24	**3c**, 89
3	*p*-ClC_6H_4 **1d**	24	**3d**, >99
4	*p*-BrC_6H_4 **1e**	24	**3e**, >99
5	*p*-$NO_2C_6H_4$ **1f**	12	**3f**, 84
6	$(CH_3)_2CH$ **1g**	24	**3g**, 70

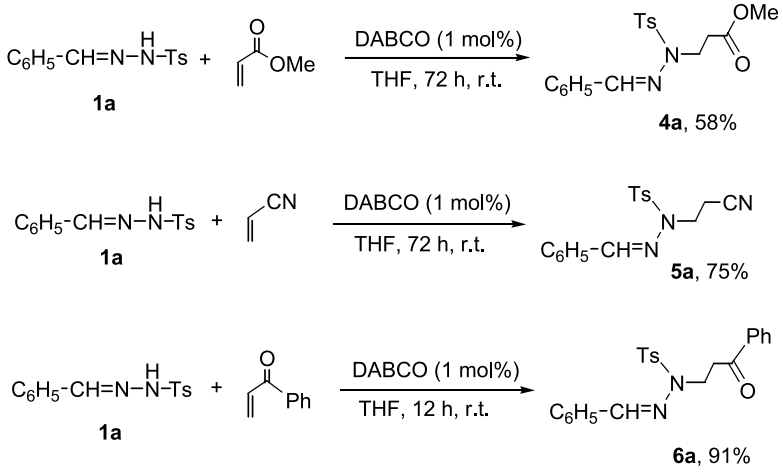
[a] Isolated yields.

reaction of **1a** with other activated olefins such as methyl acrylate, acrylonitrile, and phenyl vinyl ketone (PVK) and found that the corresponding adducts **4a**, **5a** and **6a** were also obtained in good to high yields (Scheme 1).

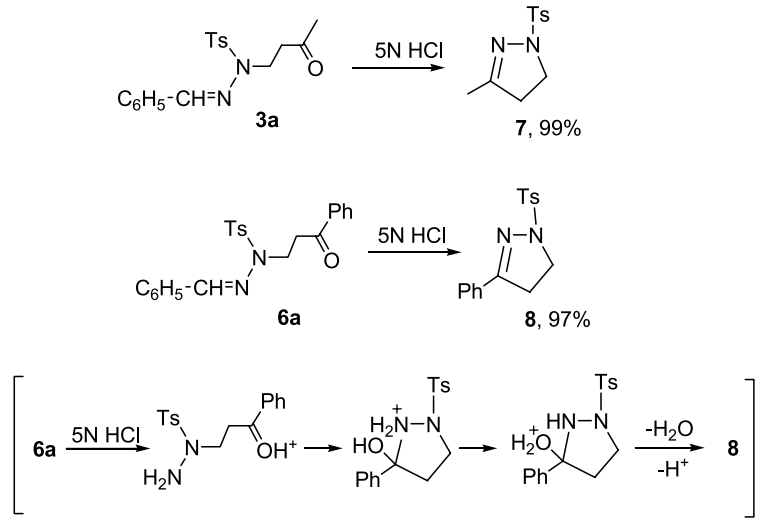
It should be emphasized here that treatment of **3a** or **6a** with 5 N HCl for 2 h gave the cyclized product **7** or **8** in high yield at room temperature (Scheme 2).

By a sequential treatment of **1** with MVK in the presence of DABCO (1.0 mmol) in THF for 24–36 h and then with 5 N HCl for 2 h, the cyclized product **7** was also obtained in good yields. The results are summarized in Table 3.

We next examined the reactions of hydrazone **2a** having a *N*-benzoyl protecting group with MVK in a variety of solvents in the presence of various organic base catalysts to

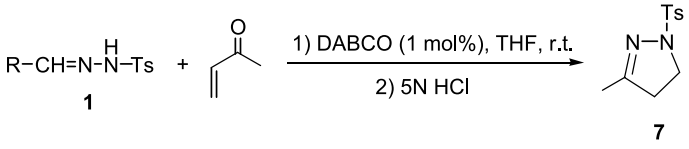


Scheme 1. Reactions of hydrazone **1a** (1.0 equiv) with other activated olefins (1.2 equiv) in the presence of DABCO (1 mol%) in THF.



Scheme 2. Cyclization of **3a** or **6a** with 5 N HCl.

Table 3. Reactions of hydrazones **1** (1.0 equiv) with MVK (1.2 equiv) in the presence of DABCO (1 mol%) and then with 5 N HCl



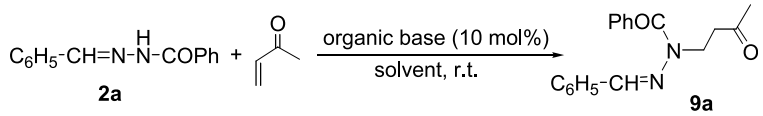
Entry	R	Time (h)	Yield (%)[a] of **7** (two steps)
1	C_6H_5 **1a**	24, 2	>99
2	*p*-MeC_6H_4 **1b**	36, 2	89
3	*p*-FC_6H_4 **1c**	24, 2	78
4	*p*-ClC_6H_4 **1d**	24, 2	>99
5	*p*-BrC_6H_4 **1e**	24, 2	95
6	$(CH_3)_2CH$ **1g**	24, 2	92

[a] Isolated yields.

optimize the reaction conditions. The result are shown in Table 4 (entries 1–9). We were pleased to find that using hydrazone **2a** as a substrate and DABCO (10 mol%) as the base catalyst in *N*,*N*-dimethylformamide (DMF), the Michael addition product **9a** can be obtained in 91% yield after a prolonged reaction time (Table 4, entry 6). The results of hydrazones **2b** and **2c** combined with **2a** under the optimized reaction conditions are summarized in Table 5. For aliphatic hydrazone **2c**, the corresponding Michael addition product **9c** was formed in 56% yield (Table 5, entry 3).

Accordingly, treatment of **2a** with MVK in the presence of DABCO in DMF for 96 h and then with 5 N HCl for 12 h, the corresponding cyclized product **10** was obtained in 98% yield (Scheme 3).

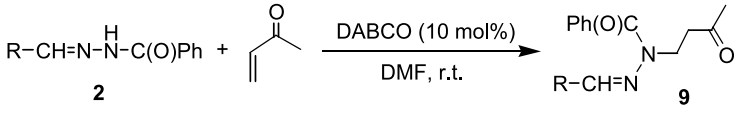
Table 4. Reactions of hydrazone **2a** (1.0 equiv) with MVK (1.2 equiv) in the presence of nitrogen containing organic base (10 mol%) at room temperature



Entry	Organic base	Solvent	Time (h)	Yield (%)[a] of **9a**
1	DABCO	THF	96	0
2	DABCO	DME	96	0
3	DABCO	EtOH[b]	96	0
4	DABCO	CH_3CN	96	Trace
5	DABCO	CH_3COCH_3	96	Trace
6	DABCO	DMF	96	91
7	DMAP	DMF	96	71
8	DBU	DMF	96	68
9	Et_3N	DMF	96	Trace

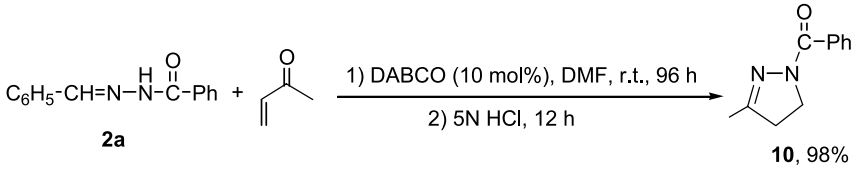
[a] Isolated yields.
[b] The reaction was carried under reflux.

Table 5. Reactions of hydrazones **2** (1.0 equiv) with MVK (1.2 equiv) in the presence of DABCO (10 mol%) at room temperature



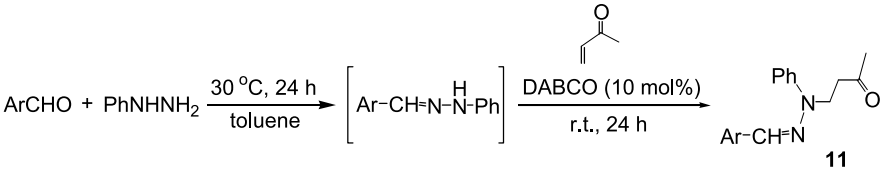
Entry	R	Time (h)	Yield (%)[a] of **9**
1	C_6H_5 **2a**	96	**9a**, 91
2	*p*-ClC_6H_4 **2b**	72	**9b**, 90
3	$(CH_3)_2CH$ **2c**	96	**9c**, 56

[a] Isolated yields.



Scheme 3. Reaction of hydrazone **2a** (1.0 equiv) with MVK (1.2 equiv) in the presence of DABCO (10 mol%) at room temperature and then with 5 N HCl.

Table 6. Reactions of aryladehyde (1.0 equiv) with phenyl hydrazine and MVK (1.2 equiv) in the presence of DABCO (10 mol%)



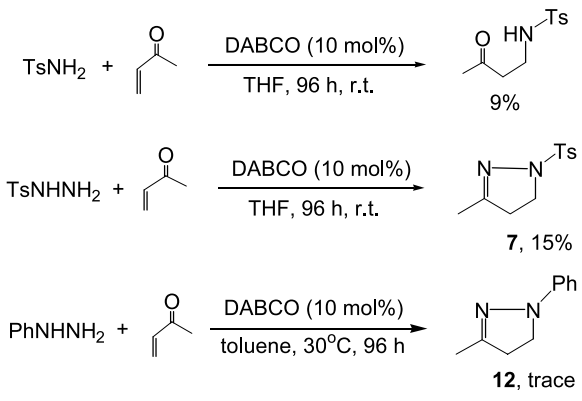
Entry	Ar	Yield (%)[a] of **11** (two steps)
1	C_6H_5	**11a**, 34
2	*p*-$CH_3C_6H_4$	**11b**, 20
3	*p*-ClC_6H_4	**11c**, 39

[a] Isolated yields.

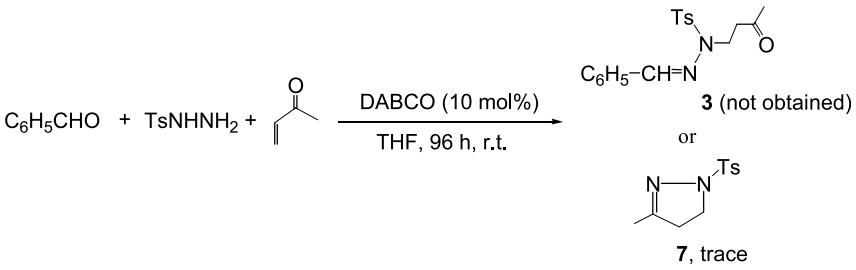
Scheme 4. Cyclization of **11a** with 5 N HCl.

Next, we examined the reactions of *N*-arylmethylidene-*N′*-phenylhydrazine (Ar–CH=N–NH–Ph)[5] prepared in situ with MVK under the similar conditions. The results are summarized in Table 6. The Michael addition adducts **11** could be obtained, but in lower yields. Cyclization of **11a** could also take place upon treating with 5 N HCl to give the cyclized product **12** in 31% yield (Scheme 4).

In order to clarify the scope and limitation of this interesting DABCO-catalyzed aza-Michael addition reaction, the reactions of $TsNH_2$,[6] $TsNHNH_2$, or $PhNHNH_2$[7] with MVK were carried out under the similar conditions in the presence of DABCO (10 mol%) (Scheme 5). However, we found that all these reactions were sluggish and the corresponding adducts were obtained in trace to only low yields even after a prolonged reaction time. Attempts to perform the one-pot reaction of aldehydes, tosylhydrazine, and MVK (Scheme 6) produced trace of cyclized product **7**, and no aza-Michael addition product **3** were obtained. These results suggest that the acidity of N–H proton in hydrazones **1** and **2** plays a significant role in this DABCO-catalyzed reaction. The *N*-tosylated or *N*-acylated hydrazones **1** and **2** can react with MVK and other activated olefins in the presence of DABCO to give the corresponding Michael addition products in good yields. This synthetic method can



Scheme 5. Reactions of $TsNH_2$, $TsNHNH_2$ $PhNHNH_2$ (1.0 equiv) with MVK (1.2 equiv) in the presence of DABCO (10 mol%).



Scheme 6. The one-pot reaction of PhCHO (1.0 equiv), $TsNHNH_2$ (1.0 equiv) with MVK (1.2 equiv) in the presence of DABCO (10 mol%).

produce pyrazoline derivatives in high yields comparing to previously reported methods.[8]

The mechanism of this interesting organic nitrogen base promoted reaction has not been unequivocally established, but on the basis of previous investigations[1,9,10] and our deuterium labeling experiments (Figs. 1–8, Schemes 7 and 8), one plausible explanation is proposed in Scheme 9.

We first carried out the following deuterium labeling experiment to clarify this mechanism. In the presence of DABCO (0.1 mmol), we found that the H/D exchange of 3-pentanone (0.1 mmol) took place rapidly in D_2O (0.5 mL)

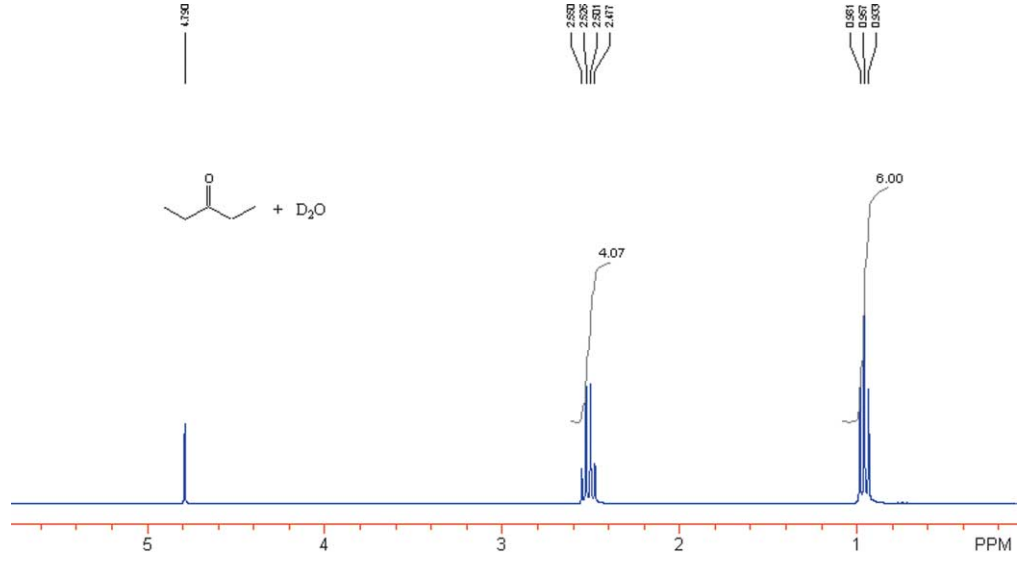


Figure 1. The ^1H NMR spectrum of 3-pentanone in D_2O.

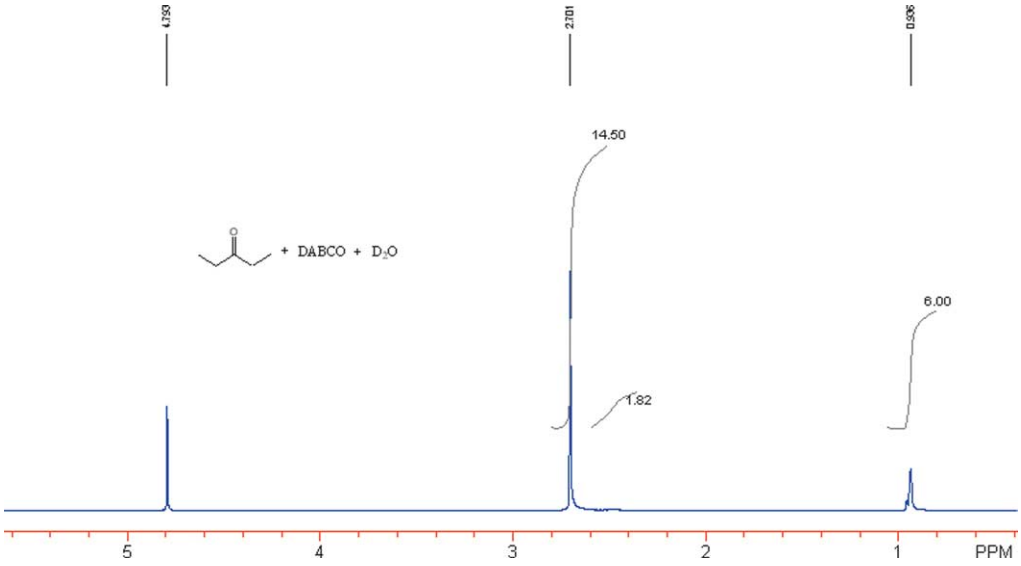


Figure 2. The ^1H NMR spectrum of 3-pentanone (0.1 mmol) and DABCO (0.1 mmol) in D_2O.

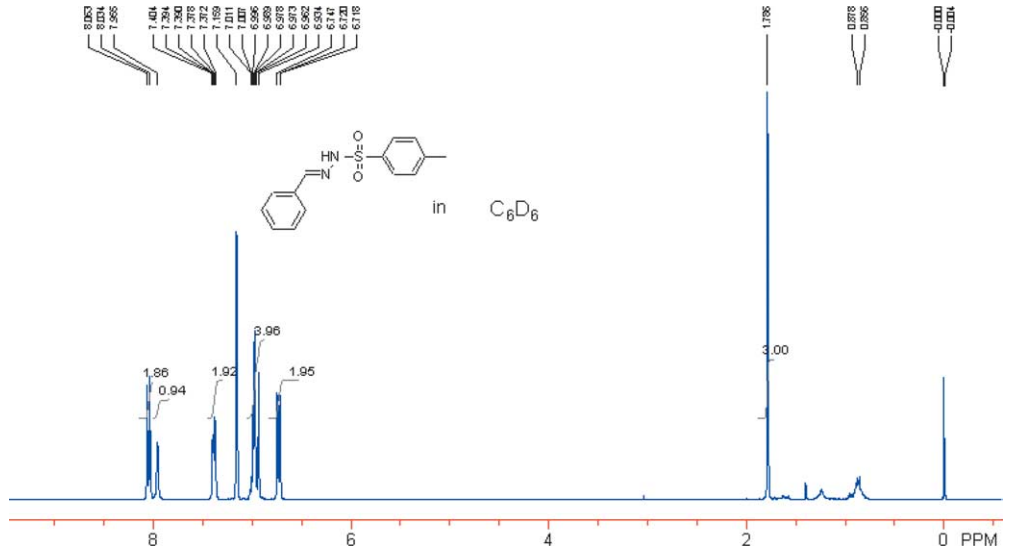


Figure 3. The ^{1}H NMR spectrum of hydrazone **1a** in C_6D_6.

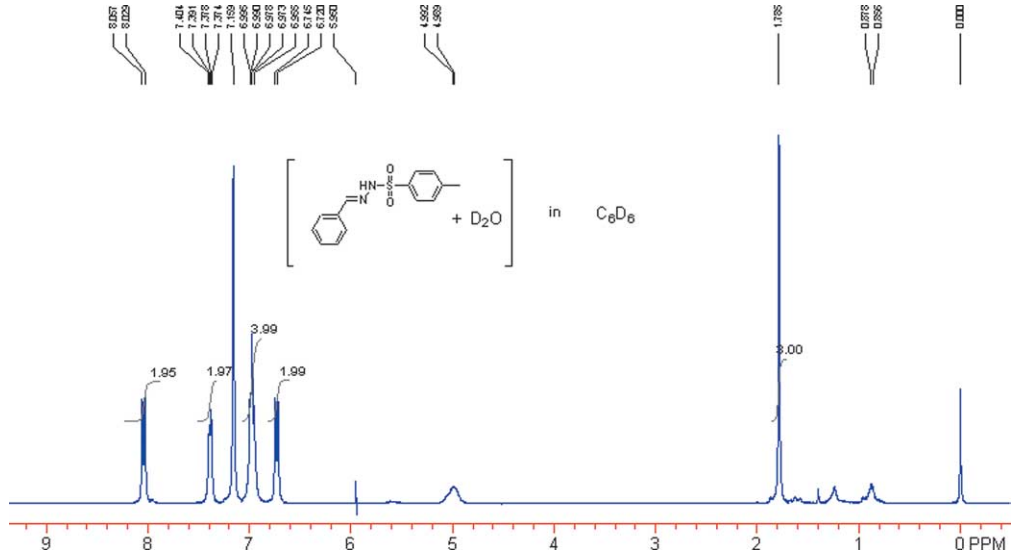


Figure 4. The ^{1}H NMR spectrum of hydrazone **1a** with D_2O in C_6D_6.

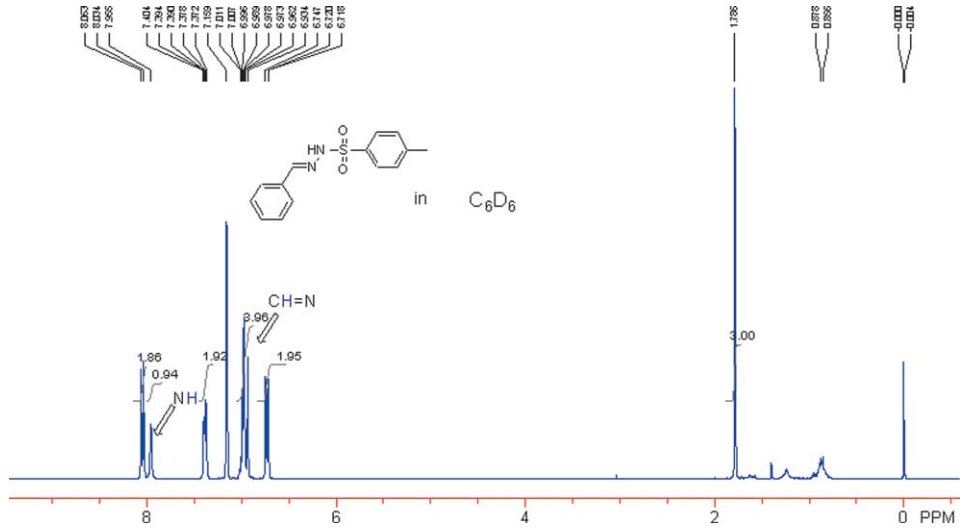


Figure 5. The ^{1}H NMR spectrum of hydrazone **1a** in C_6D_6.

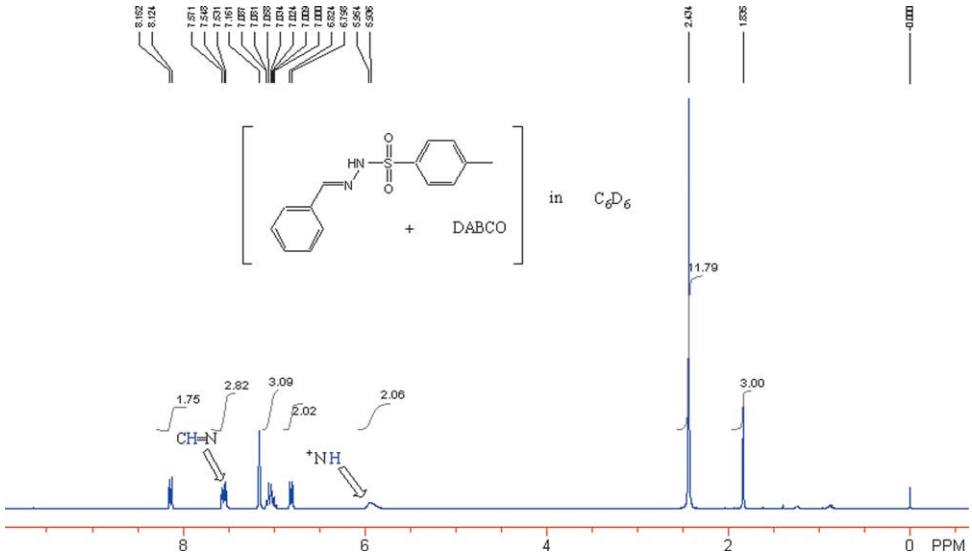


Figure 6. The ^{1}H NMR spectrum of hydrazone **1a** (0.05 mmol) with DABCO (0.05 mmol) in C_6D_6.

(Scheme 7), which could be clearly observed from ^{1}H NMR spectra shown in Figures 1 and 2. The methylene protons at 2.53 ppm (q) in Figure 1 completely disappeared in Figure 2 and the signal at δ 2.70 ppm (s) in Figure 2 was DABCO.

The deuterium labeling experiment of hydrazone **1a** (0.05 mmol) with DABCO (0.05 mmol) in C_6D_6 (0.5 mL) was also examined. Their ^{1}H NMR spectra were shown in Figures 3–6. From Figures 3, 4 and 5, we can assign the exact chemical shift of NH and CH in the ^{1}H NMR spectrum of **1a** because the signal at δ 7.97 ppm completely disappeared with the addition of deuterium oxide (D_2O) in C_6D_6. Their chemical shifts have been clearly shown in Figure 5 (δ_{NH} at 7.97 ppm and δ_{CH} at 6.93 ppm).

Next, we examined the ^{1}H NMR spectrum of **1a** in C_6D_6 with the addition of DABCO. This spectroscopic chart is shown in Figure 6. From Figure 6, we observed that the N–H proton of **1a** disappeared and a new signal appeared at 5.95 ppm which can be supposed to be $[DABCOH]^+$ (the signal at δ 2.43 ppm (s) is DABCO). Thus, we believe that DABCO functions as a base to abstract the N–H proton in **1a** directly.

Moreover, the following deuterium labeling experiment was also performed (Scheme 8). The deuterium labeled nucleophilic reagent **1a**-*d* was prepared with DCl in D_2O according to Scheme 8, which was used in the DABCO-catalyzed aza-Michael addition reaction with MVK under the similar conditions as those described above. The deuterium incorporated Michael addition product **3a**-*d* was obtained in 89% yield (D content 94%). The ^{1}H and ^{13}C NMR spectra of **3a**-*d* are given in Figures 7 and 8.

Overall, on the basis of the above spectroscopic investigations, we believe that DABCO acts as a Brønsted base

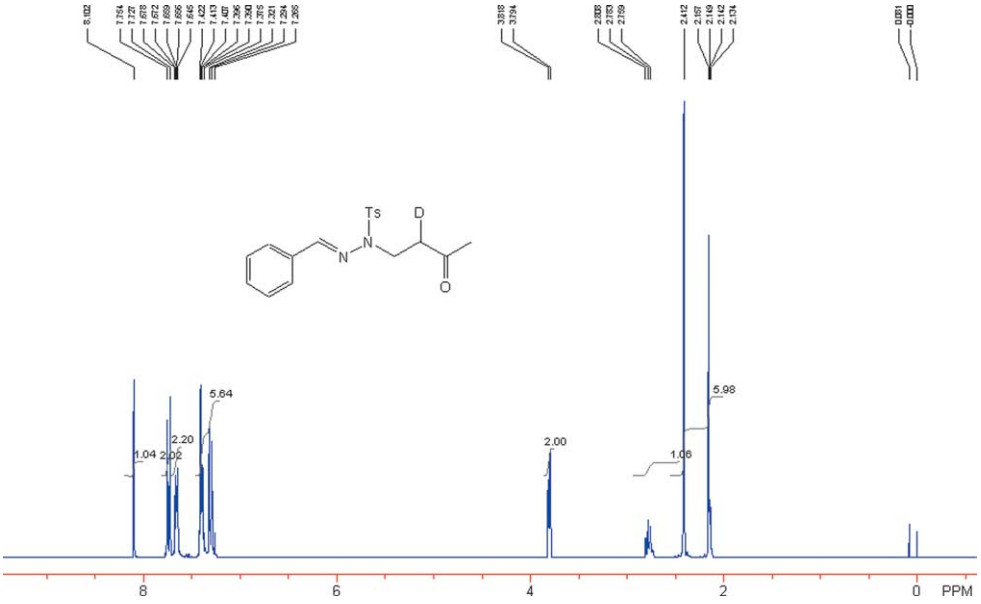


Figure 7. The ^{1}H NMR spectrum of **3a**-*d* in $CDCl_3$.

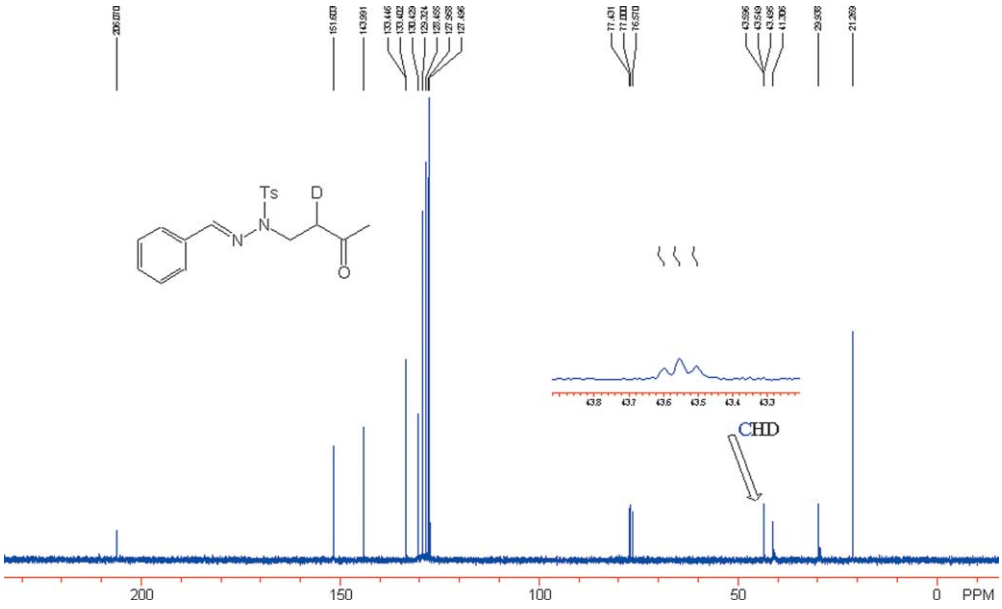
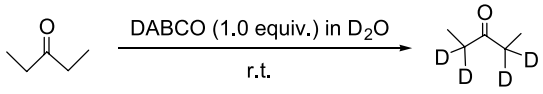
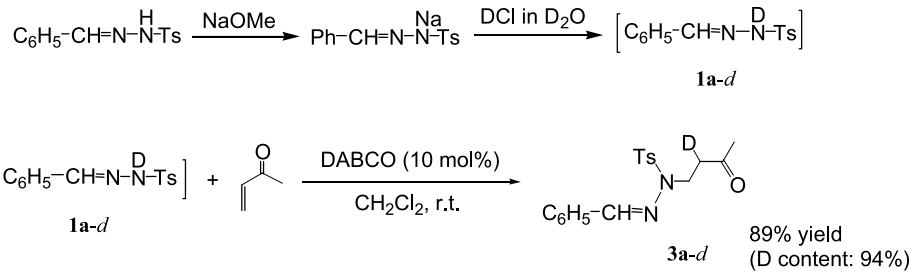


Figure 8. The ^{13}C NMR spectrum of **3a**-*d* in $CDCl_3$.



Scheme 7. DABCO-catalyzed H/D exchange of 3-pentanone in D_2O.

catalytic cycle (Scheme 9). The N–H proton of *N*-sulfonated group has higher acidity because SO_2R is a strongly electron-withdrawing group. Therefore, its proton can be easily removed by DABCO. This is why the reaction rate of **1** is remarkably higher than that of **2** and only 1.0 mol% of DABCO is enough to accomplish this catalytic reaction under otherwise identical conditions.

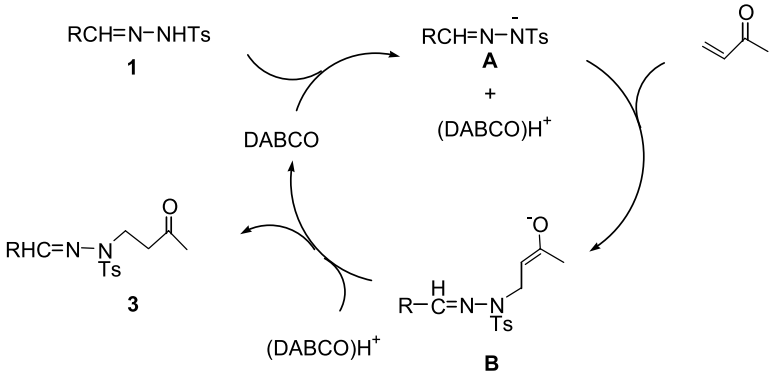


Scheme 8. The reaction of deuterium labeled **1a** (1.0 equiv) with MVK (1.2 equiv) in the presence of DABCO (10 mol%).

which abstracts a proton from hydrazone **1** or **2** to produce nucleophilic intermediate **A**. The subsequent conjugate addition of **A** to MVK generates enolate **B**. Reprotonation of enolate **B** affords **3** and regenerates DABCO to complete the

3. Conclusion

We disclosed an interesting organic nitrogen base DABCO promoted aza-Michael addition reaction of **1** or **2** with



Scheme 9. Proposed reaction mechanism of DABCO catalyzed reaction of hydrazone **1** or **2** with activated olefins.

activated olefins. The transformation is in contrast to the recently reported DABCO catalyzed aza-Baylis–Hillman reaction[3] and the reaction mechanism is different from phosphine Lewis base catalyzed Michael addition of alcohols to activated olefins.[11] Additionally, this finding can open new ways for the design of new reactions and synthesis of novel compounds by the organocatalysts in the future. The scope and limitations of this reaction have been disclosed along with the detailed investigation on the plausible reaction mechanism. Efforts are underway to elucidate the mechanistic details of this reaction and to extend the scope of those reactions in other C–C bond forming transformations thereof.

4. Experimental

4.1. General remarks

MPs were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J*-values are in Hz. Mass spectra were recorded with a HP-5989 instrument. All of the solid compounds reported in this paper gave satisfactory CHN microanalyses with a Carlo-Erba 1106 analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 200–300 mesh silica gel at medium pressure. The starting materials hydrazones **1** and **2** were prepared according to the literature.

4.2. Typical reaction procedure for the nitrogen Lewis base-catalyzed reaction of 4-methylbenzenesulfonic acid *N*-methylidene-hydrazide 1a with methyl vinyl ketone (MVK)

To a Schlenk tube with **1a** (274 mg, 1.0 mmol) and DABCO (1.0 mg, 0.01 mmol) in THF (1.0 mL) was added methyl vinyl ketone (MVK) (70 mg, 83 μL, 1.0 mmol) under an argon atmosphere and the reaction mixture was stirred for 24 h at room temperature (20 °C). The reaction mixture was diluted with dichloromethane (20 mL). The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluent: EtOAc/petroleum=1/2) to give **3a** (341 mg, 99%) as a colorless solid.

4.2.1. 4-Methylbenzenesulfonic acid *N′*-benzylidene-*N*-(3-oxobutyl)hydrazide 3a. Colorless solid; mp 55–58 °C (recrystallized from dichloromethane and petroleum ether); IR (CH_2Cl_2) ν 3296, 3062, 1716 (C=O), 1676, 1358, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.16 (3H, s, CH_3), 2.41 (3H, s, CH_3), 2.79 (2H, t, J=7.2 Hz, CH_2), 3.82 (2H, t, J=7.2 Hz, CH_2), 7.31 (2H, d, J=8.4 Hz, ArH), 7.39–7.41 (3H, m, ArH), 7.64–7.68 (2H, m, ArH), 7.74 (2H, d, J=8.4 Hz, ArH), 8.10 (1H, s, CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.5, 30.2, 41.6, 43.9, 127.7, 128.2, 128.6, 129.3, 129.5, 130.6, 133.5, 144.2, 152.5, 206.3; MS (EI) *m/z* 344 (M^+, 6.54), 189 (M^+-155, 47.72), 147 (M^+-197, 52.01), 131 (M^+-213, 73.05), 119 (M^+-225, 100); HRMS (MALDI) calcd for $C_{18}H_{20}N_2O_3SNa^{+1}$ (M^+ + Na): 367.1087. Found: 367.1074.

4.2.2. 4-Methylbenzenesulfonic acid *N′*-(4-methylbenzylidene)-*N*-(3-oxobutyl) hydrazide 3b. Colorless solid; mp 102–105 °C (recrystallized from dichloromethane and petroleum ether); IR (CH_2Cl_2) ν 3463, 3055, 1690, (C=O), 1357, 1170, 896 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.16 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.76 (2H, t, J=7.2 Hz, CH_2), 3.74 (2H, t, J=7.2 Hz, CH_2), 7.21 (2H, d, J=7.8 Hz, ArH), 7.31 (2H, d, J=7.8 Hz, ArH), 7.56 (2H, d, J=7.8 Hz, ArH), 7.71 (2H, d, J=7.8 Hz, ArH), 8.16 (1H, s, CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.5, 21.5, 30.2, 41.8, 44.5, 127.9, 128.3, 129.4, 129.5, 130.7, 133.3, 141.3, 144.1, 154.9, 206.3; MS (EI) *m/z* 358 (M^+, 5.19), 203 (M^+-155, 22.71), 161 (M^+-197, 20.25), 145 (M^+-213, 77.31), 133 (M^+-225, 100); HRMS (MALDI) calcd for $C_{19}H_{22}N_2O_3SNa^{+1}$ (M^+ + Na): 381.1243. Found: 381.1251.

4.2.3. 4-Methylbenzenesulfonic acid *N′*-(4-fluorobenzylidene)-*N*-(3-oxobutyl) hydrazide 3c. Colorless oil; IR (CH_2Cl_2) ν 3512, 3251, 1714 (C=O), 1644, 1357, 1233, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.17 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.78 (2H, t, J=7.2 Hz, CH_2), 3.78 (2H, t, J=7.2 Hz, CH_2), 7.06–7.12 (2H, m, ArH), 7.31 (2H, d, J=8.1 Hz, ArH), 7.63–7.68 (2H, m, ArH), 7.72 (2H, d, J=8.1 Hz, ArH), 8.10 (1H, s, CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.3, 30.0, 41.4, 43.8, 115.6 (d, J=21.8 Hz), 128.0, 129.4, 129.5 (d, J=8.0 Hz), 129.7 (d, J=2.9 Hz), 133.3, 144.1, 150.8, 163.9 (d, J=250.1 Hz), 206.1; MS (EI) *m/z* 362 (M^+, 7.08), 207 (M^+-155, 57.49), 165 (M^+-197, 65.52), 149 (M^+-213, 30.54), 137 (M^+-225, 100), 108 (M^+-254, 57.31); HRMS (MALDI) calcd for $C_{18}H_{19}N_2O_3FSNa^{+1}$ (M^++ Na): 385.0993. Found: 385.1012.

4.2.4. 4-Methylbenzenesulfonic acid *N′*-(4-chlorobenzylidene)-*N*-(3-oxobutyl) hydrazide 3d. Colorless solid; mp 78–80 °C (recrystallized from dichloromethane and petroleum ether); IR (CH_2Cl_2) ν 2922, 1701 (C=O), 1677, 1597, 1492, 1355, 1167, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.17 (3H, s, CH_3), 2.41 (3H, s, CH_3), 2.80 (2H, t, J=6.9 Hz, CH_2), 3.84 (2H, t, J=6.9 Hz, CH_2), 7.31 (2H, d, J=8.1 Hz, ArH), 7.36 (2H, d, J=8.1 Hz, ArH), 7.59 (2H, d, J=8.1 Hz, ArH), 7.73 (2H, d, J=8.1 Hz, ArH), 8.00 (1H, s, CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.4, 30.1, 41.5, 43.4, 128.0, 128.7, 128.8, 129.5, 132.1, 133.5, 136.2, 144.2, 148.9, 206.1; MS (EI) *m/z* 378 (M^+, 4.55), 223 (M^+-155, 27.43), 181 (M^+-197, 33.44), 165 (M^+-213, 30.54), 153 (M^+-225, 52.04), 43 (M^+-335, 100); HRMS (MALDI) calcd for $C_{18}H_{20}N_2O_3SCl^{+1}$ (M^++H): 379.0878. Found: 379.0887.

4.2.5. 4-Methylbenzenesulfonic acid *N′*-(4-bromobenzylidene)-*N*-(3-oxobutyl) hydrazide 3e. Colorless solid; mp 105–108 °C (recrystallized from dichloromethane and petroleum ether); IR (CH_2Cl_2) ν 3052, 2927, 1699 (C=O), 1674, 1356, 1093, 818 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.17 (3H, s, CH_3), 2.41 (3H, s, CH_3), 2.80 (2H, t, J=7.2 Hz, CH_2), 3.84 (2H, t, J=7.2 Hz, CH_2), 7.31 (2H, d, J=8.1 Hz, ArH), 7.51 (4H, s, ArH), 7.73 (2H, d, J=8.1 Hz, ArH), 7.97 (1H, s, CH); ^{13}C NMR ($CDCl_3$, 75 MHz,

TMS) δ 21.4, 30.1, 41.3, 43.2, 124.5, 127.9, 128.8, 129.4, 131.7, 132.5, 133.5, 144.2, 148.2, 206.1; MS (EI) *m/z* 424 (M^++2, 9.57), 422 (M^+, 9.34), 269 (M^+−153, 46.51), 267 (M^+−155, 48.85), 199 (M^+−123, 77.35), 197 (M^+−125, 81.39), 89 (M^+−333, 100); HRMS (MALDI) calcd for $C_{18}H_{19}N_2O_3SBr^{+1}$: 422.0294. Found: 422.0290.

4.2.6. 4-Methylbenzenesulfonic acid *N′*-(4-nitrobenzylidene)-*N*-(3-oxobutyl) hydrazide 3f. Colorless solid; mp 155–157 °C (recrystallized from dichloromethane and petroleum ether); IR (CH_2Cl_2) *ν* 3449, 1713 (C=O), 1639, 1343, 1166, 851 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.21 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.90 (2H, t, *J*=6.9 Hz, CH_2), 4.00 (2H, t, *J*=6.9 Hz, CH_2), 7.34 (2H, d, *J*=7.8 Hz, ArH), 7.76–7.86 (5H, m, ArH, CH), 8.24 (2H, d, *J*=9.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.5, 30.3, 41.3, 42.2, 123.9, 127.7, 128.0, 129.7, 134.0, 139.9, 141.4, 144.6, 148.2, 206.1; MS (EI) *m/z* 389 (M^+, 4.35), 234 (M^+−155, 100), 192 (M^+−197, 86.00), 91 (M^+−298, 43.70), 43 (M^+−346, 84.65); HRMS (MALDI) calcd for $C_{18}H_{19}N_3O_5SNa^{+1}$: 412.0938. Found: 412.0939.

4.2.7. 4-Methylbenzenesulfonic acid *N′*-isobutylidene-*N*-(3-oxobutyl)hydrazide 3g. Colorless oil; IR (CH_2Cl_2) *ν* 3426, 2971, 2877, 1717 (C=O), 1597, 1434, 1352, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.09 (3H, s, CH_3), 1.11 (3H, s, CH_3), 2.14 (3H, s, CH_3), 2.41 (3H, s, CH_3), 2.53–2.59 (1H, m, CH), 2.63 (2H, t, *J*=7.2 Hz, CH_2), 3.51 (2H, t, *J*=7.2 Hz, CH_2), 7.29–7.31 (2H, m, ArH), 7.61–7.66 (3H, m, ArH, CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 19.1, 21.4, 29.9, 31.9, 41.7, 44.9, 128.3, 129.2, 132.7, 144.0, 168.2, 206.2; MS (EI) *m/z* 310 (M^+, 0.25), 155 (M^+−155, 49.89), 113 (M^+−197, 23.72), 91 (M^+−219, 36.09), 43 (M^+−267, 100); HRMS (MALDI) calcd for $C_{15}H_{23}N_2O_3S^{+1}$ (M^++H): 311.1424. Found: 311.1432.

4.2.8. 3-(*N*-(4-Methylbenzenesulfonyl)-*N′*-benzylidene-hydrazino)-propionic acid methyl ester 4a. Colorless oil; IR (CH_2Cl_2) *ν* 2953, 1743 (C=O), 1598, 1439, 1352, 1162, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.42 (3H, s, CH_3), 2.63 (2H, t, *J*=7.2 Hz, CH_2), 3.67 (3H, s, OCH_3), 3.83 (2H, t, *J*=7.2 Hz, CH_2), 7.31 (2H, d, *J*=8.4 Hz, ArH), 7.39–7.43 (3H, m, ArH), 7.66–7.69 (2H, m, ArH), 7.74 (2H, d, *J*=8.4 Hz, ArH), 8.19 (1H, s, CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.1, 32.3, 44.5, 51.4, 127.4, 127.9, 128.3, 129.2, 130.4, 133.2, 133.3, 143.9, 152.6, 170.9; MS (EI) *m/z* 360 (M^+, 9.73), 205 (M^+−155, 40.85), 173 (M^+−187, 57.13), 131 (M^+−229, 100); 90 (M^+−270, 90.78); HRMS (MALDI) calcd for $C_{18}H_{21}N_2O_4S^{+1}$ (M^++H): 361.1217. Found: 361.1239.

4.2.9. 4-Methylbenzenesulfonic acid *N′*-benzylidene-*N*-(2-cyano-ethyl)-hydrazide 5a. A yellow oil; IR (CH_2Cl_2) *ν* 3060, 2923, 2850, 1598, 1356, 1266, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.38 (3H, s, CH_3), 2.57 (2H, t, *J*=6.9 Hz, CH_2), 3.61 (2H, t, *J*=6.9 Hz, CH_2), 7.27 (2H, d, *J*=8.4 Hz, ArH), 7.37–7.41 (3H, m, ArH), 7.59 (2H, d, *J*=8.4 Hz, ArH), 7.63–7.65 (2H, m, ArH), 8.46 (1H, s, CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 17.5, 21.6, 46.5, 117.1, 128.4, 128.5, 128.9, 129.8, 131.8, 132.7, 132.9, 144.8, 161.5; MS (EI) *m/z* 327 (M^+, 0.92), 222 (M^+−105, 2.25), 172 (M^+−155, 4.47), 119 (M^+−208, 26.08), 84 (M^+−243, 100); HRMS (MALDI) calcd for $C_{17}H_{18}N_3O_2S^{+1}$ (M^++H): 328.1114. Found: 328.1121.

4.2.10. 4-Methylbenzenesulfonic acid *N′*-benzylidene-*N*-(3-oxo-3-phenyl-propyl)hydrazide 6a. A yellow oil; IR (CH_2Cl_2) *ν* 3059, 1691 (C=O), 1597, 1449, 1356, 1266, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.43 (3H, s, CH_3), 3.35 (2H, t, *J*=7.2 Hz, CH_2), 4.06 (2H, t, *J*=7.2 Hz, CH_2), 7.33 (2H, d, *J*=7.8 Hz, ArH), 7.40–7.49 (5H, m, ArH), 7.56–7.58 (1H, m, ArH), 7.66–7.69 (2H, m, ArH), 7.76 (2H, d, *J*=8.4 Hz, ArH), 7.92–7.95 (2H, m, ArH), 8.12 (1H, s, CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.3, 36.7, 44.1, 127.5, 127.8, 128.0, 128.4, 128.5, 129.4, 130.4, 133.3, 133.5, 133.7, 136.0, 144.0, 150.8, 197.4; MS (EI) *m/z* 406 (M^+, 0.09), 300 (M^+−106, 23.02), 159 (M^+−247, 36.20), 145 (M^+−261, 89.02), 105 (M^+−301, 100), 77 (M^+−329, 96.97); HRMS (MALDI) calcd for $C_{23}H_{23}N_2O_3S^{+1}$ (M^++H): 407.1424. Found: 407.1408.

4.3. Typical reaction procedure for the one-pot reaction of 4-methylbenzenesulfonic acid *N*-methylidene-hydrazide 1a with methyl vinyl ketone (MVK)

To a Schlenk tube with **1a** (274 mg, 1.0 mmol) and DABCO (1.0 mg, 0.01 mmol) in THF (1.0 mL) was added methyl vinyl ketone (MVK) (70 mg, 83 μL, 1.0 mmol) under an argon atmosphere and the reaction mixture was stirred for 24 h at room temperature (20 °C). Then 5 N HCl (2 mL) was added and the reaction mixture was stirred for another 2 h at room temperature. Then the reaction mixture was extracted with dichloromethane (2×20 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (eluent: EtOAc/petroleum=1/1) to give **7** (236 mg, 99%) as a white solid.

4.3.1. 3-Methyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1*H*-pyrazole 7. Mp >300 °C (recrystallized from dichloromethane and petroleum ether); IR (CH_2Cl_2) *ν* 3434, 1712 (C=O), 1633, 1348, 988 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.96 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.65 (2H, t, *J*=9.6 Hz, CH_2), 3.50 (2H, t, *J*=9.6 Hz, CH_2), 7.32 (2H, d, *J*=8.4 Hz, ArH), 7.76 (2H, d, *J*=8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 15.9, 21.5, 36. 7, 47.9, 128.7, 129.3, 130.8, 144.1, 160.0; MS (EI) *m/z* 238 (M^+, 47.54), 155 (M^+−83, 30.26), 139 (M^+−99, 23.99), 91 (M^+−147, 100), 83 (M^+−155, 42.70). Anal. Calcd for $C_{11}H_{14}N_2O_2S$ requires C, 55.44; H, 5.92; N, 11.76%. Found: C, 55.27; H, 5.87; N, 11.63%.

4.3.2. 3-Phenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1*H*-pyrazole 8. A yellow oil; IR (CH_2Cl_2) *ν* 3055, 2986, 1356, 1266, 1171, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.60 (3H, s, CH_3), 3.28 (2H, t, *J*=9.6 Hz, CH_2), 3.88 (2H, t, *J*=9.6 Hz, CH_2), 7.48 (2H, d, *J*=7.2 Hz, ArH), 7.58–7.61 (3H, m, ArH), 7.87–7.90 (2H, m, ArH), 8.03 (2H, d, *J*=7.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.5, 32.7, 48.6, 126.8, 128.5, 128.7, 129.4, 130.4, 130.7, 130.9, 144.3, 158.3; MS (EI) *m/z* 300 (M^+, 24.11), 219 (M^+−81, 14.13), 197 (M^+−103, 38.18), 145 (M^+−155, 100), 91 (M^+−209, 75.80). Anal. Calcd for $C_{16}H_{16}N_2O_2S$ requires C, 63.98; H, 5.37; N, 9.33%. Found: C, 63.95; H, 5.30; N, 9.28%.

4.3.3. Benzoic acid *N′*-benzylidene-*N*-(3-oxobutyl)hydrazide 9a. Colorless solid; mp 107–110 °C (recrystallized from dichloromethane and petroleum ether); IR (CH_2Cl_2) ν 3441, 1713 (C=O), 1608, 1414, 1340, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.24 (3H, s, CH_3), 2.89 (2H, t, $J=7.5$ Hz, CH_2), 4.43 (2H, t, $J=7.5$ Hz, CH_2), 7.32–7.35 (3H, m, ArH), 7.43–7.50 (5H, m, ArH), 7.71–7.74 (2H, m, ArH), 7.82 (1H, s, CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 30.2, 35.8, 39.2, 127.1, 127.2, 128.6, 129.6, 129.8, 130.3, 134.4, 134.8, 142.5, 170.9, 206.5; MS (EI) *m/z* 294 (M^+, 3.13), 188 (M^+-106, 6.52), 148 (M^+-146, 17.03), 105 (M^+-189, 100), 77 (M^+-217, 37.85). Anal. Calcd for $C_{18}H_{18}N_2O_2$ requires C, 73.45; H, 6.16; N, 9.52%. Found: C, 73.40; H, 6.26; N, 9.35%.

4.3.4. Benzoic acid *N′*-(4-chlorobenzylidene)-*N*-(3-oxobutyl)hydrazide 9b. Colorless solid; mp 133–135 °C (recrystallized from dichloromethane and petroleum ether); IR (CH_2Cl_2) ν 3441, 3055, 2987, 1716 (C=O), 1658, 1414, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.24 (3H, s, CH_3), 2.89 (2H, t, $J=7.2$ Hz, CH_2), 4.41 (2H, t, $J=7.2$ Hz, CH_2), 7.27–7.32 (2H, m, ArH), 7.38–7.52 (5H, m, ArH), 7.68–7.71 (2H, m, ArH), 7.79 (1H, s, CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 30.3, 35.9, 39.3, 127.3, 128.2, 128.9, 129.8, 130.4, 133.0, 134.7, 135.4, 137.8, 170.9, 206.5; MS (EI) *m/z* 328 (M^+, 3.53), 223 (M^+-105, 0.43), 188 (M^+-140, 8.38), 105 (M^+-223, 100), 77 (M^+-251, 29.77). Anal. Calcd for $C_{18}H_{17}N_2O_2Cl$ requires C, 65.75; H, 5.21; N, 8.52%. Found: C, 65.58; H, 5.14; N, 8.61%.

4.3.5. Benzoic acid *N′*-isobutylidene-*N*-(3-oxobutyl)-hydrazide 9c. Colorless oil; IR (CH_2Cl_2) ν 2965, 1716 (C=O), 1655, 1417, 1326, 1051, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.01 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.46–2.52 (1H, m, CH), 2.78 (2H, t, $J=7.5$ Hz, CH_2), 4.24 (2H, t, $J=7.5$ Hz, CH_2), 7.12 (1H, d, $J=4.5$ Hz, CH), 7.32–7.41 (3H, m, ArH), 7.63–7.66 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 19.4, 30.0, 31.6, 35.6, 39.1, 127.0, 129.5, 129.8, 134.8, 148.2, 170.4, 206.4; MS (EI) *m/z* 261 ($M^+ +1$, 3.28), 217 (M^+-43, 57.84), 188 (M^+-72, 8.37), 105 (M^+-155, 100), 77 (M^+-183, 53.44); HRMS (MALDI) calcd for $C_{15}H_{21}N_2O_2^{+1}$ ($M^+ +H$): 261.1598. Found: 261.1599.

4.3.6. (3-Methyl-4,5-dihydropyrazol-1-yl)phenylmethanone 10. Colorless solid; mp 90–93 °C (recrystallized from dichloromethane and petroleum ether); IR (CH_2Cl_2) ν 3460, 1634 (C=O), 1454, 1375, 1169, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.04 (3H, s, CH_3), 2.85 (2H, t, $J=9.9$ Hz, CH_2), 4.09 (2H, t, $J=9.9$ Hz, CH_2), 7.37–7.45 (3H, m, ArH), 7.84–7.86 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 16.1, 35.2, 44.7, 127.5, 129.4, 130.6, 134.4, 158.4, 166.5; MS (EI) *m/z* 188 (M^+, 27.72), 105 (M^+-83, 100), 77 (M^+-111, 47.82), 51 (M^+-137, 14.09). Anal. Calcd for $C_{11}H_{12}N_2O$ requires C, 70.19; H, 6.43; N, 14.88%. Found: C, 70.13; H, 6.09; N, 14.71%.

4.3.7. 4-(*N*-Benzylidene-*N*-phenyl-hydrazino)-butan-2-one 11a. A yellow oil; IR (CH_2Cl_2) ν 3059, 3027, 1713 (C=O), 1592, 1496, 1394, 1266, 1164, 1144 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.20 (3H, s, CH_3), 2.81 (2H, t, $J=7.5$ Hz, CH_2), 4.24 (2H, t, $J=7.5$ Hz, CH_2), 6.93–6.97 (1H, m, ArH), 7.24–7.40 (7H, m, ArH), 7.50 (1H, s, CH), 7.67–7.70 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 30.46, 38.15, 39.31, 115.03, 120.79, 126.00, 127.83, 128.50, 129.13, 131.65, 136.35, 146.42, 206.88; MS (EI) *m/z* 266 (M^+, 39.39), 209 (M^+-57, 38.54), 119 (M^+-147, 41.73), 106 (M^+-160, 81.61), 77 (M^+-189, 100); HRMS (MALDI) calcd for $C_{17}H_{18}N_2O$: 266.1419. Found: 266.1413.

4.3.8. 4-[*N*-(4-Methylbenzylidene)-*N*-phenylhydrazino]-butan-2-one 11b. A yellow oil; IR (CH_2Cl_2) ν 3002, 2921, 1712 (C=O), 1592, 1498, 1363, 1221, 1143 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.19 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.80 (2H, t, $J=7.5$ Hz, CH_2), 4.23 (2H, t, $J=7.5$ Hz, CH_2), 6.92–6.96 (1H, m, ArH), 7.18 (2H, d, $J=7.8$ Hz, ArH), 7.32–7.36 (4H, m, ArH), 7.49 (1H, s, CH), 7.58 (2H, d, $J=7.8$ Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.3, 30.5, 38.3, 39.4, 115.0, 120.6, 126.0, 129.1, 129.3, 132.0, 133.6, 137.8, 146.6, 206.9; MS (EI) *m/z* 280 (M^+, 100), 223 (M^+-57, 69.40), 119 (M^+-161, 51.14), 106 (M^+-174, 90.55), 77 (M^+-203, 62.31); HRMS (MALDI) calcd for $C_{18}H_{21}N_2O^{+1}$ ($M^+ +H$): 281.1648. Found: 281.1655.

4.3.9. 4-[*N′*-(4-Chlorobenzylidene)-*N*-phenylhydrazino]-butan-2-one 11c. A yellow oil; IR (CH_2Cl_2) ν 3061, 2922, 1714 (C=O), 1596, 1497, 1404, 1145, 1087 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.21 (3H, s, CH_3), 2.82 (2H, t, $J=7.8$ Hz, CH_2), 4.24 (2H, t, $J=7.8$ Hz, CH_2), 6.96–7.00 (1H, m, ArH), 7.31–7.37 (6H, m, ArH), 7.45 (1H, s, CH), 7.60 (2H, d, $J=8.4$ Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 30.5, 38.2, 39.5, 115.2, 121.1, 127.1, 128.7, 129.2, 130.3, 133.3, 135.0, 146.3, 206.7; MS (EI) *m/z* 300 (M^+, 51.47), 243 (M^+-57, 48.44), 119 (M^+-181, 67.18), 106 (M^+-194, 71.59), 77 (M^+-223, 78.15); HRMS (MALDI) calcd for $C_{17}H_{18}N_2OCl^{+1}$ ($M^+ +H$): 301.1102. Found: 301.1114.

4.3.10. 1,3-Diphenyl-4,5-dihydro-1*H*-pyrazole 12. This a known compound.[11] ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.08 (3H, s, CH_3), 2.83 (2H, t, $J=9.6$ Hz, CH_2), 3.66 (2H, t, $J=9.6$ Hz, CH_2), 6.78–6.83 (1H, m, ArH), 6.98–7.01 (2H, m, ArH), 7.23–7.28 (2H, m, ArH); This ^1H NMR spectroscopic data is in consistent with those reported in literature.[12]

The ^1H and ^{13}C NMR spectroscopic data of **3a**-*d*: ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.16 (3H, s, CH_3), 2.41 (3H, s, CH_3), 2.76–2.81 (1H, m, CHD), 3.82 (2H, m, CH_2), 7.31 (2H, d, $J=8.4$ Hz, ArH), 7.39–7.41 (3H, m, ArH), 7.64–7.68 (2H, m, ArH), 7.74 (2H, d, $J=8.4$ Hz, ArH), 8.10 (1H, s, CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.3, 29.9, 41.3, 43.5 (t, $J=3.75$ Hz, CHD), 127.5, 128.0, 128.5, 129.3, 130.4, 133.4, 133.4, 144.0, 151.6, 205.1.

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Supplementary data

Supplementary data associated with this article can be found at 10.1016/j.tet.2005.04.071

^{1}H NMR spectra for aza-Michael addition products **3**–**6**, **9**, **11**, and cyclized products **7**, **8**, **10**, and **12**. This material is available free of charge via internet.

References and notes

1. (a) Ciganek, E. *Org. React.* **1997**, *51*, 201–350. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062. (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–892.
2. (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815–2819. (b) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972.
3. (a) Shi, M.; Xu, Y.-M. *Chem. Commun.* **2001**, 1876–1877. (b) Shi, M.; Xu, Y.-M. *Eur. J. Org. Chem.* **2002**, 696–701. (c) Shi, M.; Xu, Y.-M.; Zhao, G.-L.; Wu, X.-F. *Eur. J. Org. Chem.* **2002**, 3666–3679. (d) Shi, M.; Xu, Y.-M. *J. Org. Chem.* **2003**, *68*, 4784–4790. (e) Zhao, G. L.; Huang, J.-W.; Shi, M. *Org. Lett.* **2003**, *5*, 4737–4739.
4. DABCO-catalyzed Michael addition reaction was involved in the dimerization of propiolates: (a) Matsuya, Y.; Hayashi, K.; Nemoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 646–647. (b) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952–1958. (c) Acheson, R. M.; Ansell, P. J.; Murray, J. R. *J. Chem. Res. (S)* **1986**, 378–379. (d) Medion-Simon, M.; Pindur, U. *Helv. Chim. Acta* **1991**, *74*, 430–437. Also see: (e) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965–2983. (f) Ramachandran, P. V.; Rudd, M. T.; Reddy, M. V. R. *Tetrahedron Lett.* **1999**, *40*, 3819–3822. (g) Kice, J. L.; Lotey, H. *J. Org. Chem.* **1988**, *53*, 3593–3597. (h) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 4550–4551. (i) Lee, H. J.; Kim, T. Y.; Kim, J. N. *Synth. Commun.* **1999**, *29*, 4375–4379.
5. The reaction of phenyl hydrazone with methyl vinyl ketone was reported in the following reference. The corresponding adduct was obtained in 40% yield. Snider, B. B.; Conn, R. S. E.; Sealfon, S. *J. Org. Chem.* **1979**, *44*, 218–221.
6. For the previous literature on the Michael addition of sulfonamides to activated olefins. see: Fraser, F. A.; Proctor, G. R.; Redpathb, J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 445–448.
7. Reactions of $PhNHNH_2$ with MVK have been reported in the following references, but in very low yields. See: (a) Maire, M. *Bull. Soc. Chim. Fr.* **1908**, *3*, 277–278. (b) Blaise, E. E.; Maire, M. *C.R. Hebd. Seances Acad. Sci.* **1906**, *142*, 216–220. (c) Blaise, E. E.; Maire, M. *Bull. Soc. Chim. Fr.* **1908**, *3*, 268–270. (d) Reaction of carbazates with acrylamide has also been reported in the following reference. See: Gray, C. J.; Quibell, M.; Jiang, K.-L.; Baggett, N. *Synthesis* **1991**, 141–146.
8. (a) Auwers, K. V.; Lämmerhirt, E. *Chem. Ber.* **1921**, *54*, 1000–1024. (b) Raiford, L. C.; Entrikin, J. B. *J. Am. Chem. Soc.* **1933**, *55*, 1125–1128.
9. For a recent accounts of base promoted Michael addition, please see: Rodriguez, J. *Synlett* **1999**, 505–518.
10. For Michael addition reactions catalyzed by inorganic base, please see: (a) Ma, S.-M.; Yin, S.-H.; Li, L.-T.; Tao, F.-G. *Org. Lett.* **2002**, *4*, 505–507. (b) Khim, D. Y.; Suh, K. H.; Huh, S. C.; Lee, K. *Synth. Commun.* **2001**, 3315–3322.
11. For Michael addition reactions catalyzed by nucleophilic phosphine Lewis base, please see: (a) Bhuniya, D.; Mohan, S.; Narayanan, S. *Synthesis* **2003**, 1018–1024. (b) Phosphine-catalyzed hydration and hydroalkoxylation of activated olefins have been reported: Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696–8697 and references cited therein. (c) Wang, L.-C.; Luis, A. L.; Apapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403. (d) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405. (e) Takashi, Y.; Shojiro, S. *Chem. Lett.* **1982**, 1587–1590. (f) Islami, M. R.; Abedini-Yorghabeh, J.; Fatcmi, S. J.; Hassani, Z.; Amiry, A. *Synlett* **2004**, 1707–1710.
12. (a) Fliege, W.; Huisgen, R.; Cloris, J. S.; Knupfer, H. *Chem. Ber.* **1983**, *116*, 3039–3061. (b) Nishiyama, H.; Arai, H.; Kanai, Y.; Kawashima, H.; Itoh, K. *Tetrahedron Lett.* **1986**, *27*, 361–364.

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An efficient Stille cross-coupling reaction catalyzed by $Pd(OAc)_2$/DAB-Cy catalytic system

Jin-Heng Li,* Yun Liang and Ye-Xiang Xie

Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research, College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, China

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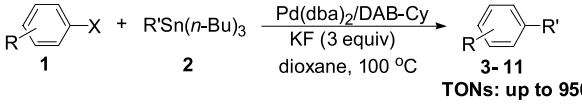
Abstract—An efficient palladium-catalyzed Stille cross-coupling reaction has been developed. In the presence of 3 mol% of $Pd(dba)_2$ and 6 mol% of DAB-Cy (1,4-dicyclohexyl-diazabutadiene), various aryl halides (iodides and bromides) were coupled with organotin compounds to afford the corresponding biaryls and alkyne in good to excellent yields. Furthermore, high TONs [turnover numbers, TONs up to 950,000 for the reaction of 1-iodo-4-nitrobenzene and tributyl(phenyl)stannane] for the Stille cross-coupling reaction were observed.

1. Introduction

The Stille cross-coupling reaction of organohalides with organotin compounds has been proven to be a useful synthetic method for carbon–carbon bond formation in organic synthesis. Consequently, many effective palladium catalytic systems have been developed for Stille cross-coupling reaction.[1–5] Generally, the combination of palladium catalysts with various phosphine ligands results in excellent yields and high efficiency.[1,2] However, phosphine ligands and their palladium complexes are often air-sensitive and are object to P–C bond degradation at elevated temperature.[6] Thus, the use of other supporting ligands for the Stille cross-coupling reaction emerged as an attractive alternative to the phosphine ligands.[3–5] Of these phosphine-free supporting ligands, only one paper has reported the use of diazabutadiene as the ligands combined with Pd(0) [Pd(Ar-BIAN)(dmfu)] to catalyze Stille cross-coupling reaction.[5] Compared with allyl halides and benzyl bromide, however, Pd(Ar-BIAN)(dmfu) showed low activity for the reaction of aromatic iodides. On the other hand, it is desirable to employ low catalyst loadings for pharmaceutical and industrial application. Although, many of the reported catalytic systems are effective, few reports employed the Stille reaction under <1 mol% loadings of palladium catalysts[2a,2c,2n–p,3a,3e–g] (general 1 to 5 mol% Pd).[1] For these reasons, the development of new and efficient phosphine-free palladium catalytic systems remains an interesting area for organic chemists.[3–5] Herein, we report a stable and efficient $Pd(dba)_2$/DAB-Cy (1,4-dicyclohexyl diazabutadiene) catalytic system for the Stille reactions of aryl halides with organotin compounds (Eq. 1).



(1)

2. Results and discussion

2.1. Palladium-catalyzed Stille cross-coupling of 4-bromoanisole with phenyltributyltin

Initially, the efficiency of diazabutadienes as the ligands for the palladium-catalyzed Stille cross-coupling reaction was evaluated, and the results were summarized in Table 1. The results showed that DAB-Cy (1,4-dicyclohexyl-diazabutadiene) was the most effective ligand for the coupling reaction of 4-bromoanisole (**1a**) with phenyltributyltin (**2a**). Without any ligands, only a 45% yield of the corresponding cross-coupled product **3** was isolated in the presence of 3 mol% of $Pd(dba)_2$ and 3 equiv of KF (entry 1). Whereas, the yield of **3** was increased sharply to 93% when 6 mol% of DAB-Cy was added (entry 3). An identical yield was observed when the amount of DAB-Cy was further increased to 12 mol% (entry 4). Other diazabutadienes as the ligands were less effective than DAB-Cy (entries 3 and 5–7). The results also demonstrated that $Pd(OAc)_2$ was inferior to $Pd(dba)_2$ (entries 3 and 8). The use of n-Bu_4NF as

Keywords: $Pd(dba)_2$/DAB-Cy; Stille cross-coupling reaction; Aryl halide; Organotin compound; Turnover number.
* Corresponding author. Tel.: +86 731 8872530; fax: +86 731 8872531; e-mail: jhli@hunnu.edu.cn

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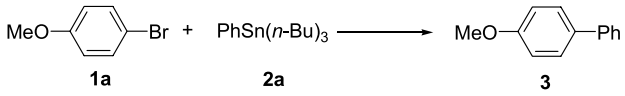
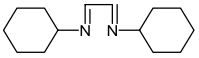
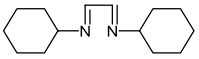
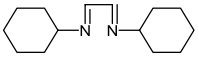
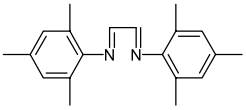
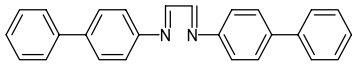
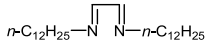
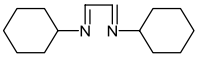
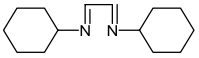
Table 1. Palladium-catalyzed Stille cross-coupling reaction of 4-bromoanisole (**1a**) with phenyltributyltin (**2a**)[a]



1a **2a** **3**

Entry	Pd	Ligand	Time (h)	Yield (%)[b]
1	$Pd(dba)_2$	—	22	45
2[c]	$Pd(dba)_2$		18	78
3	$Pd(dba)_2$		18	93
4[d]	$Pd(dba)_2$		18	94
5	$Pd(dba)_2$		22	20
6	$Pd(dba)_2$		20	79
7	$Pd(dba)_2$		21	72
8	$Pd(OAc)_2$		22	70
9[e]	$Pd(dba)_2$		18	32

[a] Under otherwise indicated, the reaction conditions were as follows: **1a** (0.30 mmol), **2a** (0.40 mmol), Pd (3 mol%), ligand (6 mol%), KF (3 equiv), and dioxane (5 mL) at 100 °C under N_2.
[b] Isolated yield.
[c] Ligand (3 mol%).
[d] Ligand (12 mol%).
[e] *n*-Bu_4NF (3 equiv) instead of KF. The reaction was not clean, and some side products were observed.

the base was also investigated, the reaction was not clean and resulted in a low isolated yield of **3** (entry 9).[7]

2.2. Palladium-catalyzed Stille cross-coupling of aryl halides with organotins

As shown in Table 2, treatment of various aryl halides **1b–g** with organotin compounds **2a–d**, respectively, afforded good to excellent yields of the corresponding cross-coupled products **3–11** in the presence of 3 mol% of $Pd(dba)_2$, 6 mol% of DAB-Cy, and 3 equiv of KF. The results indicated that $Pd(dba)_2$/DAB-Cy was an efficient catalytic system for the Stille cross-coupling reactions. For example, aryl iodide **1b** was reacted with organotin compounds including phenyltributyltin (**2a**), furan-2-yltributyltin (**2b**), thiophen-2-yltributyltin (**2c**), and 2-phenylethynyltri-butyltin (**2d**), respectively, to afford quantitative yields of the corresponding desired products **4–7** in the presence of $Pd(dba)_2$ (3.0 mol%), DAB-Cy (6 mol%), and KF (3.0 equiv) (entries 1–4). Coupling of aryl bromides **1d–g** with organotin compounds **2a** and **2b**, respectively, was also carried out smoothly and efficiently to afford the desired cross-coupled products in moderate to good yields (entries 6–10). The $Pd(dba)_2$/DAB-Cy/KF system was ineffective for the reaction of aryl chlorides **1h** and **1i** with **2a**, respectively (entries 11 and 13). The use of *n*-Bu_4NF as the base was further examined, the results showed that the activated aryl chlorides **1h** was coupled with **2a** smoothly to afford 45% yield of **4** (entry 1 in Table 1; entries 11 and 12 in Table 2). A low yield was still observed from the reaction of **1i** with **2a** under the same catalytic system (entry 14).

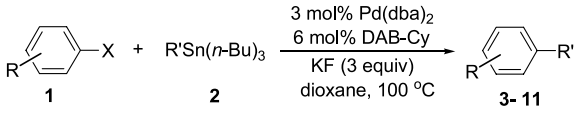
2.3. Screening the catalytic efficiency of the palladium-catalyzed Stille coupling reaction

As shown in Table 3, the catalytic efficacy of $Pd(dba)_2$/DAB-Cy was further evaluated. For coupling of aryl bromides **1a** and **1d** with **2a**, respectively, satisfied yields could still be obtained after prolonged reaction time when the catalyst loading was reduced to 0.1 mol% (entries 1 and 7). Further reduction of the catalyst, loading to 0.01 mol% led to a low yield (28%, TONs = 28,000, entry 2). For coupling of aryl iodides **1b** and **1c**, the catalytic efficiency of $Pd(dba)_2$/DAB-Cy was also excellent. For example, **1b** was coupled with **2a** smoothly to afford 95% isolated yield for 48 h when the catalyst loading was decreased to 0.0001 mol% (TONs = 950,000, entry 3).

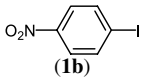
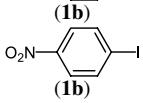
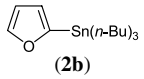
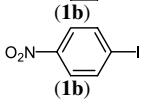
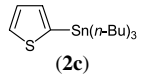
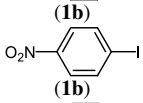
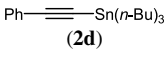
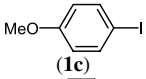
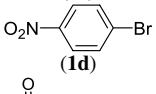
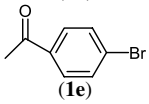
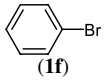
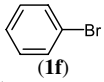
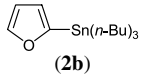
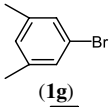
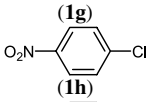
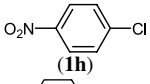
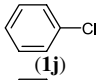
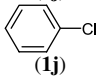
3. Conclusion

In summary, a stable and efficient $Pd(dba)_2$/DAB-Cy catalytic system for the palladium-catalyzed Stille cross-coupling reaction has been developed. In the presence of $Pd(dba)_2$ (3.0 mol%), DAB-Cy (6 mol%), and KF (3.0 equiv), the reaction of aryl halides with organotin compounds were carried out smoothly to afforded the

Table 2. Palladium-catalyzed Stille coupling reaction in the presence of DAB-Cy[a]



1 2 3- 11

Entry	ArX	R′Sn(*n*-Bu)$_3$	Time (h)	Yield (%)[b]
1	 (**1b**)	PhSn(*n*-Bu)$_3$ (**2a**)	16	98 (**4**)
2	 (**1b**)	 (**2b**)	16	100 (**5**)
3	 (**1b**)	 (**2c**)	16	100 (**6**)
4	 (**1b**)	 (**2d**)	16	100 (**7**)
5	 (**1c**)	PhSn(*n*-Bu)$_3$ (**2a**)	16	100 (**3**)
6	 (**1d**)	PhSn(*n*-Bu)$_3$ (**2a**)	18	96 (**4**)
7	 (**1e**)	PhSn(*n*-Bu)$_3$ (**2a**)	23	70 (**8**)
8	 (**1f**)	PhSn(*n*-Bu)$_3$ (**2a**)	22	85 (**9**)
9	 (**1f**)	 (**2b**)	20	52 (**10**)
10	 (**1g**)	PhSn(*n*-Bu)$_3$ (**2a**)	24	82 (**11**)
11	 (**1h**)	PhSn(*n*-Bu)$_3$ (**2a**)	24	Trace (**4**)
12[c]	 (**1h**)	PhSn(*n*-Bu)$_3$ (**2a**)	24	45 (**4**)
13	 (**1j**)	PhSn(*n*-Bu)$_3$ (**2a**)	24	Trace (**9**)
14[c]	 (**1j**)	PhSn(*n*-Bu)$_3$ (**2a**)	24	22 (**9**)

[a] Under otherwise indicated, the reaction conditions were as follows: **1** (0.30 mmol), **2** (0.40 mmol), Pd(dba)$_2$ (3.0 mol%), DAB-Cy (6.0 mol%), KF (3 equiv), and dioxane (5 mL) at 100 °C under N_2.
[b] Isolated yield.
[c] *n*-Bu$_4$NF (3 equiv) instead of KF.

Table 3. Screening the catalytic efficiency of the palladium-catalyzed Stille coupling reaction of **1** with **2**[a]

Entry	ArX	R′Sn(*n*-Bu)$_3$	Pd (mol%)	Yield (%)[b]	TON
1	**1a**	**2a**	0.1	65 (**3**)	650
2	**1a**	**2a**	0.001	28 (**3**)	28,000
3	**1b**	**2a**	0.0001	95 (**4**)	950,000
4	**1b**	**2b**	0.001	96 (**5**)	96,000
5	**1b**	**2b**	0.0001	90 (**5**)	900,000
6	**1c**	**2a**	0.0001	90 (**3**)	900,000
7	**1d**	**2a**	0.1	73 (**8**)	730

[a] Under otherwise indicated, the reaction conditions were as follows: **1** (0.30 mmol), **2** (0.40 mmol), Pd(dba)$_2$/DAB-Cy (1:2), KF (3 equiv), and dioxane (5 mL) at 100 °C under N_2 for 48 h.
[b] Isolated yield.

corresponding biaryls and alkyne in good to excellent yields (maximum TONs up to 950,000 for the reaction of 1-iodo-4-nitrobenzene and phenyltributyltin). Currently, further efforts to extend the application of these ligands and this protocol in organic synthesis are underway in our laboratory.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded on an INOVA-400 (Varian) spectrometer or a Bruker AMX-300 spectrometer with $CDCl_3$ as the solvent. All reagents were directly used as obtained commercially. All the products **3–11** are known.[8–12]

4.2. Typical experimental procedure for the palladium-catalyzed Stille cross-coupling reaction

A mixture of aryl halide **1** (0.30 mmol), organotin **2** (0.40 mmol), $Pd(dba)_2$ (3.0 mol%), DAB-Cy (6 mol%), KF (3 equiv), and dioxane (5 mL) was added to a sealed tube. Then the mixture was stirred at 100 °C under N_2 for desired time until complete consumption of starting material as judged by TLC. After the mixture was filtered and evaporated, the residue was purified by flash column chromatography (hexane or hexane/ethyl acetate) to afford **3–11**.

4.3. Typical experimental procedure for 0.0001 mol% of Pd and 0.0002 mol% of DAB-Cy-catalyzed Stille cross-coupling reaction of 1-iodo-4-nitrobenzene (1b) and phenyltributyltin (2a) (entry 3 in Table 3)

First, $Pd(dba)_2$ (4.5 mg, 0.02 mmol) was dissolved in 200 mL of dioxane, and DAB-Cy (4.5 mg, 0.04 mmol) was also dissolved in another 200 mL of dioxane. Then 3 μL of $Pd(dba)_2$ dioxane solution and 6 μL of DAB-Cy dioxane solution were added to a mixture of 1-iodo-4-nitrobenzene (**1b**) (0.30 mmol), phenyltributyltin (**2a**) (0.40 mmol), KF (3 equiv), and dioxane (5 mL) in a sealed tube (by syringe). The mixture was stirred at 100 °C under N_2 for 48 h determined by TLC. After the mixture was filtered and evaporated, the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford 95% yield of **4** (TONs: 950,000).

Acknowledgements

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References and notes

1. For reviews, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Diederich, F.; Stang, P. J. Metal-Catalyzed Cross-Coupling Reactions; Wiley-VCH: Weinheim, 1998. (c) Shirakawa, E.; Hiyama, T. *J. Organomet. Chem.* **1999**, *576*, 169. (d) Miyaura, N. Cross-Coupling Reaction; Springer: Berlin, 2002. (e) Hegedus, L. S. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, 2002; p 1123. (f) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002. (g) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (h) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
2. For recent representative papers on phosphine-palladium catalysts, see: (a) Litter, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411. (b) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119. (c) Litter, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *6343* and references cited therein. (d) Kim, Y. M.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696. (e) Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718. (f) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *J. Am. Chem. Soc.* **2003**, *125*, 14288. (g) Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292. (h) Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5079. (i) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7077. (j) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551. (k) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132. (l) Su, W.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2004**, *6*, 1421. (m) Mazzola, R. D., Jr.; Giese, S.; Benson, C.; West, F. G. *J. Org. Chem.* **2004**, *69*, 220. (n) Högenauer, K. *Synlett* **2001**, 878. (o) Scrivanti, A.; Matteoli, U.; Beghetto, V.; Antonaroli, S.; Crociani, B. *Tetrahedron* **2002**, *58*, 6881. (p) Kim, N.; Kwon, M. S.; Park, C. M.; Park, J. *Tetrahedron Lett.* **2004**, *45*, 7057.
3. For recent reviews and papers on *N*-heterocyclic carbene-palladium catalysts, see: (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (b) Yong, B. S.; Nolan, S. P. *Chemtracts: Org Chem.* **2003**, 205. (c) Herrmann, W. A.; Öfele, K.; Preysing, D. v.; Schneider, S. K. *J. Organomet. Chem.* **2003**, *687*, 229. (d) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119. (e) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69.
4. For recent representative papers on other phosphine-free ligand-palladium catalysts, see: (a) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095. (b) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823. (c) Chouday, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127. (d) Davis, J. L.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 590. (e) Amatore, C.; Bahsoun, A. A.; Jutand, A.; Meyer, G.; Ntepe, A. N.; Ricard, L. *J. Am. Chem. Soc.* **2003**, *125*, 4212. (f) Minière, S.; Cintrat, J.-C. *J. Org. Chem.* **2001**, *66*, 7385. (g) Serrano, J. L.; Fairlamb, I. J. S.; Sánchez, G.; García, L.; Pérez, J.; Vives, J.; López, G.; Crawforth, C. M.; Taylor, R. J. K. *Eur. J. Inorg. Chem.* **2004**, 2706.
5. For a representative paper on diazabutadiene-palladium catalysts [Pd(Ar-BIAN)(dmfu)] for the Stille cross-coupling reactions, see: van Asselt, R.; Elsevier, C. J. *Tetrahedron* **1994**, *50*, 323.
6. (a) *Homogeneous Catalysis with Metal Phosphine Complexes*; Pignolet, L. H., Ed.; Plenum: New York, 1983. (b) Parshall, G. W.; Ittel, S. Homogeneous Catalysis; Wiley: New York, 1992. (c) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. Principles and applications of organotransition metal chemistry; University Science: Mill Vallley, CA, 1987.
7. The reaction was not clean, and some side products were

observed. Structures of the side-products could not be determined by ^{1}H NMR and ^{13}C NMR spectra.

8. (a) Li, J.-H.; Liu, W.-J. *Org. Lett.* **2004**, *6*, 2809. (b) Tao, B.; Boykin, D. W. *J. Org. Chem.* **2004**, *69*, 4330.
9. Beadle, J. R.; Korzeniowski, S. H.; Rosenberg, D. E.; Garcia-Slanga, B. J.; Gokel, G. W. *J. Org. Chem.* **1984**, *49*, 1594.
10. Weir, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 4926.
11. Pridgen, L. N.; Jones, S. S. *J. Org. Chem.* **1982**, *47*, 1590.
12. Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3469.

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A comparison of ring-chain tautomerism in heterocycles derived from 2-aminobenzenesulfonamide and anthranilamide

Olga A. Maloshitskaya,[a] Jari Sinkkonen,[a] Valery V. Alekseyev,[b] Kirill N. Zelenin[b] and Kalevi Pihlaja[a,*]

[a]*Department of Chemistry, Structural Chemistry Group, University of Turku, FI-20014 Turku, Finland*
[b]*Russian Military Medical Academy, 194044 St. Petersburg, Russian Federation*

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Dedicated to the Memory of the late Professor Kirill N. Zelenin

Abstract—A number of anthranilamide and 2-aminobenzenesulfonamide derivatives with aromatic aldehydes and 1,3-dicarbonyl compounds were synthesized. Substituted benzaldehyde derivatives of neither aminoamides showed tautomerism in solutions. Reaction products of 2-aminobenzenesulfonamide with *p*-substituted benzoylacetic aldehydes and *p*-substituted benzoylacetones undergo ring-chain tautomerism with a good linear correlation between the ring-chain equilibrium constants (log K, where $K=$[ring]/[chain]) and the Hammett–Brown σ^+ parameters of the aromatic substituents. The equilibrium constant was measured for the reaction products of 2-aminobenzenesulfonamide with unsubstituted benzoylacetaldehyde at several temperatures which enabled the enthalpy and entropy of this reaction to be evaluated.

1. Introduction

Ring-chain tautomerism of 1,3-*N*,*N* heterocycles is currently drawing considerable attention.[1–3] Tautomeric equilibria have been described in the simplest six-membered 1,3-*N*,*N* heterocycles, 2-arylhexahydropyrimidines,[4] as well as in more complex systems which contain this structural sub-unit, such as monocyclic 2-aryl-4-methylhexahydropyrimidines,[2] *N*-alkyl-2-aryl hexahydropyrimidines[5] and condensed heterocycles. In the latter case, the hexahydropyrimidine moiety was condensed to a saturated cycloalkane (2-aryldecahydroquinazolines[6]) or to a benzo ring (2-aryltetrahydroquinazolines[3,5]). Aryl groups at C-2 were in above cases *para*-substituted phenyls (ArX). It is known that the equilibrium constants ($K_x=$[ring]/[chain]) for ring-chain equilibria depend on the electronic properties of substituents X as described by the Hammett–Brown constants σ^+: $\log K_x=\rho\sigma^+ +\log K_H$.

Variations of structural factors other than substituents X on the aryl ring can also influence the ring-chain equilibria in heterocyclic systems. An interesting case of ring-chain tautomerism of imines derived from a 1,3-diamine (2-aminomethylaniline) and β-dicarbonyl compounds has been reported.[7,8] It was shown that their linear (open-chain) tautomers were relatively more stable than the analogous imines obtained from monocarbonyl compounds. This was explained by conjugation between the imine and carbonyl double bonds in β-dicarbonyl derivatives.

In general, the greater the proportion of the enol tautomer in the starting β-dicarbonyl compound, the more stable is the enamine tautomer of its imino derivative.[9] In the case of imines derived from 1,3-diamines and β-dicarbonyl compounds, the enamine form corresponds to the linear (open-chain) tautomer. Moreover, ring-chain tautomeric equilibria of β-dicarbonyl derivatives containing a *para*-substituted phenyl ring (e.g., benzoylacetic aldehyde and benzoylacetone derivatives) also correlate with the σ^+ constants of the aryl substituents.[10]

Thus, molecular design of ring-chain tautomeric systems based on 1,3-*N*,*N*-heterocycles obtained from 1,3-diamines consists of variations both in the amine component (substitutions and ring fusions) and the carbonyl component (mono- vs. β-dicarbonyl compounds).

Imines derived from 2-aminobenzenesulfonamide and anthranilamide resemble structurally compounds discussed

Keywords: Ring-chain tautomerism; Anthranylamide; 2-Aminobenzenesulfonamide; 1,3-Dicarbonyl compounds.
* Corresponding author. Tel./fax: +358-2-3336750; e-mail: kpihlaja@utu.fi

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above. It remains to be proved, whether the ring-chain tautomerism is possible after replacing the conformationally labile –CH_2NH– fragment in 1,3-diamine derivatives with structurally more rigid amide or sulfonamide moiety. There are a few publications reporting both cyclic and open-chain tautomers for the condensation products of anthranilamide with substituted benzaldehydes.[11–14] The cyclization of linear isomers was reported to occur upon heating or acidification, but the possibility of reversible cyclization has not been previously studied, although ring-chain tautomerism has been observed in structurally related systems.[3]

The possibility of ring-chain tautomerism in 2-aminobenzenesulfonamide derivatives leading to benzo-1,2,4-thiadiazines is of considerable practical importance because many benzenesulfonamide derivatives and thiadiazines are known to possess pharmacological activity.[15,16] So far, only a few cyclic products derived from 2-aminobenzenesulfonamide and carbonyl compounds have been described in the literature.[15]

2. Results and discussion

Structures of all substances were determined by NMR spectra measured in DMSO-d_6. Tautomeric equilibria were considered as being reached when the ratio of tautomers did not change over five days (at room temperature) or in 2 h (at 80 °C) from the previous determination. Chemical shifts were assigned, in addition to the information from basic proton and carbon spectra, using gradient-selected DQF-COSY, HSQC, and HMBC (see Section 4).

2.1. Reaction of anthranilamide and 2-aminobenzenesulfonamide with aromatic aldehydes

We found that reaction products **4** derived from anthranilamide (Scheme 1) undergo irreversible cyclization to derivatives **5** regardless of the electronic properties of substituents R. Note that the latter are energetically more stable according to semiempirical MNDO calculations.[13] Contrary to what has been reported,[13] we found that melting a mixture of solid anthranilamide with *p*-nitrobenzaldehyde for 10 min initially affords the linear product **4a** (tlc control), which cyclized giving **5a** upon recrystallization from ethanol. Similar effects of recrystallization have been described previously.[12] Alternatively, cyclization of **4a** into **5a** can be achieved by heating its DMSO solution to 80 °C for 3 h. Under these conditions, however, the rate of cyclization seems to depend on the electronic properties of substituents R. Thus, the previously unknown compound **4b** (R = NMe_2) was stable in DMSO at 80 °C and cyclized only in the presence of traces of trifluoroacetic acid.

Only cyclic products **6** could be obtained from the reaction of 2-aminobenzenesulfonamide with substituted benzaldehydes (Scheme 1). The electronic properties of substituents R had no effect on the course of this reaction. Even the salicylaldehyde derivative **6c**, in which the ring form is sterically hindered by the *ortho* substitution, did not show a trace of the open-chain isomer.

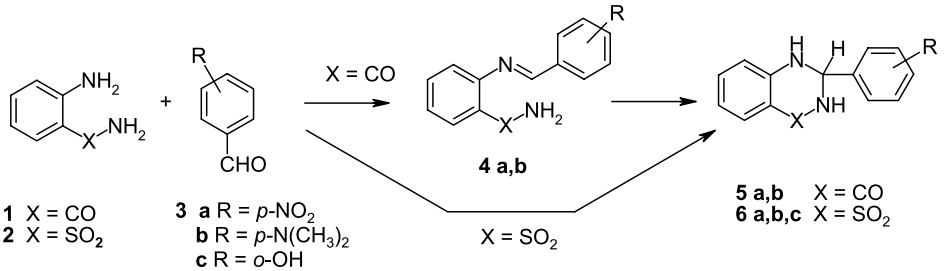
Thus, ring-chain tautomerism could not be observed in the reaction products of substituted benzaldehydes with either anthranilamide or 2-aminobenzenesulfonamide.

2.2. Reactions of anthranilamide and 2-aminobenzenesulfonamide with β-dicarbonyl compounds

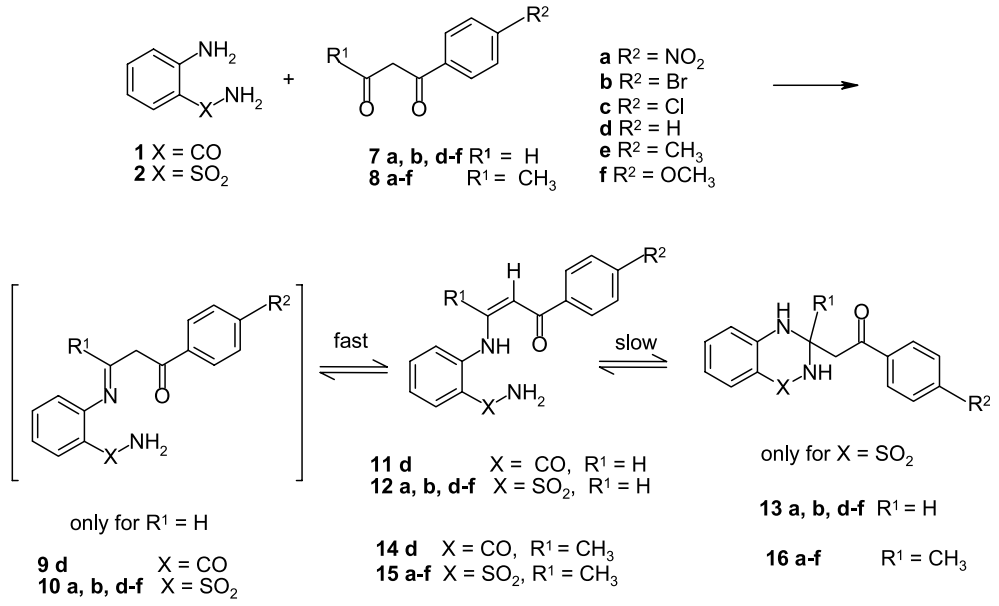
2.2.1. Reactions with *p*-substituted benzoylacetic aldehydes. Anthranilamide and 2-aminobenzenesulfonamide reacted with the title compounds as shown in Scheme 2 (R^1 = H). Reaction products **11** and **12** precipitated from methanolic solutions. In DMSO solutions they exist exclusively in the linear form (as a 10:1 mixture of *Z*- and *E*-isomers, as follows from the observed CH=CH coupling constants, J = 8.0 Hz for *Z*- and J = 12.4 Hz for *E*-isomer). The predominance of the *Z*-isomer can be explained by the hydrogen bonding between NH proton and C=O carbonyl oxygen (Scheme 2). The share of *E*-isomer reversibly increased upon heating the solutions of both **11** and **12**. This reversible *E*–*Z* isomerization indicates a tautomeric equilibrium between *Z*- and *E*-isomers, which is possible via the ketimine structures **9** and **10**, respectively. The ketimine structures are present in the equilibrium mixture at a negligibly low concentration.

A difference in the chemical behaviour between anthranilamide and 2-aminobenzenesulfonamide derivatives became apparent when they were left standing in solutions. No cyclization occurs in solutions of anthranilamide derivative **11**. Contrary, when solutions of **12** were left at room temperature, the transformation into the cyclic form **13** gradually happened, and the ring-chain equilibria were reached in few months (Scheme 2). The equilibria can be reached in 2–3 weeks if solutions are acidified with traces of trifluoroacetic acid, or in 1–2 days by heating solutions without acidification.

Compositions of the equilibrium mixtures obtained by heating the unsubstituted benzoylacetaldehyde derivative **12d** in DMSO-d_6 at different temperatures are shown in



Scheme 1.



Scheme 2.

Table 1 (K_{equil}=[ring]/[$E+Z$ chains]). Using $\Delta G=-RT\ln K$ ($=\Delta H-T\Delta S$), a very good linear correlation follows:

$$\Delta G[\mathrm{J\ mol^{-1}}] = (22.7\ \mathrm{K^{-1}} \pm 0.9\ \mathrm{K^{-1}})T - (9.9 \pm 0.3)10^3, \quad r = 0.997. \tag{1}$$

In other words the enthalpy $\Delta H=-(9.9\pm0.4)$ kJ mol^{-1} and the entropy $\Delta S=-(22.7\pm0.9)$ J mol^{-1} K^{-1} for the tautomerization between **12d** and **13d**.

Compositions of tautomeric mixtures **12**⇌**13** (Table 2) equilibrated in DMSO at 80 °C (Eq. 2) or upon acidification with traces of trifluoroacetic acid at 22 °C (Eq. 3) showed a good linear correlation with the σ^+ substituent constants:

$$\log K = -(0.41 \pm 0.06)\sigma^+ + (0.19 \pm 0.03), \quad r = 0.970(\mathrm{DMSO}, 80\ ^\circ\mathrm{C}). \tag{2}$$

$$\log K = -(0.52 \pm 0.07)\sigma^+ + (0.47 \pm 0.04), \quad r = 0.974(\mathrm{DMSO + TFA},\ 22\ ^\circ\mathrm{C}) \tag{3}$$

Table 2. Tautomeric equilibrium constants for substituted **12a**,**b**,**d–f**⇌**13a**,**b**,**d–f** and **15a–f**⇌**16a–f**

R	σ^+	K_{equil} for **12**⇌**13**, DMSO-d_6		K_{equil} for **15**⇌**16**, DMSO-d_6; 22 °C
		22 °C	80 °C	
NO_2	0.79	0.99	0.66	0.06
Br	0.15	2.39	1.29	0.16
Cl	0.11	—	—	0.16
H	0	3.64	1.92	0.24
CH_3	−0.31	4.69	2.19	0.33
OCH_3	−0.78	6.29	2.86	0.48

K_{equil}=[13]/[12, $E+Z$].

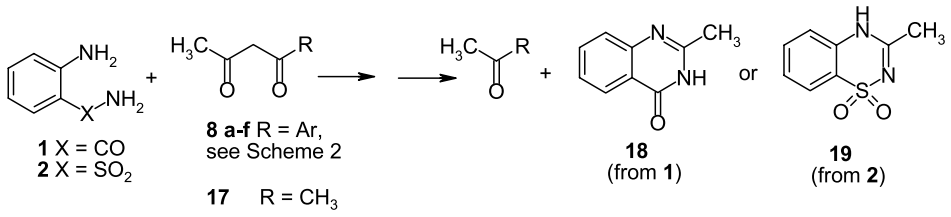
Yields and melting points of compounds **12a**,**b**,**d–f** are presented in Table 3, NMR data of *Z*-**12a**,**b**,**d–f** in Tables 4 and 5, NMR data of *E*-**12a**,**b**,**d–f** in Table 6, and NMR data of **13a**,**b**,**d–f** in Tables 7 and 8.

2.2.2. Reactions with β-diketones. *Reactions with acetylacetone* (Scheme 3). It has been reported previously[13] that the condensation of anthranilamide with acetylacetone resulted in the formation of compound **18** due to loss of an acetone molecule (Scheme 3). When repeating this experiment, we also discovered in the reaction mixture a condensation product of anthranilamide with acetone which shows a fast decomposition of the intermediate product. Acetylacetone reacted with 2-aminobenzenesulfonamide in a similar manner to form compound **19**. Its structure is confirmed by presence of only one methyl group and by absence of CO signal in carbon spectra. Spectral characteristics of **19** were identical to those published earlier.

Table 1. Temperature dependence of equilibrium constants for tautomeric equilibrium between **12d** and **13d** in DMSO-d_6

T, K	295	329	348	363	393	420
K_{equil}	3.64	2.47	1.91	1.79	1.35	1.09

K_{equil}=[**13d**]/[**12d**, $E+Z$].



Scheme 3.

According to the literature,[17] benzothiadiazine **19**, obtained by a different way, exists as the 4*H*-, and not 2*H*-isomer.

Reactions with p-substituted benzoylacetones (Scheme 2, $R^1=CH_3$). The condensation product of anthranilamide with benzoylacetone is exclusively an open-chain *Z*-enamine **14d**. When dissolved in DMSO, this compound decomposes on heating (in a few hours) or on acidification with traces of trifluoroacetic acid (in a week) to form acetophenone and compound **18** (Scheme 3). The same decomposition product **18** is obtained in reaction of anthranilamide with acetylacetone. No signals could be observed for the cyclic isomer of **14d**.

Similarly, when 2-benzenesulfonamide reacted with various substituted benzoylacetones in methanol, the products **15a–f** precipitated from the solutions. In DMSO-d_6 solutions they exist as open-chain *Z*-enamines (for yields and melting points, see Table 3). The *Z*-configuration of the products was confirmed by NOESY spectra, which showed the CH_3-group and the CH-proton to be close in space (measured for **15d**). In DMSO-d_6 solutions of **15**, however, ring-chain tautomeric equilibria **15** ⇌ **16** (Scheme 2) slowly evolved either at room temperature (during several months) or at 80 °C (during several hours), but unfortunately decomposition accompanied the tautomerization (Scheme 3). Decomposition product is the same as was obtained in reaction with acetylacetone. By acidification of DMSO solutions of **15** with traces of TFA, ring-chain tautomeric equilibria were reached at room temperature in a few days (similarly to compounds **12**) without considerable decomposition. Additional precautions were taken against possible hydrolysis by using dried DMSO and storing NMR tubes in a desiccator. When measures were taken against decomposition and hydrolysis, a reasonable linear dependence of the ring-chain equilibrium constants against Hammett σ^+ was observed (see Table 2 and Eq. 4).

$$\log K = -(0.59\pm0.06)\sigma^+ - (0.71\pm0.03), \quad r = 0.982 \tag{4}$$

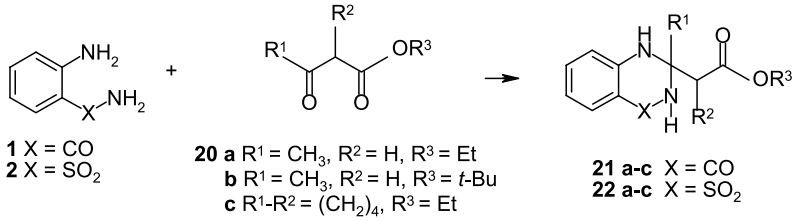
NMR data of **15a–f** are given in Tables 9 and 10, and that of **16a–e** in Tables 11–13.

It was suggested previously[8] that the relative stabilities of ring and chain forms in structurally similar ring-chain tautomeric systems can be compared by measuring the intercepts c of their ($\log K$ vs. σ^+) lines. Thus, the tautomeric ring forms **16** of the benzoylacetone derivatives ($c=-0.71$, Eq. 4) are relatively less stable than the tautomeric ring forms **13** ($c=+0.47$, Eq. 3) of the benzoylacetaldehyde derivatives under the same conditions (room temperature, traces of trifluoroacetic acid).

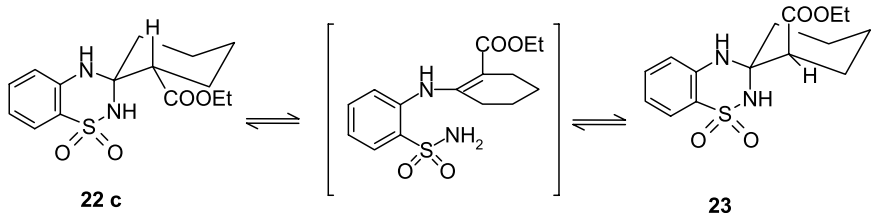
2.2.3. Reactions with β-ketoacid esters. Both anthranilamide and 2-benzenesulfonamide when reacting with β-ketoesters formed only cyclic products. The structure of compound **22a** has already been proved.[13] Cyclic isomers of condensation products of anthranilamide with ethyl acetoacetate are thought to be more stable than linear forms based on semiempirical MNDO calculations.[13] We proved that compound **22b** is also cyclic (Scheme 4).

Anthranilamide reacted with 2-carbethoxycyclohexanone **20c** to form two spirocyclic diastereomers in a 3:1 ratio. The diastereomer ratio is constant with time. The chair-conformation of the cyclohexane ring is confirmed by NOESY spectra. From ^{1}H NMR data it follows that the predominant stereoisomer has an axially oriented carbethoxy group and an equatorial H-2 (no diaxial H,H-coupling constants were observed in the H-2 multiplet, the largest constant being only 5 Hz). The axial orientation of the bulky COOEt substituent may be explained by formation of intramolecular hydrogen bonds.

Reaction of 2-benzenesulfonamide with acetoacetic esters has been previously studied,[18] and a ketoimine structure similar to **10** (Scheme 2) was erroneously assigned to the reaction products based on the IR spectra. We discovered that acetoacetic ester derivatives **22a**,**b** have cyclic structures, and no open-chain isomers were formed with time. The 2-carbethoxycyclohexanone derivative **22c** was obtained initially as a single diastereomer, in which the



Scheme 4.



Scheme 5.

COOEt group was equatorial and H-2 was axial (the coupling constants $J_{ax,ax}=11.0$ Hz and $J_{ax,eq}=3.5$ Hz were observed for the H-2 multiplet). The chair conformation of the cyclohexane ring is confirmed by NOESY spectra, which showed the H-2_{ax}, H-4_{ax} and H-6_{ax} to be close in space. However, a second diastereomer **23** slowly accumulated in solution, and the amounts of **22c** and **23** became equal after 1.5 months (Scheme 5). The build-up of **23** suggests a ring-(chain)-ring tautomeric interconversion via an open-chain form which is obviously present in a very low concentration, i.e. below the detection limits of NMR.

The presence of tautomerism in the 2-carbethoxycyclohexanone derivative and its absence in the acetoacetic ester derivatives agrees well with the observations made previously[9] on the imine derivatives of 1,3-ketoesters. It was shown then that the enamine forms of cyclic ketoesters are more stable than those of acetoacetic esters. In our case, the enamine form corresponds to the open-chain tautomer.

3. Conclusion

We have confirmed that the linear and cyclic forms of the reaction products from anthranilamide with various substituted benzaldehydes, which have been sporadically studied over the last decades, are indeed structural isomers, and not tautomers.

Replacement of monocarbonyl compounds with β-dicarbonyl compounds is known to stabilize the linear tautomers in various ring-chain equilibria due to double bond conjugation. It was proved that the products obtained from β-dicarbonyl compounds with anthranilamide show no signs of ring-chain tautomerism. On the other hand, ring-chain tautomerism was for the first time observed in the derivatives of 2-aminobenzenesulfonamide with β-dicarbonyl compounds. In a series of *p*-substituted benzoyl acetaldehydes and -acetones, the tautomeric equilibria depended linearly on the Hammett–Brown constants of the substituents on the 2-aryl group. To our knowledge, this is the first case of ring-chain tautomerism in aminoamide derivatives.

4. Experimental

4.1. NMR measurements

NMR-spectra were acquired using Bruker Avance 500 and 600 spectrometers (equipped with BBI-5 mm-Zgrad-ATM and BBO-5 mm-Zgrad probes) operating at 500.13 and 600.13 MHz for ^{1}H and 125.77 and 150.90 MHz for ^{13}C, respectively. Spectra were recorded at 25 °C using DMSO-d_6 and $CDCl_3$ as a solvent with a non-spinning sample in 5 mm NMR-tubes. Spectra were processed by a PC with Windows XP operating system and XWin NMR software. Proton and carbon spectra were referenced internally to TMS signal using value 0.00 ppm.

^{1}H NMR spectra and ^{13}C NMR proton-decoupled spectra were acquired with single-pulse excitation and 30° flip angle. 1 Hz exponential weighting was applied prior to Fourier transformation (in carbon spectra).

Gradient selected DQF-COSY spectra were acquired with cosygpmfqf pulse program (pulse programs refer to original ones installed by Bruker). Gradient selected NOESY spectra were acquired with noesygpph pulse program. Gradient selected ^{1}H–^{13}C HSQC spectra were acquired with hsqcetgpsisp.2 pulse program (using shaped pulses). Gradient selected ^{1}H–^{13}C HMBC spectra were acquired with hmbcgplpndqf pulse program.

4.2. General synthetic procedures

4.2.1. Reaction of anthranilamide with *p*-dimethylaminobenzaldehyde. Three millimoles of anthranilamide was dissolved in 4 ml of dry methanol and added to a solution of 3 mmol of *p*-dimethylaminobenzaldehyde in 4 ml of dry methanol. Reaction mixture was refluxed during 5 h and cooled to a room temperature. Crystals of two types precipitated: white thin plates (ring form) and heavy yellow cubes (chain form). Crystals were manually separated and spectroscopically characterized.

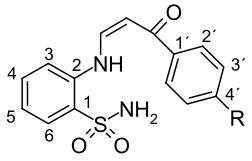
4.2.1.1. 2-(4′-Dimethylaminobenzylidenimino)anthranilamide (4b). Yield 15%, cubic yellow crystals, mp 192 °C. HRMS: $C_{16}H_{16}N_3O$ $(M-H)^+$ calcd 266.1293; obsd 266.1288. δ_H(DMSO-d_6): 3.04 (6H, s, $N(CH_3)_2$), 6.82 (2H, d, $J_{3'4'}=8.8$ Hz, H-3′, H-5′), 7.19 (1H, d, $J_{34}=7.6$ Hz, H-3), 7.28 (1H, t, $J_{45}=J_{56}=7.6$ Hz, H-5), 7.52 (1H, td, $J_{34}=J_{45}=7.0$, $J_{46}=1.2$ Hz, H-4), 7.61 (1H, br s, NH), 7.76 (2H, d, $J_{3'2'}=8.8$ Hz, H-2′, H-6′), 8.01 (1H, dd, $J_{56}=7.4$ Hz, $J_{46}=1.2$ Hz, H-6), 8.42 (1H, s, CH), 9.25 (1H, br s, NH). $\delta_C(CDCl_3)$: 39.59 ($N(CH_3)_2$), 111.48 (C-3′, C-5′), 119.25 (C-3), 122.90 (C-1′), 124.93 (C-5), 126.59 (C-1), 130.05 (C-6), 130.69 (C-2′, C-6′), 132.16 (C-4), 150.25 (C-2), 152.82 (C-4′), 161.31 (CH=N), 166.95 (C=O).

4.2.1.2. 2-(4′-Dimethylaminophenyl)-1,2,3,4-tetrahydroquinazolin-4-one (5b). Yield 50%, white plates, mp 228 °C. HRMS: $C_{16}H_{17}N_3O$ $M^{+\cdot}$ calcd 267.1372; obsd 267.1359. δ_H(DMSO-d_6): 2.90 (6H, s, $N(CH_3)_2$), 5.64 (1H, s, CH), 6.66 (1H, t, $J_{56}=J_{67}=7.3$ Hz, H-6), 6.71 (2H, d, $J_{2'3'}=8.7$ Hz, H-3′, H-5′), 6.73 (1H, m, H-8), 6.92 (1H, br s,

Table 3. Yields and physical properties of 2-aminosubstituted benzenesulfonamides **12a**,**b**,**d–f** and **15a–f**

	Yield %	Melting point °C	Colour	$M^{+\cdot}$	HRMS	
					Calculated	Observed
12a	60	198	Orange crystals	$C_{15}H_{13}N_3SO_5$	347.0576	347.0573
12b	69	186	Yellow cubic crystals	$C_{15}H_{13}N_2SO_3Br$	379.9830	379.9817
12c	87	145	Pale yellow crystals	$C_{15}H_{14}N_2SO_3$	302.0725	302.0717
12d	56	175	Yellow crystals	$C_{16}H_{16}N_2SO_3$	316.0882	316.0881
12e	75	179	Yellow crystals	$C_{16}H_{16}N_2SO_4$	332.0831	332.0823
15a	69	202	Dark orange crystals	$C_{16}H_{15}N_3SO_5$	361.0732	361.0725
15b	61	183	Yellow cubic crystals	$C_{16}H_{15}N_2SO_3Br$	393.9987	393.9975
15c	67	170	Pale yellow plate crystals	$C_{16}H_{14}N_2SO_3Cl$ (M−H)	349.0414	349.0420
15d	70	196	Pale yellow plate crystals	$C_{16}H_{16}N_2SO_3$	316.0882	316.0878
15e	51	204	Yellow crystals	$C_{17}H_{18}N_2SO_3$	330.1038	330.1023
15f	58	175	Pale yellow cubic crystals	$C_{17}H_{17}N_2SO_4$ (M−H)	345.0909	345.0910

Table 4. Proton spectra of 4′-substituted 2-(3-oxo-3-phenyl-*Z*-prop-1-enylamino) benzenesulfonamides **12a**,**b**,**d–f**



		CHCO, d	$J_{CH=CH}$	H-5, t	J_{45}	J_{35}	H-4, t	J_{34}	H-3, d	H-6, d	J_{56}
12a	NO_2	6.30	9.0	7.28	7.5	—	7.63	7.5	7.67	7.88	7.5
12b	Br	6.23	8.4	7.23	7.5	1.2	7.61	7.2	7.64	7.87	7.6
12d	H	6.26	8.0	7.23	7.2	1.6	7.62	m	7.62	7.88	7.6
12e	CH_3	6.22	8.4	7.21	7.2	2.0	7.60	m	7.60	7.85	7.6
12f	OCH_3	6.21	8.5	7.21	—	—	7.59	m	7.69	7.87	8.0
		J_{46}	NH_2, s	NC*H*, dd	J_{NH-CH}	H-3′,5′, d	$J_{2'3'}$	H-2′,6′, d	NH, d	X	
12a	NO_2	—	7.68	7.94	11.5	8.50	8.0	8.33	12.51	—	
12b	Br	0.8	7.65	7.84	12.4	7.71	8.8	7.93	12.43	—	
12d	H	1.0	7.66	7.82	12.0	7.52	8.0	7.99	12.43	7.58	
12e	CH_3	0.8	7.61	7.78	12.0	7.31	8.4	7.89	12.37	2.37	
12f	OCH_3	—	7.62	7.74	11.5	7.03	8.5	7.98	12.37	3.84	

Table 5. Carbon spectra of 4′-substituted 2-(3-oxo-3-phenyl-*Z*-prop-1-enylamino) benzenesulfonamides **12a**,**b**,**d–f**

		*C*HCO	C-3	C-5	C-6	C-1	C-4	C-2
12a	NO_2	95.74	117.56	123.27	128.27	131.07	133.59	137.65
12b	Br	95.43	117.23	122.82	128.26	130.79	133.56	137.51
12d	H	95.79	117.09	122.62	128.33	130.70	133.57	138.09
12e	CH_3	95.76	116.98	122.45	128.26	130.58	133.54	138.14
12f	OCH_3	95.73	116.83	122.30	128.29	130.49	133.55	138.24
		*C*HNH	C-2′,6′	C-3′,5′	C-4′	C-1′	CO	X
12a	NO_2	145.88	128.65	123.78	143.57	149.14	187.00	—
12b	Br	144.77	129.38	131.63	125.83	137.91	187.89	—
12d	H	144.23	127.32	128.63	131.91	138.52	189.17	—
12e	CH_3	143.84	127.41	129.18	135.93	142.02	188.89	21.07
12f	OCH_3	143.35	129.49	113.83	162.28	131.23	188.18	55.40

NH), 7.22 (1H, dt, $J_{78}=J_{67}=7.7$ Hz, $J_{75}=1.3$ Hz, H-7), 7.30 (2H, d, $J_{2'3'}=8.8$ Hz, H-2′, H-6′), 7.61 (1H, d, $J_{56}=6.8$ Hz, H-5), 8.07 (NH). δ_C(DMSO-d_6): 40.21 ($N(CH_3)_2$), 66.70 (CH), 111.97 (C-3′, C-5′), 114.43 (C-8),115.08 (C-4a), 117.00 (C-6), 127.39 (C-5), 127.79 (C-2′, C-6′), 128.62 (C-1′), 133.20 (C-7), 148.29 (C-8a), 150.74 (C-4′), 163.92 (CO).

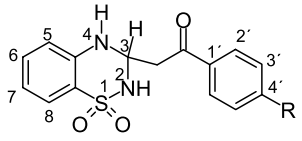
4.2.2. 3-(2′-Hydroxyphenyl)-4*H*-2,3-dihydrobenzo-1,2,4-thiadiazine-1,1-dioxide (6c). A solution of 2 mmol of 2-aminobenzenesulfonamide in 5 ml of dry methanol was added to a solution of 2 mmol of salicylic aldehyde in 2 ml of dry methanol. Reaction was completed in several hours (tlc control). Solvent was evaporated, solid recrystallized from methanol. Yield 56%, white crystals, mp 155 °C HRMS: $C_{13}H_{12}N_2O_3S$ $M^{+\cdot}$ calcd 276.0569; obsd 276.0566. δ_H(DMSO-d_6): 6.14 (1H, br. s, CH), 6.74 (1H, t, $J_{67}=J_{78}=7.6$ Hz, H-7), 6.87–6.90 (2H, m, H-5, H-5′), 6.92 (1H, d, $J_{3'4'}=8.0$ Hz, H-3′), 7.19 (1H, s, NH), 7.23 (1H, td, $J_{3'4'}=J_{4'5'}=7.6$, $J_{4'6'}=1.6$ Hz, H-4′), 7.28 (1H, td,

Table 6. Spectra of 4′-substituted 2-(3-oxo-3-phenyl-*E*-prop-1-enylamino)benzenesulfonamides **12a**,**b**,**d–f** (detected signals)

			Proton signals				
		%	CH–CO, d	J_{CH-CH}	H-5, m	NH_2, br s	CH–N*H*, t
12a	NO_2	10	6.84	12.5	n.d.	7.77	n.d.
12b	Br	11	6.82	12.8	7.21	7.76	8.15
12d	H	10	6.84	12.4	7.20	7.77	8.15
12e	CH_3	8	6.83	12.8	7.18	7.74	8.11
12f	OCH_3	10	6.86	12.5	n.d.	n.d.	8.12
			Proton signals		Carbon signals		
		%	NH, d	J_{CH-NH}	*C*H–CO	CHNH	CO
12a	NO_2	10	9.34	12.5	100.87	144.95	186.31
12b	Br	11	9.21	12.8	100.77	143.72	186.72
12d	H	10	9.17	12.8	101.22	143.16	187.85
12e	CH_3	8	9.10	12.4	101.26	142.67	187.38
12f	OCH_3	10	9.09	12.5	101.24	142.18	186.47

n.d., not detected.

Table 7. Proton spectra of 4′-substituted 3-(2-phenyl-2-oxoethyl)-2*H*,4*H*-benzothiadiazine-1,1-dioxides **13a**,**b**,**d–f**



		H-a, dd (CH_2)	H-b, dd (CH_2)	J_{gem}	J_{CH-CH2}	CH, m	H-7, t	J_{78}	J_{57}	H-5, d	J_{56}	
13a	NO_2	3.59	3.73	17.1	5.4	5.32	6.74	7.2	n.d.	6.81	7.8	
13b	Br	3.47	3.63	16.8	6.0	5.29	6.74	7.2	1.2	6.81	7.8	
13d	H	3.50	3.66	17.0	6.3	5.31	6.73	7.2	1.2	6.82	8.4	
13e	CH_3	3.43	3.60	16.8	6.3	5.28	6.73	7.2	1.2	6.82	7.8	
13f	OCH_3	3.40	3.59	16.8	6.3	5.30	6.73	7.2	n.d.	6.83	8.4	
		H-6, t	J_{67}	J_{68}	H-8, d	NH, s	NH–SO_2, d	J_{NH-CH}	H-2′,6′ d	$J_{2'3'}$	H-3′,5′ d	X
13a	NO_2	7.31	7.8	1.2	7.49	7.21	7.71	12	8.22	8.4	8.41	—
13b	Br	7.31	7.8	1.2	7.48	7.17	7.67	12	7.92	8.4	7.80	—
13d	H	7.30	8.0	1.5	7.48	7.20	7.65	12	7.99	7.5	7.58	7.69
13e	CH_3	7.30	7.2	1.8	7.48	7.16	7.64	11	7.89	7.8	7.38	2.40
13f	OCH_3	7.30	7.2	1.2	7.49	7.16	7.65	11	7.98	8.4	7.09	3.86

Table 8. Carbon spectra of 4′-substituted 3-(2-phenyl-2-oxoethyl)-2*H*,4*H*-benzothiadiazine-1,1-dioxides **13a**,**b**,**d–f**

		CH_2	CH	C-5	C-7	C-8a	C-8	C-6
13a	NO_2	43.02	62.24	115.25	115.87	121.08	123.73	132.98
13b	Br	42.45	62.38	115.89	116.48	121.06	123.71	132.93
13d	H	42.45	62.49	115.93	116.47	121.13	123.68	132.89
13e	CH_3	42.32	62.51	115.90	116.42	121.06	123.68	132.89
13f	OCH_3	42.08	62.67	115.94	116.45	121.09	123.71	132.91
		C-4a	C-3′,5′	C-2′,6′	C-4′	C-1′	CO	X
13a	NO_2	140.94	123.98	129.52	143.43	150.06	194.96	—
13b	Br	143.49	131.93	130.10	127.71	135.40	194.95	—
13d	H	143.54	128.83	128.07	133.57	136.42	195.68	—
13e	CH_3	143.55	129.37	128.31	133.95	144.04	195.14	21.19
13f	OCH_3	143.60	114.04	130.50	163.47	129.49	194.01	55.61

$J_{56}=J_{67}=7.6$ Hz, $J_{68}=1.4$ Hz, H-6), 7.51 (1H, d, $J_{78}=8.0$ Hz, H-8), 7.64 (1H, dd, $J_{5'6'}=7.6$, $J_{4'6'}=1.2$ Hz, H-6′), 7.71 (1H, m, NH), 9.96 (1H, br s, OH). δ_C(DMSO-d_6): 61.75 (CH), 115.28 (C-3′), 116.11 (C-5), 116.28 (C-7), 118.92 (C-5′), 121.35 (C-8a), 123.27 (C-1′), 123.68 (C-8), 128.10 (C-6′), 129.82 (C-4′), 132.57 (C-6), 144.12 (C-4a), 154.39 (C-2′).

4.2.3. Procedure A (compounds 11d, 12a,b,d–f, 14d, 15a–f). A solution of 2 mmol of β-dicarbonyl compounds in 5 ml of dry methanol was added to a solution of 2 mmol of aminoamide in 5 ml of dry methanol at room temperature. In several days a precipitate developed. It was filtered off, washed with methanol, and recrystallized from methanol if necessary.

Table 9. Proton spectra of 4′-substituted 2-(1-methyl-3-oxo-3-phenyl-*Z*-prop-1-enylamino)benzenesulfonamides **15a–f**

		CH_3	CH–CO	H-5, t	J_{45}	J_{35}	H-3, d	J_{34}	H-4, t	H-6, d
15a	NO_2	2.10	6.27	7.50	7.5	n.d.	7.55	7.5	7.67	7.95
15b	Br	2.06	6.17	7.45	7.6	0.8	7.50	7.8	7.63	7.93
15c	Cl	2.07	6.19	7.46	8.0	n.d.	7.51	8.0	7.64	7.93
15d	H	2.08	6.20	7.44	7.5	n.d.	7.50	n.d.	7.63	7.95
15e	CH_3	2.06	6.17	7.43	7.5	1.0	7.49	8.0	7.62	7.92
15f	OCH_3	2.07	6.16	7.42	7.5	7.5	7.47	7.5	7.62	7.94
		J_{56}	J_{46}	NH_2, s	H-3′, H-5′, d	$J_{2'3'}$	H-2′, H-6′, d	NH, s	X	
15a	NO_2	7.5	n.d.	7.55	8.32	8.7	8.19	12.87	—	
15b	Br	7.8	1.6	7.49	7.70	8.0	7.89	12.72	—	
15c	Cl	8.0	1.0	7.52	7.54	8.5	7.98	12.73	—	
15d	H	n.d.	1.0	7.52	7.50	n.d.	7.96	12.77	7.53	
15e	CH_3	1.5	1.5	7.48	7.28	8.0	7.86	12.69	2.37	
15f	OCH_3	7.5	n.d.	7.48	7.02	9.0	7.95	12.67	3.83	

Table 10. Carbon spectra of 4′-substituted 2-(1-methyl-3-oxo-3-phenyl-*Z*-prop-1-enylamino)benzenesulfonamides **15a–f**

		CH_3	*C*HCO	C-5	C-6	C-3	C-4	C-2	C-1
15a	NO_2	20.06	95.61	126.43	127.52	128.53	132.60	135.20	137.89
15b	Br	20.09	95.15	126.08	127.57	128.44	132.59	135.60	137.80
15c	Cl	20.13	95.22	126.10	127.58	128.48	132.63	135.63	137.81
15d	H	20.14	95.53	125.93	127.60	128.42	132.62	135.83	137.75
15e	CH_3	20.02	95.33	125.68	127.46	128.22	132.48	135.81	137.56
15f	OCH_3	20.15	95.34	125.64	127.59	128.25	132.59	136.06	137.59
		CH_3C=	C-2′,6′	C-3′,5′	C-4′	C-1′	CO	X	
15a	NO_2	163.15	128.22	123.55	144.55	148.70	184.46	—	
15b	Br	161.83	129.09	131.38	125.00	138.28	185.76	—	
15c	Cl	161.82	128.92	128.48	136.03	137.95	185.66	—	
15d	H	161.22	127.04	128.42	131.25	139.26	187.26	—	
15e	CH_3	160.61	127.01	128.89	136.49	141.11	186.95	20.92	
15f	OCH_3	161.80	129.09	113.63	160.19	131.84	186.54	55.34	

Table 11. Proton spectra of 4′-substituted 3-methyl-3-(2-phenyl-2-oxoethyl)-2*H*,4*H*-benzothiadiazine-1,1-dioxides **16d–f**

		CH_3, s	H-a, d (CH_2)	H-b, d (CH_2)	J_{gem}	H-7, t	J_{78}	H-5, d	J_{56}	NH,s
16d	H	1.78	3.62	3.85	17.5	6.73	7.2	6.84	8.0	7.11
16e	CH_3	1.69	3.54	3.74	16.8	6.71	7.6	6.78	8.0	7.09
16f	OCH_3	1.70	3.53	3.72	16.3	6.72	7.2	6.80	8.4	7.08
		H-6, t	J_{67}	J_{68}	H-8, d	$NH–SO_2$, s	H-2′, H-6′	H-3′, H-5′	X	
16d	H	7.28	8.0	1.6	7.5(m)	7.83	7.93	7.5(m)	7.6	
16e	CH_3	7.3m	7.6	n.d.	7.6(m)	7.75	7.81	7.3(m)	2.36	
16f	OCH_3	7.27	7.2	1.8	7.48(m)	7.77	7.94(m)	7.02	3.84	

Compounds **7a**,**b**,**d–f** and **8b–f** were obtained from corresponding acetophenones by Claisen condensation using standard synthetic protocol (e.g., see Ref. 19), and compound **8a**—according to Ref. 20.

4.2.3.1. *N*-(3-Oxo-3-phenyl-*cis*-prop-1-enyl)anthranilamide (11d). Yield 45%, yellow crystals, mp 199 °C. HRMS: $C_{16}H_{14}N_2O_2$ $M^{+\cdot}$ calcd 266.1055, obsd 266.1047. δ_H(DMSO-d_6): 6.13 (1H, d, $J_{CH–CH}$=8.0 Hz, C*H*–CO), 7.10 (1H, t, $J_{56}=J_{45}$=7.2 Hz, H-5), 7.45–7.65 (6H, m, H-3, H-4, H-3′, H-4′, H-5′, NH from NH_2), 7.71 (1H, d, J_{56}= 7.6 Hz, H-6), 7.80 (1H, dd, $J_{CH–CH}$=8.0, $J_{CH–NH}$=12,6 Hz, C*H*–NH), 7.96 (2H, d, $J_{2'3'}$=7.2 Hz, H-2′, H-6′), 8.09 (1H, broad s, NH from NH_2), 13.09 (1H, d, $J_{NH–CH}$=12.8 Hz, NH). δ_C(DMSO-d_6): 94.54 (*C*H–CO), 115.09 (C-3), 121.42 (C-1), 121.86 (C-5), 127.06 (C-2′, C-6′), 128.44 (C-3′, C-5′), 128.85 (C-6), 131.51 (C-4′), 132.07 (C-4), 138.80 (C-1′), 140.46 (C-2), 143.54 (CH–NH), 169.47 (CO–NH_2), 188.32 (*C*O–Ph).

4.2.3.2. *N*-(3-Oxo-3-phenyl-*trans*-prop-1-enyl)anthranilamide (*trans*-11d). Conc. 16%, detected signals: δ_H (DMSO-d_6): 6.75 (1H, d, $J_{CH–CH}$=12.4 Hz, C*H*–CO), 7.05 (1H, m, H-5), 8.23 (1H, t, $J_{CH–CH}=J_{CH–NH}$= 13.0 Hz, C*H*–NH), 8.29 (1H, broad s, NH from NH_2), 11.49 (1H, d, $J_{NH–CH}$=13.2 Hz, NH). δ_C(DMSO-d_6): 100.06 (*C*H–CO), 142.59 (*C*H–NH), 170.55 (CO–NH_2), 187.58 (*C*O–Ph).

4.2.3.3. *N*-(1-Methyl-3-oxo-3-phenyl-*cis*-prop-1-enyl)-anthranilamide (14d). Yield 60%, light-yellow crystals, mp 160 °C. HRMS: $C_{17}H_{16}N_2O_2$ $M^{+\cdot}$ calc 280.1212, obsd

Table 12. Carbon spectra of 4′-substituted 3-methyl-3-(2-phenyl-2-oxoethyl)-2*H*,4*H*-benzothiadiazine-1,1-dioxides **16d–f**

		CH_3	CH_2	N–*C*–N	C-5	C-7	C-8a	C-8	C-6
16d	H	26.54	46.08	69.87	116.34	116.48	120.24	123.56	132.97
16e	CH_3	26.42	45.86	69.80	116.26	116.37	120.10	123.52	132.95
16f	OCH_3	26.37	45.58	69.90	116.24	116.32	120.13	123.46	132.86
		C-4a	C-3′,5′	C-2′,6′	C-4′	C-1′	CO	X	
16d	H	142.38	128.63	127.93	133.24	137.24	196.98	—	
16e	CH_3	142.34	129.20	128.10	134.77	143.69	196.47	21.12	
16f	OCH_3	142.32	113.76	130.33	163.20	130.12	195.42	55.46	

Table 13. Spectra of 4′-substituted 3-methyl-3-(2-phenyl-2-oxoethyl)-2*H*,4*H*-benzothiadiazine-1,1-dioxides **16a–c** (concentration less than 20%, detected signals)

		Proton signals								
		CH_3, s	H-a, d (CH_2)	H-b, d (CH_2)	J_{gem}	H-7, t	$J_{78}=J_{67}$	H_5, d	J_{56}	NH, s
16a	Cl	1.70	3.52	3.79	16.8	6.71	7.2	6.77	7.6	7.13
16b	Br	1.70	3.51	3.78	16.8	6.71	7.2	6.77	8.4	7.13
16c	NO_2	1.74	3.56	3.92	17.0	6.72	7.5	6.78	n.d.	7.19
		Carbon signals								
		CH_3	CH_2	N–*C*–N	C=O					
16a	Cl	n.d.	45.87	69.53	195.69					
16b	Br	26.40	45.89	69.54	194.32					

280.1208. δ_H(DMSO-d_6): 3.00 (3H, s, CH_3), 6.06 (1H, s, C*H*–CO), 7.29 (1H, dt, $J_{56}=J_{45}=7.2$ Hz, $J_{35}=1.0$ Hz, H-5), 7.39 (1H, d, $J_{34}=8.0$ Hz, H-3), 7.45–7.51 (5H, m, H-4, H-3′, H-4′, H-5′, NH from NH_2), 7.54 (1H, dd, $J_{56}=$ 7.5 Hz, $J_{46}=1.5$ Hz, H-6), 7.91 (3H, m, H-2′, H-6′, NH from NH_2), 12.88 (1H, s, NH). δ_C(DMSO-d_6): 20.08 (CH_3), 94.45 (*C*H–CO), 125.13 (C-5), 126.16 (C-3), 126.78 (C-2′, C-6′), 127.05 (C-6), 128.25 (C-3′, C-5′), 128.98 (C-4), 130.90 (C-4′), 131.52 (C-1), 136.06 (C-2), 139.41 (C-1′), 160.95 (=*C*–CH_3), 168.82 (CO–NH_2), 186.53 (*C*O–Ph).

4.2.4. Procedure B (compounds 21a–c, 22a–c). 2 mmol of aminoamide was dissolved in 6 mmol of β-ketoester, and one drop of concentrated HCl was added on stirring. A white solid developed in approx. 15 min. It was washed with cold hexane and recrystallized from hexane–benzene.

4.2.4.1. 2-(2-Methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)acetic acid, ethyl ester (21a). Yield 47%, white powder, mp 109 °C (lit. 103 °C, Ref. 13).

4.2.4.2. 2-(2-Methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)acetic acid, *tert*-butyl ester (21b). Yield 72%, white powder, mp 163 °C. HRMS: $C_{15}H_{21}N_2O_3$ $(M+H)^+$ calcd 277.1552; obsd 277.1562. δ_H(DMSO-d_6): 1.31 (9H, s, $(CH_3)_3C$), 1.48 (3H, s, CH_3), 2.50 (1H, m, H-a from CH_2), 2.58 (1H, d, $J_{gem}=13.8$ Hz, H-b from CH_2), 6.64 (1H, t, $J_{67}=J_{56}=7.2$ Hz, H-6), 6.67 (1H, d, $J_{78}=7.8$ Hz, H-8), 6.70 (1H, br s, NH), 7.22 (1H, t, $J_{78}=J_{67}=7.2$ Hz, H-7), 7.57 (1H, d, $J_{56}=7.8$ Hz, H-5), 7.94 (1H, br s, NH). δ_C(DMSO-d_6): 27.42 ($(CH_3)_3C$), 27.85(CH_3), 47.18 (CH_2CO), 67.69 (N–*C*–N), 80.10 ($(CH_3)_3C$), 113.55 (C-4a), 114.13 (C-8), 116.57 (C-6), 127.02 (C-5), 133.20 (C-7), 146.30 (C-8a), 162.44 (CO), 168.60 (COO).

4.2.4.3. 4′-Oxo-1′,2′,3′,4′-tetrahydrospiro[cyclohexane-1,2′-quinazoline]-2-carboxylic acid, ethyl ester (21c) (a mixture of two diastereomers). Yield 73%, white powder, mp 146 °C, HRMS: $C_{16}H_{20}N_2O_3$ $M^{+\cdot}$ calcd 288.1474; obsd 288.1472. Major component (carbethoxy group in axial position): δ_H ($CDCl_3$): 1.20 (3H, t, $J_{CH3-CH2}=$ 7.2 Hz, CH_3CH$_2$), 1.46 (2H, m, both H-4 or H-4 and H-5), 1.64 (2H, m, both H-5 or H-4 and H-5), 1.78 (1H, m, H-6ax), 1.91 (1H, m, H-3 ax or eq), 1.99.(1H, m, H-3 ax or eq), 2.25 (1H, m, H-6eq), 2.91 (1H, m, $J_{2eq3ax}=5.2$ Hz, H-2e), 4.06 (2H, m, CH_2CH$_3$), 5.36 (1H, s, NH), 6.67 (1H, d, $J_{7'8'}=$ 7.8 Hz, H-8′), 6.80 (1H, t, $J_{5'6'}=J_{6'7'}=7.2$ Hz, H-6′), 7.06 (1H, br.d, NH), 7.26 (1H, td, $J_{6'7'}=J_{7'8'}=7.8$ Hz, $J_{5'7'}=$ 1.2 Hz, H-7′), 7.85 (1H, m, H-5′). δ_C($CDCl_3$): 14.05 (*C*H$_3$CH$_2$), 21.30 (C-5), 22.27 (br, C-4), 25.01 (C-3), 36.22 (br, C-6), 49.86 (br, C-2), 60.91 (CH$_3$*C*H$_2$), 69.18 (N–*C*–N), 114.71 (C-4′a), 115.38 (C-8′), 118.79 (C-6′), 128.07 (C-5′), 134.00 (C-7′), 145.59 (C-8′a), 164.07 (CO), 173.04 (COO). Minor component (carbethoxy group in equatorial position, concentration approx. 30%): δ_H ($CDCl_3$): 1.15 (3H, t, $J_{CH3-CH2}=7.2$ Hz, CH_3CH$_2$), 1.24 1.40 (2H, m, H-5ax, H-4ax), 1.65–2.05 (5H, m, cyclohexane H), 2.35 (1H, m, H-6eq), 2.77 (1H, $J_{H\text{-}2ax-H\text{-}3ax}=9.0$ Hz, $J_{H\text{-}2ax-H\text{-}3eq}=3.6$ Hz, H-2ax), 4.00 (2H, m, CH_2CH$_3$), 4.86 (1H, s, NH), 6.65 (1H, d, $J_{7'8'}=7.8$ Hz, H-8′), 6.74 (1H, br.d, NH), 6.78 (1H, m, H-6′), 7.26 (1H, m, H-7′), 7.84 (1H, m, H-5′). δ_C($CDCl_3$): 14.00 (*C*H$_3$CH$_2$), 21.24 (C-5), 22.67 (br, C-4), 25.15 (C-3), 37.73 (br, C-6), 51.79 (br, C-2), 60.93 (CH$_3$*C*H$_2$), 69.20 (N–*C*–N), 114.75 (C-4′a), 115.06 (C-8′), 118.68 (C-6′), 128.20 (C-5′), 133.90 (C-7′), 145.34 (C-8′a), 163.70 (CO), 172.34 (COO).

4.2.4.4. 2-Methyl-2-(2*H*,4*H*-1,1-dioxo-benzo-1,2,4-thiadiazin-3-yl)acetic acid, ethyl ester (22a). Yield 47%, white powder, mp 110 °C (lit. 109 °C, Ref. 18). δ_H(DMSO-d_6): 1.18 (3H, t, $J=7.2$ Hz, CH_3CH$_2$), 1.63 (3H, s, CH_3),

2.83 (1H, d, J_{gem}=15.6 Hz, H-a from CO–CH_2), 3.02 (1H, d, J_{gem}=15.6 Hz, H-b from CO–CH_2), 4.08 (2H, m, CH_2CH$_3$), 6.72 (1H, t, J_{67}=J_{78}=7.2 Hz, H-7), 6.79 (1H, d, J_{56}=8.4 Hz, H-5), 7.08 (1H, broad s, NH), 7.28 (1H, dt, J_{56}=J_{67}=8.4 Hz, J_{68}=1.8 Hz, H-6), 7.45 (1H, d, J_{78}=7.2 Hz, H-8), 7.72 (1H, s, SO$_2$N*H*). δ_C(DMSO-d_6): 13.90 (*C*H$_3$CH$_2$), 26.08 (CH$_3$), 43.33 (*C*H$_2$CO), 59.89 (*C*H$_2$CH$_3$), 68.95 (N–*C*–N), 116.10 (C-5), 116.38 (C-7), 120.01 (C-8a), 123.42 (C-8), 132.87 (C-6), 142.15 (C-4a), 168.97 (CO).

4.2.4.5. 2-Methyl-2-(2*H*,4*H*-1,1-dioxo-benzo-1,2,4-thiadiazin-3-yl)acetic acid, *tert*-butyl ester (22b). Yield 77%, white powder, mp 151 °C. HRMS: $C_{14}H_{20}N_2O_4S$ $M^{+\cdot}$ calcd 312.1144; obsd 312.1155. δ_H(DMSO-d_6): 1.40 (9H, s, (C*H*$_3$)$_3$C), 1.62 (3H, s, CH$_3$), 2.72 (1H, d, J_{gem}=15.0 Hz, H-a from CO–CH_2), 2.93 (1H, d, J_{gem}=15.0 Hz, H-b from CO–CH_2), 6.72 (1H, t, J_{67}=J_{78}=7.2 Hz, H-7), 6.80 (1H, d, J_{56}=8.4 Hz, H-5), 7.04 (1H, broad s, NH), 7.28 (1H, dt, J_{56}=J_{67}=7.8 Hz, J_{68}=1.8 Hz, H-6), 7.45 (1H, dd, J_{78}=8.4 Hz, J_{68}=1.2 Hz, H-8), 7.67 (1H, s, SO$_2$N*H*). δ_C(DMSO-d_6): 26.02 (CH$_3$), 27.61 ((*C*H$_3$)$_3$C), 44.37 (*C*H$_2$CO), 69.01 (N–*C*–N), 80.22 ((CH$_3$)$_3$*C*), 116.15 (C-5), 116.38 (C-7), 120.11 (C-8a), 123.45 (C-8), 132.84 (C-6), 142.16 (C-4a), 168.40 (CO).

4.2.4.6. 2′-Carbethoxy-2*H*,4*H*-spiro(benzo-1,2,4-thiadiazine-3,1′-cyclohexane(-1,1-dioxide (22c) (equatorial carbethoxy group). Yield 68%, white powder, mp 161 °C. HRMS: $C_{15}H_{20}N_2O_4S$ $M^{+\cdot}$ calcd 324.1144; obsd 324.1152. δ_H(DMSO-d_6): 1.18 (3H, t, $J_{CH3-CH2}$=7.2 Hz, C*H*$_3$CH$_2$), 1.34 (2H, m, H-6′ax, H-4′ax), 1.56 (1H, m, H-5′ax or H-5′eq), 1.66 (2H, m, H-4′eq, H-5′eq or H-5′ax), 1.76 (1H, m, H-3′ax), 1.83 (1H, m, H-3′eq), 2.64 (1H, dm, J_{gem}=14.0 Hz, H-6′eq), 2.78 (1H, dd, $J_{2'ax3'ax}$=11.0 Hz, $J_{2'ax3'eq}$=3.5 Hz, H-2′ax), 4.12 (2H, m, CH_2CH$_3$), 6.74 (dt, J_{78}=J_{67}=7.5 Hz, J_{57}=1.0 Hz, H-7), 6.79 (1H, d, J_{56}=8.0 Hz, H-5), 6.86 (1H, broad s, NH), 7.29 (1H, dt, J_{67}=J_{56}=7.8 Hz, J_{68}=1.5 Hz, H-6), 7.37 (1H, s, SO$_2$N*H*), 7.45 (1H, dd, J_{78}=7.8 Hz, J_{68}=1.3 Hz, H-8). δ_C(DMSO-d_6): 13.82 (*C*H$_3$CH$_2$), 20.90 (C-5′), 23.44 (br, C-4′), 25.71 (C-3′), 34.01 (br, C-6′), 49.72 (br, C-2′), 60.76 (*C*H$_2$CH$_3$), 71.07 (N–*C*–N), 116.48 (C-5), 117.01 (C-7), 120.30 (C-8a), 123.64 (C-8), 133.15 (C-6), 142.36 (C-4a), 174.32 (br, CO).

4.2.4.7. 2′-Carbethoxy-2*H*,4*H*-spiro(benzo-1,2,4-thiadiazine-3,1′-cyclohexane)-1,1-dioxide (23) (axial carbethoxy group), interpreted signals. δ_H(DMSO-d_6): 1.13 (3H, t, $J_{CH3-CH2}$=7.2 Hz, C*H*$_3$CH$_2$), 1.45–1.85 (4H, m, cyclohexane ring), 1.76 (1H, m, H-3′ax or H-3′eq), 1.93 (1H, m, H-3′ax or H-3′eq), 1.96 (1H, m, H-6′eq), 2.29 (1H, td, $J_{6'ax-5'ax}$=J_{gem}=13.2 Hz, $J_{6'ax-5'eq}$=4.2 Hz, H-6′ax), 3.73 (1H, m, H-2′eq), 4.06 (2H, m, CH_2CH$_3$), 6.70 (1H, dt, J_{78}=J_{67}=7.5 Hz, J_{57}=0.6 Hz, H-7), 6.84–6.92 (m, NH, H-5), 7.25 (1H, dt, J_{67}=J_{56}=7.8 Hz, J_{68}=1.5 Hz, H-6), 7.44 (1H, dd, J_{78}=7.8 Hz, J_{68}=1.3 Hz, H-8). δ_C(DMSO-d_6): 13.90 (*C*H$_3$CH$_2$), 20.00 (C-5′), 23.44 (br, C-4′), 24.36 (C-3′), 32.56 (br, C-6′), 45.22 (C-2′), 59.89 (*C*H$_2$CH$_3$), 70.70 (N–*C*–N), 116.29, 116.36 (C-5, C-7), 120.01 (C-8a), 123.47 (C-8), 132.80 (C-6), 142.32 (C-4a), 172.12 (br, CO).

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References and notes

1. Lázár, L.; Fülöp, F. *Eur. J. Org. Chem.* **2003**, 3025–3042 and references therein.
2. Maloshitskaya, O.; Sinkkonen, J.; Ovcharenko, V. V.; Zelenin, K. N.; Pihlaja, K. *Tetrahedron* **2004**, *60*, 6913–6921.
3. Sinkkonen, J.; Zelenin, K. N.; Potapov, A.-K.A.; Lagoda, I. V.; Alekseyev, V. V.; Pihlaja, K. *Tetrahedron* **2003**, *59*, 1939–1950.
4. (a) Zelenin, K. N.; Alekseyev, V. V.; Ukraintsev, I. V.; Tselinsky, I. V. *Org. Prep. Proc. Int.* **1998**, *30*, 53–61. (b) Zelenin, K. N.; Ukraintsev, I. V. *Khim. Geterotsikl. Soed.* **1996**, 1137.
5. Göblyös, A.; Lásár, L.; Fülöp, F. *Tetrahedron* **2002**, *58*, 1011–1016.
6. Lázár, L.; Göblyös, A.; Martinek, T. A.; Fülöp, F. *J. Org. Chem.* **2002**, *67*, 4734–4741.
7. Zelenin, K. N.; Potapov, A.-K.A.; Lagoda, I. V.; Alekseyev, V. V.; Sinkkonen, J.; Pihlaja, K. *Chem. Heterocycl. Comp.* **2002**, *38*, 1148–1149.
8. Zelenin, K. N.; Potapov, A.-K.A.; Lagoda, I. V. *Khim. Geterotsikl. Soed.* **2004**, *7*, 1052–1060. English translation: Chem. Heterocycl. Comp. in press.
9. Yakimovich, S. I.; Zelenin, K. N. *Zh. Obshch. Khim.* **1995**, *65*(5), 705–727.
10. (a) Yakimovich, S. I.; Zerova, I. V. *Zh. Org. Khim.* **1978**, *14*, 42–48. (b) Yakimovich, S. I.; Zerova, I. V. *Zh. Org. Khim.* **1978**, *14*, 266–274. (c) Yakimovich, S. I.; Zerova, I. V.; Brundina, S. S. *Zh. Org. Khim.* **1979**, *15*, 2295–2301. (d) Yakimovich, S. I.; Zerova, I. V. *Zh. Org. Khim.* **1993**, *29*, 905–910.
11. Smith, T. A. K.; Stephen, H. *Tetrahedron* **1957**, *1*, 38–44.
12. Bonola, G.; Sianesi, E. *Chem. Ber.* **1969**, *102*, 3735–3738.
13. Lessel, J. *Arch. Pharm.* **1994**, *327*, 571–579.
14. Lessel, J. *Pharm. Acta Helv.* **1996**, *71*, 109–119.
15. Phillips, D.; Sonnenberg, J.; Arai, A. C.; Vaswani, R.; Krutzik, P. P.; Kleisli, T.; Kessler, M.; Granger, R.; Lynch, G.; Chamberlin, A. R. *Bioorg. Med. Chem.* **2002**, *10*, 1229–1248.
16. Braghiroli, D.; Puia, G.; Cannazza, G.; Tait, A.; Parenti, K.; Losi, G.; Baraldi, M. *J. Med. Chem.* **2002**, *45*, 2355–2357 and references therein.
17. Jakobsen, P.; Treppendahl, S. *Tetrahedron* **1979**, *35*, 2151–2153.
18. Solomko, Z. F.; Fedenko, V. S.; Avramenko, V. I.; Bozhanova, N.; Ya, . *Zh. Org. Khim.* **1979**, *15*, 134–138.
19. Auwers, K.; von Schmidt, W. *Ber.* **1925**, *58*, 528–543.
20. Görlitz, G.; Hartmann, H. *Heteroatom Chem.* **1997**, *8*, 147–155.

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Synthesis of bridged aza-rebeccamycin analogues

Samir Messaoudi,[a] Fabrice Anizon,[a] Bruno Pfeiffer[b] and Michelle Prudhomme[a,*]

[a]*Université Blaise Pascal, Synthèse et Etude de Systèmes à Intérêt Biologique, UMR 6504 du CNRS, 63177 Aubière, France*
[b]*Institut de Recherches Servier, Division Recherche Cancérologie, 125 Chemin de ronde, 78290 Croissy sur Seine, France*

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Abstract—The syntheses of rebeccamycin analogues possessing a 7-azaindole moiety instead of an indole unit, and with both indole and azaindole moieties linked to the carbohydrate are described. In these bridged aza compounds, the oxygen of the pyranose heterocycle is oriented towards either the indole, or the azaindole unit. In these series, compounds bearing a free imide nitrogen were synthesized by coupling the corresponding aglycones with a sugar pre-tosylated in 2-position via a Mitsunobu reaction. To obtain a precursor for bridged aza-rebeccamycin analogues substituted in 6-position on the sugar moiety, a 2,6-ditosylated sugar was used.

1. Introduction

Rebeccamycin, isolated from cultures of *Saccharothrix aerocolonigenes*, contains an indolocarbazole framework, an imide upper heterocycle and a sugar part linked to one of the indole nitrogens like other natural products such as some tjipanazoles E, F1 and F2 and AT2433-A1 and B1 but unlike staurosporine and UCN-01 in which the carbohydrate moiety is linked to both indole nitrogens (Fig. 1).[1–4] Rebeccamycin is a topoisomerase I inhibitor without inhibitory properties toward kinases such as CDK1/cyclinB, CDK5/p25 and PKC whereas staurosporine and UCN-01 are not topoisomerase I poisons but exhibit inhibitory properties against a variety of kinases.[5–7] In the course of structure–activity relationship studies on rebeccamycin analogues, we have synthesized 7-aza-rebeccamycin analogues in which one or both indole moieties have been replaced by a 7-azaindole unit.[8,9] When only one azaindole was introduced, the sugar part was linked either to the indole or to the azaindole (Fig. 2). Important differences in DNA binding properties and in topoisomerase I poisoning were observed between the two series. Compounds with the sugar moiety attached to the indole moiety exhibited strong DNA binding and topoisomerase I inhibitory properties whereas with compounds in which the sugar was attached to the azaindole, DNA binding and topoisomerase I poisoning were highly weakened or completely abolished. However, compounds in both series could exhibit strong in vitro cytotoxicities toward some tumor cell lines with IC_{50} values in the nanomolar range, suggesting other biological targets

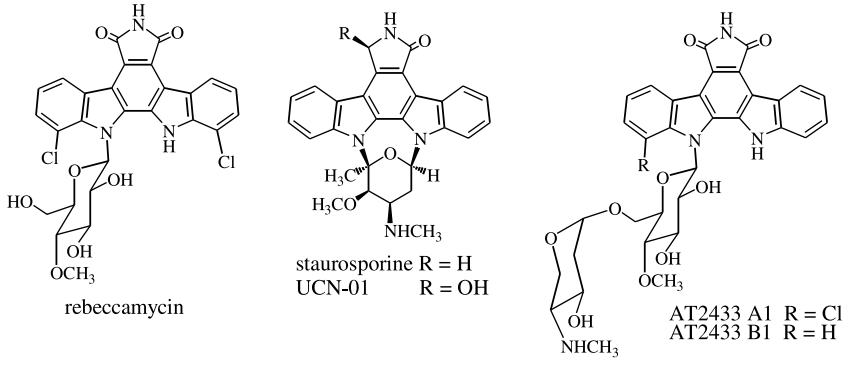

Figure 1. Chemical structures of the bacterial metabolites rebeccamycin, staurosporine, UCN-01, AT2433 A1 and B1.

Keywords: Staurosporine; Rebeccamycin; 7-Azaindole; Antitumor compounds; Enzyme inhibitors.
* Corresponding author. Tel.: +33 4 73 40 71 24; fax: +33 4 73 40 77 17; e-mail: Michelle.PRUDHOMME@univ-bpclermont.fr

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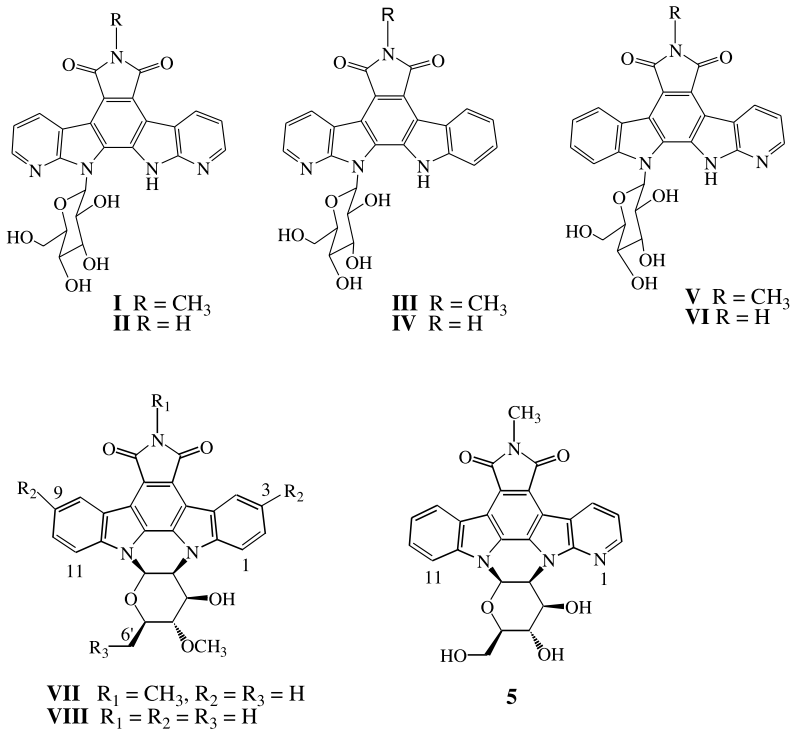
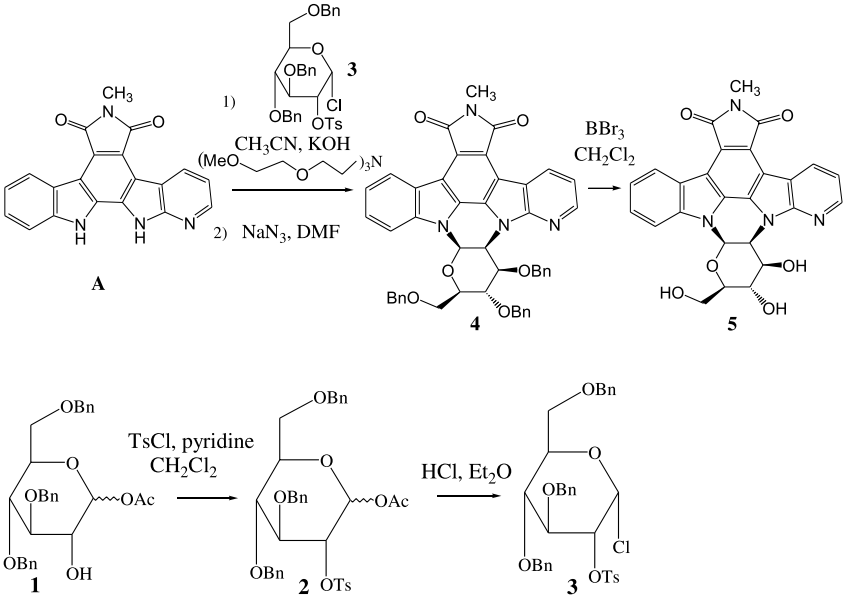


Figure 2. Aza-rebeccamycin analogues previously described.

than DNA and topoisomerase I for compounds in which the sugar is linked to the azaindole. To get an insight into the structural parameters inducing enzyme selectivity, we have synthesized staurosporine analogues from rebeccamycin by coupling the sugar moiety to the second indole nitrogen in non aza series at first and recently, one *N*-methylated compound has been prepared in 7-azaindole series.[10–12] In a previous brief communication, we described the synthesis of the 7-aza staurosporine analogue **5** with the sugar attached to both indole and azaindole nitrogens, with a methyl group on the imide nitrogen and with the oxygen heteroatom of the sugar ring oriented toward the indole unit (Fig. 2).[12] This compound was synthesized by coupling an α-1-chloro-glucose on the *N*-methylated indolocarbazole aglycone in the presence of a phase transfer catalyst. As deduced from the crystal structures of staurosporine in complex with various kinases, a free nitrogen in the upper heterocycle seems to be necessary to establish a hydrogen bond with the carbonyle of glutamate 81 in the ATP binding pocket of the kinases.[13,14] In this paper, the syntheses of new 7-aza bridged compounds, without the methyl group on the imide nitrogen and with the oxygen of the sugar ring oriented either toward the indole or toward the azaindole moiety, are reported. The replacement of an indole moiety



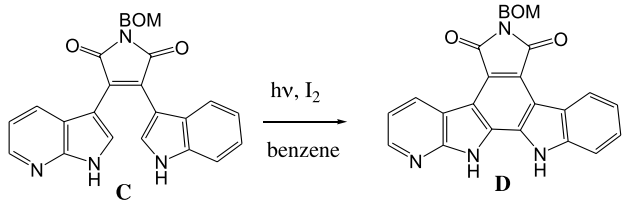
Scheme 1. Synthetic scheme for compound **5**.

by an azaindole in the bridged series could increase the affinity for the binding site of the target enzyme(s) and modify the electronic distribution on the aromatic framework and the lipophilicity. Because, it has been shown that substitutions in 6-position of the sugar unit can modify the biological target[15,16], we use a sugar unit ditosylated in 2- and 6-positions allowing access to bridged aza compounds substituted in 6-position of the sugar moiety with an azido group, a precursor for amino and amido substituents.

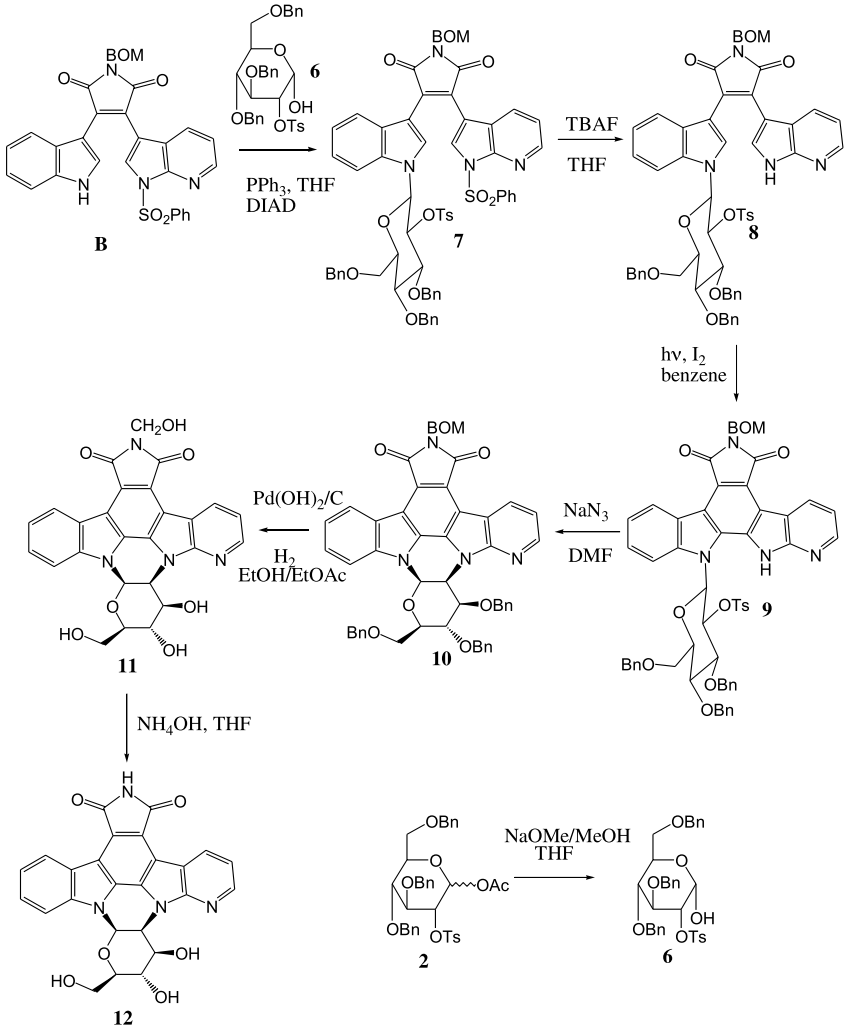
2. Results and discussion

2.1. Chemistry

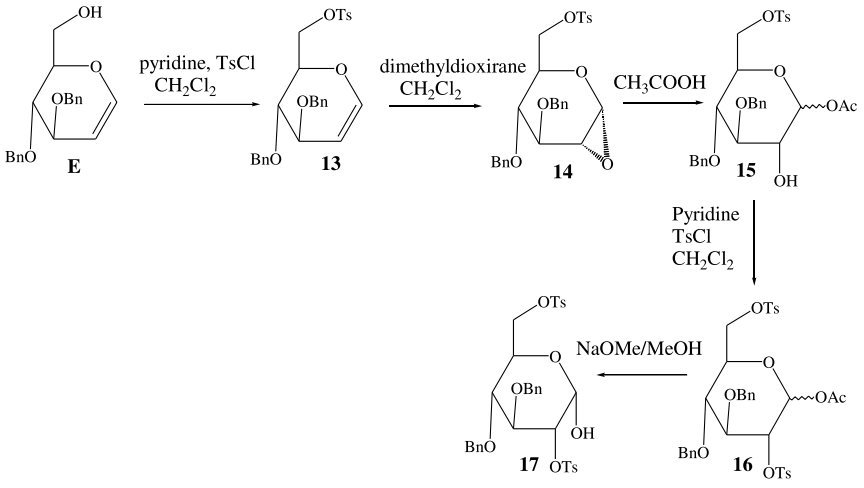
The synthesis of compound **5** is outlined in Scheme 1. The chloro sugar **3** was prepared from acetylated compound **1** which could be obtained from the commercial triacetylated glycal as described in literature.[17–19] Tosylation of **1** yielded tosylate **2** as a mixture of both α and β anomers, which was further treated with HCl gas to give the α-chloro anomer **3**.[12] This chloro sugar was coupled to the aglycone **A**[20] using potassium hydroxide and a phase transfer catalyst to yield the required coupling product, which was further treated with sodium azide to give the bridged compound **4** formed via a nucleophilic attack of the deprotonated azaindolic nitrogen on the carbon bearing the tosyl group. Elimination of the benzyl protecting groups of the sugar moiety was carried out using boron tribromide. For the synthesis of compound **12** (Scheme 3), the same procedure as described for the synthesis of **5** was tried from aglycone **D**, which was obtained from **C**[9] by oxidative photocyclization (Scheme 2). However, the coupling reaction with the chloro sugar **3** did not work. A Mitsunobu reaction was then performed from aglycone **B**[9] and sugar **6** prepared from **2** by reaction with MeONa/MeOH in THF (Scheme 3). Compound **7** was obtained in 88% yield. After deprotection of the azaindole nitrogen, oxidative photocyclization in the presence of iodine gave **9** in 62% yield. Reaction of **9** with sodium azide led to the bridged compound **10** in 72% yield. Unlike for compound **4**, debenzylation of **10** using boron



Scheme 2. Photocyclization of aglycone **C**.



Scheme 3. Synthesis of compound **12**.

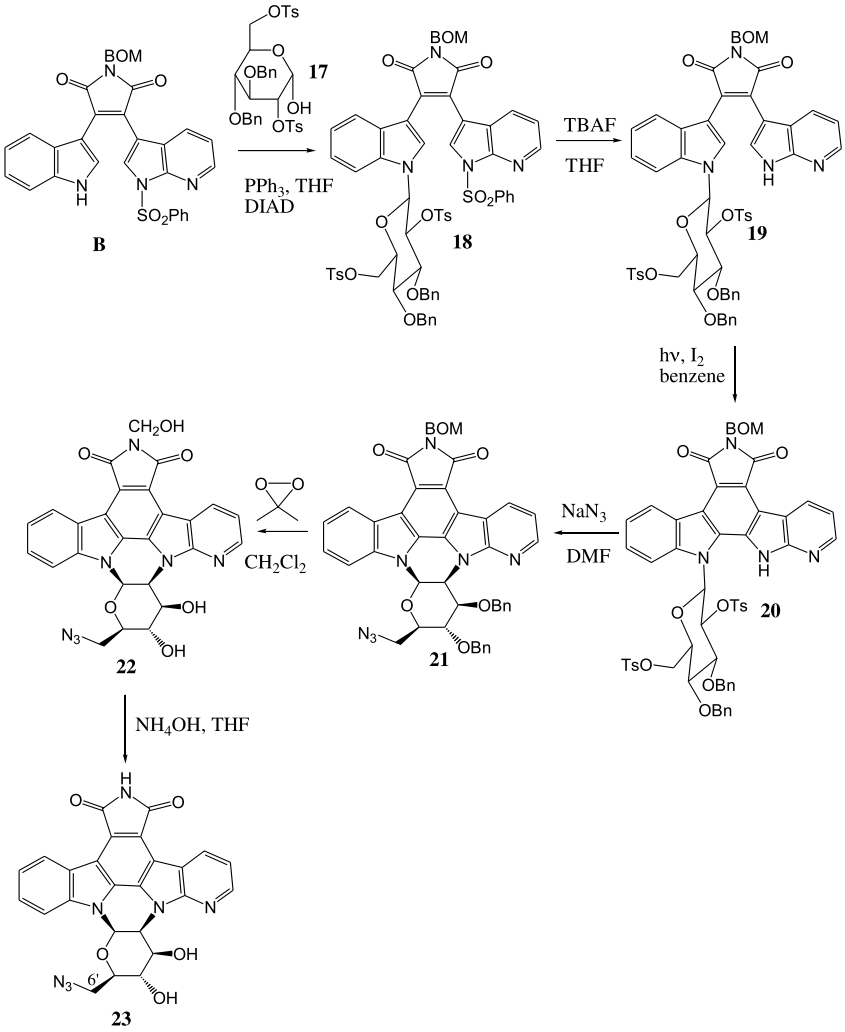


Scheme 4. Synthesis of di-tosylated sugar **17**.

tribromide gave an inexploitable mixture. Removal of the protective groups was achieved in two steps: hydrogenolysis with $Pd(OH)_2/C$ as the catalyst leading to **11** in 52% yield, followed by aminolysis giving the required compound **12** in 71% yield.

To introduce substituents selectively in 6′ position on the sugar moiety of **12**, the Mitsunobu reaction was carried out using 2,6-ditosyl-sugar **17**, which was prepared from glycal **E** as shown in Scheme 4.

Glycal **E** was prepared according to known procedures.[21] Tosylation of **E** at 6-position led to compound **13**. Epoxidation performed using dimethyldioxirane provided



Scheme 5. Synthesis of 6′-azido compound **23**.

the anhydro sugar **14** as the major isomer. Reaction of **14** with glacial acetic acid gave compound **15** in 77% yield as a mixture of both α and β anomers in 0.3:2 ratio, respectively. Tosylation of **15** led to a mixture of both α and β anomers in 1:3.9 ratio, respectively, in only 24% yield. 31% of the unreacted β anomer was recovered. The final step was deacetylation with sodium methoxide/methanol affording **17** in 66% yield. The Mitsunobu reaction between **17** and aglycone **B** led to compound **18** in 52% yield. Deprotection of the azaindole nitrogen using tetrabutylammonium fluoride gave **19** in 83% yield. Compound **19** was further photocyclized to give **20**. Reaction of **20** with sodium azide in DMF induced the coupling of the sugar part with the azaindole nitrogen and concomitant substitution at 6′-position to give **21** (Scheme 5). Contrary to compound **10**, debenzylation by hydrogenolysis could not be achieved with compound **21**. A mixture of compounds reduced on the aromatic rings was obtained. Debenzylation carried out using dimethyldioxirane[22,23] afforded the required compound **22** in 45% yield. Removal of the hydroxymethyl substituent by aminolysis gave **23** in 77% yield.

Because in non-bridged aza rebeccamycins, important differences in the biological activities were observed between compounds in which the carbohydrate was linked either to the indole nitrogen or to the azaindole unit, bridged compounds with a nitrogen atom in 11-position instead of 1-position in the azaindolocarbazole were also synthesized (Scheme 6). A similar sequence of reactions as for the synthesis of **12** was performed from aglycone **F**[9] until elimination of the benzenesulfonyl protective group leading to **25**. Photocyclization of **25** in the presence of iodine did not afford the required compound **26**, only degradation was observed. Cyclization was successfully achieved in 56% yield using palladium triflate in DMF at 90 °C according to a method described by Faul et al.[24] for the synthesis of rebeccamycin. Reaction of **26** with sodium azide led to **27** in 93% yield. Debenzylation carried out using trifluoroacetic acid or dimethyldioxirane or by hydrogenolysis proved to be unsuccessful. The required compound **28** was finally obtained in 27% yield by debenzylation with boron tribromide followed by aminolysis.

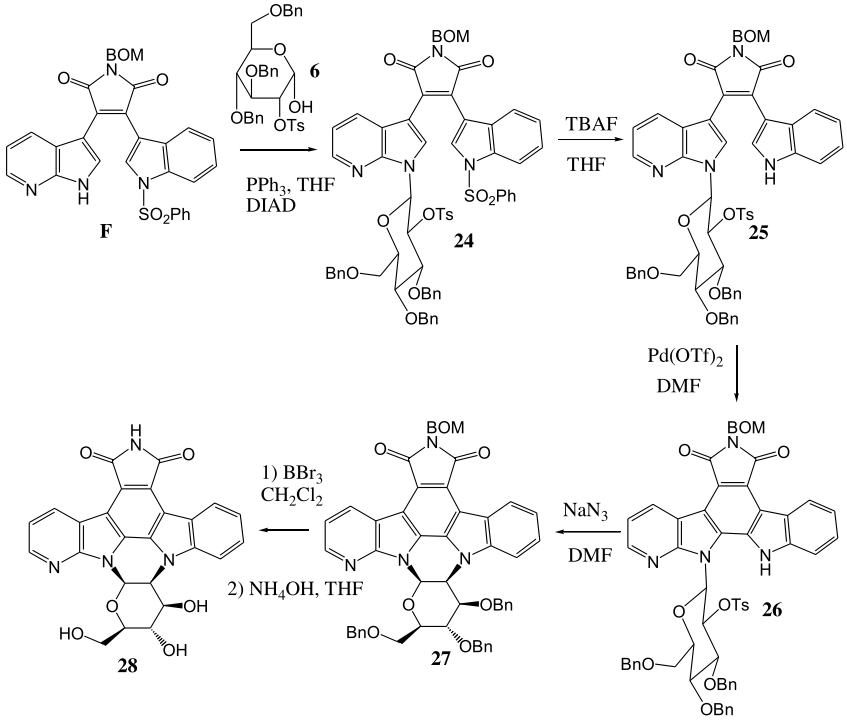
3. Conclusion

In conclusion, we have developed methods to synthesize bridged aza-rebeccamycin analogues from 2-*O*-tosyl-glucopyranose. Both analogues in which the anomeric carbon of the sugar part is linked to either the azaindole or the indole moiety have been synthesized. The use of 2,6-*O*-ditosyl-glucopyranose, in the Mitsunobu reaction, allowed the introduction of an azido group in 6′-position. This method can also be applied for introducing a wide range of substituents in 6-position of the sugar moiety. The cytotoxicities and the inhibitory activities of these new compounds toward various kinases are now under investigation.

4. Experimental

4.1. Chemistry

IR spectra were recorded on a Perkin Elmer 881 spectrometer. NMR spectra were performed on a Bruker AVANCE 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) (chemical shifts δ in ppm, the following abbreviations are used: singlet (s), doublet (d), triplet (t), pseudo-triplet (pt), doubled triplet (dt), multiplet (m), br s (broad signal), tertiary carbons (C tert), quaternary carbons (C quat). The signals were assigned from ^{1}H–^{1}H COSY and ^{13}C–^{1}H correlations.



Scheme 6. Synthesis of the bridged compound **28**.

Low-resolution mass spectra (ESI+ and APCI+) were determined on a MS Hewlett Packard engine. HRMS spectra (FAB+) were determined on a high resolution Fisons Autospec-Q spectrometer at CESAMO (Talence, France). Chromatographic purifications were performed by flash silicagel Geduran SI 60 (Merck) 0.040–0.063 mm or Kieselgel 60 (Merck) 0.063–0.200 mm column chromatography. For purity tests, TLC were performed on fluorescent silica gel plates (60 F_{254} from Merck).

4.1.1. 1-*O*-Acetyl-2-*O*-tosyl-3,4,6-tri-*O*-benzyl-α and β-D-glucopyranose 2. To a solution of **1** (548 mg, 1.11 mmol, α/β ratio 3:10) in pyridine (6 mL) and CH_2Cl_2 (15 mL) was added tosyl chloride (766 mg, 5.55 mmol). After refluxing for 72 h, 2 N HCl (15 mL) was added. After extraction with EtOAc, the organic phase was washed with saturated aqueous $NaHCO_3$ and then with brine. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 9:1 to 7:3) to give **2** as a colorless oil (603 mg, 0.93 mmol, 84% yield) as a mixture of β and α anomers in 8:5 ratio, respectively. Unreacted **1** (β anomer, 150 mg) was recovered.

Compound **2**. IR (NaCl film), $\nu_{C=O}$ 1739, 1760 cm^{-1}. HRMS (FAB+) $[M+Na]^+$, calcd for $C_{36}H_{38}NaO_9S_1$ 669.2134, found 669.2147. ^1H NMR (400 MHz, $CDCl_3$): $^{\beta}$ major anomer, $^{\alpha}$ minor anomer 1.92 ($3H^{\beta}$, s, CH_3), 2.11 ($3H^{\alpha}$, s, CH_3), 2.35 ($3H^{\beta}$, s, CH_3), 2.39 ($3H^{\alpha}$, s, CH_3), 3.54–3.86 ($5H^{\beta}+5H^{\alpha}$, m), 4.43–4.82 ($7H^{\beta}+7H^{\alpha}$, m), 5.65 ($1H^{\beta}$, d, $J=8.0$ Hz, H_1), 6.18 ($1H^{\alpha}$, d, $J=3.5$ Hz, H_1), 7.04–7.10 ($2H^{\beta}+2H^{\alpha}$, m), 7.14–7.36 ($15H^{\beta}_{arom}+15H^{\alpha}_{arom}$), 7.73–7.79 ($2H^{\beta}+2H^{\alpha}$, m). ^{13}C NMR (100 MHz, $CDCl_3$): 20.7, 20.9, 21.6, 21.8 (CH_3), 67.7, 67.8 (C_6), 73.6, 73.7, 75.2, 75.4, 75.5, 75.7 (CH_2), 72.6, 75.8, 77.0, 77.4, 78.1, 79.5, 79.7, 82.4, 89.6, 91.5 (C_1, C_2, C_3, C_4, C_5), 127.6–128.6, 129.7, 130.0 (C tert arom), 133.2, 134.7, 137.6, 137.7, 137.8, 137.9, 144.7, 145.3 (C quat arom), 168.6, 169.3 (C=O).

4.1.2. 1-Chloro-1-deoxy-2-*O*-tosyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranose 3. HCl gas was bubbled for 20 min in a solution of **2** (444 mg, 0.69 mmol) in diethylether. After stirring for 48 h at room temperature, the solvent was removed, the residue was dissolved in CH_2Cl_2 then the solvent was removed. The residue was purified by flash chromatography (eluent cyclohexane/EtOAc 7:3) to give **3** (α anomer) as a colorless oil (272 mg, 0.438 mmol, 66% yield). Unreacted α anomer **2** (56 mg) was recovered. The reaction performed with pure β anomer **2** afforded **3** in 86% yield.

Compound **3**. IR (NaCl film) $\nu_{S=O}$ 1739 cm^{-1}. HRMS (FAB+) $[M+Na]^+$, calcd for $C_{34}H_{35}ClNaO_7S$ 645.1690, found 645.1699. ^1H NMR (400 MHz, $CDCl_3$): 2.39 (3H, s, CH_3), 3.66 (1H, dd, $J_1=11.0$ Hz, $J_2=2.0$ Hz), 3.76–3.83 (2H, m), 4.05 (1H, t, $J=9.5$ Hz), 4.10 (1H, m), 4.48 (1H, d, $J=10.5$ Hz), 4.49 (1H, d, $J=12.0$ Hz), 4.60 (1H, d, $J=12.0$ Hz), 4.61 (1H, dd, $J_1=9.5$ Hz, $J_2=4.0$ Hz), 4.69 (1H, d, $J=11.0$ Hz), 4.74 (1H, d, $J=11.0$ Hz), 4.75 (1H, d, $J=10.5$ Hz), 6.21 (1H, d, $J=4.0$ Hz, H_1), 7.08–7.11 (2H, m), 7.16–7.23 (4H, m), 7.25–7.37 ($11H_{arom}$), 7.80 (2H, d, $J=8.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 21.7 (CH_3), 67.4 (C_6), 73.6, 75.4, 75.6 (CH_2), 73.4, 76.6, 78.6, 79.1, 91.8 (C_1, C_2, C_3, C_4, C_5), 127.7, 127.8–128.1, 128.3, 128.4, 128.5 (C tert arom), 133.0, 137.5, 137.6, 137.7, 145.3 (C quat arom).

4.1.3. 6-Methyl-5,7-dihydro-12,13-(3,4,6-tri-*O*-benzyl-β-D-mannopyranose-1,2-diyl)-pyrrolo[3,4-*c*]pyrido[2′,3′:4,5] pyrrolo[2,3-*a*]carbazole-5,7-dione 4. To a solution of aglycone **A** (73 mg, 0.214 mmol) in acetonitrile (8.5 mL) were added powdered KOH (92 mg) and tris[2-(2-methoxyethoxy) ethyl]amine (34 μL). After stirring at room temperature for 15 min, a solution of **3** (290 mg, 0.466 mmol) in acetonitrile (4.5 mL) was added dropwise. The mixture was stirred at room temperature for 48 h. After acidification with 1 N HCl (10 mL), the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent was removed. The residue was partly purified by flash chromatography (eluent cyclohexane/EtOAc from 9:1 to 5:5 then EtOAc 100%) to give a mixture of glycosylated compounds (24 mg). To the mixture of the glycosylated compounds in DMF (1 mL) was added NaN_3 (32 mg, 0.50 mmol). After stirring at 70 °C for 48 h, water was added and the mixture was extracted with EtOAc. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 9:1 to 5:5 then EtOAc 100%) affording **4** (20 mg, 0.026 mmol, 12% yield from **A**) as a yellow solid.

Compound **4**. Mp 67–69 °C. IR (KBr) $\nu_{C=O}$ 1700 cm^{-1}. HRMS (FAB+) $[M+H]^+$, calcd for $C_{47}H_{39}N_4O_6$ 755.2870, found 755.2871. The ^1H NMR signals were assigned from ^1H–^1H COSY correlations. ^1H NMR (400 MHz, $CDCl_3$): 3.30 (3H, s, CH_3), 3.79 (1H, d, $J=11.0$ Hz), 3.91 (1H, dd, $J_1=10.5$ Hz, $J_2=5.5$ Hz, $H_{6'}$), 3.96–4.03 (2H, m, $H_{3'}$, $H_{6'}$), 4.09 (1H, t, $J=9.5$ Hz, $H_{4'}$), 4.42 (1H, m, $H_{5'}$), 4.43 (1H, d, $J=11.0$ Hz), 4.64 (1H, d, $J=11.0$ Hz), 4.66 (1H, d, $J=12.0$ Hz), 4.75 (1H, d, $J=11.5$ Hz), 4.91 (1H, d, $J=11.0$ Hz), 5.52 (1H, m, $H_{2'}$), 6.15 (1H, d, $J=3.5$ Hz, $H_{1'}$), 6.45 (2H, d, $J=7.0$ Hz), 6.89 (2H, t, $J=7.5$ Hz), 7.03 (1H, t, $J=7.5$ Hz), 7.14–7.18 (2H, m), 7.24–7.30 (3H, m), 7.32–7.39 (2H, m), 7.40–7.47 (6H, m), 7.99 (1H, m), 8.52 (1H, dd, $J_1=4.0$ Hz, $J_2=1.0$ Hz), 8.82 (1H, m), 8.95 (1H, dd, $J_1=8.0$ Hz, $J_2=1.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 23.9 (NCH_3), 58.3, 74.5, 78.3, 80.4, 85.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 68.9 ($C_{6'}$), 73.8, 75.1, 75.9 (CH_2), 110.4, 113.3, 116.5, 117.7, 121.9, 125.3, 127.4, 130.2, 136.1, 137.6, 137.9, 143.3, 152.3 (C quat arom), 113.6, 117.3, 122.9, 125.6, 127.7–128.7, 134.1, 146.5 (C tert arom), 170.0, 170.1 (C=O).

4.1.4. 6-Methyl-5,7-dihydro-12,13-(β-D-mannopyranose-1,2-diyl)-pyrrolo[3,4-*c*]pyrido[2′,3′:4,5]pyrrolo[2,3-*a*]-carbazole-5,7-dione 5. To a solution of **4** (10 mg, 0.013 mmol) in CH_2Cl_2 (5 mL) cooled to −78 °C was added 1 M BBr_3 in CH_2Cl_2 (87 μL, 0.08 mmol). After stirring for 10 min at −78 °C, water was added, the mixture was allowed to reach room temperature then it was extracted with EtOAc. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent from EtOAc 100% to EtOAc/MeOH 9:1) to give **5** (5.6 mg, 0.012 mmol, 90% yield) as a yellow solid.

Compound **5**. Mp 245–250 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1700 cm^{-1}, ν_{OH} 3040–3680 cm^{-1}. HRMS (FAB+) $[M+H]^+$, calcd for $C_{26}H_{21}N_4O_6$ 485.1461, found 485.1465. ^1H NMR (400 MHz, DMSO-d_6): 3.19 (3H, s, NCH_3), 3.59–3.66 (2H, m), 3.79 (1H, m), 3.97 (1H, m), 4.06 (1H, m), 5.18–5.28 (3H, m, 2OH, $H_{2'}$), 5.40 (1H, d, J= 5.5 Hz, OH), 6.42 (1H, d, J=4.0 Hz, $H_{1'}$), 7.49 (1H, dd, J_1=8.0 Hz, J_2=5.0 Hz), 7.51 (1H, t, J=7.5 Hz), 7.64 (1H, dt, J_1=7.5 Hz, J_2=1.0 Hz), 8.24 (1H, d, J=8.0 Hz), 8.63 (1H, dd, J_1=5.0 Hz, J_2=1.5 Hz), 8.72 (1H, d, J=7.5 Hz), 8.89 (1H, dd, J_1=8.0 Hz, J_2=1.5 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 23.6 (CH_3), 61.1 ($C_{6'}$), 59.2 ($C_{2'}$), 70.1, 73.6, 76.8 ($C_{3'}$, $C_{4'}$, $C_{5'}$), 84.6 ($C_{1'}$), 109.2, 114.6, 116.1, 120.1, 120.9, 124.4, 127.6, 130.2, 143.0, 152.8 (C quat arom), 114.1, 116.9, 122.1, 124.2, 127.7, 132.1, 146.9 (C tert arom), 169.5, 169.6 (C=O).

4.1.5. 2-Benzyloxymethyl-5,7-dihydro-12*H*,13*H*-pyrrolo[3,4-*c*]pyrido[2′,3′:4,5]pyrrolo[2,3-*a*]carbazole-5,7-dione D. To a solution of aglycone **C** (218 mg, 0.486 mmol) in benzene (300 mL) was added iodine (1.32 g, 5.32 mmol). The mixture was irradiated for 7 h with a medium pressure mercury lamp (400 W). The solvent was removed, and the residue dissolved in EtOAc (250 mL) and washed with saturated aqueous sodium thiosulfate (100 mL) and then with brine. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent EtOAc/cyclohexane 5:5) to give **D** (120 mg, 0.267 mmol, 55% yield) as a yellow solid.

Compound **D**. Mp >290 °C (degradation). IR (KBr) $\nu_{C=O}$ 1700, 1750 cm^{-1}, ν_{NH} 3000–3600 cm^{-1}. Mass (ESI+) $[M+H]^+$ 447. ^1H NMR (400 MHz, DMSO-d_6): 4.67 (2H, s, CH_2), 5.08 (2H, s, CH_2), 7.24–7.43 (7H, m), 7.57 (1H, t, J=7.5 Hz), 7.78 (1H, d, J=8.0 Hz), 8.55 (1H, d, J= 3.5 Hz), 8.90 (1H, d, J=8.0 Hz), 9.05 (1H, d, J=7.5 Hz), 11.45 (1H, s, NH), 12.08 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 66.4, 70.3 (CH_2), 112.1, 116.6, 120.4, 124.1, 127.1, 127.4, 127.5 (2C), 128.2 (2C), 132.1, 147.3 (C tert arom), 113.0, 114.1, 116.1, 118.5, 118.8, 121.1, 127.8, 128.8, 137.8, 140.2, 151.8 (C quat arom), 168.9, 169.0 (C=O).

4.1.6. 2-*O*-Tosyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranose 6. To a solution of **2** (300 mg, 0.462 mmol, anomeric ratio α/β 5:8) in THF/MeOH (5 mL, 1:1 v/v) at 0 °C was added dropwise 1 M NaOMe/MeOH (60 μL). The mixture was stirred at 0 °C for 1 h, the solvent was removed and the residue purified by flash chromatography (eluent cyclohexane/EtOAc 7:3) affording **6** (204 mg, 0.038 mmol, 73% yield) as a white solid.

Compound **6**. Mp 118–120 °C. IR (KBr) ν_{OH} 3240–3600 cm^{-1}. Mass (ESI+) $[M+H]^+$ 604, $[M+Na]^+$ 627. ^1H NMR (400 MHz, $CDCl_3$): 2.17 (3H, s, CH_3), 3.35–3.50 (4H, m), 3.80–3.90 (2H, m), 4.23 (1H, d, J=10.0 Hz), 4.24 (1H, d, J=11.5 Hz), 4.30 (1H, d, J=12.0 Hz), 4.39 (1H, d, J=11.5 Hz), 4.48 (2H, s), 4.53 (1H, d, J=11.0 Hz), 5.24 (1H, br s, H_1), 6.85–6.89 (2H, m), 6.94–6.98 (4H, m), 7.04–7.16 ($11H_{arom}$), 7.58 (2H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 21.7 (CH_3), 68.3 (C_6), 73.5, 75.1, 75.2 (CH_2), 70.0, 77.9, 79.0, 80.0, 90.9 (C_1, C_2, C_3, C_4, C_5), 127.5–128.5, 129.6, 129.8 (C tert arom), 133.3, 137.6, 137.8, 138.0, 144.9 (C quat arom).

4.1.7. 1-Benzyloxymethyl-2,5-dihydro-3-[1-(2-*O*-tosyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranos-1-yl)-indol-3-yl]-4-[1-phenylsulfonyl-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 7. To a solution of **B** (89 mg, 0.152 mmol) in THF (8 mL) were added **6** (205 mg, 0.338 mmol) and triphenylphosphine (89 mg, 0.338 mmol). The mixture was cooled to −78 °C then diisopropyl azodicarboxylate (DIAD) (65.5 μM, 0.338 mmol) was added dropwise. The mixture was allowed to reach room temperature then was stirred for 18 h. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2) to give **7** (156 mg, 0.133 mmol, 88% yield) as a red solid.

Compound **7**. Mp 47–50 °C. IR (KBr) $\nu_{C=O}$ 1710, 1770 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1175. ^1H NMR (400 MHz, $CDCl_3$): 1.93 (3H, s, CH_3), 3.53–3.59 (2H, m), 3.63 (1H, dd, J_1=9.0 Hz, J_2=3.5 Hz), 3.70 (1H, t, J= 9.0 Hz), 3.84 (1H, t, J=9.5 Hz), 4.34 (1H, d, J=12.0 Hz), 4.42 (1H, d, J=12.0 Hz), 4.43–4.47 (2H, m), 4.57 (2H, s), 4.58 (1H, d, J=8.5 Hz), 4.62 (1H, d, J=10.5 Hz), 5.03 (1H, d, J=9.0 Hz), 5.07 (2H, s), 5.34 (1H, d, J=9.0 Hz, $H_{1'}$), 6.19–6.28 (2H, m), 6.56 (2H, d, J=8.0 Hz), 6.62 (1H, dd, J_1=8.0 Hz, J_2=3.5 Hz), 6.82 (1H, t, J=8.0 Hz), 6.91–6.97 (2H, m), 7.02–7.19 ($20H_{arom}$), 7.23 (2H, d, J=8.0 Hz), 7.31 (2H, t, J=7.5 Hz), 7.43 (1H, dt, J_1=8.0 Hz, J_2=1.0 Hz), 7.90 (1H, s), 7.96 (2H, d, J=8.0 Hz), 7.98 (1H, s), 8.07 (1H, d, J=5.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 22.0 (CH_3), 67.4, 68.0 (CH_2), 71.8, 73.5, 75.2, 75.4 ($C_{6'}+CH_2$), 70.1, 77.5, 78.2, 79.9, 83.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 119.3, 121.4, 121.5, 123.0, 127.2, 127.5–128.5, 129.1, 129.3, 131.4, 134.1, 145.4 (C tert arom), 106.5, 109.5, 123.6, 126.0, 131.1, 133.3, 135.6, 137.5, 137.6, 137.7, 137.8, 138.0, 144.3, 146.6 (C quat arom), 170.7 (2 C=O).

4.1.8. 1-Benzyloxymethyl-2,5-dihydro-3-[1-(2-*O*-tosyl-3,4,6-*O*-benzyl-β-D-glucopyranos-1-yl)-indol-3-yl]-4-[1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 8. To a solution of **7** (160 mg, 0.136 mmol) in THF (5 mL) was added a 1.1 M solution of tetrabutylammonium fluoride in THF (409 μL, 0.448 mmol). The mixture was stirred for 2.5 h at room temperature. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 3:2) to give **8** (114 mg, 0.110 mmol, 81% yield) as a red solid.

Compound **8**. Mp 75–80 °C. IR (KBr) $\nu_{C=O}$ 1765, 1710 cm^{-1}, ν_{NH} 3240–3600 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1035. ^1H NMR (400 MHz, $CDCl_3$): 2.12 (3H, s, CH_3), 3.72–3.86 (3H, m), 3.94 (1H, t, J=9.0 Hz), 4.04 (1H, t, J= 9.0 Hz), 4.53 (1H, d, J=12.0 Hz), 4.60 (1H, d, J=12.0 Hz), 4.67 (1H, d, J=11.0 Hz), 4.80 (4H, s+m), 4.85 (1H, d, J= 10.5 Hz), 5.30 (3H, s+m), 5.56 (1H, d, J=9.0 Hz, $H_{1'}$), 6.69–6.78 (5H, m), 7.02 (1H, m), 7.15–7.21 (2H, m), 7.26–7.40 (19H), 7.47 (2H, d, J=7.5 Hz), 7.55 (1H, t, J= 8.0 Hz), 8.00 (2H, d, J=9.5 Hz), 8.14 (1H, d, J=4.5 Hz), 12.4 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 67.2, 68.2 (CH_2), 71.7, 73.5, 75.3, 75.4 ($C_{6'}+CH_2$), 77.6, 78.2, 80.1, 83.1 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 116.7, 120.9, 122.1, 122.8, 127.0, 127.5–128.5, 129.1, 129.8, 131.4, 142.8 (C tert

arom), 105.3, 107.4, 119.0, 126.4, 126.9, 133.2, 135.6, 137.5–137.9, 144.2, 148.6 (C quat arom), 171.3, 171.7 (C=O).

4.1.9. 6-Benzyloxymethyl-12-(3,4,6-tri-*O*-benzyl-2-*O*-tosyl-β-D-glucopyranos-1-yl)-5,7-dihydro-13*H*-pyrido-[3′,2′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione 9. To a solution of **8** (50 mg, 0.048 mmol) in benzene (150 mL) was added iodine (18 mg, 0.071 mmol). The mixture was irradiated for 1.5 h with a medium pressure mercury lamp (400 W). The solvent was removed, and the residue was dissolved in EtOAc (250 mL) and washed with saturated aqueous sodium thiosulfate (50 mL) and then with brine. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent EtOAc/cyclohexane 3:7) to give **9** (31 mg, 0.030 mmol, 62% yield) as a yellow solid.

Compound **9**. Mp 37–40 °C. IR (KBr) $\nu_{C=O}$ 1710, 1755 cm^{-1}, ν_{NH} 3200–3600 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1033. ^1H NMR (400 MHz, $CDCl_3$): 2.10 (3H, s, CH_3), 3.65 (1H, dd, $J_1=10.0$ Hz, $J_2=2.5$ Hz), 3.81 (1H, d, $J=10.0$ Hz), 3.93 (1H, d, $J=10.0$ Hz), 3.99 (1H, t, $J=9.0$ Hz), 4.17 (1H, d, $J=10.5$ Hz), 4.44 (1H, d, $J=10.0$ Hz), 4.47 (1H, d, $J=9.0$ Hz), 4.70 (1H, d, $J=10.5$ Hz), 4.74 (2H, s), 4.76 (1H, d, $J=11.5$ Hz), 5.00 (1H, d, $J=10.5$ Hz), 5.03 (1H, d, $J=13.5$ Hz), 5.15 (1H, t, $J=9.0$ Hz), 5.30 (2H, s), 5.99 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.37 (2H, d, $J=8.0$ Hz), 6.46 (2H, d, $J=8.0$ Hz), 6.74 (2H, d, $J=7.5$ Hz), 6.76–6.83 (2H, m), 6.90 (1H, m), 6.95–7.00 (3H, m), 7.10–7.45 (14H), 7.50 (2H, dd, $J_1=7.5$ Hz, $J_2=0.5$ Hz), 8.56 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz), 9.02 (1H, d, $J=8.0$ Hz), 9.43 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 11.10 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 65.2, 66.9 (CH_2), 71.6, 73.2, 75.3, 76.2 ($C_{6'}+CH_2$), 76.3, 78.4, 79.7, 82.3, 83.4 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.4, 115.3, 115.7, 115.8, 117.5, 120.5, 120.8, 121.5, 125.9, 126.0, 126.6, 126.7, 127.2, 127.3, 127.6, 127.8–129.3, 129.7, 130.3, 133.8, 148.3 (C tert arom), 119.3, 120.5, 120.8, 121.9, 132.2, 137.2, 137.3, 137.6 (2C), 140.7, 144.3, 153.5 (C quat arom), 169.4 (2C, C=O).

4.1.10. 6-Benzyloxymethyl-5,7-dihydro-12,13-(3,4,6-tri-*O*-benzyl-β-D-mannopyranose-1,2-diyl)-pyrrolo[3,4-*c*]-pyrido[2′,3′:4,5]pyrrolo[2,3-*a*]carbazole-5,7-dione 10. To a solution of **9** (60 mg, 0.06 mmol) in DMF (2 mL) was added NaN_3 (37 mg, 0.60 mmol). The mixture was stirred for 48 h at 70 °C, then water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 4:1) to give **10** (37 mg, 0.043 mmol, 72% yield) as a yellow solid.

Compound **10**. Mp 38–40 °C. IR (KBr) $\nu_{C=O}$ 1700, 1750 cm^{-1}. Mass (ESI+) $[M+H]^+$ 861. ^1H NMR (400 MHz, $CDCl_3$): 3.60 (1H, dd, $J_1=10.0$ Hz, $J_2=4.5$ Hz), 3.63 (1H, d, $J=11.5$ Hz), 3.70 (1H, d, $J=12.0$ Hz), 3.71 (1H, m), 3.76 (1H, m), 4.23 (1H, d, $J=12.0$ Hz), 4.31 (1H, d, $J=11.5$ Hz), 4.32 (1H, m), 4.49 (1H, d, $J=12.0$ Hz), 4.57 (1H, m), 4.58 (1H, d, $J=12.0$ Hz), 4.68 (2H, s), 5.16 (2H, AB system, $J=11.0$ Hz, $\Delta\nu=13.0$ Hz), 5.56 (1H, dd, $J_1=5.5$ Hz, $J_2=3.5$ Hz, $H_{2'}$), 6.18 (2H, t, $J=8.0$ Hz), 6.20 (1H, d, $J=6.0$ Hz, $H_{1'}$), 6.71 (2H, t, $J=7.5$ Hz), 6.86 (1H, t, $J=7.5$ Hz), 7.10–7.38 (17H, m), 7.42 (1H, dt, $J_1=7.5$ Hz, $J_2=1.0$ Hz), 7.85 (1H, d, $J=8.0$ Hz), 8.36 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz), 8.71 (1H, d, $J=7.5$ Hz), 8.84 (1H, dd, $J_1=7.5$ Hz, $J_2=1.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 52.6, 72.8, 72.9, 75.4, 80.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 66.7 ($C_{6'}$), 70.2, 71.5, 71.8, 72.3, 73.2 (CH_2), 109.3, 114.2, 117.5, 120.2, 120.4, 124.6, 128.8, 129.0, 136.1, 137.4, 137.8, 138.0, 142.5, 151.7 (C quat arom), 113.4, 117.3, 122.3, 125.3, 127.4, 127.6–128.7, 133.4, 146.6 (C tert arom), 169.6 (2 C=O).

4.1.11. 6-Hydroxymethyl-5,7-dihydro-12,13-(β-D-mannopyranose-1,2-diyl)-pyrrolo[3,4-*c*]pyrido[2′,3′:4,5]-pyrrolo[2,3-*a*]carbazole-5,7-dione 11. To a suspension of **10** (50 mg, 0.058 mmol) in EtOH/EtOAc (5 mL, 4:1 v/v) was added $Pd(OH)_2/C$ (20%) (50 mg). The mixture was hydrogenated under pressure (40 psi) at room temperature for 3 days. After filtration over Celite, the filtrate was evaporated. The residue was purified by flash chromatography (eluent CH_2Cl_2/MeOH 95:5) to give **11** (15 mg, 0.030 mmol, 52% yield) as a yellow solid. 16 mg of a mixture of partially debenzylated compounds could be recovered and recycled.

Compound **11**. Mp >200 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1700, 1750 $cm^{-1;}$ ν_{OH} 3100–3600 cm^{-1}. HRMS (FAB+) $[M+H]^+$, calcd for $C_{26}H_{20}N_4O_7$ 501.1410, found 501.1416. ^1H NMR (400 MHz, DMSO-d_6): 3.33 (1H, m, $H_{6'}$), 3.47–3.61 (2H, m, $H_{4'}+H_{6'}$), 3.70 (1H, m, $H_{5'}$), 4.30 (1H, m, $H_{3'}$), 4.35 (1H, t, $J=5.5$ Hz, $OH_{6'}$), 5.10 (2H, d, $J=6.5$ Hz, CH_2OH), 5.35 (1H, d, $J=2.5$ Hz, $H_{2'}$), 5.48 (1H, d, $J=5.0$ Hz, $OH_{4'}$), 6.46 (1H, t, $J=7.0$ Hz, CH_2OH), 6.97 (1H, s, $H_{1'}$), 7.55 (1H, t, $J=8.0$ Hz), 7.66 (1H, dd, $J_1=8.0$ Hz, $J_2=5.0$ Hz), 7.74 (1H, dt, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 8.04 (1H, d, $J=8.0$ Hz), 8.20 (1H, d, $J=12.5$ Hz, $OH_{3'}$), 8.68 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz), 8.71 (1H, d, $J=7.5$ Hz), 9.06 (1H, dd, $J_1=7.5$ Hz, $J_2=1.5$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 59.8, 59.9 ($C_{6'}$, CH_2), 64.5 ($C_{2'}$), 66.6 ($C_{4'}$), 73.0 ($C_{3'}$), 79.8 ($C_{1'}$), 80.6 ($C_{5'}$), 109.6, 113.4, 117.2, 120.2, 120.3, 123.3, 129.7, 130.2, 140.8, 151.7 (C quat arom), 111.8, 117.5, 122.1, 124.4, 127.7, 133.7, 144.9 (C tert arom), 168.5, 168.6 (C=O).

4.1.12. 5,7-Dihydro-12,13-(β-D-mannopyranose-1,2-diyl)-6*H*-pyrrolo[3,4-*c*]pyrido[2′,3′:4,5]pyrrolo[2,3-*a*]-carbazole-5,7-dione 12. To a solution of **11** (30 mg, 0.060 mmol) in THF (6 mL) was added 28% aqueous NH_4OH (12 mL). The mixture was stirred overnight at room temperature. The solvent was removed and the residue was purified by flash chromatography (eluent CH_2Cl_2/MeOH 95:5) to give **12** (20 mg, 0.0425 mmol, 71% yield) as a yellow solid.

Compound **12**. Mp >300 °C. IR (KBr) $\nu_{C=O}$ 1620, 1670 cm^{-1}, $\nu_{NH,OH}$ 3200–3500 cm^{-1}. Mass (APCI+) $[M+H]^+=471$. HRMS (FAB+) $[M+H]^+$, calcd for $C_{25}H_{18}N_4O_6$ 471.1304, found 471.1300. ^1H NMR (400 MHz, DMSO-d_6): 3.30 (1H, m, $H_{6'}$), 3.46–3.59 (2H, m, $H_{4'}+H_{6'}$), 3.70 (1H, m, $H_{5'}$), 4.29 (1H, dt, $J_1=12.5$ Hz, $J_2=3.0$ Hz, $H_{3'}$), 4.35 (1H, t, $J=5.5$ Hz, $OH_{6'}$), 5.28 (1H, d, $J=2.0$ Hz, $H_{2'}$), 5.47 (1H, d, $J=5.0$ Hz, $OH_{4'}$), 6.93 (1H, s, $H_{1'}$), 7.48 (1H, t, $J=7.5$ Hz), 7.60 (1H, dd, $J_1=7.5$ Hz,

J_2=5.0 Hz), 7.68 (1H, t, J_1=8.0 Hz), 8.00 (1H, d, J=8.0 Hz), 8.22 (1H, d, J=12.0 Hz, $OH_{3'}$), 8.60–8.67 (2H, m), 9.00 (1H, d, J=7.5 Hz), 11.17 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 59.9 ($C_{6'}$), 64.4, 66.6, 73.0, 79.8, 80.6 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.5, 113.4, 117.4, 121.5, 121.6, 123.5, 129.6, 130.1, 140.8, 151.7 (C quat arom), 111.8, 117.3, 122.0, 124.5, 127.5, 133.9, 144.7 (C tert arom), 170.6 (2 C=O).

4.1.13. 3,4-Di-*O*-benzyl-6-*O*-tosyl-D-glucal 13. To a solution of glucal **E** (700 mg, 2.14 mmol) in pyridine (3 mL) and CH_2Cl_2 (7.5 mL) was added tosyl chloride (1.45 g, 7.6 mmol). The mixture was refluxed overnight, then 2 N HCl (15 mL) was added. After extraction with EtOAc, the organic phase was washed with saturated aqueous $NaHCO_3$ then with brine, dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 9:1) to give **13** (503 mg, 1.048 mmol, 49% yield) as a colorless oil.

Compound **13**. IR (NaCl film) $\nu_{C=O}$ 1647, 1733 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 503. ^{1}H NMR (400 MHz, $CDCl_3$): 2.45 (3H, s, CH_3), 3.84 (1H, dd, J_1=8.0 Hz, J_2=6.0 Hz, H_4), 4.16 (1H, m, H_5), 4.22 (1H, m, H_3), 4.34 (1H, dd, J_1=11.0 Hz, J_2=2.5 Hz, H_6), 4.45 (1H, dd, J_1=11.0 Hz, J_2=5.5 Hz, H_6), 4.57 (1H, d, J=12.0 Hz), 4.68 (1H, d, J=11.0 Hz), 4.69 (1H, d, J=11.0 Hz), 4.89 (1H, d, J=11.0 Hz), 4.96 (1H, dd, J_1=6.5 Hz, J_2=3.0 Hz, H_2), 6.35 (1H, d, J=6.0 Hz, H_1), 7.30–7.45 (12H, m), 7.85 (2H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 21.7 (CH_3), 68.2, 70.4, 73.5 (C_6+2CH_2), 73.4, 74.5, 74.7 (C_3, C_4, C_5), 100.1 (C_2), 127.6–128.9, 129.9 (C tert arom), 144 (C_1), 132.8, 137.9, 138.2, 145.0 (C quat arom).

4.1.14. 1-*O*-Acetyl-3,4-di-*O*-benzyl-6-*O*-tosyl-α- and β-D-glucopyranose 15. To a solution of **13** (291 mg, 0.606 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added a solution of dimethyldioxirane in acetone (0.07–0.09 M, 20 mL). The mixture was stirred at 0 °C for 1 h, the solvent was removed at room temperature and compound **14** was dried under vacuum for 2 h. Glacial acetic acid (6 mL) was added to **14** under nitrogen atmosphere. The mixture was stirred at room temperature overnight. After evaporation of acetic acid, the residue was dissolved in CH_2Cl_2 then saturated aqueous $NaHCO_3$ was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give **15** (258 mg, 0.465 mmol, 77% yield from **E**) as a colorless oil. The anomeric ratio calculated from ^{1}H NMR spectrum on $H_{1'}$ at 5.98 ppm (α anomer) and 5.34 ppm (β anomer) was 0.3:2, respectively.

Compound **15**. IR (NaCl film) $\nu_{C=O}$ 1710, 1757 cm^{-1}, ν_{OH} 3517 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 579. ^{1}H NMR (400 MHz, $CDCl_3$) of the major anomer: 2.00 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.54 (1H, br s, OH), 3.49 (4H, br s), 4.11 (1H, d, J=10.5 Hz), 4.17 (1H, d, J=10.0 Hz), 4.43 (1H, d, J=10.5 Hz), 4.73 (1H, d, J=10.5 Hz), 4.77 (1H, s), 4.78 (1H, d, J=8.5 Hz), 5.34 (1H, d, J=7.0 Hz, H_1), 7.08–7.29 (12H, m), 7.67 (2H, d, J=8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) of the major anomer: 20.9, 21.6 (CH_3), 67.8 ($C_{6'}$), 74.9, 75.3 (CH_2), 72.8, 73.5, 76.1, 84.3, 93.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 127.6–128.6, 129.9 (C tert arom), 132.6, 137.5, 138.2, 145.0 (C quat arom), 169.4; 169.5 (C=O).

4.1.15. 1-*O*-Acetyl-3,4-di-*O*-benzyl-2,6-di-*O*-tosyl-α- and β-D-glucopyranose 16. To a solution of **15** (558 mg, 1.00 mmol) in pyridine (2 mL) and CH_2Cl_2 (4 mL) was added tosyl chloride (315 mg, 1.65 mmol). The mixture was refluxed for 72 h, then 2 N HCl (15 mL) was added. After extraction with EtOAc, the organic phase was washed with saturated aqueous $NaHCO_3$ then with brine, dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give **16** (171 mg, 0.241 mmol, 24% yield) as a colorless oil. The anomeric ratio calculated from ^{1}H NMR spectrum on $H_{1'}$ at 6.15 ppm, (α anomer) and 5.62 ppm (β anomer) was 1:3.9, respectively. 171 mg of unreacted **15** (β anomer) was recovered.

Compound **16**. $^{\beta}$Major anomer, $^{\alpha}$minor anomer. IR (NaCl film) $\nu_{C=O}$ 1737, 1767 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 733. ^{1}H NMR (400 MHz, $CDCl_3$): 2.06 (3H$^{\beta}$, s, CH_3), 2.09 (3H$^{\alpha}$, s, CH_3), 2.35 (3H$^{\beta}$, s, CH_3), 2.39 (3H$^{\alpha}$, s, CH_3), 2.42 (3H$^{\beta}$, s, CH_3), 2.43 (3H$^{\alpha}$, s, CH_3), 3.58–4.01 (m, 3H$^{\beta}$+3H$^{\alpha}$), 4.19–4.32 (2H$^{\beta}$+2H$^{\alpha}$, m), 4.43–4.52 (1H$^{\alpha}$+1H$^{\beta}$, m), 4.64–4.73 (3H$^{\beta}$+3H$^{\alpha}$, m), 4.74–4.80 (1H$^{\beta}$+1H$^{\alpha}$, m), 5.62 (1H$^{\beta}$, d, J=8.0 Hz, H_1), 6.15 (1H$^{\alpha}$, d, J=3.5 Hz, H_1), 7.10–7.40 (10H$^{\beta}$+10H$^{\alpha}$), 7.77 (2H$^{\beta}$+2H$^{\alpha}$, pt, J=8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 20.5, 20.7 (CH_3), 21.5, 21.6 (CH_3), 67.3, 67.5 ($C_{6'}$), 75.2, 75.5 (CH_2), 70.7, 73.5, 76.2, 76.3, 77.6, 79.2, 82.1, 89.1, 91.1 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 127.4–128.5, 129.7, 129.9 (C tert arom), 132.4, 132.5, 132.8, 134.0, 137.1, 137.4, 137.6, 144.8, 145.1, 145.4 (C quat arom), 168.3 (C=O).

4.1.16. 3,4-*O*-Benzyl-2,6-di-*O*-tosyl-α-D-glucopyranose 17. To a solution of **16** (170 mg, 0.24 mmol) in THF/MeOH (2 mL, 1:1) at 0 °C was added dropwise 1 M MeONa/MeOH (31 μL). The mixture was stirred at 0 °C for 2 h, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 7:3) affording **17** (106 mg, 0.158 mmol, 66% yield) as a colorless oil.

Compound **17**. IR (NaCl film), $\nu_{C=O}$ 1589, 1735 cm^{-1}, ν_{OH} 3500 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 691. ^{1}H NMR (400 MHz, $CDCl_3$): 2.26 (3H, s, CH_3), 2.31 (3H, s, CH_3), 3.40 (1H, t, J=9.5 Hz), 3.55 (1H, m), 3.89 (1H, t, J=9.5 Hz), 3.94 (1H, d, J=10.0 Hz), 4.06 (1H, dd, J_1=10.5 Hz, J_2=1.5 Hz), 4.13 (1H, dd, J_1=11.0 Hz, J_2=3.5 Hz), 4.21 (1H, dd, J_1=10.0 Hz, J_2=3.5 Hz), 4.32 (1H, d, J=10.5 Hz), 4.54 (2H, s), 4.61 (1H, d, J=10.5 Hz), 5.24 (1H, d, J=3.0 Hz, H_1), 6.97–7.23 (14H), 7.66 (4H, pt, J=10.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 21.6 (CH_3), 68.3 ($C_{6'}$), 75.1, 75.3 (CH_2), 68.4, 77.0, 78.8, 79.6, 90.8 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 127.4–128.5, 129.9 (C tert arom), 132.6, 133.0, 137.4, 137.8, 145.1 (2C) (C quat arom).

4.1.17. 1-Benzyloxymethyl-2,5-dihydro-3-[1-(3,4-di-*O*-benzyl-2,6-di-*O*-tosyl-β-D-glucopyranos-1-yl)-indol-3-yl]-4-[1-phenylsulfonyl-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 18. To a solution of **B** (41 mg, 0.070 mmol) in THF (4 mL) were added **17** (104 mg, 0.155 mmol) and triphenylphosphine (41 mg, 0.155 mmol). The mixture was

cooled to −78 °C then diisopropyl azodicarboxylate (DIAD) (30 μM, 0.155 mmol) was added dropwise. The mixture was allowed to reach room temperature then was stirred for 18 h. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2 then CH_2Cl_2/EtOAc 9:1) to give **18** (45 mg, 0.036 mmol, 52% yield) as a red solid.

Compound **18**. Mp 65–68 °C. IR (KBr) $\nu_{C=O}$ 1708, 1760 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 1261. ^1H NMR (400 MHz, $CDCl_3$): 2.02 (3H, s, CH_3), 2.19 (3H, s, CH_3), 3.68 (1H, m), 3.75–3.84 (2H, m), 4.05 (1H, dd, $J_1=11.0$ Hz, $J_2=2.0$ Hz), 4.17 (1H, dd, $J_1=11.0$ Hz, $J_2=4.0$ Hz), 4.53 (2H, t, $J=10.5$ Hz), 4.64 (1H, d, $J=11.0$ Hz), 4.67 (2H, s), 4.73 (1H, d, $J=10.5$ Hz), 5.10 (1H, m), 5.17 (2H, AB system, $J=11.0$ Hz, $\Delta\nu=5$ Hz), 5.37 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.34–6.42 (2H, m), 6.66 (2H, d, $J=8.0$ Hz), 6.71 (1H, dd, $J_1=8.0$ Hz, $J_2=5.0$ Hz), 6.94 (1H, dt, $J_1=7.0$ Hz, $J_2=1.5$ Hz), 7.03 (2H, d, $J=8.0$ Hz), 7.05–7.10 (2H, m), 7.11–7.29 (14H), 7.30–7.35 (3H, m), 7.42 (2H, t, $J=8.5$ Hz), 7.53 (1H, t, $J=7.5$ Hz), 7.63 (2H, d, $J=8.0$ Hz), 7.90 (1H, s), 8.07 (2H, dd, $J_1=8.5$ Hz, $J_2=1.5$ Hz), 8.10 (1H, s), 8.16 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 21.6 (CH_3), 67.4, 67.5 (CH_2), 71.8 ($C_{6'}$), 75.3, 75.5 (CH_2), 75.9, 76.6, 79.4, 82.9 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 119.4, 121.5, 123.2, 127.0–130.0, 131.4, 134.2, 145.5 (C tert arom), 106.9, 109.4, 121.2, 124.1, 126.0, 130.8, 132.1, 133.1, 135.6, 136.8, 137.4, 137.6, 138.0, 144.5, 145.1, 146.6 (C quat arom), 170.6 (C=O).

4.1.18. 1-Benzyloxymethyl-2,5-dihydro-3-[1-(3,4-di-*O*-benzyl-2,6-di-*O*-tosyl-β-D-glucopyranos-1-yl)-indol-3-yl]-4-[pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 19. To a solution of **18** (45 mg, 0.036 mmol) in THF (2 mL) was added a 1.1 M solution of tetrabutylammonium fluoride in THF (109 μL, 0.120 mmol). The mixture was stirred for 2.5 h at room temperature. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent CH_2Cl_2/EtOAc 4:1) to give **19** (33 mg, 0.030 mmol, 83% yield) as a red solid.

Compound **19**. Mp 105–107 °C. IR (KBr) $\nu_{C=O}$ 1708, 1764 cm^{-1}, ν_{NH} 3402 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1099, $[M+Na]^+$ 1121. ^1H NMR (400 MHz, $CDCl_3$): 2.01 (3H, s, CH_3), 2.18 (3H, s, CH_3), 3.68 (1H, m), 3.72–3.85 (2H, m), 4.11 (2H, br s), 4.50 (1H, d, $J=10.5$ Hz), 4.64 (2H, s), 4.68 (2H, s), 4.74 (1H, d, $J=10.5$ Hz), 5.13 (1H, t, $J=8.5$ Hz), 5.18 (2H, s), 5.37 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.60–6.70 (5H, m), 6.93 (1H, m), 7.02 (2H, d, $J=8.0$ Hz), 7.06–7.11 (2H, m), 7.13–7.28 (14H), 7.34 (2H, d, $J=7.5$ Hz), 7.43 (1H, d, $J=8.0$ Hz), 7.62 (2H, d, $J=8.0$ Hz), 7.78 (1H, s), 7.89 (1H, s), 8.03 (1H, br s), 11.57 (1H, br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 21.6 (CH_3), 67.3, 67.5 (CH_2), 71.7 ($C_{6'}$), 75.4 (2C) (CH_2), 75.8, 75.9, 76.7, 79.6, 83.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 116.9, 121.1, 122.1, 123.0, 127.0–130.0, 131.5, 143.0 (C tert arom), 105.5, 107.6, 119.0, 126.4, 127.0, 132.2, 133.1, 135.6, 136.9, 137.5, 137.7, 144.4, 144.5, 145.1, 148.3 (C quat arom), 171.3, 171.6 (C=O).

4.1.19. 12-(3,4-Di-*O*-benzyl-2,6-di-*O*-tosyl-β-D-glucopyranos-1-yl)-13*H*-2,5-dihydro-pyrido[3′,2′:4,5]pyrrolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-5,7-dione 20. To a solution of **19** (381 mg, 0.346 mmol) in benzene (300 mL) was added iodine (137 mg, 0.52 mmol). The mixture was irradiated for 1 h with a medium pressure mercury lamp (400 W). The solvent was removed, and the residue dissolved in EtOAc (250 mL) and washed with saturated aqueous sodium thiosulfate (50 mL) and then with brine. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent CH_2Cl_2/EtOAc 9:1) to give **20** (228 mg, 0.208 mmol, 60% yield) as a yellow solid.

Compound **20**. Mp 82–85 °C. IR (KBr) $\nu_{C=O}$ 1710, 1760 cm^{-1}, ν_{NH} 3300–3500 cm^{-1}. Mass (APCI+) $[M]^+$ 1097. ^1H NMR (400 MHz, $CDCl_3$): 1.99 (6H, s, CH_3), 3.84 (1H, t, $J=6.0$ Hz, $H_{4'}$), 4.19 (1H, t, $J=5.5$ Hz, $H_{3'}$), 4.28 (1H, m, $H_{5'}$), 4.34 (2H, d, $J=11.0$ Hz), 4.42 (1H, dd, $J_1=11.0$ Hz, $J_2=5.5$ Hz), 4.61 (1H, d, $J=11.5$ Hz), 4.70 (1H, d, $J=9.0$ Hz), 4.72 (2H, s), 5.06 (1H, dd, $J_1=9.0$ Hz, $J_2=4.5$ Hz), 5.15 (1H, d, $J=11.0$ Hz), 5.27 (2H, s), 6.04 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.19 (2H, d, $J=8.0$ Hz), 6.47 (2H, d, $J=7.5$ Hz), 6.69 (2H, d, $J=8.0$ Hz), 7.10–7.30 (19H, m), 7.50 (2H, d, $J=7.5$ Hz), 8.50 (1H, d, $J=4.5$ Hz), 8.99 (1H, d, $J=8.0$ Hz), 9.33 (1H, d, $J=8.0$ Hz), 10.07 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 21.1 (CH_3), 21.4 (CH_3), 66.9, 68.4, 71.7, 73.7, 74.0 (CH_2), 74.6, 78.6, 79.0, 79.6, 81.3 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.3, 117.6, 121.9, 125.7, 126.1, 127.0–129.0, 129.4, 133.7, 148.3 (C tert arom), 114.7, 116.4, 119.1, 119.9, 120.8, 121.7, 126.9, 131.1, 132.4, 136.4, 136.7, 137.6, 140.6, 144.5, 144.8, 152.7 (C quat arom), 169.2 (2 C=O).

4.1.20. 6-Benzyloxymethyl-5,7-dihydro-12,13-(6-azido-3,4-di*O*-benzyl-6-deoxy-β-D-mannopyranose-1,2-diyl)-pyrido[3′,2′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione 21. To a solution of **20** (12.5 mg, 0.011 mmol) in DMF (1 mL) was added NaN_3 (7.3 mg, 0.112 mmol). The mixture was stirred overnight at 70 °C. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent CH_2Cl_2 100% to CH_2Cl_2/EtOAc 9:1) to give **21** (7.5 mg, 0.0094 mmol, 82% yield) as a yellow solid.

Compound **21**. Mp 45–47 °C. IR (KBr) $\nu_{C=O}$ 1704, 1754 cm^{-1}, ν_{N3} 2100 cm^{-1}. Mass (ESI+) $[M+H]^+$ 796. ^1H NMR (400 MHz, $CDCl_3$): 3.62 (1H, dd, $J_1=13.0$ Hz, $J_2=6.0$ Hz, $H_{6'}$), 3.66 (1H, dd, $J_1=13.0$ Hz, $J_2=7.0$ Hz, $H_{6'}$), 3.79 (1H, m, $H_{4'}$), 3.76 (1H, m), 3.81 (1H, d, $J=13.0$ Hz), 3.87 (1H, d, $J=12.0$ Hz), 4.22 (1H, dd, $J_1=11.0$ Hz, $J_2=6.5$ Hz, $H_{5'}$), 4.53 (1H, d, $J=12.0$ Hz), 4.69 (1H, m, $H_{3'}$), 4.70 (1H, d, $J=11.5$ Hz), 4.78 (2H, s), 5.32 (2H, s), 5.69 (1H, dd, $J_1=5.5$ Hz, $J_2=3.5$ Hz, $H_{2'}$), 6.34 (1H, d, $J=6.0$ Hz, $H_{1'}$), 6.37 (2H, d, $J=7.5$ Hz), 6.87 (2H, t, $J=7.5$ Hz), 6.99 (1H, t, $J=7.5$ Hz), 7.20–7.50 (11H, m), 7.60 (1H, t, $J=7.5$ Hz), 7.94 (1H, d, $J=8.0$ Hz), 8.48 (1H, dd, $J_1=5.0$ Hz, $J_2=1.0$ Hz), 8.85 (1H, d, $J=8.0$ Hz), 8.99 (1H, dd, $J_1=7.5$ Hz, $J_2=0.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 52.5 ($C_{6'}$), 52.6, 73.0, 73.4, 75.0, 80.8 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 66.8, 71.5, 72.1, 72.5 (CH_2), 109.5, 114.4, 117.6, 120.3, 120.7, 124.7, 128.6, 135.9, 137.0, 137.8, 142.3, 151.7

(C quat arom), 113.0, 117.4, 122.5, 125.5, 127.7–128.9, 133.6, 146.7 (C tert arom), 169.6 (2 C=O).

4.1.21. 6-Hydroxymethyl-5,7-dihydro-12,13-(6-azido-6-deoxy-β-D-mannopyranos-1,2-diyl)-pyrido[3′,2′:4,5]-pyrrolo[2,3-*a*] pyrrolo[3,4-*c*]carbazole-5,7-dione 22. To a solution of **21** (96 mg, 0.120 mmol) in CH_2Cl_2 (6 mL) was added a solution of dimethyldioxirane in acetone (0.07–0.09 M, 60 mL) during 7 days. After removal of the solvent, the residue was purified by flash chromatography (eluent from cyclohexane/EtOAc 2:8 to EtOAc 100%) to give **22** (28.3 mg, 0.054 mmol, 45% yield).

Compound **22**. Mp 145–148 °C. IR (KBr) $\nu_{C=O}$ 1702, 1753 cm^{-1}, ν_{N3} 2100 cm^{-1}, ν_{OH} 3038–3653 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 3.15 (1H, dd, $J_1=13.5$ Hz, $J_2=6.0$ Hz, $H_{6'}$), 3.37 (1H, m, $H_{6'}$), 3.50 (1H, m, $H_{4'}$), 3.97 (1H, m, $H_{5'}$), 4.34 (1H, dt, $J_1=12.5$ Hz, $J_2=3.0$ Hz, $H_{3'}$), 4.90 (2H, m, CH_2OH), 5.32 (1H, d, $J=2.5$ Hz, $H_{2'}$), 5.76 (1H, d, $J=5.0$ Hz, $OH_{4'}$), 6.37 (1H, t, $J=7.0$ Hz, CH_2OH), 7.03 (1H, s, $H_{1'}$), 7.47 (1H, t, $J=8.0$ Hz), 7.57 (1H, dd, $J_1=8.0$ Hz, $J_2=5.0$ Hz), 7.70 (1H, dt, $J_1=8.5$ Hz, $J_2=1.0$ Hz), 7.98 (1H, d, $J=8.5$ Hz), 8.26 (1H, d, $J=12.0$ Hz, $OH_{3'}$), 8.57 (1H, d, $J=8.0$ Hz), 8.60 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 8.90 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 50.1 ($C_{6'}$), 59.6 (CH_2OH), 64.2, 67.4, 72.6, 78.8, 79.6 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.6, 113.6, 117.1, 120.2, 123.4, 129.5, 130.0, 139.1, 140.8, 151.5 (C quat arom), 111.7, 117.5, 122.2, 124.4, 127.7, 133.7, 144.9 (C tert arom), 168.3, 168.4 (2 C=O).

4.1.22. 12,13-(6-Azido-6-deoxy-β-D-mannopyranos-1,2-diyl)-6*H*-pyrido[3′,2′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7-dione 23. To a solution of **22** (28 mg, 0.053 mmol) in THF (6 mL) was added 28% aqueous NH_4OH (11 mL). The mixture was stirred for 5 h at room temperature. The solvent was removed and the residue was purified by flash chromatography (eluent EtOAc 100%) to give **23** (20 mg, 0.041 mmol, 77% yield) as a yellow solid.

Compound **23**. Mp >200 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1719, 1746 cm^{-1}, ν_{N3} 2100 cm^{-1}, $\nu_{NH,OH}$ 3138–3618 cm^{-1}. HRMS (ESI+) $[M+H]^+$, calcd for $C_{25}H_{18}N_7O_5$ 496.1369, found 496.1372. ^1H NMR (400 MHz, DMSO-d_6): 3.20 (1H, dd, $J_1=13.5$ Hz, $J_2=6.0$ Hz, $H_{6'}$), 3.40 (1H, dd, $J_1=13.5$ Hz, $J_2=2.0$ Hz, $H_{6'}$), 3.54 (1H, m, $H_{4'}$), 3.99 (1H, dt, $J_1=9.0$ Hz, $J_2=2.0$ Hz, $H_{5'}$), 4.31 (1H, dt, $J_1=13.0$ Hz, $J_2=3.0$ Hz, $H_{3'}$), 5.40 (1H, d, $J=2.5$ Hz, $H_{2'}$), 5.76 (1H, d, $J=5.0$ Hz, $OH_{4'}$), 7.05 (1H, s, $H_{1'}$), 7.53 (1H, dt, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 7.67 (1H, dd, $J_1=8.0$ Hz, $J_2=5.0$ Hz), 7.73 (1H, dt, $J_1=7.5$ Hz, $J_2=1.0$ Hz), 8.03 (1H, d, $J=8.0$ Hz), 8.33 (1H, d, $J=12.0$ Hz, $OH_{3'}$), 8.66–8.72 (2H, m), 9.08 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 11.25 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 50.2 ($C_{6'}$), 64.2, 67.5, 72.7, 78.8, 79.6 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.6, 113.6, 117.3, 121.1, 121.6, 123.5, 129.5, 130.0, 140.7, 151.6 (C quat arom), 111.7, 117.4, 122.1, 124.5, 127.5, 133.9, 144.7 (C tert arom), 170.5 (2 C=O).

4.1.23. 1-Benzyloxymethyl-3-(1-phenylsulfonyl-1*H*-indol-3-yl)-4-[1-(2-*O*-tosyl-3,4,6-tri-*O*-benzyl-β-D-gluco-pyranos-1-yl)-pyrrolo[2,3-*b*]pyridin-3-yl]-2,5-dihydro-pyrrole-2,5-dione 24. To a solution of **F** (200 mg, 0.341 mmol) in THF (18 mL) were added **6** (459 mg, 0.76 mmol) and triphenylphosphine (199 mg, 0.76 mmol). The mixture was cooled to −78 °C then diisopropyl azodicarboxylate (DIAD) (147 μM, 0.76 mmol) was added dropwise. The mixture was allowed to reach room temperature then was stirred for 18 h. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent CH_2Cl_2/EtOAc 9:1) to give **24** as the major product of the reaction (190 mg, 0.161 mmol, 47% yield) as a red solid.

Compound **24**. Mp 80–82 °C. IR (KBr), $\nu_{C=O}$ 1711 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1175. ^1H NMR (400 MHz, $CDCl_3$): 2.13 (3H, s, CH_3), 3.69–3.80 (2H, m), 3.77 (1H, d, $J=9.5$ Hz), 3.91–3.99 (2H, m), 4.55 (1H, d, $J=12.0$ Hz), 4.62 (1H, d, $J=10.5$ Hz), 4.63 (1H, d, $J=12.5$ Hz), 4.65 (1H, d, $J=12.5$ Hz), 4.75 (1H, d, $J=13.5$ Hz), 4.76 (2H, s), 4.80 (1H, d, $J=10.5$ Hz), 5.20 (1H, m, $H_{2'}$), 5.27 (2H, s), 6.19 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.34 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 6.65 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 6.75 (2H, d, $J=8.0$ Hz), 6.84 (1H, t, $J=7.5$ Hz), 7.02 (1H, d, $J=8.0$ Hz), 7.07–7.13 (2H, m), 7.16 (1H, t, $J=8.0$ Hz), 7.21–7.40 (18H), 7.42 (2H, d, $J=7.5$ Hz), 7.51 (2H, t, $J=8.0$ Hz), 7.63 (1H, t, $J=7.5$ Hz), 7.95–8.01 (3H, m), 8.06 (1H, d, $J=1.5$ Hz), 8.08 (1H, s), 8.34 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 67.5, 68.2, 71.9, 73.5, 75.3, 75.4 ($C_{6'}+5CH_2$), 77.7, 78.2, 80.5, 83.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 113.5, 117.2, 122.5, 124.0, 125.3, 127.0–128.6, 128.7, 129.5, 129.7, 130.5, 134.2, 143.7 (C tert arom), 105.8, 112.4, 118.6, 124.7, 130.8, 133.5, 134.4, 137.5, 137.7, 137.9, 144.2, 147.8 (C quat arom), 170.5 (2C, C=O).

4.1.24. 1-Benzyloxymethyl-3-(1*H*-indol-3-yl)-4-[1-(2-*O*-tosyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo[2,3-*b*]pyridin-3-yl]-2,5-dihydro-pyrrole-2,5-dione 25. To a solution of **24** (160 mg, 0.136 mmol) in THF (5 mL) was added a 1.1 M solution of tetrabutylammonium fluoride in THF (409 μL, 0.448 mmol). The mixture was stirred for 2.5 h at room temperature. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent from CH_2Cl_2 100% to CH_2Cl_2/EtOAc 9:1) to give **25** (90 mg, 0.087 mmol, 64% yield) as a red solid.

Compound **25**. Mp 38–40 °C. IR (KBr) $\nu_{C=O}$ 1706, 1743 cm^{-1}, ν_{NH} 3163–3608 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1035. ^1H NMR (400 MHz, $CDCl_3$): 2.13 (3H, s, CH_3), 3.67 (1H, d, $J=10.0$ Hz), 3.72–3.80 (2H, m), 3.92 (1H, t, $J=9.0$ Hz), 3.97 (1H, t, $J=9.0$ Hz), 4.47 (1H, d, $J=12.0$ Hz), 4.55 (1H, d, $J=12.0$ Hz), 4.62 (1H, d, $J=11.0$ Hz), 4.80 (3H, s+m), 4.82 (1H, d, $J=10.5$ Hz), 5.00 (1H, m), 5.27 (3H, s+m), 6.17 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.45 (1H, br s), 6.67 (1H, dd, $J_1=7.5$ Hz, $J_2=4.5$ Hz), 6.72 (2H, d, $J=8.0$ Hz), 6.82 (1H, t, $J=8.0$ Hz), 7.00–7.40 (23H), 7.44 (2H, d, $J=7.5$ Hz), 7.71 (1H, d, $J=2.0$ Hz), 8.08 (2H, s), 8.88 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 22.0 (CH_3), 67.3, 68.3, 71.7, 73.5, 75.3, 75.5 ($C_{6'}+5CH_2$), 70.1, 77.7, 78.1, 80.7, 83.1 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 111.4, 116.9, 121.1, 122.1, 122.8, 126.8–129.1, 129.7, 130.5, 143.4 (C tert arom), 106.5, 106.6, 118.9, 125.3, 126.2, 133.5, 135.9,

137.6, 137.7, 137.8, 138.0, 143.9, 147.7 (C quat arom), 171.2, 171.5 (C=O).

4.1.25. 6-Benzyloxymethyl-13-(2-*O*-tosyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranos-1-yl)-5,7-dihydro-12*H*-pyrido[3′,2′:4,5]pyrrolo[3,2-*a*]-pyrrolo[3,4-*c*]carbazole-5,7-dione 26. To a solution of **25** (54 mg, 0.052 mmol) in DMF (2 mL) was added $Pd(OTf)_2$ (52 mg, 0.158 mmol). The mixture was stirred at 90 °C for 5 h. EtOAc was added, then 0.5 N HCl (10 mL). After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent from cyclohexane/CH_2Cl_2 3:7 to CH_2Cl_2 100%) to give **26** (30 mg, 0.029 mmol, 56% yield) as a yellow solid.

Compound **26**. Mp 147–149 °C. IR (KBr) $\nu_{C=O}$ 1710, 1760 cm^{-1}, ν_{NH} 3200–3600 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 1055. ^1H NMR (400 MHz, $CDCl_3$): 2.02 (3H, s, CH_3), 3.55 (1H, d, $J=10.0$ Hz), 3.75 (1H, d, $J=10.5$ Hz), 3.84 (1H, d, $J=10.0$ Hz), 3.96 (1H, t, $J=8.5$ Hz), 4.26 (1H, d, $J=9.5$ Hz), 4.31 (1H, d, $J=11.0$ Hz), 4.46 (2H, t, $J=12.0$ Hz), 4.58 (1H, d, $J=10.0$ Hz), 4.62 (2H, s), 4.81 (1H, d, $J=10.0$ Hz), 4.83 (1H, d, $J=10.5$ Hz), 5.05 (1H, dt, $J_1=9.0$ Hz, $J_2=1.0$ Hz), 5.18 (2H, s), 6.35 (2H, d, $J=8.0$ Hz), 6.41 (2H, d, $J=7.5$ Hz), 6.67 (1H, dd, $J_1=9.5$ Hz, $J_2=1.0$ Hz), 6.95–7.30 (25H), 8.28 (1H, d, $J=5.0$ Hz), 9.03 (1H, d, $J=8.0$ Hz), 9.06 (1H, d, $J=8.0$ Hz), 10.31 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 66.6, 67.0, 71.7, 74.2, 75.6, 76.5 (CH_2), 76.4, 77.9, 79.7, 80.4, 83.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 112.0, 117.7, 121.6, 125.7, 126.1 (2C), 127.5–129.0, 134.0, 146.8 (C tert arom), 115.2, 116.3, 119.3, 120.3, 121.0, 122.6, 127.0, 130.1, 133.0, 136.6, 137.3, 137.6, 137.8, 141.8, 144.3, 151.4 (C quat arom), 169.3, 169.4 (C=O).

4.1.26. 6-Benzyloxymethyl-5,7-dihydro-13,12-(3,4,6-tri-*O*-benzyl-β-D-mannopyranose-1,2-diyl)-pyrido[3′,2′:4,5]pyrrolo[2,3-*a*] pyrrolo[3,4-*c*]carbazole-5,7-dione 27. To a solution of **26** (15 mg, 0.0145 mmol) in DMF (1 mL) was added NaN_3 (10 mg, 0.154 mmol). The mixture was stirred overnight at 70 °C. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 4:1 then CH_2Cl_2/EtOAc 9:1) to give **27** (11.6 mg, 0.0137 mmol, 93% yield) as a yellow solid.

Compound **27**. Mp 59–61 °C. IR (KBr) $\nu_{C=O}$ 1700, 1750 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 883. ^1H NMR (400 MHz, $CDCl_3$): 3.34 (1H, dd, $J_1=10.0$ Hz, $J_2=4.0$ Hz), 3.47 (1H, dd, $J_1=11.0$ Hz, $J_2=2.5$ Hz, $H_{6'}$), 3.58 (1H, dd, $J_1=11.5$ Hz, $J_2=4.0$ Hz, $H_{6'}$), 3.95 (1H, m, $H_{5'}$), 3.97 (2H, s), 4.11 (1H, t, $J=8.5$ Hz, $H_{4'}$), 4.30 (1H, dd, $J_1=9.0$ Hz, $J_2=3.0$ Hz, $H_{3'}$), 4.56 (1H, d, $J=11.0$ Hz), 4.65 (2H, s), 4.74 (2H, s), 4.84 (1H, d, $J=11.0$ Hz), 5.08 (1H, s, $H_{2'}$), 5.11 (1H, d, $J=3.5$ Hz), 6.41 (1H, s, $H_{1'}$), 6.64 (2H, d, $J=8.0$ Hz), 6.91 (2H, t, $J=7.5$ Hz), 7.02 (1H, t, $J=7.5$ Hz), 7.12 (1H, t, $J=7.5$ Hz), 7.15–7.35 (15H, m), 7.40 (1H, t, $J=8.0$ Hz), 7.47 (1H, t, $J=8.0$ Hz), 8.43–8.48 (2H, m), 8.88 (1H, d, $J=7.5$ Hz), 8.91 (1H, d, $J=6.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 60.5, 73.1, 78.6, 80.0, 80.5 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 66.7, 68.2, 71.5, 73.1, 73.3, 75.0 (CH_2), 114.5, 118.2, 122.0, 125.8, 127.4–129.4, 133.7, 146.8 (C tert arom), 111.0, 115.2, 120.3, 120.9, 124.5, 129.2, 131.3, 136.6, 137.7, 142.9, 151.8 (C quat arom), 169.3, 169.4 (C=O).

4.1.27. 5,7-Dihydro-13,12-(β-D-mannopyranose-1,2-diyl)-6*H*-pyrido[3′,2′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7-dione 28. To a suspension of **27** (135 mg, 0.157 mmol) in CH_2Cl_2 (18 mL) at −78 °C was added a 1 M solution of BBr_3 in CH_2Cl_2 (3.16 mL). The mixture was stirred at −78 °C for 30 min, then it was allowed to reach room temperature. After extraction with EtOAc, the organic phase was dried over $MgSO_4$ and the solvent was removed. The residue was dried under vacuum for 1 h. To a solution of the residue (56 mg) in THF (6 mL) was added 28% aqueous NH_4OH (12 mL). The mixture was stirred overnight at room temperature. The solvent was removed and the residue was purified by flash chromatography (eluent from EtOAc 100% to EtOAc/MeOH 95:5) to give **28** (20 mg, 0.0425 mmol, 27% yield) as a yellow solid.

Compound **28**. Mp >300 °C. IR (KBr) $\nu_{C=O}$ 1703, 1747 cm^{-1}, $\nu_{NH,OH}$ 3038–3619 cm^{-1}. Mass (ESI+) $[M+H]^+$ 471. HRMS (FAB+) $[M+H]^+$, calcd for $C_{25}H_{18}N_4O_6$ 471.1304, found 471.1291. ^1H NMR (400 MHz, DMSO-d_6): 3.30 (1H, dd, $J_1=12.5$ Hz, $J_2=5.5$ Hz, $H_{6'}$), 3.55 (1H, dd, $J_1=12.5$ Hz, $J_2=1.5$ Hz, $H_{6'}$), 3.70 (1H, d, $J=9.5$ Hz, $H_{5'}$), 3.76 (1H, m, $H_{4'}$), 4.43 (1H, t, $J=5.5$ Hz, $OH_{6'}$), 4.58 (1H, m, $H_{3'}$), 5.16 (1H, d, $J=2.0$ Hz, $H_{2'}$), 5.60 (1H, br s, $OH_{4'}$), 6.74 (1H, d, $J=4.0$ Hz, $OH_{3'}$), 6.90 (1H, s, $H_{1'}$), 7.47 (1H, t, $J=7.5$ Hz), 7.60 (1H, dd, $J_1=8.0$ Hz, $J_2=5.0$ Hz), 7.64 (1H, dt, $J_1=7.0$ Hz, $J_2=1.5$ Hz), 8.68 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 8.84 (1H, d, $J=8.0$ Hz), 8.94 (1H, dd, $J_1=7.5$ Hz, $J_2=1.5$ Hz), 9.08 (1H, d, $J=8.5$ Hz), 11.17 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 60.2 ($C_{6'}$), 64.3, 65.8, 72.3, 79.5, 80.9 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.3, 113.6, 117.0, 120.9, 121.4, 123.4, 129.1, 131.1, 143.0, 151.0 (C quat arom), 116.4, 118.0, 121.0, 124.2, 127.0, 132.6, 146.7 (C tert arom), 170.7, 171.0 (2 C=O).

References and notes

1. Bush, J. A.; Long, B. H.; Catino, J. J.; Bradner, W. T.; Tomita, K. *J. Antibiot.* **1987**, *40*, 668–678.
2. Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397–402.
3. Matson, J. A.; Claridge, C.; Bush, J. A.; Titus, J.; Bradner, W. T.; Doyle, T. W.; Horan, A. C.; Patel, M. *J. Antibiot.* **1989**, *42*, 1547–1555.
4. Takahashi, I.; Kobayashi, E.; Asano, K.; Yoshida, M.; Nakano, H. *J. Antibiot.* **1987**, *40*, 1782–1784.
5. Rodrigues Pereira, E.; Belin, L.; Sancelme, M.; Prudhomme, M.; Ollier, M.; Rapp, M.; Sevère, D.; Riou, J-F. ; Fabbro, D.; Meyer, T. *J. Med. Chem.* **1996**, *39*, 4471.
6. Moreau, P.; Gaillard, N.; Marminon, C.; Anizon, F.; Dias, N.; Baldeyrou, B.; Bailly, C.; Pierré, A.; Hickman, J.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Bioorg. Med. Chem.* **2003**, *11*, 4871.

7. Prudhomme, M. *Curr. Pharm. Des.* **1997**, *3*, 265–290.
8. Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Renard, P.; Prudhomme, M. *Bioorg. Med. Chem.* **2003**, *11*, 679–687.
9. Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Joubert, A.; Bailly, C.; Renard, P.; Hickman, J.; Prudhomme, M. *J. Med. Chem.* **2003**, *46*, 609–622.
10. Anizon, F.; Moreau, P.; Sancelme, M.; Voldoire, A.; Prudhomme, M.; Ollier, M.; Sevère, D.; Riou, J-F. ; Bailly, C.; Fabbro, D.; Meyer, T.; Aubertin, A-M. *Bioorg. Med. Chem.* **1998**, *6*, 1597–1604.
11. Marminon, C.; Anizon, F.; Moreau, P.; Léonce, S.; Pierré, A.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *J. Med. Chem.* **2002**, *45*, 1330–1339.
12. Messaoudi, S.; Anizon, F.; Pfeiffer, B.; Golsteyn, R.; Prudhomme, M. *Tetrahedron Lett.* **2004**, *45*, 4643–4647.
13. Gray, N.; Détivaud, L.; Doerig, C.; Meijer, L. *Curr. Med. Chem.* **1999**, *6*, 859–875.
14. Zhao, B.; Bower, M. J.; McDewitt, P. J.; Zhao, H.; Davis, S. T.; Johanson, K. O.; Green, S. M.; Concha, N. O.; Zhou, B. B. *J. Biol. Chem.* **2002**, *277*, 46609–46615.
15. Anizon, F.; Moreau, P.; Sancelme, M.; Laine, W.; Bailly, C.; Prudhomme, M. *Bioorg. Med. Chem.* **2003**, *11*, 3709–3722.
16. Prudhomme, M. *Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4*, 509–521.
17. Bovin, N. V.; Zurabyan, S. E.; Khorlin, A. Y. *Carbohydr. Res.* **1981**, *98*, 25–35.
18. Timer, C. M.; van Straten, N. C. R.; van der Marel, G. A.; van Boom, J. H. *J. Carbohydr. Chem.* **1998**, *17*, 471–487.
19. Takahashi, T.; Ebata, S.; Yamada, H. *Synlett* **1998**, 381–382.
20. Routier, S.; Ayerbe, N.; Mérour, J.-Y.; Coudert, G.; Bailly, C.; Pierré, A.; Pfeiffer, B.; Caignard, D.-H.; Renard, P. *Tetrahedron* **2002**, *58*, 6621–6630.
21. Alonso, R. A.; Vite, G. D.; McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 573–584.
22. Marples, B. A.; Muxworthy, J. P.; Baggaley, K. H. *Synlett* **1992**, 646.
23. Csuk, R.; Dörr, P. *Tetrahedron* **1994**, *50*, 9983–9988.
24. Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1999**, *64*, 2465–2470.