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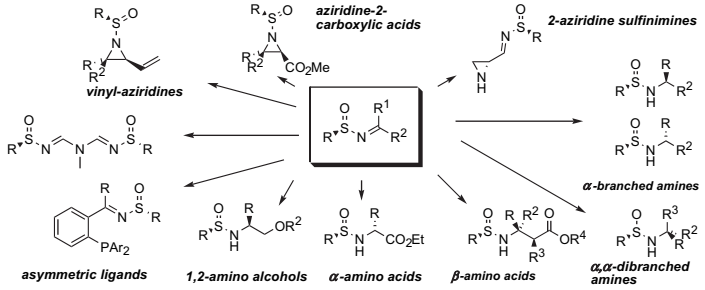
Contents

REPORT



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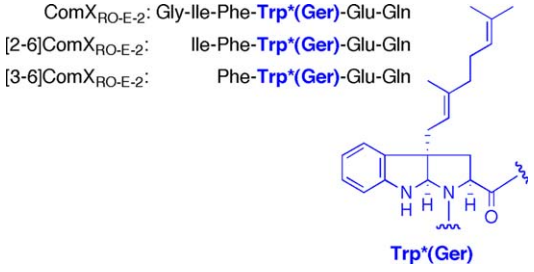
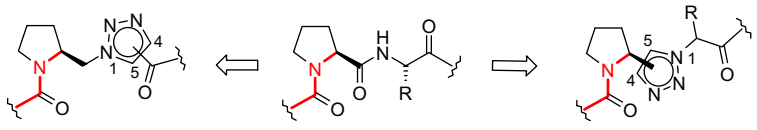
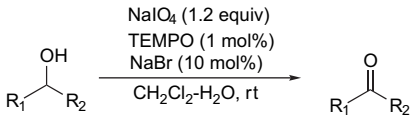
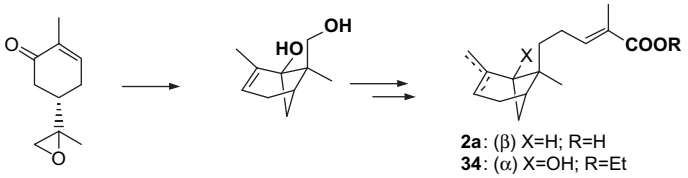
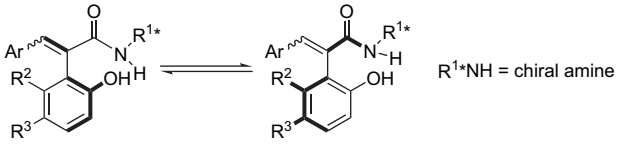
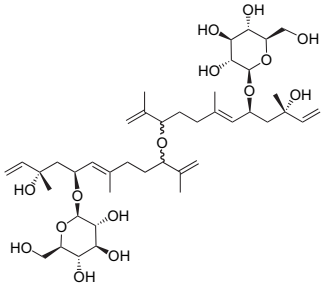


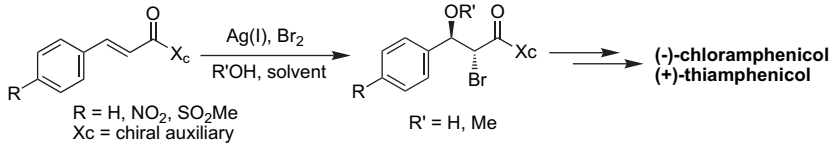


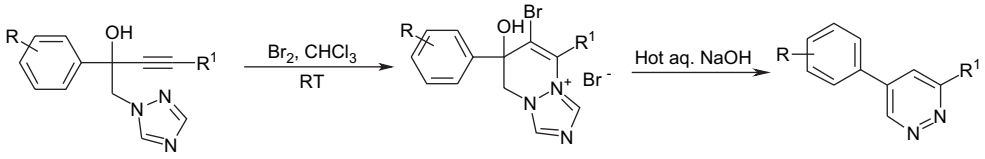


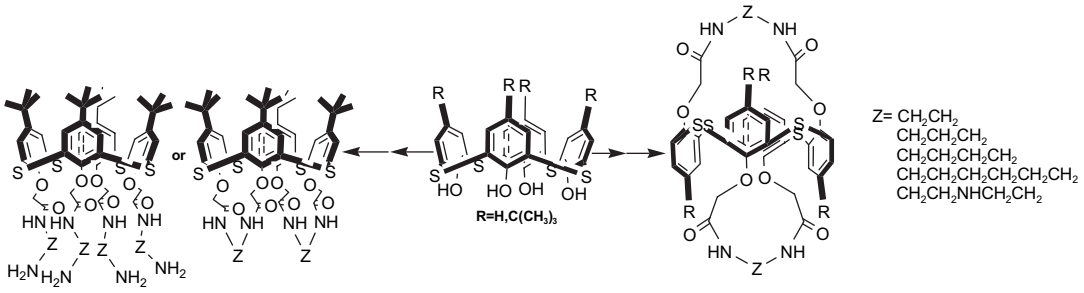


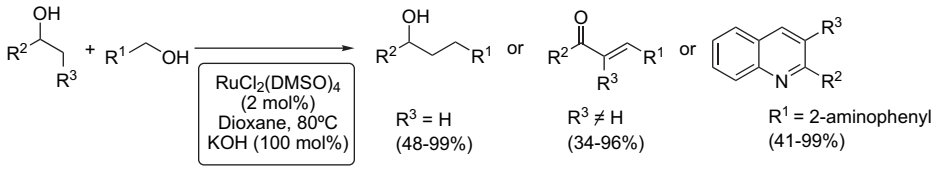


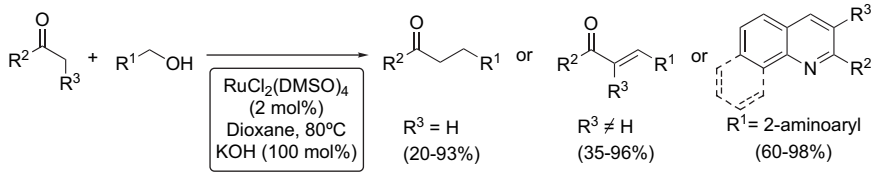


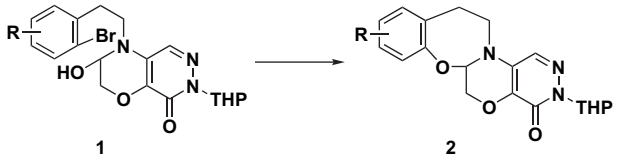


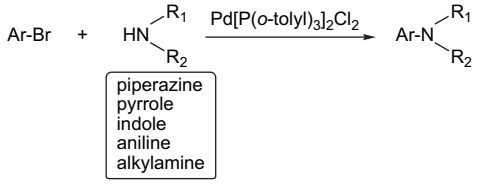


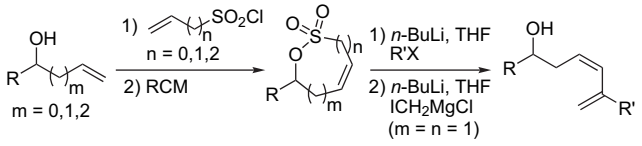


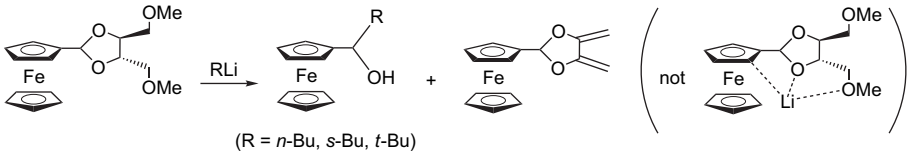


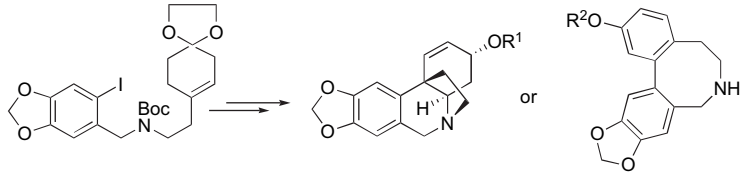


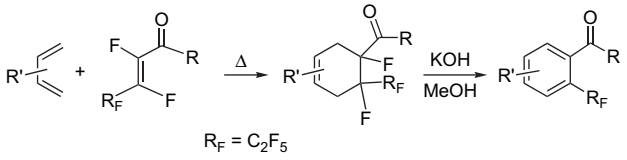


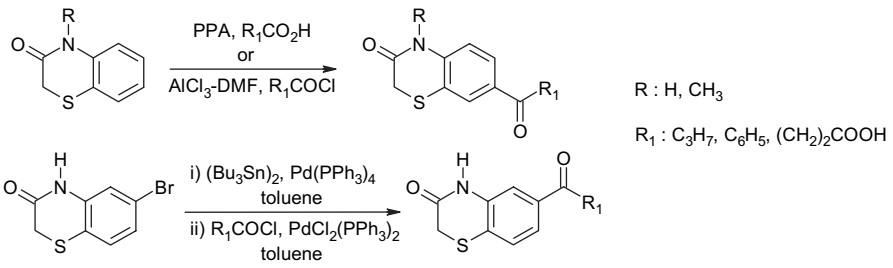


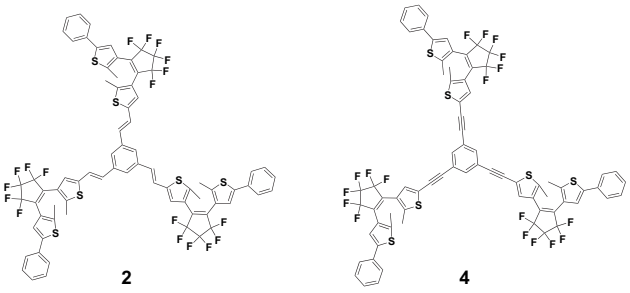


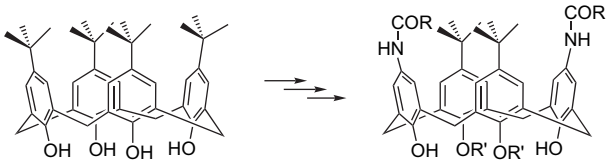




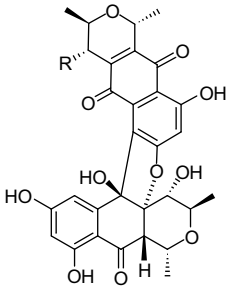








Functionalisation of calix[4]arene was carried out such that metal complexation could occur at both the wide and narrow rims, a rare occurrence in calixarene chemistry.



uroleuconaphin A_1 (**1**): R = H
uroleuconaphin B_1 (**2**): R = OH

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Prolyl *cis/trans* isomerisation plays a crucial role in various biological processes. Employing a divergent synthetic pathway, four different subtypes of triazolopeptides were obtained and examined by means of NMR and IR spectroscopy. Depending on the orientation and the mode of insertion of the triazole moiety, the building blocks allow a gradual adjustment of the prolyl *cis/trans* ratio, thus offering a molecular toolkit for peptide mimetic research. *Tetrahedron* **2006**, *62*, 8919–8927.

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Chiral non-racemic sulfinimines: versatile reagents for asymmetric synthesis

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Contents

1. Introduction

Amines represent one of the nature's key functionalities. Their incorporation into a wide variety of motifs, from drugs and biologically active molecules to ligands for asymmetric catalysis, underlines their importance to modern chemistry. Despite their abundance in both natural and un-natural systems, however, methods for the preparation of chiral amines can often be difficult. This deficiency in synthetic methodology has been efficiently addressed in recent years through the emergence of enantiopure sulfoxide *N*-protecting groups, versatile substituents that can be incorporated into a wide range of imines and influence the stereochemistry of a variety of reactions, introducing high levels of stereocontrol.

While it is recognised that 1,2-nucleophilic additions to imine double bonds represent one of the most flexible approaches to amines and, more specifically chiral amines, N-substitution is generally required to domesticate the capricious nature of the imines. This has prompted the development of electronically and structurally diverse *N*-substituents. To be effective tools for the synthetic chemist, these substituents are required to be inexpensive and easy to synthesise, to provide direct preparation of stable imines from a broad spectrum of aldehyde and ketone precursors, to

Keywords: Sulfinimine; Sulfinyl imine; Imine; Amine; Asymmetric; Amino acids; Amino alcohols; Aziridines.
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furnish activation of the imine double bond for nucleophilic attack, to ideally act as a chiral directing group and finally, once their role is complete, to be amenable to facile removal.

2. Background

N-Sulfinyl-imines (sulfinimines) represent an exceptional class of imines.[1] Their widespread application since their inception has led to the development of an array of chiral sulfinyl motifs, offering the opportunity to fine-tune the reactivity of the sulfinimines towards specific requirements (Fig. 1).

Sulfinimines, albeit in racemic form, were first introduced over 30 years ago with the synthesis of *p*-toluene-sulfinimines (*p*-TS-imines, **1**), through the oxidation of *p*-toluene-sulfenimines with *m*-CPBA, by Davis and co-workers.[2] The first synthesis of enantiomerically pure *p*-TS-imines was accomplished by Cinquini et al. in 1982 via reaction of metal ketimines with the Andersen reagent **7** (Scheme 1).[3] Applications of this budding class of chiral *N*-substituent were, however, slow to emerge, primarily due to the difficulty associated with their preparation. New methods were developed to overcome this hurdle, and their application began to spread. This new-found interest prompted investigations into varying the structural and electronic chemistry of the sulfoxide. Garcia Ruano et al. recognised that substitution of the *p*-toluene motif with a *tert*-butyl group significantly increased the stereoinduction observed in the aziridination of sulfinimines.[4] This substitution was perceived to also infer a subtle alteration in the electronic chemistry of the species, specifically with respect to interactions with Grignard reagents. At the time of this work, however, the synthesis of *tert*-butyl-sulfinimines (*t*-BS-imines, **2**) was not straightforward.

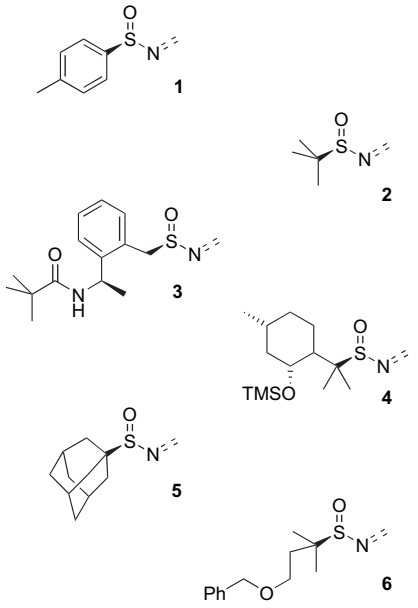
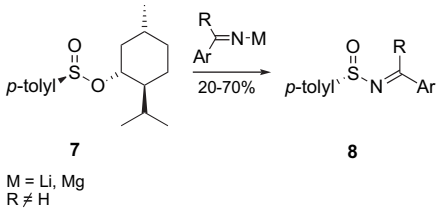


Figure 1.



Scheme 1.

It was in the mid-1990s that sulfinimine chemistry really blossomed; *p*-TS-imines were becoming recognised as valuable chiral ammonium synthons, and a novel direct entry into the *t*-BS-imines was developed. During their efforts to develop a new linker for solid-phase synthesis, Ellman et al. recognised a potential route for accessing *t*-BS-imines and subsequently reported the straightforward synthesis of *tert*-butyl-sulfinamide (*t*-BSA),[5] condensation of which with aldehydes and ketones provided direct entry to a broad range of *t*-BS-aldimines and *t*-BS-ketimines,[6] circumventing many of the problems previously associated with the preparation of sulfinimines.

At around the same time, other groups were investigating modifications of this concept. Wills et al. reported the synthesis of a recyclable chiral sulfinyl *N*-substituent, **3**, recycling of the chiral motif combined with the high stereocontrol induced making it particularly attractive.[7] Kawecki et al., emerging from a series of investigations focused on the interactions of sulfoxides with Lewis acids, described the development, generation and application of a novel chiral sulfoxide **4**.[8] Senanyake et al. have in the past three years developed an extremely facile entry to a broad, diverse range of chiral sulfoxides, each with individual, distinct chemical features (**5**, **6**).[9] In spite of these advances, however, the *p*-TS- and *t*-BS-imines remain the most popular substrates and have been applied in a panoply of asymmetric reactions. This work seeks to provide a general overview of the role of chiral sulfinimines in asymmetric synthesis, providing a taste for the chronological trends exhibited by these chiral synthons up until January 2006.

3. Synthesis of chiral sulfinimines

For any motif to be truly valuable as a synthetic tool, it is vital for it to be readily available. To this end, there has been a strong focus on the development of efficient routes for the direct, inexpensive synthesis of chiral sulfinimines. Examination of the chiral sulfinimine reveals three obvious disconnections, asymmetric oxidation, iminolysis of sulfinate esters and condensation of a sulfinamide with aldehydes and ketones (Fig. 2).

Each of these synthetic routes has been explored towards the development of an efficient synthesis of chiral sulfinimines.

3.1. Iminolysis

While the first sulfinimines were prepared by Davis et al.[2] it was Cinquini and co-workers who accomplished the first

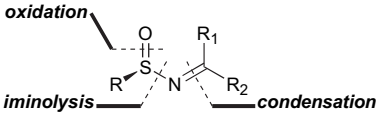
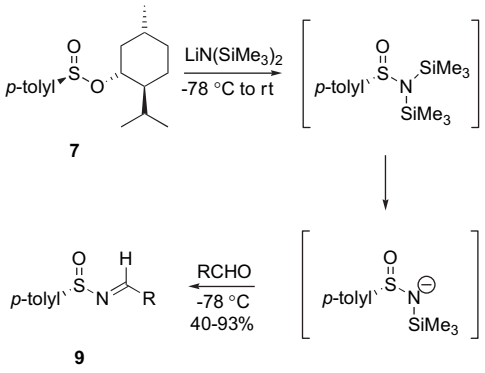


Figure 2.

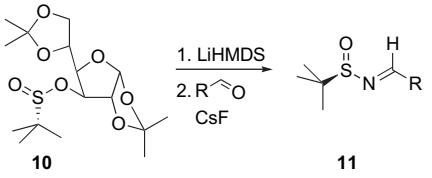
asymmetric synthesis of these chiral synthons.[3] Reaction of metal ketimines with the Andersen reagent **7** furnished a variety of sulfinimines **8** in 20–70% yield and high enantiopurity (Scheme 1).

While this methodology provided access to chiral sulfinimines, the scope of the reaction was severely limited, with only aromatic metallo-ketimines being suitable reagents, and the more sensitive aromatic and aliphatic aldehydes were precluded. In order to address this issue and expand the scope of accessible sulfinimines, Davis et al. developed a one-pot synthesis of sulfinimines from **7**, for the first time providing an efficient entry (40–93% yield, and >96% ee) to sulfinimines **9** derived from both aliphatic and aromatic aldehydes (Scheme 2).[10]



Scheme 2.

Exploiting the stereodirecting influence of the diacetone-D-glucose (DAG) developed by Alcudia et al.,[11] it is possible to prepare enantiomerically pure *t*-BS-imines (Scheme 3).[12] Both enantiomers of *S*-alkyl sulfinate ester **10** are accessible through judicious choice of conditions, subsequent fluoride-promoted condensation with both aldehydes and ketones revealing access to a range of *t*-BS-imines **11**.



Scheme 3.

More recently, Wills et al. have described the iminolysis of the recyclable chiral cyclic sulfinamide **12**.[7] Addition of metallo-imines to cyclic sulfinamide **12** resulted in the clean formation of aromatic sulfin-ketimines **13**. Subsequent removal of the sulfinyl group gave chiral amines **14** and chiral sulfinic acid **15**, which could be regenerated to the chiral cyclic sulfinamide **12** (Scheme 4). Many of the constraints associated with previous iminolysis methodologies were, however apparent, with only ketimines being suitable addition substrates and more sensitive, enolisable structures being precluded.

While the iminolysis of sulfinate esters provides access to a wide range of enantiopure sulfinimines, there are, unfortunately, a number of problems associated with this chemistry. The primary consideration is a practical one, isolation of the enantiomerically pure sulfinimines from the complex mixture of reagents and chiral auxiliaries employed prohibiting large-scale preparation using either Andersen's reagent or the DAG methodology.

3.2. Oxidation

Possibly the most rational approach to chiral sulfinimines **17** is through the asymmetric oxidation of sulfenimines **16**. There are two distinct methods for the introduction of asymmetry into the oxidation process (Fig. 3). One strategy is through the introduction of a stereo-inducing chiral centre into the sulfenimine, and thus an achiral oxidant can be employed. The alternative technique is to use a chiral oxidant, introducing asymmetry into achiral sulfenimines.

The first efficient chemo- and enantioselective oxidation of sulfenimines **18** was described by Davis et al. in 1992. Chiral *N*-sulfonyloxaziridines **20** were used as chiral oxidants to prepare both *R*- and *S*-sulfinimines **19** in 72–95% yield and 88–90% ee (Scheme 5).[13]

Davis demonstrated the generality of this procedure through the oxidation of a range of achiral sulfenimines. The

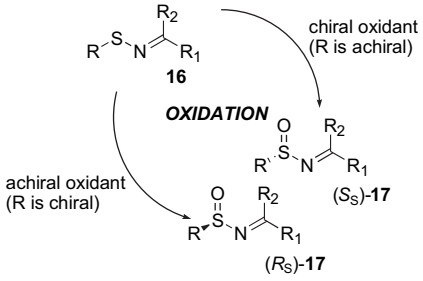
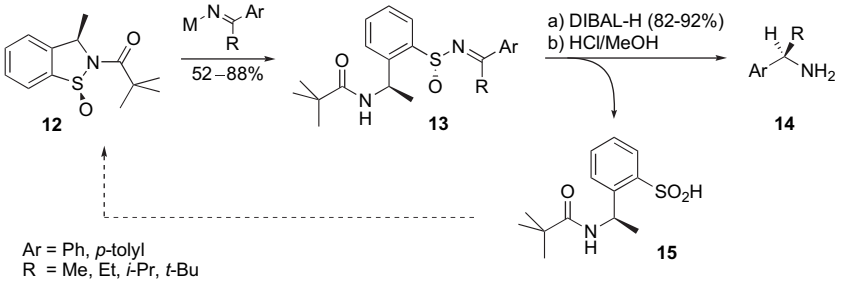
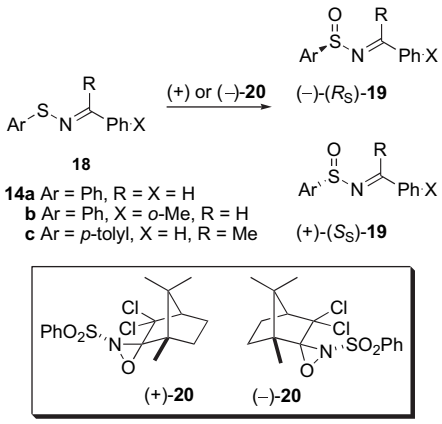


Figure 3.



Scheme 4.



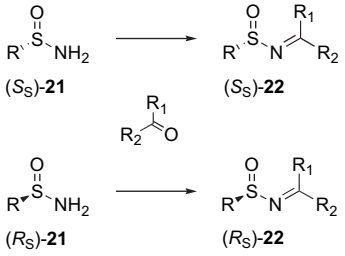
Scheme 5.

alternative approach, the diastereomeric oxidation of chiral, non-racemic sulfenimines, has also been reported.[14]

While asymmetric oxidation was found to provide access to a range of chiral sulfinimines in high ees, their application was limited, primarily due to the difficulty associated with the preparation of chiral *N*-sulfonyloxaziridines or the chiral sulfenimine starting materials.

3.3. Condensation

The most common and versatile method for the preparation of generic imines is through the condensation of an aldehyde or ketone with an amine, providing access to a diverse range of substituted imines. Thus, the obvious progression for the preparation of chiral sulfinimines **22** was the synthesis of chiral sulfinamides **21**, substrates for condensation with aldehydes and ketones (Scheme 6).

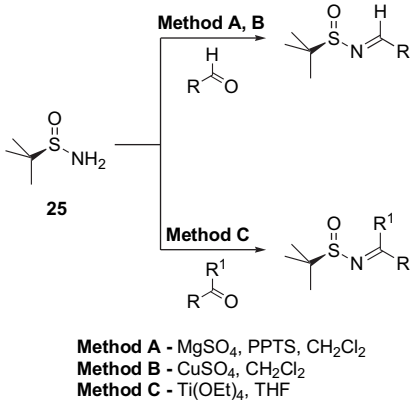


Scheme 6.

The first non-racemic sulfinamide was synthesised by Davis et al. in 1997. Isolated as a side product of their one-pot procedure for the direct preparation of chiral sulfinimines, *p*-toluene-sulfinamide (*p*-TSA) was found to condense with *p*-nitrobenzaldehyde in the presence of CsF. Other less reactive aldehydes were, however, found not to react with *p*-TSA, and it therefore appeared that the reaction was applicable to only a narrow range of substrates.

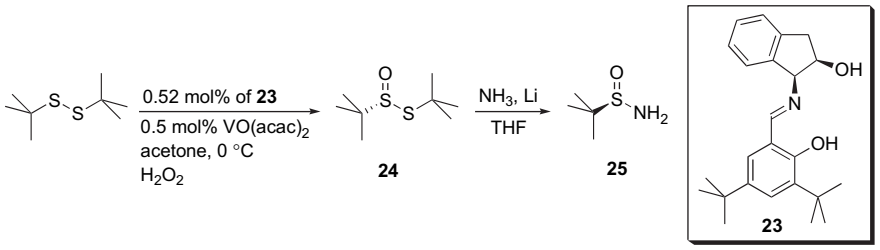
In the same year, Ellman et al. described the preparation and reaction of *t*-BSA **25**. The enantiomerically pure sulfinamide was synthesised through the reaction of lithium amide with chiral *tert*-butanethiosulfinate **24** (Scheme 7).

Although the initial procedure for acquiring the optically active *tert*-butanethiosulfinate **24** was found not to be amenable to large-scale preparation, subsequent investigations using the chiral ligand **23** have furnished conditions that allow the preparation of both enantiomers on the multi-kilogram scale in 68% overall yield and >99% ee.[15] Ellman's focus then switched to the condensation reaction between *t*-BSA and aldehydes and ketones (Scheme 8).[16] Direct condensation of *t*-BSA with aldehydes in the presence of $MgSO_4$ and PPTS provided both aromatic and aliphatic *t*-BS-imines in high yield (84–96%), with no sign of racemisation (Method A, Scheme 8). Under these conditions, however, large excesses of aldehydes were required, especially with unreactive substrates and efforts to react ketones met with little success. Use of the more Lewis-acidic $CuSO_4$ as both a desiccant and catalyst provided efficient access to *t*-BS-imines (40–96%), with many of the unreactive substrates only requiring small excesses of this reagent to provide satisfactory yields (Method B, Scheme 8). Despite the efficiency of $CuSO_4$, condensation with ketones was still not possible. To effect the condensation of *t*-BSA with ketones, a range of titanium(IV) salts were investigated (Method C, Scheme 8).



Scheme 8.

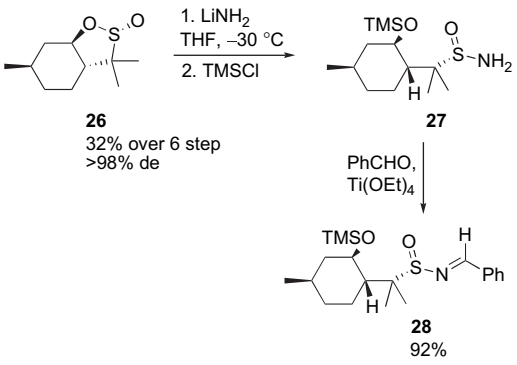
Ellman's studies revealed that $Ti(OEt)_4$ provided the best results, the condensation of unreactive aldehyde substrates being performed at room temperature, with mild warming



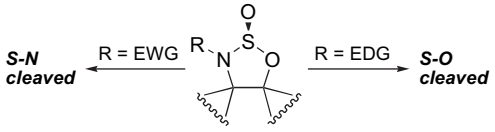
Scheme 7.

required to promote condensation with a wide range of ketones. This work established an efficient and reliable route for obtaining both *t*-BS-aldimines and *t*-BS-ketimines, significantly expanding the potential of chiral sulfinimines. The generality observed in the preparation of *t*-BS-imines through condensation of aldehydes and ketones with *t*-BSA was found to be true for the condensation with *p*-TS-amide (*p*-TSA).[17] Davis et al. screened a wide range of conditions for this condensation, finding that 4 Å molecular sieves or $Ti(OEt)_4$ were efficient desiccants for the procedure. Further to these investigations, a number of other conditions have been examined for the condensation reaction,[18,19] although few have approached the generality offered by those developed by Ellman and Davis.

From their experience gained in examining the interaction between chiral sulfinimines and Lewis acids,[8] Kawecki et al. proposed and developed the synthesis of a novel, recoverable chiral sulfinyl protecting group (Scheme 9).[8] Sultine **26**, prepared in six steps and 32% yield (>98% de), was reacted with lithium amide furnishing sulfinamide **27**. Condensation of **27** with benzaldehyde in the presence of $Ti(OEt)_4$ afforded sulfinimine **28** in 92% yield.



Scheme 9.



Scheme 10.

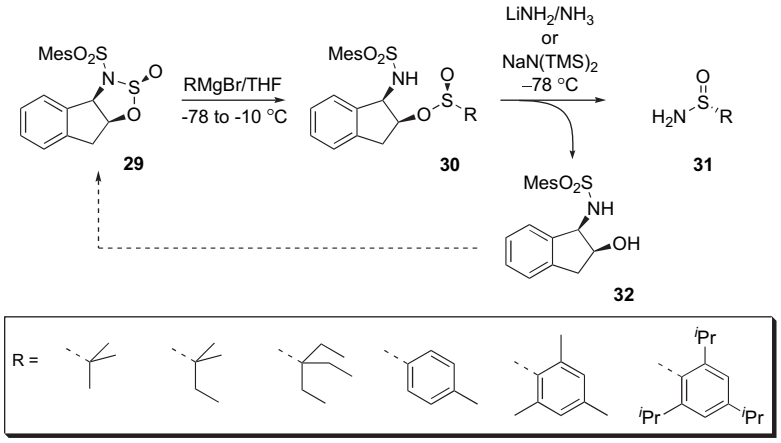
During their synthesis of the enantiomerically pure drug (*S*)-cetirizine, Senanayake et al. found that chiral sulfinimines, specifically *t*-BS-imines, were the most suitable intermediates for the drug's construction.[20] While the *t*-BS-imines provided acceptable results, however, their synthetic strategy required the preparation of structurally diverse aryl and alkyl sulfinamides for the fine-tuning of the diastereoselectivity of the organometallic addition. To fulfil this need, a general and practical modular synthesis of enantiopure tertiary alkyl and aryl sulfinamides was developed. Their approach was based upon the use of cyclic sulfinyl transfer agents. Over 30 years ago, Wudl and Lee demonstrated the utility of the (−)-ephedrine-derived *N*-methyl-1,2,3-oxathiazolidine-2-oxide in the synthesis of chiral sulfoxides. Exposure to carbon nucleophiles selectively cleaved the more reactive S–O bond (Scheme 10).

Senanayake et al. reasoned that a modification of the structure of the cyclic sulfinate would provide access to chiral sulfinamides. By building an electron-withdrawing group (EWG) rather than an electron-donating group (EDG) onto the nitrogen, the S–N bond would be activated and, thus upon exposure to a carbon nucleophile, the S–N bond would be cleaved in preference to the S–O bond giving silfinylester **30** (Scheme 11).

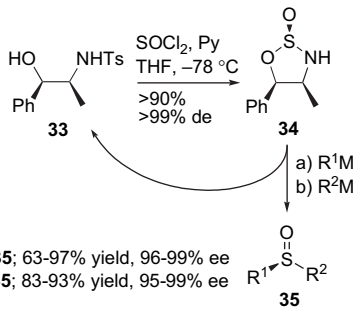
Not only does this chemistry provide access to a diverse range of chiral sulfinamides **31** in high yields and excellent enantiopurity, but, in addition, the valuable chiral amino alcohol **32** can be recovered and recycled to the cyclic sulfinate **29**, significantly increasing the efficiency of this chemistry.

More recent investigations have evaluated the use of other *N*-sulfonylamino alcohols as oxathiazolidine-oxide precursors. The inexpensive and readily available *N*-toluenesulfonylnorephedrine (*R*,*S*)-**33** was reported to be an excellent precursor to the corresponding oxathiazolidine-oxide **34**, exposure of which to a series of nucleophiles demonstrated its applicability to the preparation of chiral sulfoxides **35** (Scheme 12).

Condensation of aldehydes and ketones with chiral sulfinamides has become the most prevalent route for the preparation of chiral sulfinimines. With methods established for access to a variety of both sulfinyl and imine substituents, the versatility of condensation as a preparative procedure



Scheme 11.



Scheme 12.

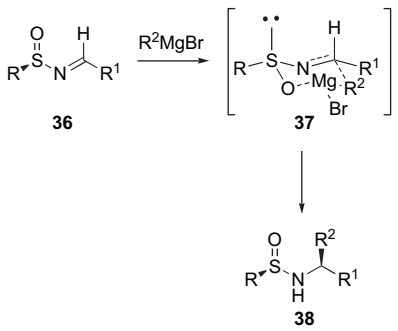
has significantly expanded the application of chiral sulfinimines in asymmetric synthesis.

4. Application of chiral sulfinimines as substrates in asymmetric synthesis

Since their inception, chiral non-racemic sulfinimines have played an increasingly significant role in the preparation of enantiopure amines. Their stereodirecting nature, the facile preparation of a diverse range of substrates and the subsequent possible removal of the protecting group have provoked widespread interest in their application. This section aims to provide a general overview of the role of chiral sulfinimines in asymmetric synthesis.

4.1. Synthesis of chiral amines

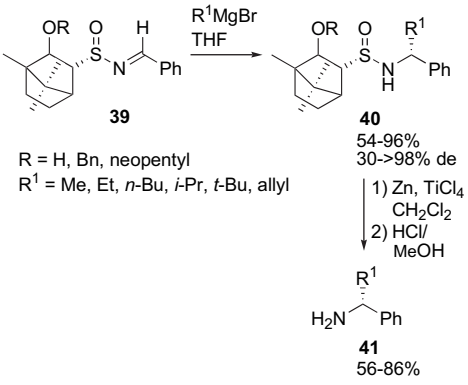
Nucleophilic 1,2-addition to an imine double bond is one of the most versatile and popular methods for the preparation of functionalised amines. With the incorporation of a stereodirecting motif in sulfinimines, the potential for the synthesis of chiral amines is evident. The typical means for such additions is through the reaction of aryl and alkyl carbanions, classically, Grignard reagents. Thus, it was proposed that addition of Grignard reagents to chiral sulfinimines **36** should, through transition state **37**, yield amines **38** with a high degree of stereoselectivity (Scheme 13).



Scheme 13.

The initial efforts to synthesise chiral amines from *p*-TS-imines, however, encountered problems. A prime example was reported in 1997 by Moreau et al., examining the addition of Grignard reagents to chiral *p*-TS-imines as a route for the synthesis of optically active 1,2-diphenylethylamines.[21] While the addition of benzylmagnesium bromide to the *p*-TS-imines furnished the desired sulfinamides in modest yield (55–76%) and stereoselectivity (60–74% de), exposure of the *p*-TS-imines under the same conditions to the more nucleophilic methylmagnesium bromide resulted in the displacement of the sulfinyl auxiliary and yielded none of the desired addition product.

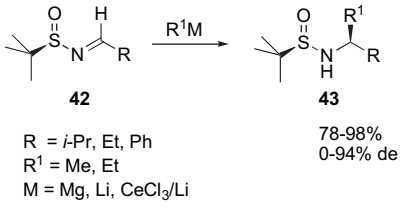
Thus, it became generally accepted that the more reactive Grignard reagents added exclusively to the sulfur of *p*-TS-imines, furnishing the *p*-tolyl methyl sulfoxides. These issues were overcome by the work of Yang et al. through the examination of an alternative *S*-substituent.[14] Reaction of the camphor-derived sulfinimines **39** with Grignard and other organometallic reagents was found to occur solely at the desired imine double bond, with no displacement being observed (Scheme 14).



Scheme 14.

A number of chemically diverse Grignard reagents were found to be suitable nucleophiles for this transformation, furnishing the chiral sulfinamides **40** in good yield and stereoselectivity. In addition, removal of the camphor-derived sulfinyl group was achieved in good yield to furnish the chiral amines **41**, with no loss in enantiopurity.

In 1997, Ellman et al. demonstrated the utility of *t*-BS-imines by the preparation of α-branched amines through the addition of Grignard reagents to these imines.[5] Ellman and co-workers later disclosed a report detailing the exploration of the synthesis of chiral amines through the addition of organometallic reagents to *t*-BS-imines.[22] They demonstrated that chiral amines **43** could be prepared in high yield (78–98%) and good diastereoselectivity (0–94% de) from the reaction of a diverse range of *t*-BS-imines **42** with a number of organometallic reagents (Scheme 15).



Scheme 15.

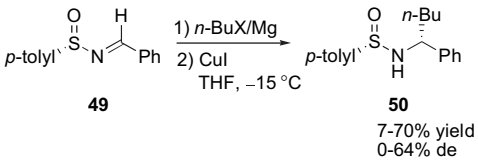
This work was further extended to encompass the reaction of *t*-BS-ketimines. Initial investigations found that both the rate and selectivity of the addition were disappointing. In order to both promote the rate and improve the selectivity of the reaction, a series of Lewis-acid additives were investigated.

The early results indicated that Me_3Al was the Lewis acid of choice, providing yields of 26–93% with 26–99% de.[23] Further investigations, however, provided a more elegant solution.[24] It was found that employing $Ti(OEt)_4$ as a Lewis acid in the addition of organometallics to *t*-BS-imines promoted the rate and improved the diastereoselectivity of the reaction. With $Ti(OEt)_4$ being used to drive the condensation of *t*-BSA with ketones, the one-pot asymmetric synthesis of chiral *t*-BS-amines was realised (Scheme 16).

The use of $Ti(OEt)_4$ as the promoter in both condensation and reduction meant that chiral amines **48** could be prepared directly in one pot, with *t*-BS-ketimine **44** or *t*-BS-imines **45** and **46** not being isolated. Furthermore, Ellman and coworkers described the removal of the *t*-BS protecting group through acid-promoted methanolysis, a protocol shown to be applicable to an array of *t*-BS-aldimines and -ketimines. Addition of Grignard (M=MgBr) and organolithium (M=Li) reagents to the *t*-BS-ketimines followed by subsequent deprotection provided an efficient route to a wide range of chiral tertiary amines **48**. The stereochemical outcome of all their investigations were in keeping with the chelating transition state **37**.

While *t*-BS-imines are the preferred substrates for reactions with organometallic reagents due to the propensity for attack at the sulfur atom of *p*-TS-imines, a shrewd choice of both substrates and conditions has revealed a number of methods for organometallic addition to *p*-TS-imines. A prime example was reported by Chan et al. on the addition of *n*-butylmagnesium bromide to *p*-TS-imine **49** (Scheme 17).[25] Initial investigations gave the desired amine **50** in only 7% yield and as a 1:1 diastereomeric mixture, with the major product resulting from attack at the sulfur of the *p*-TS-imine. It was found, however, that premixing of the organometallic reagent with copper iodide not only improved the yield to 70%, but, in addition, increased the diastereoselectivity to 64% de. Thus, copper-mediated organometallic addition to *p*-TS-imines provides an efficient route to α-branched chiral amines.

Prakash et al. made use of the high stereodirecting nature of the *t*-BS-auxiliary in their synthesis of trifluoromethylated allylic amines.[26] Reaction of α,β-unsaturated *t*-BS-imines with $TMSCF_3$ in tetrahydrofuran furnished the corresponding allylic amines in 50–80% yield and >99% de. The



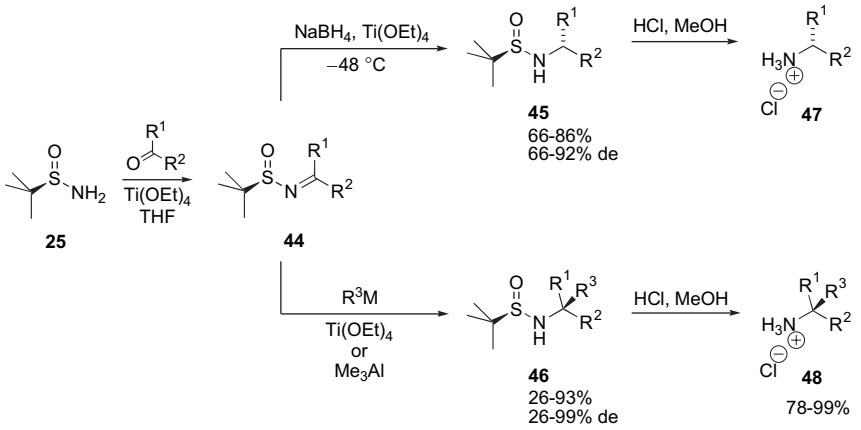
Scheme 17.

application of this protocol to the *p*-TS-imines was later explored by Dolbier et al., but the yields (54–86%) and stereochemical induction (44–88% de) were observed to be significantly lower.[27]

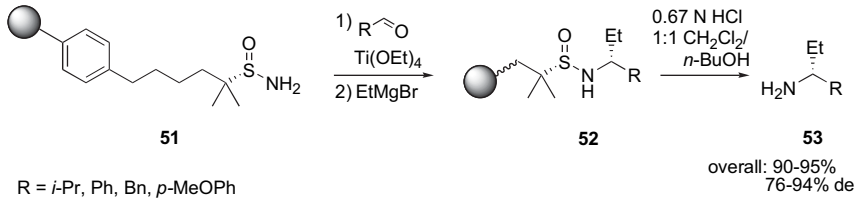
The routes of Ellman's interest in the field of chiral sulfinimines stem from research into the development of a novel solid-phase linker. In 2001, Ellman et al. reported on the synthesis and utility of a support-bound *tert*-butylsulfinamide derivative **51** (Scheme 18).[28] While many support-bound linkers have been developed for amines, few had incorporated the possibility to impart stereochemical information. Prepared in high yield, enantiopure **51** represents a stereodirecting solid-support linker, incorporating all the advantages displayed by the solution-phase *t*-BSA.

To correlate the solid- and solution-phase synthetic methods and demonstrate the practicality of the new technology, Ellman assessed the synthesis of chiral α-branched amines. Imine formation and addition of ethylmagnesium bromide were carried out under solution-phase optimised conditions. Subsequent cleavage from the solid-support-bound derivative **52** furnished the chiral amines **53** in near-quantitative yield over the three steps, albeit in a lower diastereomeric excess than the solution-phase counterparts. The utility of **51** was further demonstrated through the multistep synthesis of the more complex pavine and *iso*-pavine alkaloids.

Plobeck et al., during their investigations into the preparation of chiral diarylmethylamines, found that it was possible to implement a switch in the diastereoselectivity of the addition of the organometallic derivatives to *t*-BS-imines through judicious choice of reagents and conditions (Scheme 19).[29] While the addition of Grignard reagents afforded the expected *S*-amines **54**, reaction of the organolithium reagents in tetrahydrofuran furnished the *R*-amines **55**. To justify this change in stereochemical induction, which was observed

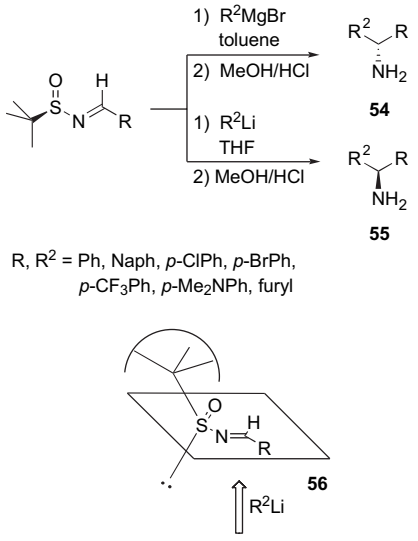


Scheme 16.



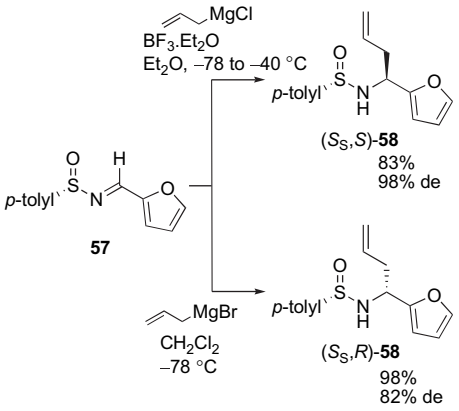
Scheme 18.

in a number of other instances, an open transition state **56** was adopted.



Scheme 19.

Shimizu et al. reported the addition of the more reactive allyl Grignard reagents to *p*-TS-imines.[30] An informed choice of the Grignard reagent and reaction conditions uncovered methods that furnished high diastereoselectivity and a reversal in the configuration of the newly formed chiral centre (Scheme 20). Addition of allylmagnesium bromide to **57** in CH_2Cl_2 furnished **58** in 98% yield with (S_S,*R*)-**58** in 82% de. On the other hand, in the addition of allylmagnesium chloride in ether, with $BF_3\cdot OEt_2$ as an additive, (S_S,*S*)-**58** was observed to be the major diastereomer in 98% de and 83% yield.



Scheme 20.

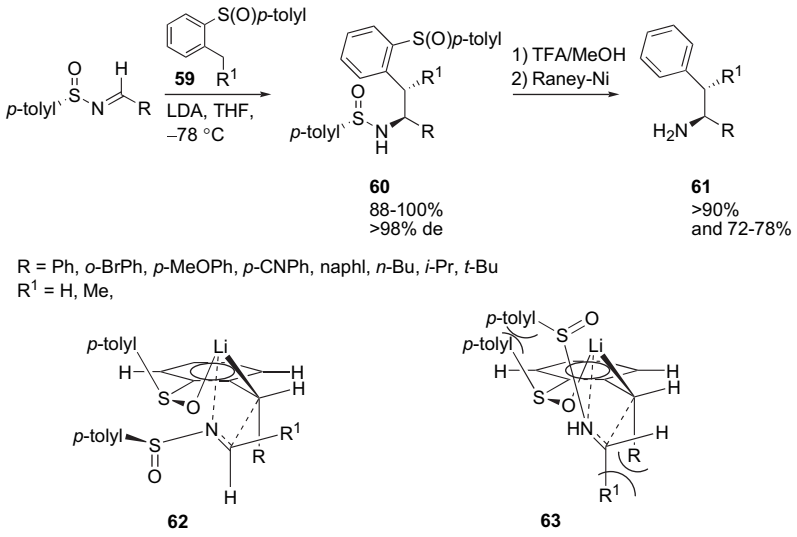
Prompted by reports of the difficulty of incorporating the benzyl motif into chiral amines through 1,2-nucleophilic addition to sulfinimines, primarily due to an unacceptably low stereoselectivity, Garcia Ruano et al. developed a new protocol to improve the stereoselective synthesis of 1,2-diaryl (and 1-alkyl-2-aryl) ethyl and propylamines (Scheme 21).[31] Proposing that the inclusion of a chiral substituent at the *ortho*-position of the benzyl carbanion would increase the stereoselectivity of the reaction through a double stereodifferentiation effect, the reaction of the anion generated by deprotonation of sulfoxide **59** with a range of both aromatic and aliphatic *p*-TS-imines was examined.

Both aromatic and aliphatic sulfinimines proved to be suitable substrates for the procedure, affording sulfinamides **60** in high yield and exceptional stereoselectivity. Sequential removal of the *N*-sulfinyl group and the sulfoxide afforded the benzyl chiral amines **61** in good yield and optical purity. The exceptional stereoselectivity was rationalised by invoking a double stereodifferentiation effect. The matched pairing was found to be the *S*-isomer of the benzyl carbanion and the *S*-sulfinimine. In this instance, the reaction can proceed through either transition state **62** or **63**, but there are significantly less unfavourable steric interactions present in **62**, and thus the new chiral centre is formed almost exclusively as the *S*-isomer.

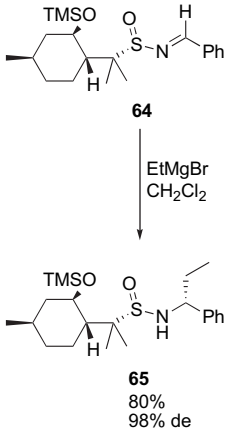
To demonstrate the utility of his new chiral sulfinamide, Kawecki explored the synthesis of chiral amines through the reaction of ethylmagnesium bromide with sulfinimine **64** (Scheme 22).[8] Comparative studies found that the reaction of sulfinimine **64** in CH_2Cl_2 furnished sulfinamide **65** in a comparable yield to the reaction of *t*-BS-imines, but notably with a higher diastereoselectivity (84% vs 98% de). The 8-menthylsulfinyl moiety was removed under acidic conditions, affording the desired amine and sulfinate **26**, which could be recycled.

During a programme of research directed towards the stereoselective synthesis of organosilanes, Scheidt et al. reported the highly diastereoselective addition of silyl anions to *t*-BS-imines (Scheme 23).[32] Both aryl and branched alkyl *t*-BS-imines **66** were found to be suitable substrates for the addition, affording α-organosilanes **67** in good yield and stereoselectivity.

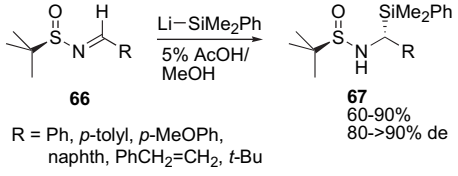
While the addition of Grignard and lithium reagents has proved to be a reliable method for the synthesis of chiral amines, these methods were, in general, intolerant to highly functionalised substrates. One example of the addition of a Grignard reagent to a complex, functionalised substrate was described by Overhand et al., where the addition of phenylmagnesium chloride to a sugar-based *t*-BS-imine provided the desired chiral amine in high stereoselectivity.[33] Full protection of the sugar alcohols was, however, required.



Scheme 21.



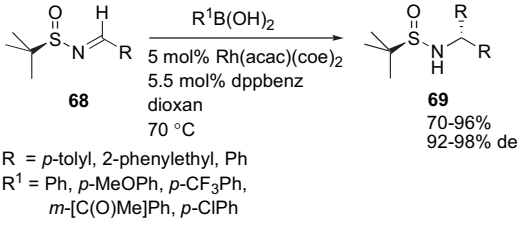
Scheme 22.



Scheme 23.

To address this issue, Ellman et al. investigated the addition of arylboronic acids to *t*-BS-imines.[34] While arylboronic acids are poor nucleophiles, rhodium(I)–phosphine complexes have been found to effectively catalyse their addition to *N*-sulfonyl-imines, and, thus, Ellman reasoned that *t*-BS-imines would be suitable substrates (Scheme 24).

The addition of arylboronic acids to both aliphatic and aromatic *t*-BS-imines **68** to form **69** was achieved in good yield (70–96%) and with high diastereoselectivity (92–98% de). Notably, Ellman reports the first rhodium(I)-catalysed addition of arylboronic acids to aliphatic imines **68** (R=2-phenylethyl), and demonstrates the functional group tolerance of the procedure with the addition of relatively sensitive substrates



Scheme 24.

(R^1=3-acetylphenyl). The efficiency of the protocol was enhanced through the development of a one-pot procedure, leading from the aldehydes directly to the chiral amines **55**.

Recently, Batey et al. have disclosed their investigations on the rhodium-catalysed addition of arylboronic acids to chiral *t*-BS-imines, with conditions that require only room-temperature reaction and provide more facile practical conditions.[35]

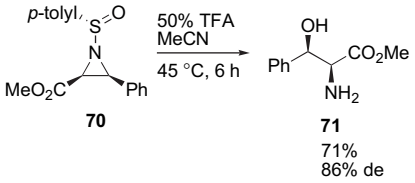
While it is clear that *t*-BS-imines have emerged as the favoured substrates for the synthesis of chiral amines, due to the lack of reaction of organometallics at sulfur, conditions have been established for the addition of organometallics to *p*-TS-imines. With the emergence of new techniques for nucleophilic addition to chiral sulfinimines, the range of substrates suitable for this transformation is set to expand.

4.2. Synthesis of chiral α-amino acids

The existence of α-amino acids as the building blocks of proteins and peptides in biological systems combined with their application as chiral synthons in modern organic chemistry has justified the continued efforts for the development of new and efficient methods for the preparation of an ever-expanding pool of these valuable chiral amines.

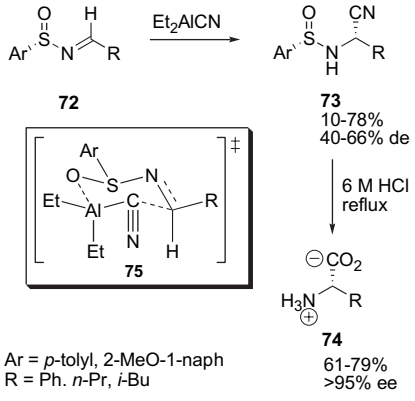
The first α-amino acid derived from a chiral sulfinimine was synthesised by Davis et al. in 1994.[36] To demonstrate the activating nature of the *p*-TS-sulfinyl group to promote the ring opening of an aziridine ring, exposure of aziridine **70** to 50%

aqueous TFA furnished the *syn*-β-phenylserine derivative **71** in 71% yield (Scheme 25).



Scheme 25.

While this reaction demonstrated the activating ability of the *p*-TS-group towards aziridine ring opening, it does not represent an efficient synthesis of α-amino acids. In the same year, however, Davis et al. published the first of a series of articles on the development of a highly efficient route to chiral α-amino acids.[37] The asymmetric Strecker synthesis of α-amino acids has become a cornerstone of this field of chemistry. The addition of cyanide to a chiral imine and subsequent hydrolysis of the nitrile furnishes the desired amino acid. The auxiliary controlled nucleophilic addition of cyanide to non-racemic imines had, however, encountered several hurdles; only modest levels of diastereoselectivity had been observed (22–60% de) and, subsequently, the removal of the *N*-substituent without decomposition or epimerisation of the α-amino acid proved challenging. Prompted by these shortcomings, Davis et al. investigated the use of enantiopure *p*-TS-imines in the Strecker synthesis[37] (Scheme 26). Their initial efforts using common cyanide sources such as KCN, CuCN and TMSCN met with disappointing results and, in general, there was no reaction, with only poor yields being obtained when addition did occur, even in the presence of Lewis-acid catalysts. Undeterred, diethylaluminium cyanide (Et_2AlCN) was examined as a source of cyanide. While there was only limited precedence for this reagent, Davis rationalised that the strong Lewis-acid nature of the reagent would increase the likelihood of addition to *p*-TS-imines **72**; complexation with the sulfinyl oxygen would not only activate the imine double bond to addition, but would also provide a mechanism for the intramolecular delivery of cyanide **75**.



Scheme 26.

The major diastereomeric α-amino nitriles **73** could be isolated by chromatography, and interestingly the sulfinimines with the 2-methoxy-1-naphthyl substituent were not only easier to separate but the addition appeared to proceed with higher diastereoselectivity. Removal of the sulfinyl group and hydrolysis of the nitrile were achieved in refluxing HCl, and hence, both aromatic and aliphatic chiral α-amino acids **74** were prepared in good yield and excellent enantiopurity.

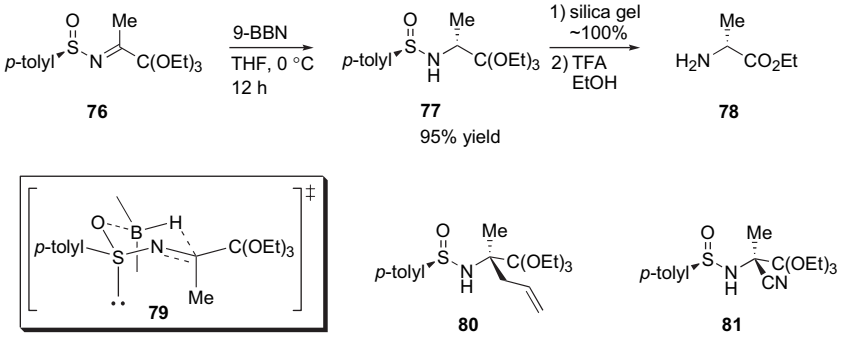
Hua et al. adopted an alternative approach to chiral α-amino acids (Scheme 27).[38] Reduction of *p*-TS-imine **76** was carried out with a number of reagents, both lithium aluminium hydride and diisobutylaluminium hydride giving a mixture of *R*-and *S*-diastereomers. However, reduction with 9-BBN yielded exclusively (R_S,*R*)-**77**. Hydrolysis of the *ortho* ester **77** on silica gel followed by ethanolysis afforded the alanine ethyl ester **78**.

An explanation for the stereoselective reduction was proposed in the form of the six-membered transition state **79**. The boron chelates with the sulfinyl oxygen, and hence the hydride reagent approaches from the *si*-face of the sulfinimine. Hua's investigations were extended by examining the addition of alternative nucleophiles to *p*-TS-imine **76**. Sulfinimine **76** underwent a completely stereoselective addition of allylmagnesium bromide to give **80** in 95% yield, subsequent deprotection and hydrolysis affording the corresponding α-amino acid. Treatment of **76** with Et_2AlCN gave a 92% yield of both the *S*- and *R*-diastereomers of nitrile **81** in a 7:4 ratio.

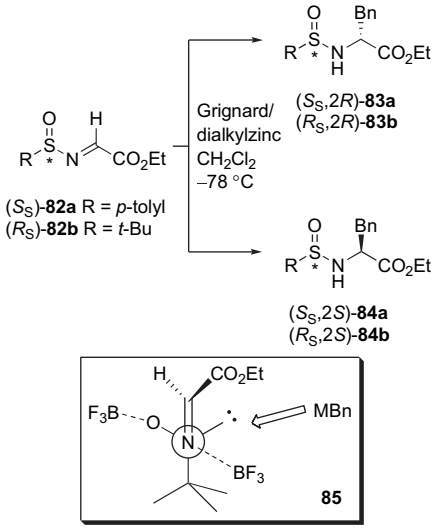
While the *p*-TS-imine asymmetric Strecker reaction provided access to a range of chiral α-amino acids, the diastereoselectivities were still only modest at best. Seeking to improve the stereoselectivity of this reaction, Davis et al. examined the reaction conditions.[39] Having realised that the Lewis acidity of the cyanide source was significant to this reaction, this aspect was considered. It was observed that pre-complexation of the Et_2AlCN with 2-propanol resulted in a dramatic improvement in the diastereoselectivity, from 40–66% to 82–86% de, of the *p*-TS-imine Strecker reaction. Addition of 2-propanol to Et_2AlCN results in the formation of an ethylaluminium cyanide, alkoxide Et(*i*-PrO)AlCN. It is thought that the lower Lewis acidity of the alkoxide complex relative to the Et_2AlCN is responsible for the greater diastereoselectivity observed.

An alternative disconnection investigated by Davis et al. for the synthesis of α-amino acids provided some interesting results that furnished a procedure complementary to the *p*-TS-imine-based Strecker modification.[40] Glyoxylate imines have previously been employed in the preparation of un-natural α-amino acids, but the effectiveness of this route has been hampered by a lack of stereoselectivity. Proposing that the attachment of a sulfinyl group to the imino-nitrogen could introduce a level of stereocontrol over the reaction, Davis investigated the reaction of a series of glyoxylate sulfinimines (Scheme 28).

Initial investigations revolved around the reaction of *p*-TS-imine **82a** and, while the addition of BnMgCl occurred regioselectively at the desired imino carbon providing a diastereomeric mixture of amines **83** and **84**, with **83a** as the major diastereomer (*R*/*S* 82:12) in 56% yield, the mixture was found to be inseparable. The modest yield was attributed to a competing oligomerisation pathway and the associated sulfinyl displacement reaction recurrent in *p*-TS-imine



Scheme 27.

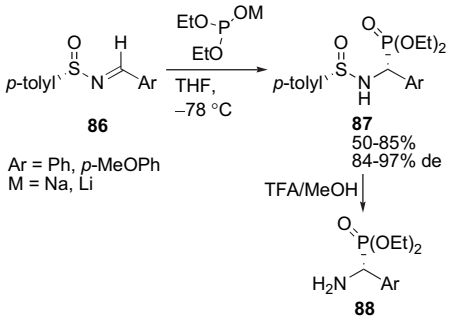


Scheme 28.

chemistry. Introduction of 2 equiv of the Lewis acid, $BF_3 \cdot OEt_2$, to the reaction significantly decreased not only the oligomerisation, but, unfortunately, also the yield of the amino acid. It was thought that overactivation of the sulfinyl group promoted displacement of the sulfoxide by the organometallic reagent. Davis envisaged that the more sterically demanding *t*-BS-imine would reduce the likelihood of reaction at sulfur.

Initial results from the reaction of BnMgCl with *t*-BS-imine **82b** were disappointing, with significant levels of both oligomerisation and displacement at sulfur observed, but the diastereoselectivity was seen to have improved and the isomers were found to be separable by chromatography. Further investigation found that the addition of 2 equiv of $BF_3 \cdot OEt_2$ and the use of 2 equiv of the organometallic reagent provided conditions that effectively eliminated oligomerisation and the displacement of the sulfoxide, delivering the protected α-amino acid **83b** in 88% de and 70% isolated yield. These conditions were found to be efficient for a number of both aromatic and aliphatic organometallic reagents (Bn, Ph, Et, Me). The sense of stereoinduction is opposite to that previously observed. To rationalise this observation, Davis proposed the open transition state **85**. Coordination of BF_3 to the sulfinyl oxygen and to the imino-nitrogen sterically shields the *si*-face of the imine to afford the Cram product. This observed difference is due to the presence of the ester functionality, and it was speculated that chelation of the incoming organometallic reagent with the ester carbonyl disrupts and prevents the formation of the commonly favoured chelated transition state. This inversion of the observed stereoinduction provides a method complementary to Davis's modification of the Strecker reaction. This chemistry was more recently put to interesting use *en route* to the synthesis of the un-natural amino acid, L-α-(1-cyclobutenyl)glycine.[41] Thus, the chiral centre was set up through the asymmetric directing power of the chiral sulfinyl group on the addition of 1-cyclobutenylmagnesium chloride on the *t*-BS-imine glyoxylate.

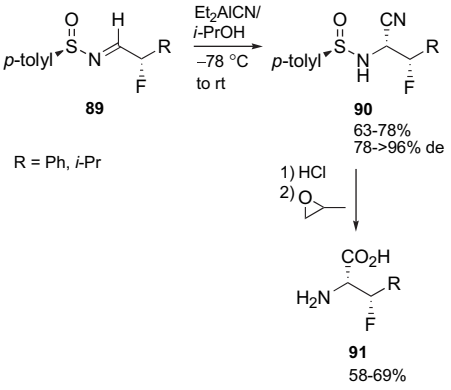
The wide range of biological activity exhibited by α-amino phosphonic acids as surrogate α-amino acids, primarily as antagonists in the metabolism of amino acids, has resulted in a number of routes for their preparation. In 1997, Evans et al. took advantage of the stereodirecting nature of the *p*-TS auxiliary in the synthesis of these biologically interesting compounds (Scheme 29).[42] Both lithium and sodium phosphites were added to a range of aromatic *p*-TS-imines **86**, with the corresponding *p*-TS-α-amino phosphonates **87** isolated in high yield and diastereoselectivity. The lithium phosphites were observed to provide marginally better yields and stereoselectivities, with the stereoinduction consistent with an open, non-chelating transition state. Subsequent deprotection was accomplished in high yield, furnishing the desired α-amino acid surrogates **88**.



Scheme 29.

As a continuation of their studies into the application of the sulfinimine-mediated asymmetric Strecker synthesis and, in particular, its application to the preparation of β-substituted α-amino acids, Davis et al. published a series of papers in 1999–2000 detailing the synthesis of structurally diverse β-substituted α-amino acids.

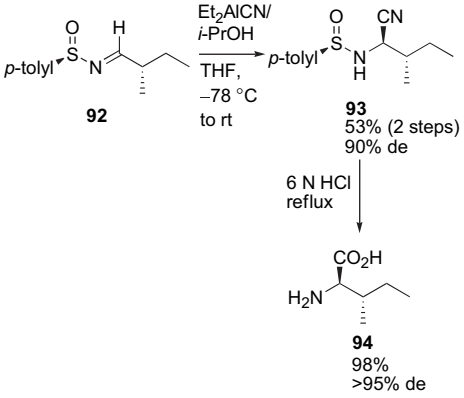
Shrewd inclusion of a fluorine atom into a structure has the capacity to significantly enhance the biological properties and, in this respect, β-fluoro α-amino acids are of particular interest. Many of the previous strategies for synthesising these halogenated amines displayed low yields and a tendency for defluorination during the deprotection of the amine. In 1999, Davis et al. described a direct approach to these biologically interesting compounds (Scheme 30).[43]



Scheme 30.

Addition of cyanide to α-fluoro *p*-TS-imines **89** through optimised reaction of Et_2AlCN/*i*-PrOH furnished β-fluoro α-amino nitriles **90** in high yield (63–78%) and diastereomeric excess (78 to >96% de). Subsequent treatment with 6 N HCl and propylene oxide afforded β-fluoro α-amino acids **91** in good yield with no racemisation observed. Notably, the stereoselectivity of the reaction was observed to be unaffected by the presence of the α-fluoro chiral centre, with the sulfinyl group found to be the sole influence over the topicity of the nucleophilic cyanide addition.

In 1999, Joullié et al. disclosed the synthesis of the β-methyl α-amino acid (2*R*,3*S*)-alloisoleucine via the sulfinimine-mediated Strecker reaction (Scheme 31).[44] Addition of cyanide to the crude *p*-TS-imine **92** afforded α-amino nitrile **93** in good yield and high diastereoselectivity. It was observed that, in accordance with previous findings, the adjacent chiral centre played no role in the stereoselectivity of the reaction, and rather the sulfinyl group was the sole influence on the topicity of the cyanide delivery. Subsequent deprotection under standard conditions provided the un-natural α-amino acid **94** in high yield.



Scheme 31.

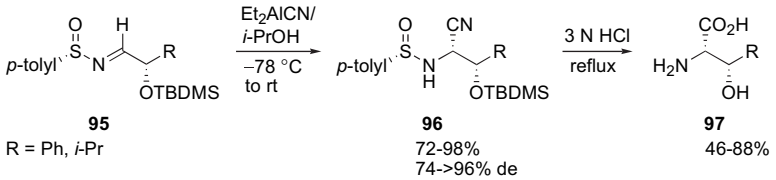
β-Hydroxy α-amino acids are not only an important class of biologically active compounds, but, in addition, they are useful chiral building blocks in organic synthesis. In 2000, Davis et al. described a general route to β-hydroxy α-amino acids (Scheme 32).[45] Reaction of *p*-TS-imines **95** under the optimised Strecker conditions afforded α-amino nitriles **96** in good yield (72–98%) and good diastereoselectivity (74–96% de). Davis et al. demonstrated the generality of this procedure through preparation of all four stereoisomers of phenylserine and (2*R*,3*S*)-β-hydroxyleucine. Investigation of the factors influencing the stereoselectivity of the reaction revealed that a double stereodifferentiation effect was present, where the chirality of the resident hydroxyl moiety influences the asymmetric induction. This effect was, however, observed to be relatively weak, with the mismatched pair proceeding with 74% and 87% de, while the matched pair presented >96% de. It is suggested that the reason this double stereodifferentiation effect is observed for these substrates, yet not for the α-methyl or α-fluoro substrates, is due to the greater steric presence of the TBDMS protecting group.

Hydrolysis of the diastereomerically pure α-amino nitriles was accomplished by refluxing with 3 N HCl, delivering amino acids **97** in 46–88% yield and >95% enantiomerically pure.

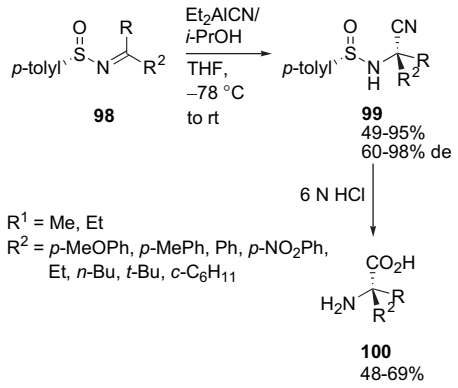
Davis successfully prepared the surrogate β-hydroxy α-amino phosphonates through the addition of metal dialkyl phosphites to *O*-protected α-hydroxy *p*-TS-imines.[46] The chiral motifs were prepared in good yield (68–74%) and high diastereoselectivity (86 to >94% de). The addition was observed to be subject to a similar double stereodifferentiation effect, though again the sulfinyl group was found to exert the primary influence.

Another avenue of structural investigation for α-amino acids is the investigation of α-alkyl α-amino acids. Davis proposed that application of the sulfinimine-mediated asymmetric Strecker reaction to sulfin-ketimines would provide a straightforward route for the synthesis of these sterically congested amines (Scheme 33).[47]

Reaction of ethylaluminium cyanoisopropoxide with *p*-TS-ketimines **98** gave α-amino nitriles **99** in good yield (49–95%) and diastereoselectivity (60–98%), with the



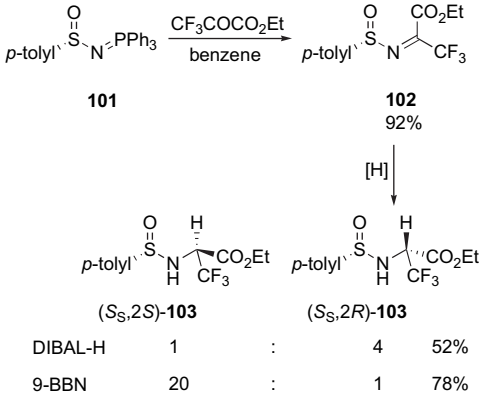
Scheme 32.



Scheme 33.

stereoselectivity of the reaction in accordance with the chelating six-membered transition state **75**. Hydrolysis to α-alkyl α-amino acids **100** was achieved through refluxing in 6 N HCl. To ascertain the effect of a more sterically demanding sulfinyl group on the diastereoselectivity of the reaction, Davis examined the cyanide addition to *t*-BS-ketimines. While the crude yield and diastereoselectivities (64–84% de) were comparable, unlike the *p*-TS-α-amino nitriles, the *t*-BS analogues could not be easily separated by flash chromatography. In addition, removal of the *t*-BS protecting group was found to be challenging. Later in the same year, this chemistry was applied to the synthesis of the di-α-amino acids, (2*S*,6*S*)-diaminopimelic acid and *meso*-(2*S*,6*R*)-diaminopimelic acid, providing an efficient entry to these biologically interesting compounds.[48]

Zanda et al. developed a novel, *p*-TS-imine-mediated synthesis of trifluorinated α-amino acids **103** (Scheme 34).[49] The Staudinger reaction of **101** proceeded in high yield, affording *p*-TS-imine **102**. The sulfinyl group was found to



Scheme 34.

direct the stereoselectivity of the reduction of imine **102**. The sense and extent of the reduction were observed to be dependent upon the hydride source employed.

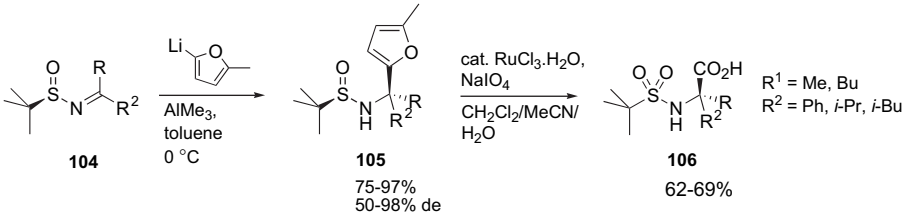
Reduction with 9-BBN occurred in high yield and stereoselectivity, rationalised by the six-membered transition state **79** proposed by Hua, while DIBAL-H proceeded with significantly lower yield and diastereoselectivity, the fact that both diastereomers are readily accessible from the same enantiomer of the *p*-TS-imine making this as an attractive route. Hydrolysis afforded 3,3,3-trifluoroalanine.

Ellman et al. also considered the synthesis of α,α-disubstituted amino acids **106** from sulfin-ketimines **104**, but an alternative disconnection was examined (Scheme 35).[50] Nucleophilic addition of a masked carboxylic acid to sulfin-ketimines and subsequent oxidation and deprotection provides direct access to α,α-disubstituted amino acids.

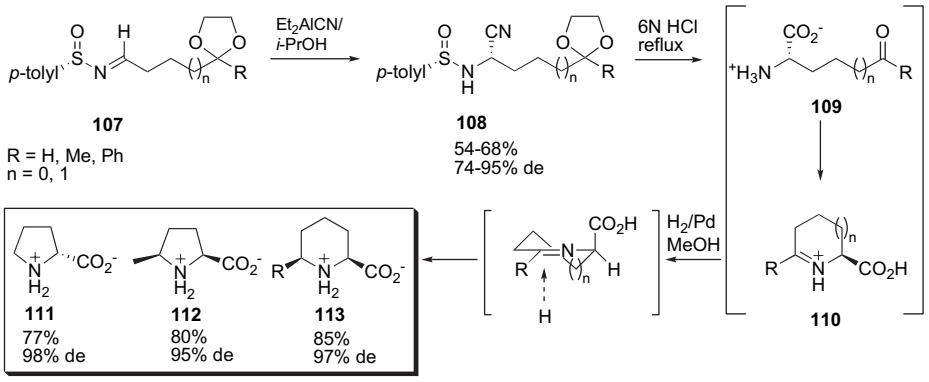
Addition of 5-methylfuryllithium at 0 °C furnished **105** in good yield (75–90%) and excellent diastereoselectivity (50–98% de), and the reaction was found to be general over a range of both aromatic and aliphatic substrates. Oxidation of both the sulfinyl and furyl groups afforded the *tert*-butylsulfonyl- (Bus-) protected α,α-disubstituted amino acids **106** in good yield (62–69%), with no racemisation observed. The utility of Bus-protected α,α-disubstituted amino acids in peptide synthesis was then examined, with two coupling conditions evaluated, in both instances the protecting group remaining untouched. Removal of the Bus protection was achieved through exposure to TfOH/CH_2Cl_2 in good yield (65%).

In 2001, Davis et al. focused their interest on the application of the sulfinimine-mediated Strecker reaction on the synthesis of cyclic α-amino acids.[51] Previous methods for the synthesis of these structurally interesting motifs had been hampered by their reliance upon proteinogenic amino acids as building blocks, hence making access to both enantiomers difficult. The Davis strategy revolved around the Strecker reaction of masked oxo *p*-TS-imines **107** (Scheme 36).

Treatment of the masked oxo sulfinimines **107** with Et_2AlCN/*i*-PrOH afforded α-amino nitriles **108** in good yield (54–68%) and high diastereoselectivity (74–95% de). Hydrolysis of the diastereomerically pure α-amino nitriles in refluxing HCl accomplished a number of operations in a single pot; hydrolysis of the sulfinyl group was accompanied by conversion of the nitrile into the acid, and the protected acetal is unmasked to give the intermediate aldehydes/ketone **109**, which undergoes cyclisation in situ, furnishing the iminium ion **110**, which was carried through a hydrogenation crude, producing the cyclic α-amino acids **111–113** in high



Scheme 35.



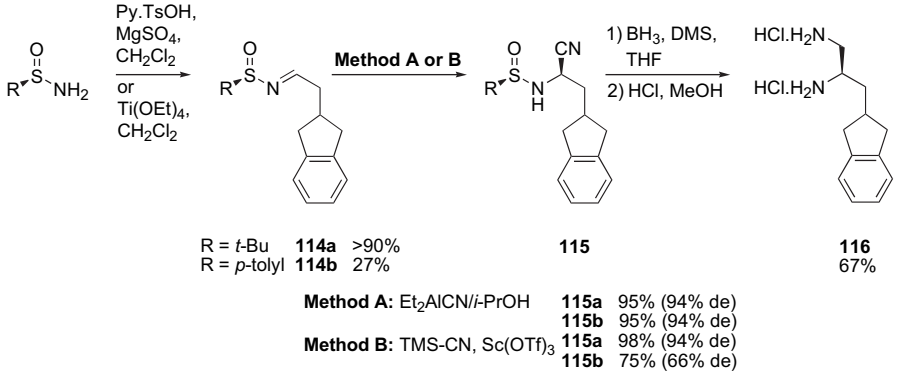
Scheme 36.

yield (77–85%) and excellent diastereoselectivity (95–98% de).

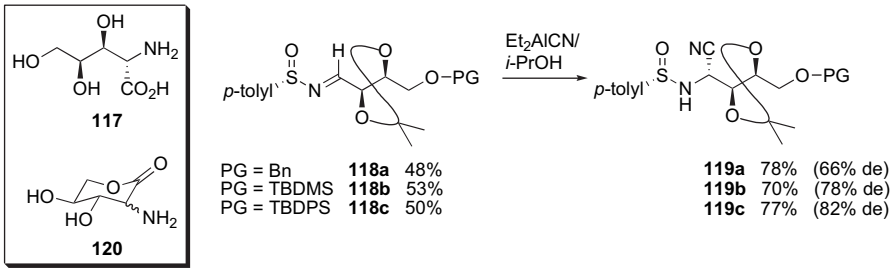
During a programme of research directed towards the preparation of imidazoles as potential antidepressants, Cordi et al. investigated the application of the sulfinimine-mediated asymmetric Strecker reaction as a facile method for the preparation of one of the key intermediates.[52] During these investigations, the suitabilities of the *p*-tolyl- and *t*-BS-imines were compared and an alternative cyanide source was investigated (Scheme 37).

Condensation with *t*-BSA to form sulfinimine **114a** occurred in high yield, and it was noted that the sulfinimine was highly stable and easily isolated, while condensation with *p*-TSA under typical conditions furnished sulfinimine **114b** in disappointing yield and the sulfinimine itself was found to readily decompose. Two cyanide-delivery reagents were examined. The Strecker conditions developed by Davis et al. afforded α-amino nitriles **115a** and **115b** in high yield and diastereoselectivity (Method A). The second delivery agent examined was TMSCN, previously thought to be inactive towards sulfinimines, and it was found to react at temperatures above 10 °C in the presence of an activating Lewis acid. After extensive screening, scandium triflate was found to deliver the best yield and diastereoselectivity (Method B). Subsequent reduction and deprotection efficiently provided the desired di-amine intermediate **116**.

Through a series of reports, Davis et al. have demonstrated that the sulfinimine-mediated Strecker synthesis is an efficient, versatile and stereoselective method for the synthesis of a diverse range of α-amino acids. There were, however, limitations highlighted, primarily the ability to prepare the desired sulfinimine, and the compatibility of the functional groups with the hydrolysis conditions. To this end, Davis sought a highly substituted α-amino acid that would provide a good test for these criteria. Thus, the synthesis of polyoxamic acid **117** was investigated (Scheme 38).[53] Sulfinimine **118** was prepared in modest yield, with the extent of the



Scheme 37.



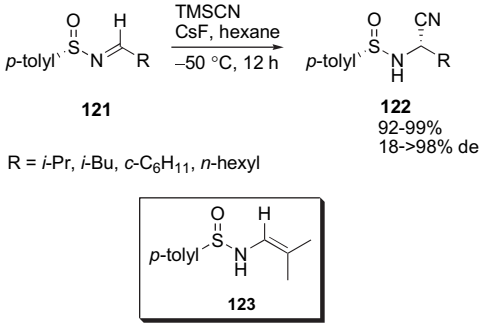
Scheme 38.

condensation found to be almost independent of the protecting group employed.

Hydrocyanation of **118a–c** afforded the corresponding α-amino nitriles **119a–c** in good yield (70–78%) and modest to good diastereoselectivity (66–82% de). Alteration of the conditions failed to provide a significant improvement. Stereochemical investigations revealed that the chiral sulfinyl moiety was the sole stereodirecting factor with no double stereodifferentiation effect observed.

In previous examples of the sulfinimine-mediated Strecker reaction, the hydrolysis of the nitrile and concomitant removal of the sulfinyl group is accomplished in a simple one-pot operation. Application of the normal conditions to **119a** resulted in decomposition. Exposure of **119a** to moist ethereal HCl removed both the ketal and sulfinyl moieties, but conditions could not be found for the reductive removal of the benzyl group. Exposure of **119c** to refluxing HCl also resulted in decomposition, as did exposure to moist ethereal HCl. Thus sequential removal of the TBDPS with TBAF and the sulfinyl moiety with ethereal HCl was accomplished. Hydrolysis of the nitrile functionality was executed using moist ethereal HCl, but rather than the desired acid, lactone **120** was isolated. Efforts to remove the TBDMS group in **119b** were unsuccessful.

Recently, an alternative, yet complementary, approach to Davis's modification to the Strecker synthesis was reported by Hou and Dai.[54] Whilst Davis's work was efficient in the generation of α-amino acids, there were some practical considerations and limitations evident in the generality in the procedure, and thus Hou and Dai sought to address these by the consideration of an alternative source for the cyanide anion. While Davis's early work had established that when aromatic *p*-TS-imines were treated with TMSCN and CsF in tetrahydrofuran no reaction occurred, from previous experience Hou and Dai had observed that the presence of a fluoride anion acted as a trigger to promote the reaction of silicon reagents. On revisiting the conditions initially investigated by Davis et al., it was observed that TMSCN, in the presence of CsF, successfully adds to the C=N bond of *p*-TS-imines **121**, provided that there is an enolisable proton α to the imine bond (Scheme 39).



Scheme 39.

With yields of the α-amino nitriles **122** >90% and the diastereoselectivities >95%, the application of the more robust TMSCN as a cyanide-delivery reagent has only one obvious limitation. Identification of enamine **123** from the reaction mixture suggests it is an intermediate in the mechanism, lending weight to the argument that only enolisable imines are suitable substrates for these conditions, a rationale further supported by the lack of reaction with non-enolisable *p*-TS-imines.

Extending their work on the synthesis of cyclic α-amino acids, Davis et al. reported the construction of cyclic α-amino phosphonic acids via masked oxo *p*-TS-imines (Scheme 40).[55] Reaction of the masked oxo *p*-TS-imines **124** with 2 equiv of lithium diethyl phosphate furnished the α-amino phosphonates **125** in high yield and diastereoselectivity. Subsequent hydrolysis and hydrogenation of the major diastereomers **126** afforded the cyclic α-amino phosphonates **127–129** in modest to good yield with no loss of enantiopurity observed.

Further to these investigations, Davis examined the reaction of masked oxo *p*-TS-ketimines towards the asymmetric synthesis of quaternary cyclic α-amino phosphonates. While the masked oxo *p*-TS-ketimines did prove to be suitable substrates for this reaction, lower yields and diastereoselectivities were observed.

Recently, Avenoza et al. have exploited the sulfinimine-mediated Strecker synthesis for the straightforward preparation of both (*S*)- and (*R*)-α-phenylserine.[56] Hydrocyanation of the *t*-BS-imines afforded the corresponding α-amino nitriles in only modest yield (52%) and stereoselectivity (62% de). Subsequent deprotection and hydrolysis provided rapid access to the structurally interesting α,α-disubstituted amino acids.

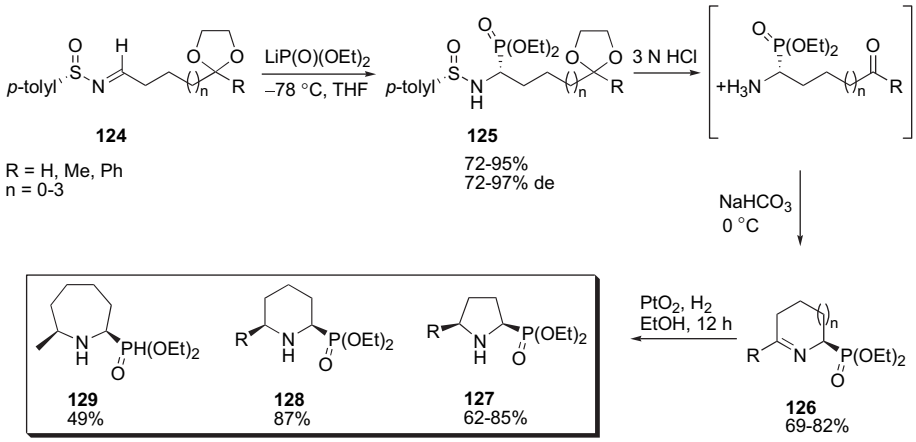
The sulfinimine-mediated asymmetric Strecker synthesis developed by Davis et al. has provided a direct and efficient route to a wide range of chiral non-racemic α-amino acids. Modifications have extended the applicability of this procedure, and alternative cyanide sources have been investigated. Both *p*-TS- and *t*-BS-imines have been shown to be suitable chiral precursors for α-amino acids.

4.3. Synthesis of chiral β-amino acids

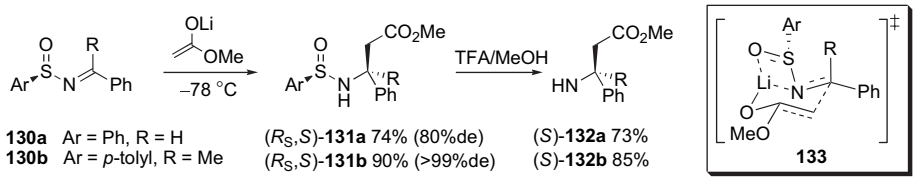
β-Amino acids have recently received significant attention as the fundamental building blocks of β-peptides. Previous methods for their preparation have relied upon either the homologation of α-amino acids or the addition of various nucleophiles to imines. While these methods have been effective, efficient and more general means are still sought.

In 1992, Davis et al. first described the synthesis of enantiomerically pure *p*-TS-imines through the asymmetric oxidation of sulfenimines with chiral oxaziridines.[13] To demonstrate the capacity of the *p*-TS-imines towards asymmetric synthesis, the preparation of non-racemic β-amino acids was tackled (Scheme 41).

Thus, addition of lithium enolate to enantiopure sulfinimines **130a**,**b** furnished the sulfinamides **131a**,**b** in good yield and diastereoselectivity and, notably, the *p*-tolyl-sulfinyl group afforded significantly higher levels of diastereoselectivity. Further, no enolisation of **130b** was observed. Hydrolysis, with no loss of enantiopurity, was achieved with TFA in methanol, affording β-amino acids **132a**,**b** in good yield.



Scheme 40.

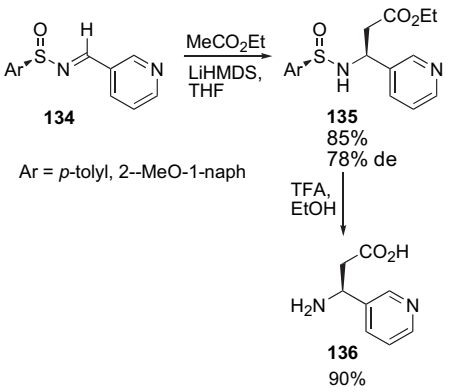


Scheme 41.

Davis proposed the Zimmerman–Traxler-type six-membered transition state **133** to rationalise the stereochemical outcome. Chelation of the incoming lithium enolate with the sulfinyl oxygen ensures delivery to the *si*-face of the sulfinimine.

During studies towards the synthesis of (*R*)-β-phenylalanine, an important constituent of a number of biologically interesting compounds, Davis et al. re-examined the conditions of enolate addition to *p*-TS-imines.[57] While the lithium enolate in tetrahydrofuran afforded the corresponding sulfinamide in 74% yield and 80% de, the use of the sodium enolate in diethyl ether boosted the yield to 84% in >96% de. Thus, sodium enolates became the favoured reagents.

Extending the scope of their β-amino acid protocol, Davis et al. reported the asymmetric synthesis of (*S*)-ethyl-β-amino-3-pyridinepropanoate **136**, a key building block of a peptidomimetic of fibrinogen and an orally active antiplatelet agent (Scheme 42).[58] It was anticipated that the basic pyridine unit



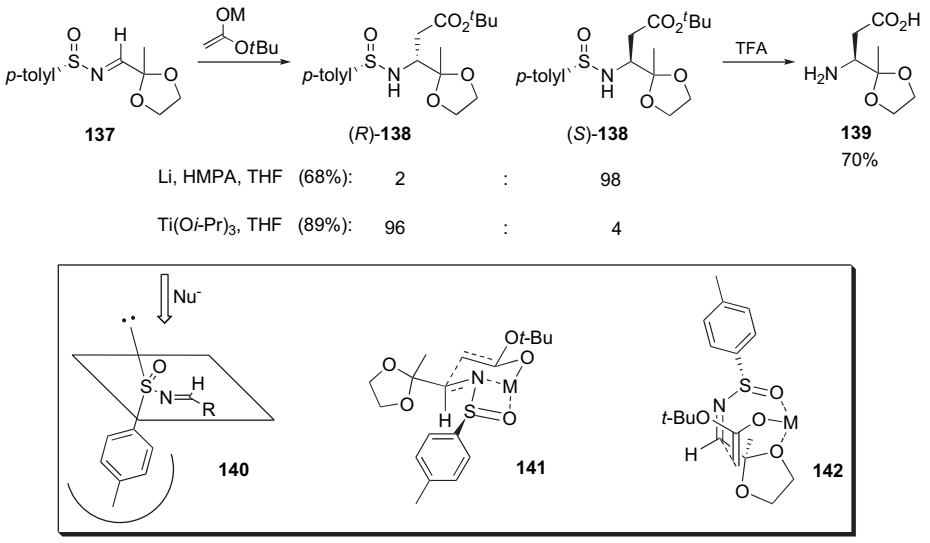
Scheme 42.

would present complications, and thus this synthesis provided a test of the robustness of the procedure. Hence, while the sodium enolate in diethyl ether had been established as the most efficient conditions, the insolubility of sulfinimine **134** precluded these conditions. Therefore a re-examination of the conditions was required.

While it was found that the lithium enolate of ethyl acetate effected the desired transformation in acceptable yield, the *p*-tolyl-substituted sulfinamide diastereomers were found to be inseparable. Fortunately however, the 2-methoxynaphthyl derivatives were found to be readily separable by flash chromatography. Hydrolysis of sulfinimine **135** with TFA presented β-amino acid **136**, in 90% yield, with the enantiomeric purity shown to be >97% ee.

En route towards the synthesis of chiral β-lactams, Fujisawa et al. observed an interesting feature of the reactivity of different metal enolates with *p*-TS-imines to make β-amino acids.[59] It was realised that it was possible to control the sense of stereoinduction through judicious choice of reagent, thus effectively making both enantiomers of the newly formed stereocentre available from the same starting material (Scheme 43). A rationale for the observed switchover in stereoselectivity was provided through a consideration of the chelated and non-chelated transition states. Addition of the lithium enolate in tetrahydrofuran with HMPA as an additive causes the counterion effect to be negated by solvent effects, and thus the open transition state **140** predominates, resulting in *si*-face attack of sulfinimine **137**.

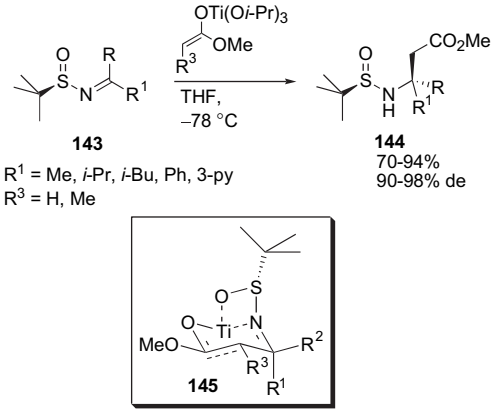
On the other hand with the titanium enolate, however, the more covalent nature of the bonding interactions leads to the predominance of the Zimmerman–Traxler-type six-membered transition state **141** and/or the seven-membered counterpart **142**, delivering the enolate to the *re*-face of the



Scheme 43.

sulfinimine. Both sets of conditions furnish sulfinamide **139** in good yield and high diastereoselectivity. Hydrolysis of (*S*)-**138** afforded the β-amino acid that was taken forward for the synthesis of β-lactams.

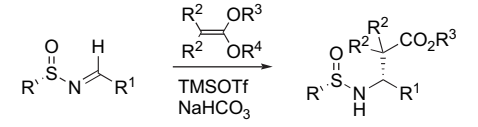
The synthesis of β-amino acids through the addition of metal enolates to *p*-TS-imines prompted Ellman et al. to examine the application of *t*-BS-imines **143**, proposing that the greater stereodirecting influence of the *tert*-butyl-sulfinyl group would result in the preparation of highly enantio-enriched β-amino acids **144**.[60] Having screened a series of both metals and solvents, Ellman established that the reaction of titanium enolates in tetrahydrofuran provided both the best yield and stereoselectivity (Scheme 44). Notably, a significant improvement in diastereoselectivity (74–96% de) was observed upon increasing the number of equivalents of titanium from 1 to 2. The scope of the reaction was then examined, and aryl, branched alkyl and unbranched alkyl *t*-BS-imines were all found to be suitable substrates for titanium enolate addition.



Scheme 44.

The stereochemical outcome of these transformations was in agreement with the previously proposed Zimmerman–Traxler-type six-membered transition state **145**. In addition to these studies, Ellman evaluated the impact of a substituent on the enolate (R^3). Preliminary results indicated that more substituted enolates remained efficient nucleophiles. Further work examined the application of the *t*-BS auxiliary as a Boc surrogate in the synthesis of more elaborate structures, where it proved to be both efficient and easy to remove.

An alternative approach to enantiopure β-amino acids was taken by Kawecki, investigating the addition of silyl ketene acetals to chiral *p*-TS-imines (Scheme 45).[61] A range of Lewis acids were screened to promote the reaction, with the most efficient system proving to be in the presence of TMSOTf. With efficient conditions in hand, the substituent tolerance for both the *p*-TS-imine and ketene was examined, and both aromatic and aliphatic substituted structures were observed to be suitable substrates. Focus then turned to the addition of silyl ketene acetals to 10-isobornyl-sulfinimines.



Scheme 45.

Addition of the silyl ketene acetal to the 10-isobornyl-sulfinimines was seen to only occur under the optimised conditions in the presence of TMSOTf. Upon reaction, however, the protected β-amino acid derivatives were provided in good yield and stereoselectivity. Subsequent to Kawecki's work, Skrydstrup et al. reported on the reaction of a similar system with *t*-BS-imines.[62] Reaction of silyl ketene acetals with *t*-BS-imines was found to proceed with similar yields (50–95%) and stereoselectivities (60–94% de).

Silverman et al. disclosed a protocol for the traceless solid-phase synthesis of chiral 3-aryl β-amino acid-containing peptides in 2000.[63] The key chiral-inducing step was a *t*-BS-imine-mediated titanium enolate addition, which

proceeded in high yield (79%) and excellent diastereoselectivity (>99% de).

In 2002, Ellman et al. disclosed a full account of their investigations into the asymmetric addition of enolates to *t*-BS-imines.[64] It was found that *t*-BS-imines **149** were ideal precursors for the synthesis of β-substituted α,β- and β,β-disubstituted, α,β,β- and α,α,β-trisubstituted and α,α,β,β-tetrasubstituted β-amino acid derivatives (Scheme 46).

Screening of the enolate addition conditions primarily with acetate enolates (R^3=R^4=H) furnished a series of the β-amino esters **149** in high yield (70–95%) and excellent diastereoselectivity (90–98% de) and firmly established the optimal conditions for the reaction. Application of these conditions to facilitate the addition of α-substituted ester enolates (R^3=Me, Bn, *p*-MeOPh; R^4=H) to *t*-BS-imines afforded access to α-substituted β-amino acids in high yield (65–96%) and generally good diastereoselectivity (18–92% de). Further it was found that α,α-disubstituted enolates (R^3=R^4=Me, –$(CH_2)_5$–) could be employed, providing α,α,β-trisubstituted and α,α,β,β-tetrasubstituted β-amino esters in moderate to good yield (65–86%) and excellent diastereoselectivity (98% de in all cases). In all instances, the major diastereomer was correctly predicted by the Zimmerman–Traxler six-membered transition state **150** previously invoked. With a diverse range of variously substituted β-amino acid derivatives to hand, Ellman's focus turned to the application of the *t*-BS group as a versatile protecting group, providing the means for incorporating *t*-BS-β-amino esters into a series of more complex structures.

4.4. Synthesis of chiral non-racemic amino alcohols

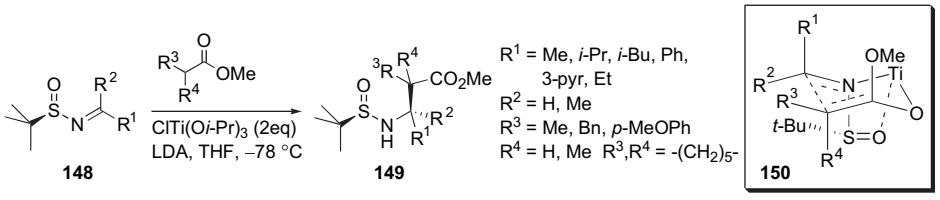
The 1,2- and 1,3-amino alcohol motifs are recurrent throughout drugs and natural products and have been widely employed in many chiral ligands for asymmetric catalysis. While many methods have been developed for the asymmetric synthesis of these valuable structural patterns, their varied applications warrant continued interest in new and diverse methods for their preparation.

Expanding upon the work of Bravo et al.,[65] Garcia Ruano and co-workers sought to develop a general procedure for the synthesis of chiral 1,2-amino alcohols via the Pummerer reaction of β-amino sulfoxides.[66] For this to be efficient, an expedient route to β-amino sulfoxides was required, and thus Garcia Ruano chose to examine the reaction of lithium anions with chiral *p*-TS-imines (Scheme 47). Building upon their previous experience, a chiral sulfoxide was incorporated into nucleophile **152** to induce a double stereodifferentiation effect, their reasoning being that this would increase the diastereoselectivity of the reaction.

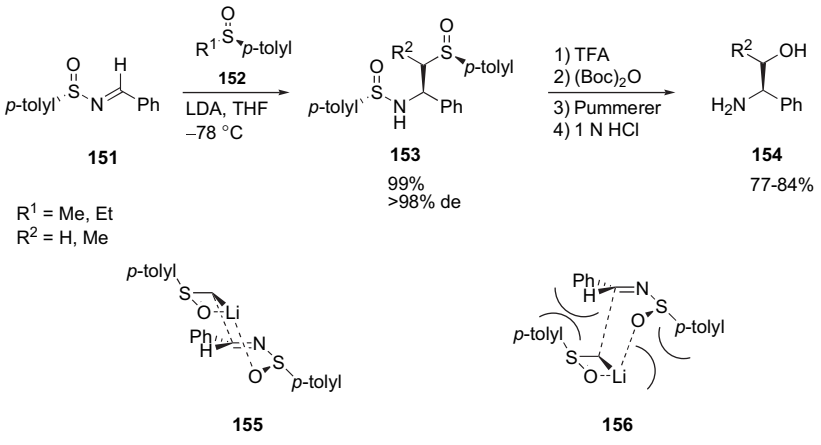
Reaction of the lithium anions of **152** with *p*-TS-imine **151** furnished chiral sulfinamides **153** in near-quantitative yield and excellent diastereoselectivity. The transition states **155** and **156** are for the matched pair, which, in this case, was found to be the *S*-sulfinimine and *R*-sulfoxide. Chelation of the incoming nucleophile is preferred for **155**, due to significantly reduced steric interactions. Exchange of the nitrogen protecting group and subsequent Pummerer reaction afforded the 1,2-amino alcohols **154** in good yield.

Barrow et al., through an adaptation of the methodologies developed by Davis and Ellman, described a novel *t*-BS-imine-mediated asymmetric synthesis of 1,2-amino alcohols **160** from protected α-alkoxy imines **157** and **158** in 2001 (Scheme 48).[67]

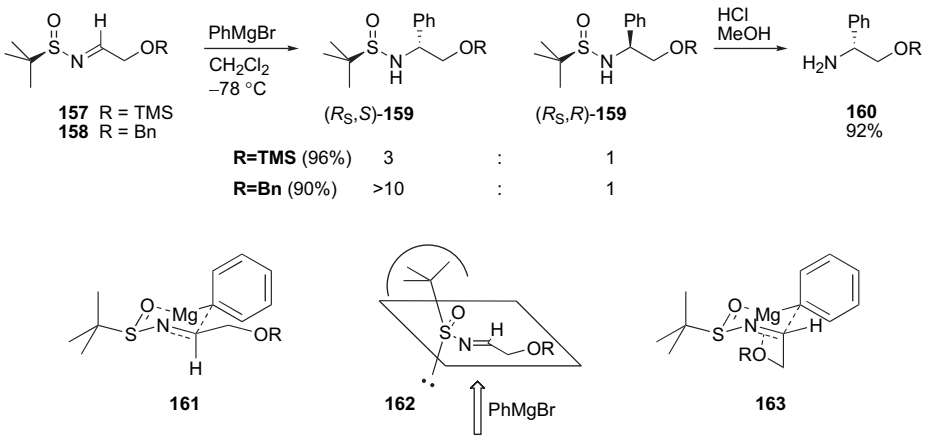
Initially, Barrow screened a range of conditions for the addition of phenylmagnesium bromide or phenyllithium to



Scheme 46.



Scheme 47.

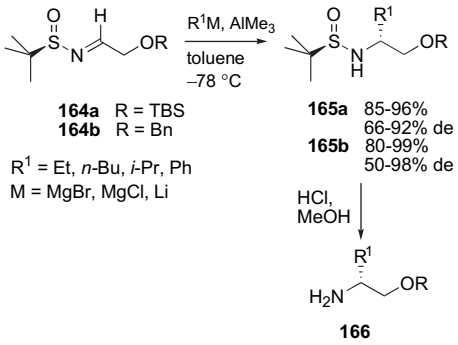


Scheme 48.

t-BS-imines **157** and **158**. In general, the yield of sulfinamide **159** was high (>80%), but the diastereoselectivity of the reaction was found to be highly dependent on the conditions employed. With tetrahydrofuran present in the solvent system, a modest selectivity towards the expected (R_S,*R*)-**159** was observed, which was thought to proceed through transition state **161**. Reactions performed in CH_2Cl_2, however, favoured the formation of the (R_S,*S*)-**159** isomer. This reversal in selectivity has been previously observed, and the open transition state **162** was used to rationalise the stereochemistry. Barrow put forward the chelated bicyclic transition state **163**, in which the imine has isomerised to the *Z*-conformation, the behaviour which has previously been observed.[22] Further support for this premise was found when sulfinimine **158** was subjected to the reaction conditions. It was found that sulfinimine **158** was significantly more selective and less dependent upon the solvent environment, thought to be due to the superior co-ordinating power of the benzyloxy group, hence stabilising **163**. Once the optimal conditions were established, the scope of the reaction was examined, with a series of both aryl and alkyl Grignard reagents adding to sulfinimines **158** in good yield (44–100%) and modest stereoselectivity (23–80% de).

Later in the same year, Ellman et al. published their findings on the synthesis of 1,2-amino alcohols **166** from *t*-BS-imines.[68] These workers employed the substrates previously examined by Barrow for their investigations. Preliminary studies focused on screening the conditions for the addition. Drawing on previous experience, it was observed that the addition of a Lewis acid improved not only the yield of the reaction, but also the stereocontrol of the addition. The addition of *tert*-butylmagnesium chloride was found to proceed most satisfactorily in toluene in the presence of aluminium trichloride (Scheme 49).

These conditions were found to be the most efficient for both the benzyl and silyl ethers, affording sulfinamides **165** in high yields and stereoselectivities. The stereoinduction observed was in line with Barrow's results, and thus Ellman invoked a similar argument. Further results, however, highlighted that the true mechanism was still not fully understood. Addition to a *t*-BS-ketimine was found to proceed in modest yield (42–52%) and diastereoselectivity (44–70% de), yet the stereochemistry of the resulting sulfinamides was the reverse

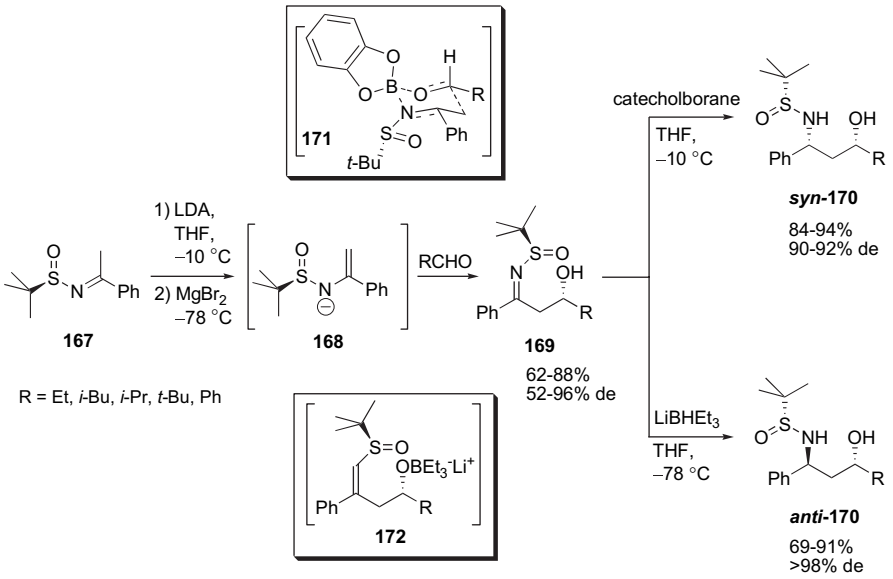


Scheme 49.

of the aldimine substrates and, in line with previous Grignard additions, was presumably via transition state **150**, the α-chelating group therefore having no effect on the facial selectivity of *t*-BS-ketimines.

In 2002, Ellman et al. disclosed a report detailing their work on a remarkable new feature of chiral sulfinimine chemistry.[69] While the asymmetric addition to sulfinimines had been used extensively, despite the importance of metalloenamines as enolate equivalents, the use of metalloenamines derived from sulfinimines had not previously been described. Ellman proposed that the addition of a *t*-BS-metalloenamine to an aldehyde would occur stereoselectively, furnishing the chiral β-hydroxyl *t*-BS-imines, which, upon reduction and subsequent deprotection would afford direct entry to a wide range of chiral 1,3-amino alcohols (Scheme 50).

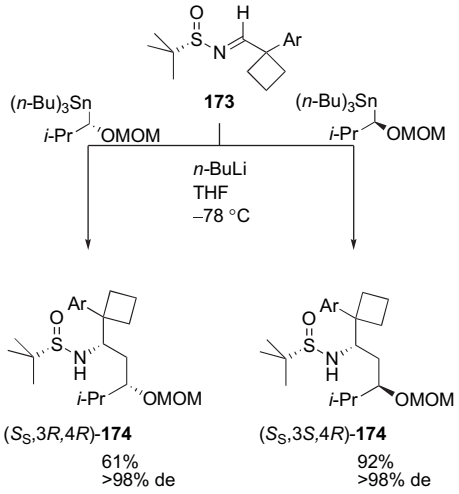
Generation of the *t*-BS-metalloenamine **168** from **167** was found to be best accomplished with lithium diisopropylamine, the addition of $MgBr_2$ significantly increasing both the yield and stereoselectivity of the transformation. Addition to a number of both aryl and alkyl aldehydes to form **169** was accomplished in good yield and diastereoselectivity. Reduction to the 1,3-amino alcohols was found to be highly dependent upon the reagent employed. Both catecholborane and $LiBHEt_3$ carried out the reduction in high yield, with catecholborane affording *syn*-**170** and $LiBHEt_3$ presenting the *anti*-**170**. It was proposed that chelation of the catecholborane with the sulfinyl group (**171**) stabilised isomerisation of the imine to the *Z*-geometry, hence the *anti*-stereoselectivity,



Scheme 50.

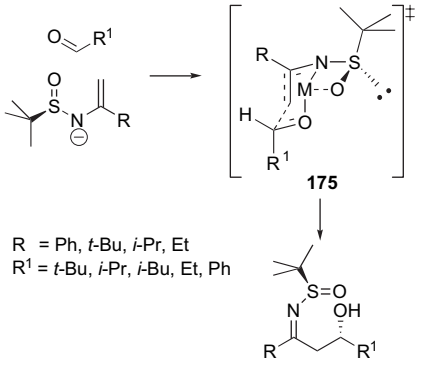
while no such stabilisation is present upon reaction with $LiBHEt_3$ (**172**).

Senanayake et al. developed an efficient method for the synthesis of both *syn*- and *anti*-1,2-amino alcohols from a common *t*-BS-imine starting material **173** (Scheme 51).[70] Addition of the stannanes proceeded in good yield (61–92%) and excellent diastereoselectivity (>98%), affording the protected 1,2-amino alcohols **174**. Deprotection through exposure to HCl in methanol furnishes the desired chiral 1,2-amino alcohols in 83–89% yield.



Scheme 51.

In 2003, Ellman et al. disclosed a detailed account of their extended studies on the formation of *t*-BS-metalloenamines and their application in the synthesis of 1,3-amino alcohols.[71] Having established the optimal conditions in the preliminary report,[69] Ellman's focus turned to the scope of the reaction. A range of both aryl and alkyl aldehydes were found to be suitable substrates for the addition reaction, as were a series of more complex *t*-BS-metalloenamines, with both aryl and alkyl side chains incorporated. In all cases, the reaction proceeded in good to high yield (50–92%) and high stereoselectivity (54–98% de). To rationalise the stereochemical outcome, Ellman proposed the transition state **175** to access the major diastereomer (Scheme 52).

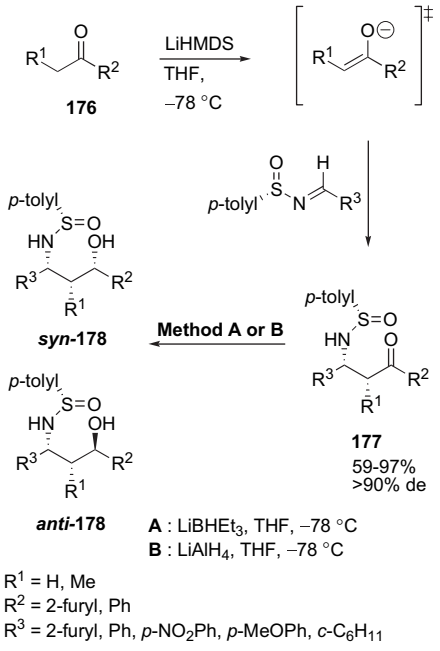


Scheme 52.

The practical nature of the reaction of *t*-BS-metalloenamines was further exemplified by Ellman through the synthesis of two alkaloid natural products (−)-halosaline and (−)-8-epi-halosaline.

Nelson et al. employed an alternative strategy for the construction of 1,3-amino alcohols.[72] Addition of ketone enolates **176** to *p*-TS-imines was found to occur stereoselectively, to afford the corresponding chiral β-amino ketones **177**. Subsequent reduction provided direct access to amino alcohols **178** (Scheme 53).

The addition of a number of ketone enolates to a range of aryl- and alkyl-*p*-TS-imines was achieved in high yield (59–97%) and generally excellent diastereoselectivity (>90%). A range of conditions were screened for the reduction and, while the majority of conditions were efficient, two sets in particular afforded noteworthy results. Reduction with $LiBHEt_3$ in tetrahydrofuran furnished the 1,3-amino alcohols **178** in a 92:8 ratio in favour of the *syn*-isomer (Method A). On



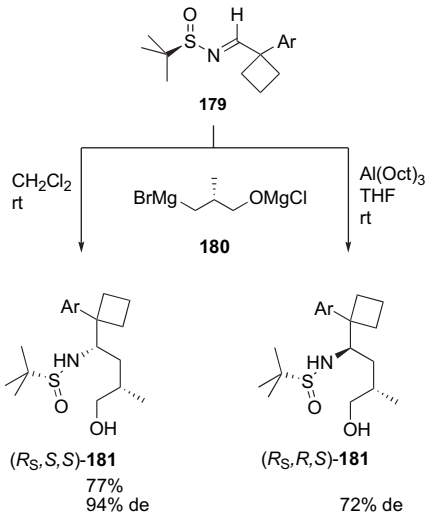
Scheme 53.

the other hand, reduction with $LiAlH_4$ in tetrahydrofuran provided the amino alcohols in a 29:71 population in favour of the *anti*-isomer (Method B). Hence, a careful choice of conditions allows selection between the *syn*- and *anti*-isomer from the same starting material.

In a recent report, Garcia Ruano et al. expand upon their investigations into the synthesis of chiral 1,2-amino alcohols through the reaction of chiral lithium anions with *p*-TS-imines.[73] Further to their previous studies, the reaction of the *p*-TS-ketimine derived from acetophenone was investigated and the influence of the sulfinyl substituent examined. As observed before, the excellent diastereoselectivity of the reaction was the result of a double stereodifferentiation effect, with the *S*-sulfinimine and *R*-sulfoxide making up the matched pair. The addition to the sulfinimine occurred with high yield (67–83%) and excellent stereoselectivity (>98% de). Interestingly, changing to the naphthyl-sulfinimine in place of the *p*-TS-imine produced some anomalous results, with disappointing yields and diastereoselectivities observed.

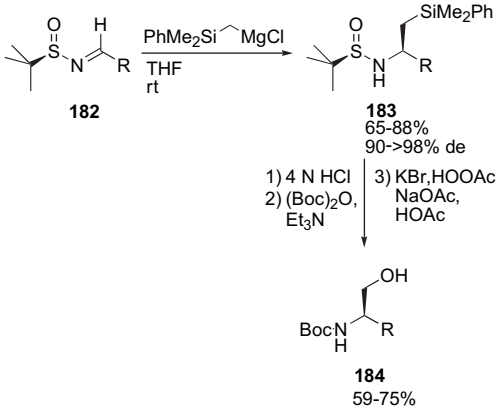
En route to the synthesis of biologically active sibutramine analogues, Senanayake et al. exploited the chiral influence of the *t*-BS-auxiliary in the preparation of 1,4-amino alcohols.[74] Seeking to analyse the biological potential of all stereoisomers of the target molecule, Senanayake reported the efficient stereoselective synthesis of all four stereoisomers (Scheme 54). It was observed that it was possible to obtain both enantiomers of 1,4-amino alcohols **181** from a single enantiomer of *t*-BS-imine **179**. Addition of the Grignard reagents (*S*)-**180** or (*R*)-**180** to a common sulfinimine led to a new chiral centre with the *R*-configuration.

The same reaction carried out in CH_2Cl_2, however, led to a new stereocentre with *S*-configuration being formed. Subsequent deprotection afforded the corresponding 1,4-amino alcohols.



Scheme 54.

Very recently, Kim et al. reported their findings on the development of an alternative route to chiral 1,2-amino alcohols.[75] Using the dimethylphenylsilyl group as a masked hydroxy equivalent, the addition of [(dimethylphenylsilyl)-methyl]magnesium chloride to *t*-BS-imines **182** and subsequent Fleming–Tamao oxidation of silanes **183** was found to provide an effective entry to the desired chiral alcohols **184** (Scheme 55).



Scheme 55.

A screen of the conditions established that the most efficient reaction, in terms of both the yield and stereoselectivity, was carried in tetrahydrofuran at room temperature. The configuration of the newly formed chiral centre was found to favour the *R*-isomer, which is in accordance with the six-membered chelated transition state commonly invoked for the addition of Grignard reagents. With these conditions established, the focus was turned to the scope of the reaction. Both alkyl and aryl *t*-BS-imines were found to be suitable substrates, undergoing the addition in good yield (65–88%) and excellent diastereoselectivity (90 to >98% de). Subsequent conversion into the Boc-protected amine and Fleming–Tamao oxidation afforded the chiral 1,2-amino alcohols in good yield (59–75%).

Thus through the addition of a variety of organometallic reagents or the development of a new aspect to sulfinimine

chemistry in the case of Ellman's metalloenamine chemistry, it has been shown that a variety of chiral 1,2-, 1,3- and 1,4-amino alcohols are readily accessible in only a few steps from sulfinimines.

4.5. Synthesis of chiral 1,2-amino sulfides

1,2-Amino sulfides have, in recent years, received a good deal of interest from the synthetic community; not only have they found application as N, S ligands in asymmetric synthesis, but they are also common as a subunit in a number of biologically active molecules. In 2005, drawing upon their previous experience,[76] Garcia Ruano et al. published an expedient synthesis of chiral 1,2-amino sulfides **186** through the addition of a suitably substituted benzyl carbanion to chiral *p*-TS-imines **185** (Scheme 56).[77]

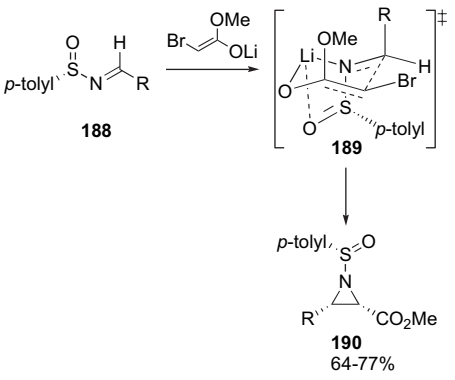
Under optimised conditions, the addition of the benzyl carbanion to the *p*-TS-imine was found to be a rapid and efficient reaction. It was observed that there was a double stereodifferentiation effect at work, with the matched pair having the *S*-configuration around both the *p*-TS-imine and the chiral sulfoxide present in the nucleophile; under these conditions, exceptional stereoselectivity was observed. Using *tert*-butyllithium to remove the sulfoxide, with subsequent deprotection of the amine with HCl, revealed direct access to chiral *anti*-1,2-amino sulfides **187**.

4.6. Synthesis of chiral aziridines

Aziridines are a representative of the first, and most simple of, heterocyclic systems, characterised by the presence of two carbon atoms and one heteroatom. Their simplicity, however, belies their importance to organic chemistry. Aziridines and, in particular chiral aziridines, are increasingly being exploited in organic synthesis. Elaboration via ring opening or ring expansion provides direct access to a host of structural motifs.[78]

Combining a long-standing interest in aziridines and the application of chiral *p*-TS-imines, Davis et al. developed the asymmetric aza-Darzens reaction for the synthesis of *cis*-*p*-TS-aziridine-2-carboxylic acids **190** (Scheme 57).[36] The addition of the lithium enolate of methyl-2-bromoacetate was found to add selectively to a series of both non-enolisable and enolisable *p*-TS-imines **188** in good yield (64–77%), with, in most cases, only the cis-isomer being observed. The high cis-stereoselectivity was rationalised by invoking the six-membered transition state **189**.

To demonstrate the application of *p*-TS-aziridines, Davis investigated the reaction of **190**. It was demonstrated that the

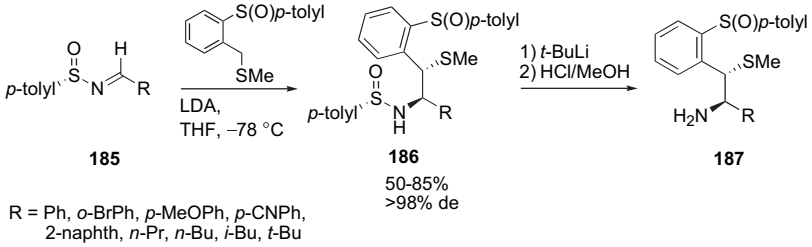


Scheme 57.

sulfinyl auxiliary could be easily oxidised to the toluenesulfonyl group, thus making it a substrate for the plethora of ring-opening reactions previously established for that motif. Removal of the sulfinyl group upon exposure to TFA revealed direct access to N–H aziridines, versatile intermediates in synthesis. Further, it was shown that the *p*-TS auxiliary provides enough activation to the aziridine ring to direct ring opening, thus bypassing the need to oxidise to the more-electron-withdrawing sulfonyl substituent.

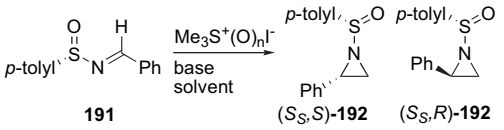
Supplementary to their report on the synthesis of *cis*-*p*-TS-aziridine-2-carboxylic acids, Davis et al. demonstrated the practicality of these small molecules through the synthesis of the antibiotic, (+)-thiamphenicol, using the chiral aziridine backbone to install the stereochemistry of this molecule.[79]

In 1995, Garcia Ruano et al. reported the results of their evaluation of a *p*-TS-imine-mediated modification of the classic Corey–Chaykovsky methylene-transfer reaction.[80] Reaction of the activated sulfonium ylides, dimethylsulfonium methylide and dimethyloxosulfonium methylide with chiral non-racemic *p*-TS-imines **191** was found to furnish chiral aziridines **192** in good yield (Scheme 58). From screening the reaction conditions, two clear trends emerged, it was observed that the nature of the major diastereomer was dependent upon the methylene-transfer reagent employed, with the reaction with dimethylsulfonium methylide selecting for the *S*-isomer and dimethyloxosulfonium methylide for the *R*-isomer. The solvent polarity was found to have a significant effect upon the diastereoselectivity; as the polarity of the solvent was increased, the diastereoselectivity of the reaction was improved, with solvents such as DMSO and DMF for dimethylsulfonium methylide and toluene for dimethyloxosulfonium methylide proving optimal. Further, it was



Scheme 56.

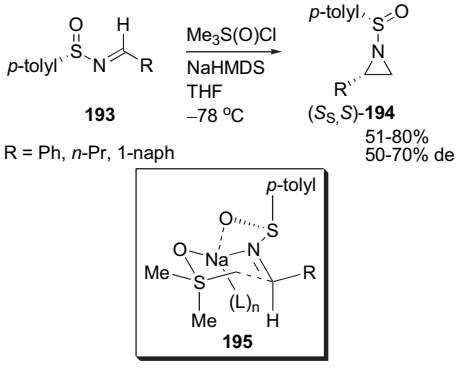
found that the stereoselectivity of the reaction was independent of the metal ion present.



Scheme 58.

Deprotection of the chiral aziridines was accomplished through treatment with methyllithium, affording the N–H aziridine, through which the stereochemical assignments were made. In an ensuing report in the same year, however, these assignments were brought into question.

Diversifying from the development of the sulfinimine-mediated aza-Darzens aziridine synthesis, Davis et al. reported their findings on the addition of dimethyloxosulfonium methylide to *p*-TS-imines (Scheme 59).[81] Having screened a number of conditions for the reaction of the activated ylide with both alkyl- and aryl-*p*-TS-imines **193**, it was observed that the use of solvents other than tetrahydrofuran resulted in significantly lower yields. The optimal base in terms of both yield and stereoselectivity was found to be sodium bis(trimethylsilyl)amine (NaHMDS).



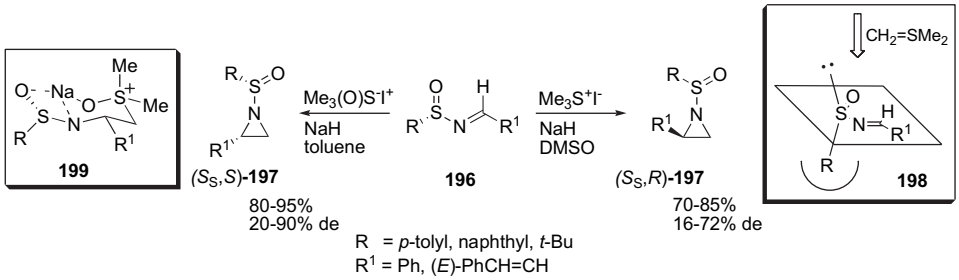
Scheme 59.

While the extent of the diastereoselectivity was not astonishing, *p*-TS-aziridine **194** diastereomers were separable. The absolute assignment of stereochemistry was achieved through oxidation to the known *N*-tosyl-aziridine with *m*-CPBA, establishing that the reaction of dimethyloxosulfonium methylide with (*S*)-*p*-TS-imine is selective towards (S_S,*S*)-**194** isomer, not (S_S,*R*)-**194** isomer as previously thought. The stereochemical outcome was in agreement with a six-membered transition state **195** proposed by Davis. Further confirmation of the assignment was gained upon removal of the *p*-TS-auxiliary, with methyllithium affording the known (*S*)-phenylaziridine.

In 1996, Garcia Ruano et al. disclosed a report containing a full account of their investigations into the reaction of activated sulfur ylides with sulfinimines.[12] Prompted by the disappointing diastereoselectivity observed both by themselves and Davis on the reaction of *p*-TS-imines with methylene-transfer reagents, Garcia Ruano et al. examined the influence of the substituent on the sulfinyl sulfur on the stereochemical outcome of the aziridination. Using the optimal conditions discovered in their previous investigations, the reaction of both dimethylsulfonium methylide and dimethyloxosulfonium methylide with *p*-TS-, naphthyl- and *t*-Bu-imines **196** was investigated (Scheme 60). A number of trends became clear from their enquiries. Again, it was realised that, for all substrates, an opposite sense of diastereoselection occurred at the newly formed C-2 carbon when using different methylene-transfer reagents. Thus, (S_S,*S*)-**197** are the major products with dimethyloxosulfonium methylide in toluene, while (S_S,*R*)-**197** are formed preferentially upon reaction with dimethylsulfonium methylide in DMSO. These stereochemical assignments are in line with Davis's previous observation.

With respect to the influence of the sulfur substituent on the stereoselectivity of the aziridination, it was observed that an increase in the steric bulk of the substituent was accompanied by an increase in the diastereoselection. Thus, changing from the *p*-TS-imines to the naphthyl-sulfinimines resulted in an increase in the diastereomeric excess with both ylides, the improvement being much more pronounced when the *t*-BS-imines were examined, providing even greater levels of stereocontrol. Garcia Ruano proposed that the observed disparity in the stereochemical outcome of the reaction with the two ylides was attributable to the difference in the chelating character of the reagents. With the non-chelating dimethylsulfonium methylide, the nucleophilic attack is directed to the least-hindered face of sulfinimine **198**. The presence of the oxygen on the dimethyloxosulfonium methylide, however, provides the opportunity for the intermediate betaine to be stabilised through chelation with sodium. Thus, the conformation of the transition state **199** is favoured over the more hindered form in which the R group would clash with the axial methyl of the ylide.

Such was the success of the sulfinimine-mediated aza-Darzens protocol developed by Davis et al. that it was investigated whether aziridine-2-phosphonates could be prepared



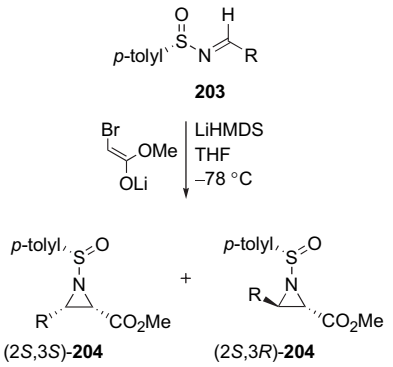
Scheme 60.

by an analogous method.[82] As surrogates for carboxylic acids, amino phosphonates have received significant interest and, it was for these reasons, that aziridine-2-phosphonates were thought to be valuable targets.[83] Using the conditions previously optimised for the aza-Darzens chemistry, the reaction between *p*-TS-imines **200** and the lithium anion of diethyl chloromethylphosphonate was found to give none of the desired aziridines **202** (Scheme 61). Rather, the major products were the α-chloro-β-amino adducts **201**. Isolation and treatment of the sulfinamide diastereomers **201** with 2 equiv of sodium hydride furnished the aziridine-2-phosphonates **202** in good yield.

The stereochemical outcome observed was consistent with previous phosphite and α-phosphonate additions to chiral sulfinimines, the nucleophile attacking the least-hindered face in an open, non-chelated transition state. Treatment of the *cis*-aziridine-2-phosphonates **201** with 50 equiv of TFA removed the sulfinyl group in 84% yield. Interestingly, under similar conditions, the less stable *trans*-aziridines were found to afford mainly the ring-opened product, while conducting the reaction at 0 °C with only 5 equiv of TFA delivered the N–H aziridine in 91% yield. Davis demonstrated the potential of the aziridine-2-phosphonates through ring opening to afford the α-amino phosphonates and hydrogen abstraction to give the azirine-2-phosphonates.

To demonstrate the practicality of the sulfinimine-mediated aza-Darzens synthesis of the aziridine-2-carboxylate esters, it was applied as a key step in the synthesis of a variety of chiral amine motifs. In 1999, Davis published a report summarising these applications and describing their exploration of this simple aziridination procedure (Scheme 62).[84] A wide range of α-haloesters were screened to find the best conditions for the addition to *p*-TS-imine. While, in general, these reactions occurred with high stereoselectivities (68–98% de), the yields were disappointing. The best results were observed for the lithium enolate of methyl α-bromoacetate, with high selectivity (>90% de) and yield. Aziridination was found to be general for aromatic, aliphatic and α,β-unsaturated *p*-TS-imines **203** furnishing the *cis*-aziridines **204** in good yield (50–77%).

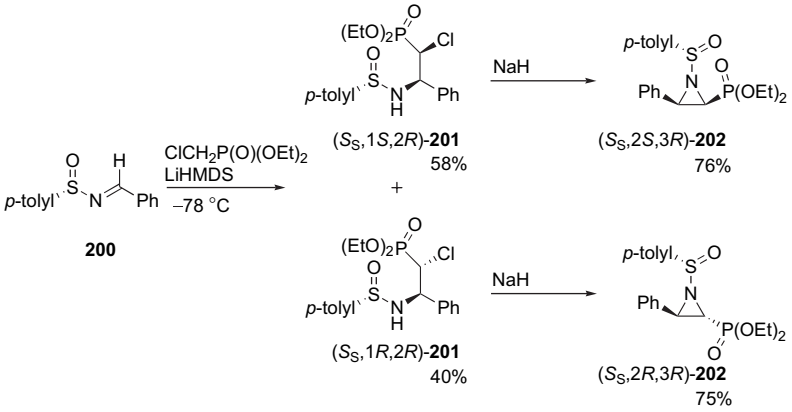
The preparation of aziridines directly from the Andersen derivative that is the sulfinimine precursor was investigated and, while the aziridines could be prepared in high yields



Scheme 62.

(55–93%), the stereoselectivity observed was significantly lower (42–90% de). In addition, the reaction of the enolates with *p*-TS-ketimines was briefly examined. Reaction with the sulfinimine derived from acetophenone proved sluggish, however, and required thermal encouragement. There were also significant side reactions competing with the desired aziridination, primarily the formation of the *p*-TS-imine enolate and further side reactions which markedly reduced the yield. To demonstrate the aziridine-2-carboxylate motif's potential for further elaboration, a number of transformations were carried out on the chiral cis-substrates. Deprotection of the ring nitrogen was achieved through exposure to either TFA or methylmagnesium bromide. The ring opening of the chiral aziridines was shown to provide direct access to chiral α-amino acids, a strategy previously employed by Davis. Oxidation of the sulfinyl group was shown to furnish the corresponding *N*-tosyl aziridines, the activating nature of which is key to many aziridine transformations.

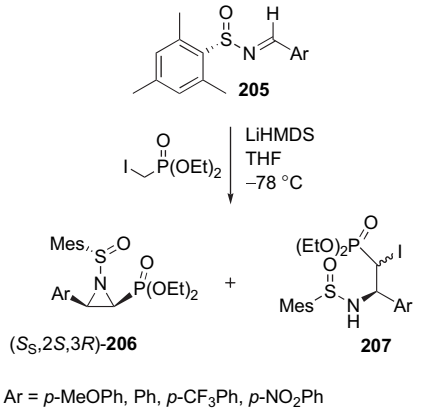
Building upon their preliminary results on the synthesis of *p*-TS-aziridine-2-phosphonates, Davis et al. published a detailed report on their extended investigations.[85] While, at this stage, it remained necessary to isolate the intermediate α-chloro-β-amino adducts and subsequently cyclise them to synthesise the aziridines in acceptable yields and stereoselectivities, the protocol was shown to be practical for a wide range of aromatic *p*-TS-imines. Further, the influence of the sulfinyl auxiliary on the reaction was investigated. Reaction of the anion derived from either iodo or tosyl phosphonate with *t*-BS-phenyl-imine and LiHMDS formed the aziridine-2-phosphonate directly, as a single isomer in 82% and



Scheme 61.

32% yield, respectively. Unfortunately, however, removal of the *tert*-butylsulfinyl auxiliary proved challenging. Thus, Davis's investigations into the synthesis of aziridine-2-phosphonates from sulfinimines were continued.

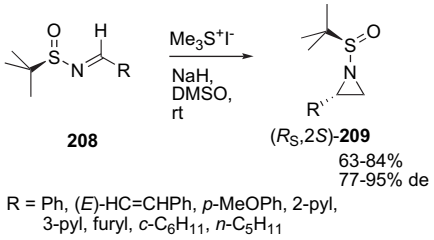
In a report later in 2003, Davis disclosed an improved synthesis of aziridine-2-phosphonates.[86] Seeking to combine the advantageous features of both the *t*-BS- and *p*-TS-imines, *N*-sulfinyl auxiliaries large enough to produce high diastereoselectivities in the aza-Darzens reaction and to allow selective deprotection using Grignard reagents. Thus the *N*-(2,4,6-trimethylphenylsulfinyl) (Mes-sulfinyl) auxiliary was examined (Scheme 63). Using a modification of the procedure developed by Senanayake, in which LiHMDS was favoured over NaHMDS as it proved to impart better enantioselectivity, Davis prepared a range of Mes-sulfinimines **205**.



Scheme 63.

Under the previously optimised conditions, reaction of Mes-sulfinimines containing the phenyl and *para*-methoxyphenyl motif underwent aziridination to form aziridine-2-phosphonates **206** as single diastereomers, in one pot with 75% and 78% isolated yield, respectively. Substrates containing electron-withdrawing functionalities, such as *p*-trifluoromethylphenyl and *p*-nitrophenyl Mes-sulfinimines, however, reacted to produce a complex mixture of the desired aziridine diastereomers and isomeric mixtures of the β-amino-α-iodophosphonates **207**, which could not be separated. This was in contrast to the *p*-TS analogues, which were found to be separable; this divergence in physical properties is thought to be due to the increased lipophilicity associated with the Mes-sulfinyl group. Exposure of the Mes-aziridine-2-phosphonates to 2 equiv of methylmagnesium bromide furnished the deprotected N–H aziridines in 72–77% yield with no loss of optical purity. Though the application of Mes-sulfinimines appears not to be general, the diastereoselectivities associated with the system provided a significant improvement on those associated with the *p*-TS-imines and, with the demonstrated facile removal of the Mes-sulfinyl auxiliary, this is an efficient and direct route to the synthesis and further elaboration of chiral aziridine-2-phosphonates.

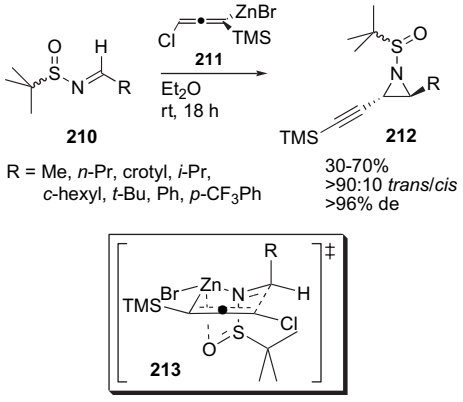
To determine the functionality tolerated by the sulfur ylide-mediated aziridination of chiral sulfinimines, Stockman et al. explored the reaction of *t*-BS-imines with dimethylsulfonium methylide in greater detail (Scheme 64).[87] Their initial investigations screened a series of conditions to determine the optimal reaction of dimethylsulfonium methylide with *t*-BS-imines. In line with the findings of Garcia Ruano et al., deprotonation with sodium hydride in DMSO provided both the best yield and stereoselectivity.



Scheme 64.

Both aromatic and enolisable aliphatic *t*-BS-imines **208** were found to be suitable substrates for the procedure, affording aziridines (R_S,2*S*)-**209** in high yields and stereoselectivities. Notably, the reactions were found to be complete within 10 h, signifying a remarkably more rapid process than those observed by both Davis and Garcia Ruano. The selective formation of the *S*-chiral centre within the aziridine ring is in line with the previously observed reaction, where it was proposed that the selectivity originated from an open transition state with the *si*-face protected by the steric bulk of the auxiliary and the nucleophile attacking the open *re*-face. The stereochemical assignments were confirmed by an X-ray crystal structure.

Extending their previous experience in the synthesis of *N*-benzyl and *N*-TMS ethynylaziridines, Ferreria et al. examined the reaction of allenylzinc **211** with racemic *t*-BS-imines **210** (Scheme 65).[88] With their established procedures only requiring minor modifications, both aromatic and aliphatic *t*-BS-imines were found to be suitable substrates, accessing the corresponding ethynylaziridines **212** in generally good yield (35–70%), high trans/cis selectivity (>90:10) and excellent diastereoselectivity (>96% de of the trans-isomer). Further, the procedure was found to be applicable to a limited range of *t*-BS-ketimines, albeit in lower yields. In all cases, however, the reaction was found to be rather sluggish, requiring 18 h and with the allenylzinc reagents required in significant excesses (3–6 equiv).

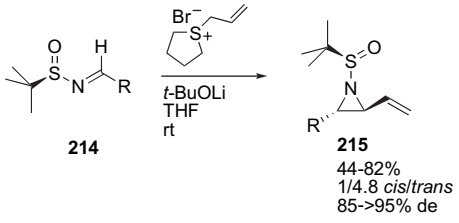


Scheme 65.

The relative stereochemistry of the aziridines was confirmed through comparison with the X-ray crystal structure of the

t-BS-phenyl-ethynylaziridine. The high predilection for the trans-isomer was rationalised through the Zimmerman–Traxler-type transition state **213**. While these preliminary investigations were carried out on racemic *t*-BS-imines, the scope of the reaction was established and the stereoselectivities observed revealed the potential for the synthesis of optically pure chiral ethynylaziridines.

Building upon their previous investigations into the reaction of activated sulfur ylides with *t*-BS-imines, Stockman et al. disclosed their exploration of the reaction of *S*-allyl sulfur ylides with chiral *t*-BS-imines for the synthesis of chiral vinylaziridines **215** (Scheme 66).[89] Initial investigations revolved around the optimisation of the conditions; a series of solvents and bases were analysed, with generation of the ylide with LiO*t*-Bu in tetrahydrofuran providing the best balance of high yield and good cis/trans selectivity. In all cases examined, irrespective of base or solvent, the diastereoselectivity observed was excellent (generally >95%).

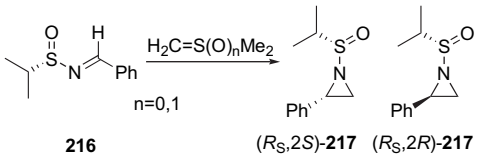


Scheme 66.

With efficient conditions established, the focus was turned to the generality of the reaction. Aromatic, heterocyclic and branched and cyclic aliphatic *t*-BS-imines **214** were all found to be suitable substrates, providing the corresponding *t*-Bs-vinylaziridines **215** in good yield and excellent diastereoselectivity. The excellent diastereoselectivity was rationalised by invoking an open transition state, with the ylide attacking the less hindered *re*-face of the (*R*)-*t*-BS-imine. The removal of the *t*-BS-auxiliary was achieved through exposure to HCl in dioxan, furnishing the stable hydrochloride salt of the N–H aziridine in >90% yield, thus increasing the potential for elaboration of the chiral vinylaziridines.

Prompted by their initial results on the reaction of allenylzinc **211** with racemic *t*-BS-imines, Ferreira et al. took the logical progression and examined the reaction with enantiomerically pure *t*-BS-imines.[90] As expected, the non-racemic substrates performed with similar reactivity to their racemic counterparts, with both aromatic and aliphatic *t*-BS-imines furnishing the ethynylaziridines in good yield (54–70%) displaying a high predilection for the trans-isomer (90:10) and excellent diastereoselectivity (>96% de). In an effort to reduce the long reaction time and large excesses of allenylzinc required to achieve these reactions, Ferreira considered the reaction of *p*-TS-imines. While the *p*-TS-imines all exhibited a much higher reactivity, consequently requiring less allenylzinc (1.5–3 equiv) and being complete in significantly shorter times, disappointing levels of diastereoselectivity were observed. Removal of the *t*-BS-auxiliary was achieved through treatment with HCl in methanol. Overall, a series of aromatic and aliphatic chiral, non-racemic ethynylaziridines were prepared in good yield and stereoselectivity.

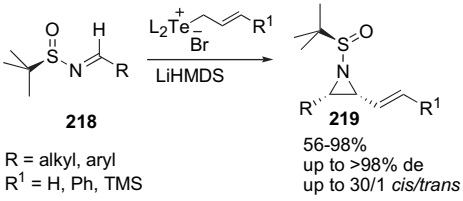
Recently, Fernandez et al. re-examined the reaction of chiral sulfinimines with the activated sulfonium ylides, dimethylsulfonium methylide and dimethyloxosulfonium methylide, to demonstrate the application of a new class of chiral sulfinimines.[91] Fernandez reports on the development of the *iso*-propyl-sulfinyl (*i*-PS) auxiliary **216**, and its application to the synthesis of chiral terminal aziridines **217** (Scheme 67). Recognising that the trend was towards more sterically encumbered sulfur substituents, the *i*-PS-imines were designed to play an intermediary role between the *p*-TS- and the *t*-BS-imines.



Scheme 67.

The results reported suggest that the *i*-PS auxiliary does indeed react with a rapid nature with the *p*-TS-imines and induces stereoinfluence similar to that of the *t*-BS-imines. The aziridines were formed with the same sense of stereoinduction as previously observed for the addition of activated sulfur ylides to sulfinimines.

Very recently, Tang et al. disclosed a report on the reaction of telluronium ylides with *t*-BS-imines **218** in the synthesis of chiral, non-racemic *cis*-vinylaziridines **219** (Scheme 68).[92] Optimisation of the conditions provided an efficient protocol that was applied to the synthesis of a diverse range of aromatic, aliphatic and unsaturated aliphatic *cis*-vinylaziridines. In addition, the *t*-BS-ketimine derived from acetophenone underwent the aziridination in good yield (76%) and high stereoselectivity (30/1 cis/trans, >98% de). Further studies examined the aziridination mediated by different telluronium ylides. Interestingly, replacing the TMS group with a proton diminished both the yield and stereoselectivity.



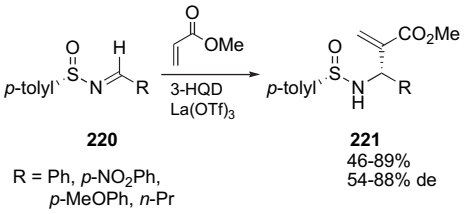
Scheme 68.

Aziridines have been shown to be efficient precursors to a number of interesting motifs, and, with their potential for elaboration, either through ring expansion or ring opening, and now through the reaction of chiral non-racemic sulfinimines, a number of efficient routes for the preparation of the valuable chiral aziridines have been developed.

4.7. Synthesis of chiral β-hydroxy-α-methylene esters

The Baylis–Hillman reaction provides an efficient direct entry into substituted esters, ketones and nitriles. In an effort to assert stereocontrol over the reaction, Aggarwal et al. investigated whether the *N*-sulfinimines **220** would be activated

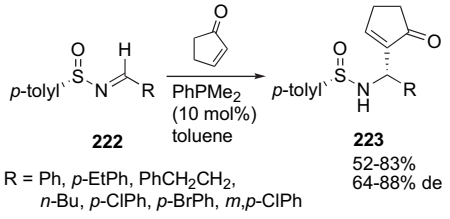
enough to undergo the coupling reaction to **221** (Scheme 69).[93] A range of conditions were examined for the addition of methyl acrylate to *p*-TS-phenyl-imine, and it was observed that the most efficient reaction was achieved in the presence of 3-hydroxyquinuclidine (3-HQD) as an amine catalyst and lanthanide-based Lewis acids, affording the desired β-hydroxy-α-methylene ester in high yield (89%) and modest diastereoselectivity (64% de). It was also observed that the major isomer had the *S*-configuration around the new chiral centre, rationalised by a six-membered Zimmerman–Traxler-type transition state.



Scheme 69.

In an effort to improve the rather disappointing diastereoselectivity of the transformation, the reaction with the bulkier *t*-BS-imines was examined. Reaction with the *t*-BS-analogues furnished increased levels of diastereoselection, but the yields were significantly diminished, leading to the conclusion that the *p*-TS-imines were the most suitable substrates for the Baylis–Hillman reaction.

In the same year, Shi et al. reported their findings on the sulfinimine-mediated catalytic asymmetric Baylis–Hillman reaction (Scheme 70).[94] Drawing upon their previous experience with the catalytic Baylis–Hillman reaction, a range of conditions were screened. Reaction of **222** in toluene in the presence of 10 mol % of the Lewis acid dimethylphenylphosphine, afforded the β-hydroxy-α-methylene amides **223** in high yield (83%) and good diastereoselectivity (86% de).

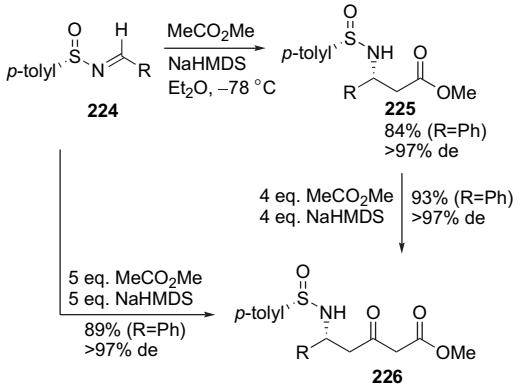


Scheme 70.

The scope of the reaction was then examined and both alkyl and aryl-*p*-TS-imines were found to be suitable substrates for the addition.

5. Chiral sulfinimines as building blocks for synthesis

Designed polyfunctionalised chiral building blocks (DPFCBs) have been developed to overcome the problems associated with using chiral-pool derivatives. The DPFCBs are engineered to avoid many of the manipulations and protecting-group transformations inherent in the use of natural sources. Spurred on by the growing popularity of chiral sulfinimines in asymmetric synthesis, Davis et al. introduced a new class of DPFCBs; *N*-sulfinyl δ-amino β-keto esters such as **226**.[95] The utility of these new building blocks for the synthesis of alkaloids was illustrated in the concise synthesis of (*R*)-2-phenylpiperidine **229** (see Scheme 72) and (−)-SS20846A **232** (see Scheme 73). A flexible approach for the synthesis of these highly functionalised systems was adopted and two routes were developed from **224**, allowing a modular design of the substrates (Scheme 71).



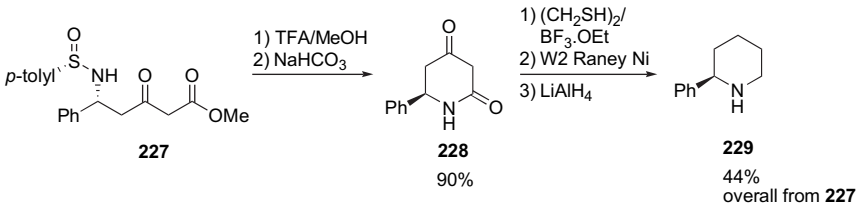
Scheme 71.

While the one-step procedure is more succinct, the two-step route was envisioned to provide the opportunity, where the initial enolate addition is not selective enough, to enrich the optical purity of the intermediate **225**. Notably, it was observed that, in solution, 5–10% of the δ-amino β-keto esters existed in the enol form. Thus having established an efficient route for the synthesis of chiral δ-amino β-keto esters, Davis's focus turned to the application of the building blocks (Scheme 72).

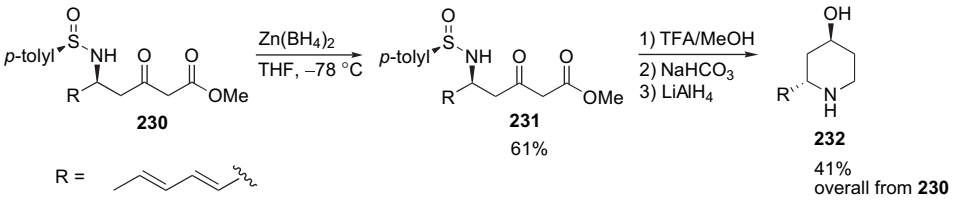
Deprotection and subsequent cyclisation of **227** afforded piperidinedione **228** as a single isomer. Succeeding transformations afforded (*R*)-2-phenylpiperidine **229** in 44% overall yield over four steps from δ-amino β-keto ester **227**. The modular nature of these building blocks allows the incorporation of motifs at different stages of the synthesis, and hence (2*S*,4*S*)-SS20846A **232** was synthesised in 41% overall yield over four steps, via **231**, from **230** (Scheme 73).

These concise, efficient asymmetric syntheses demonstrate the power of the δ-amino β-keto esters as chiral building blocks.

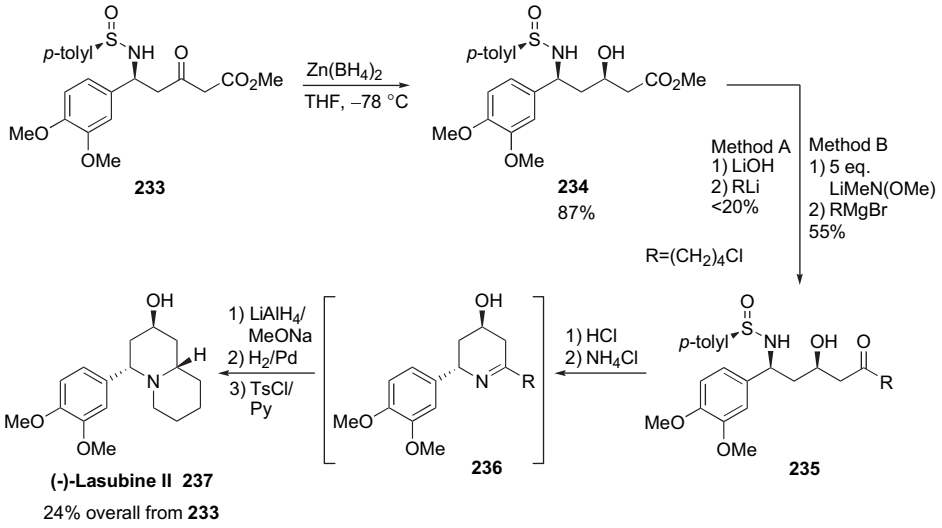
To further demonstrate the practicality of the δ-amino β-keto esters to asymmetric synthesis, Davis embarked upon the synthesis of the challenging (−)-lasubine II skeleton **237**, one of the lythracease class of alkaloids (Scheme 74).[96] During the course of their synthesis, it was found necessary to incorporate the benzyl chain at the β-amino alcohol **234** stage, as efforts to introduce this structure further in the synthesis met with disappointing results. Thus hydrolysis of the ester with subsequent addition of the corresponding organolithium reagent afforded ketone **235**, though in only 20% yield (Method A). As an alternative route, conversion into the Weinreb amide and addition of the corresponding Grignard reagent furnished ketone **235**, albeit in two steps, in 55% yield (Method B).



Scheme 72.



Scheme 73.



Scheme 74.

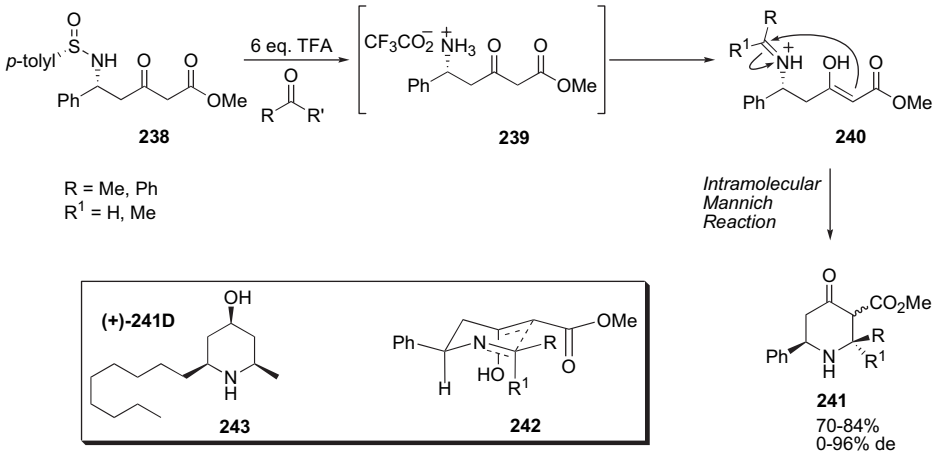
Deprotection of the sulfinyl group and subsequent elaboration of the resulting cyclised product provided direct access to (−)-lasubine II **237** in 24% overall yield in six steps from δ-amino β-keto ester **233** as a single isomer.

In a modification to the synthesis of (−)-lasubine II **237**, Davis et al. described the synthesis of *trans*-2,6-disubstituted piperidines, and thereafter the preparation of (−)-lasubine I.[97] Screening a set of conditions for the reduction of **236**, they found that using a mixture of diisobutylaluminium hydride and *n*-butyllithium afforded the trans-isomer, rather than the previously favoured cis-ring system, in 68% yield and 98% de.

Stemming from the observation that 5–10% of the δ-amino β-keto esters exist as the enol form in solution, Davis sought to exploit this property in the application of the δ-amino β-keto esters towards new chiral skeletons.[98] It was reasoned that if an iminium ion could be generated, it would react with the enol form via an intramolecular Mannich reaction, providing direct access to the 2,3,4,6-tetrasubstituted piperidine skeleton (Scheme 75). It was found that, after removal of the sulfinyl group of **238**, an iminium ion **240** could be generated from **239** and a number of different aldehydes and ketones. The intramolecular Mannich reaction furnished piperidines **241** in high yield (70–84%) with generally good stereoselectivity (1:1 to 98:2 cis/trans). The high predilection for the cis-isomer was rationalised by invoking the chelated six-membered transition state **242**, in which the sterically large substituents preferentially occupy the equatorial positions, leading to the cis-isomer.

The efficacy of the intramolecular Mannich reaction was further demonstrated by Davis et al. through the asymmetric synthesis of the dendrobate alkaloid (+)-241D **243**, achieved in five steps from the δ-amino β-keto ester in 36% yield and >97% de.

As a test of the intramolecular Mannich reaction of the sulfinimine-derived δ-amino β-keto esters, Davis et al. embarked upon the synthesis of the quinolizidine alkaloids, (−)-epimyrtine and (+)-myrtine.[99] *En route* to these functionalised piperidines, the scope of the reaction was briefly examined. Overall, the expediency of this procedure was



Scheme 75.

again highlighted, providing a short and efficient asymmetric synthesis of these alkaloids, with (−)-epimyrtine synthesised in six steps and 41% overall yield from the corresponding sulfinimine.

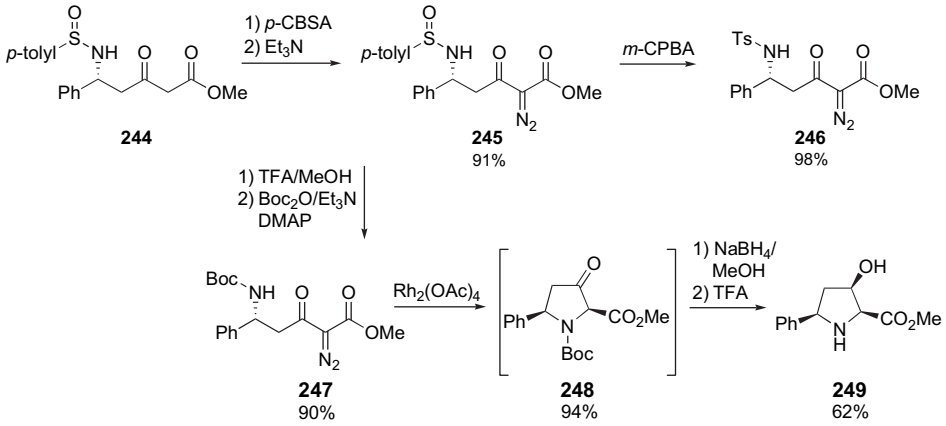
Seeking to expand the versatility of the new δ-amino β-keto ester building blocks, a method for the coupling of the δ-amino with the α-carbon was reported by Davis et al., providing expedient entry to the proline skeleton. To accomplish the desired cyclisation, Davis chose to exploit metal carbenoid chemistry (Scheme 76).[100] The requisite chiral diazo compound **245** was synthesised in high yield from δ-amino β-keto ester **244**. As metal carbenoid insertion into the N–H bond of a sulfinamide was unprecedented, however, preliminary investigations revolved around insertion into the corresponding *N*-tosyl derivative **246**, accessed through oxidation of the sulfoxide. Unfortunately, treatment of the *N*-tosyl derivative with 3 mol % $Rh_2(OAc)_4$ resulted in a complex mixture of inseparable products. Hence, sulfinamides **245** were converted into the *N*-Boc derivative **247**, which, upon treatment with 3 mol % $Rh_2(OAc)_4$ afforded the desired oxo-proline **248** in near-quantitative yield and as a single diastereomer. It was observed, however, that the stereochemical purity of the compound eroded in solution and upon further purification, and thus proline **248** was taken on directly, reduction, deprotection and subsequent purification affording the major cis-isomer **249** in 62% yield.

The effectiveness of this new strategy for the synthesis of the chiral proline skeleton was demonstrated through the concise synthesis of (2*R*,5*R*)-5-phenylpyrrolidine-2-carboxylate, a key structural feature of (+)-RP66803, a non-peptide cholecystokinin antagonist.

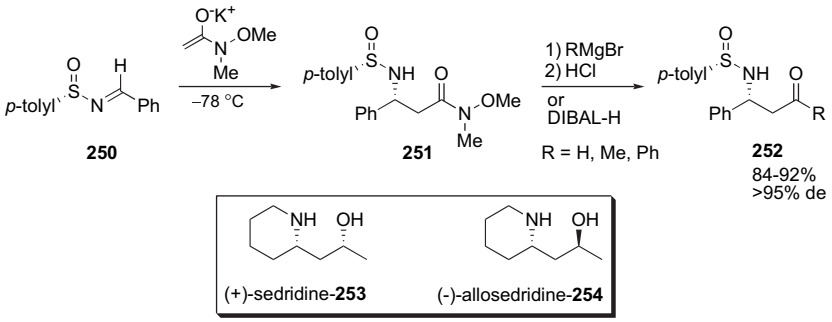
In 2003, Davis et al. published a detailed report on their exploration of the scope and limitations of the rhodium-mediated N–H insertion of δ-amino α-diazo compounds.[101] It was found that the exceptional cis-stereoselectivity was general to a wide range of substituent patterns. Further, it was found that many of the substrates examined possessed greater stability relative to Davis's previous results.

A further illustration of the potential of the α-diazo δ-amino β-keto ester building blocks was presented in 2004, through the efficient asymmetric synthesis of the potent antifungal and antibiotic agent, (+)-preussin.[102] The asymmetric synthesis was accomplished in seven steps and 23% overall yield from the δ-amino β-keto ester.

Prompted by previous results of their work, Davis et al. reported a general solution to the construction of enantiopure β-amino carbonyl compounds via the new sulfinimine-derived chiral building blocks, *N*-sulfinyl β-amino Weinreb amides.[103] Addition of the potassium enolate of the commercially available *N*-methoxy-*N*-methylacetamide to chiral



Scheme 76.

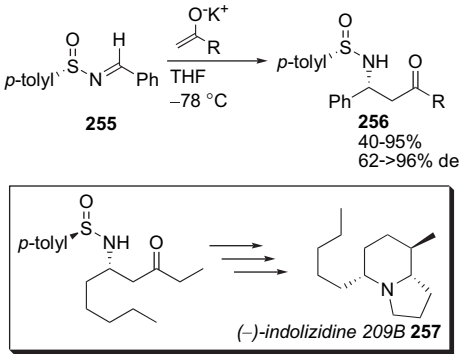


Scheme 77.

p-TS-imine **250** was found to provide β-amino amide **251** in good yield and high diastereoselectivity (Scheme 77). Addition to *p*-TS-phenyl-imine, however, afforded low diastereoselectivities (56% de), though this was observed to be the exception. Variation of the sulfinyl substituent resulted in a reduction in both yields and stereoselection.

It was found that the β-amino Weinreb amides **251** react well with a variety of organometallic reagents to afford the corresponding β-amino carbonyl compounds **252** in good yield (84–92%), with no loss in stereochemical purity. As a demonstration of the virtue of these new building blocks, the asymmetric synthesis of the sedum alkaloids, (+)-sedridine **253** and (−)-allosedridine **254**, was completed, indicating the potential access to a wide range of enantiopure β-amino carbonyl compounds.

In 2003, Davis et al. published an alternative approach to the β-amino carbonyl chiral building blocks.[104] Rather than synthesis via the Weinreb amide as previously described, the direct addition of methyl ketone enolates to enantiopure sulfinimines **255** was found to provide direct access to the protected amino ketones **256** (Scheme 78). The reaction of a number of ketones was investigated. Through a screen of the conditions, it was found that the potassium enolates provided both the highest yields and diastereoselectivities. The stereochemical outcome was found to be in accordance with the established six-membered chelated transition state. To illustrate the utility of their methodology, Davis et al. described the concise asymmetric synthesis of (−)-indolizidine 209B **257**, a member of the dendrobatide family of alkaloids.



Scheme 78.

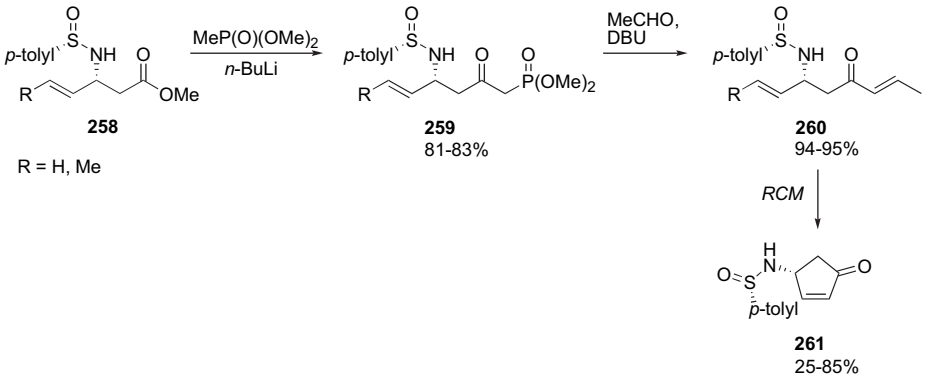
During their studies towards the asymmetric synthesis of carbocyclic nucleoside building blocks, Davis et al. described a new modification of the sulfinimine-derived δ-amino β-keto ester motif.[105] Seeking to synthesise a substrate for ring-closing metathesis (RCM) that incorporated the possibility for flexible substitution at both the alkenes and nitrogen to activate the system to metathesis, δ-amino β-ketophosphonates **259** were examined (Scheme 79).

Treatment of the *p*-TS imine-derived β-amino esters **258** with lithium dimethyl methylphosphonate furnished β-ketophosphonates **259** in high yield. Subsequent reaction with acetaldehyde provided direct access to the α,β-unsaturated amino ketones **260** in very high yield. A wide screen of conditions for the ring-closing metathesis was conducted, including both the first- and second-generation catalysts and analysing the effect of the sulfur substituent. Reaction of **260**, however, provided carbocycle **261** in good yield as a single isomer.

Expanding on their interest in the asymmetric synthesis of α-amino phosphonic acids as surrogate amino acids, Davis et al. described the efficient asymmetric synthesis of cis-5-substituted pyrrolidine-2-phosphonates from β-ketophosphonates (Scheme 80).[106] Conversion of the sulfinyl β-ketophosphonate into the *N*-Boc derivative occurred in high yield (80–90%) and, after some optimisation, the diazo functionality was efficiently installed (83–91%). Treatment of **264** with 4 mol % of $Rh_2(OAc)_4$ delivered the corresponding 3-oxopyrrolidine phosphonate **265** in high yield (65–88%), with the cis/trans ratio of the crude product varying between 81:19 and >99:1.

The new β-ketophosphonate building block provides efficient entry to chiral, non-racemic *cis*-5-substituted pyrrolidine-2-phosphonates, valuable proline surrogates, during which the first metal carbenoid N–H insertion reaction from a α-diazophosphonate was reported.

Very recently, Davis et al. introduced a new perspective to their intramolecular Mannich reaction of δ-amino β-keto esters.[107] Seeking to find an entry into the 2,4,5-trisubstituted piperidine ring system, Davis rationalised that an initial reaction with formaldehyde or its equivalent would set up the requisite Mannich precursor. Initial investigations revolved around the reaction of a number of formaldehyde equivalents to the δ-amino β-keto esters and, while the iminium ion was detected in a number of these instances, it was in unacceptably low yields, with a number of undesired side reactions competing. Thus, Davis's focus turned to the reaction of δ-amino β-keto ester enaminones **267** (Scheme 81).



258

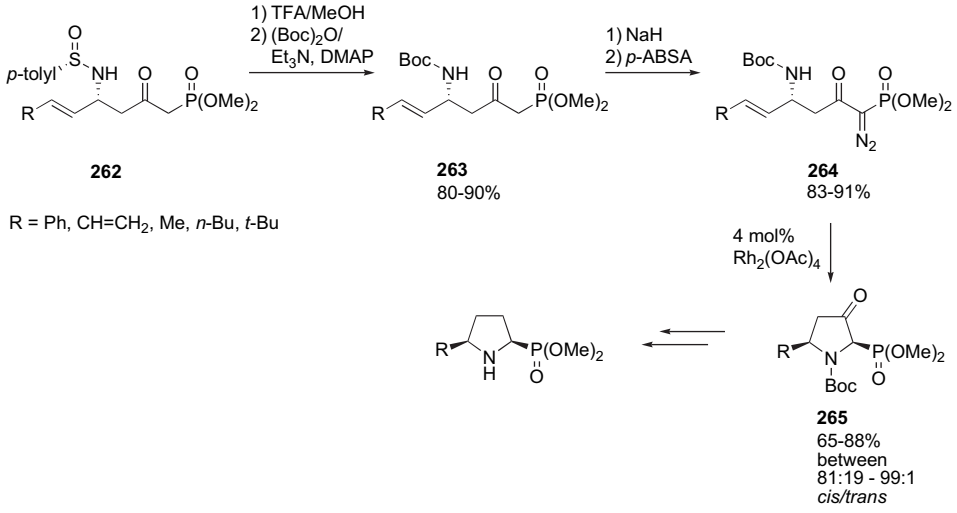
R = H, Me

259
81-83%

260
94-95%

261
25-85%

Scheme 79.



262

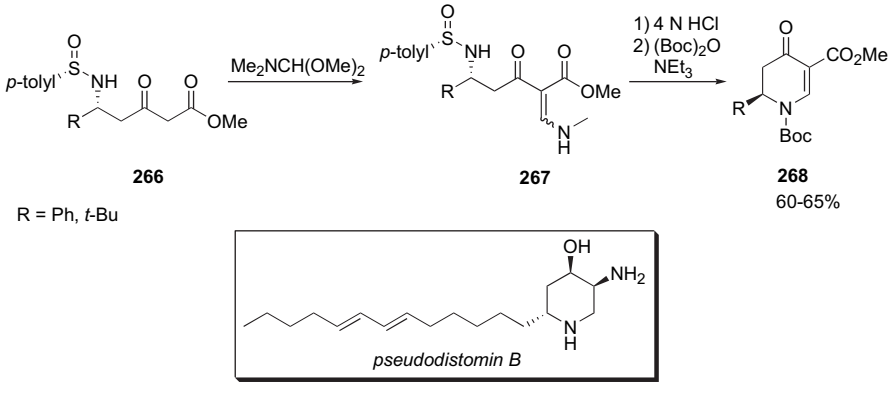
R = Ph, $CH=CH_2$, Me, *n*-Bu, *t*-Bu

263
80-90%

264
83-91%

265
65-88%
between
81:19 - 99:1
cis/trans

Scheme 80.



266

R = Ph, *t*-Bu

267

268
60-65%

Scheme 81.

Treatment of δ-amino β-keto esters **266** with 10 equiv of dimethylformamide dimethyl acetal furnished the desired enaminones **267**, which, upon direct deprotection and treatment with Boc anhydride, afforded piperidines **268** in 60–65% from the δ-amino β-keto esters as a single isomer.

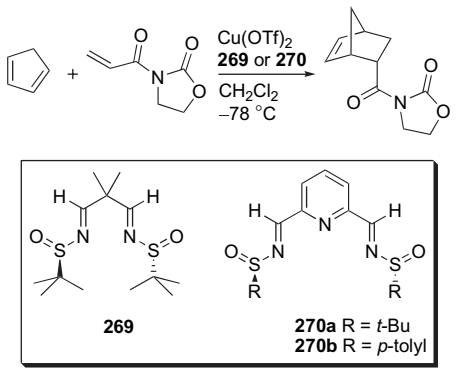
The practicality of this strategy for the construction of 2,4,5-trisubstituted piperidines was demonstrated through the synthesis of pseudodistomin B, one of the first isolated piperidine marine alkaloids.

6. Application of chiral sulfinimines as ligands for asymmetric synthesis

The drive towards the development of catalytic methods is particularly apparent in the field of asymmetric synthesis, primarily as it provides the opportunity to introduce asymmetry through the use of sub-stoichiometric amounts of valuable chiral-inducing agents. One of the most widely employed methods is through the use of chiral ligands. In the vast majority of chiral ligands, the stereodirecting effect

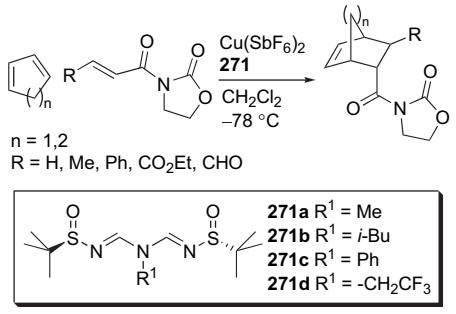
relies upon stereocentres located at carbon. While the construction of ligands incorporating chiral sulfoxides as the stereodirecting moiety had been observed,[108] the chemistry was relatively underdeveloped. It was Ellman et al. who instigated a series of investigations into the practicality of chiral ligands based upon sulfinimines for asymmetric Lewis-acid catalysis.

Ellman's initial investigations into the application of sulfinimines in chiral ligands focused on the construction of the C_2-symmetric ligands **269** and **270**,[109] designed to be analogous to the highly successful bisoxazoline ligands (Scheme 82).[110] The reaction they chose in order to test the activity of these novel catalytic systems was the Lewis-acid-catalysed Diels–Alder reaction. Their initial results showed that, while the novel ligands proved to present good catalytic activity, the asymmetric induction was disappointing.



Scheme 82.

Reaction with ligand **269** showed good conversion (100% yield), but with essentially no stereoselectivity (80% de, 6% ee). Ligand **270a** was found to be less active (35–100% yield), but did present moderate levels of stereoinduction (88% de, 30–72% ee). Reaction in the presence of **270b** proceeded in both low yield (50%) and stereoinduction (88% de, 37% ee), and this discrepancy is thought to be due to the decreased steric presence of the *p*-tolyl group, in comparison to the *tert*-butyl-group. Developing their strategy further, Ellman et al. sought to synthesise a ligand that contained a rigid backbone, which contained a more basic donor atom to increase the co-ordinating capability of the ligand. To this end, the bis(sulfinyl)imidoamidine (SIAM) ligand **271** was prepared (Scheme 83).

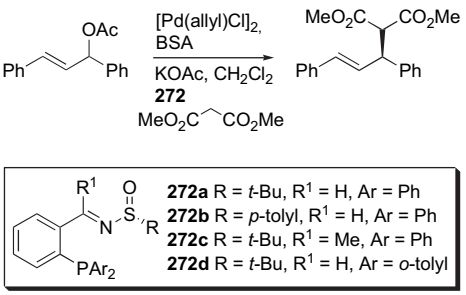


Scheme 83.

It was found that reaction in the presence of the complex of **271a** with $Cu(SbF_6)$ resulted in a greatly accelerated reaction (100% conversion in 0.1–16 h) with exceptional levels of both enantio- and diastereoselectivity (32 to >98% ee, 90 to >98% de). A range of dienophiles were examined to give a preliminary determination of the substrate tolerance of the catalyst system. Even with less electrophilic substrates, it was possible to find conditions that afforded high yields and stereoinduction. Notably, having observed that the use of excess ligand with respect to the amount of copper employed did not slow down the reaction, as had been seen in previously more established systems, it was deduced that the Cu(II)-SIAM complex exists as a rare M_2L_4 quadruple-stranded helicate.

Such was the success of their preliminary studies that Ellman et al. expanded their investigations on the development of sulfinimine-based ligands for asymmetric Lewis-acid catalysis, summarised in a full account in 2003.[111] Further to their introductory report, the full range of ligands examined was detailed. In addition, exploration of the SIAM ligands was described. A range of C_2-symmetric ligands **271a–d** were synthesised to investigate the impact of differential substitution at the internal nitrogen upon the ligand activity. Interestingly, substitution on the internal nitrogen appeared to have no detrimental effects, with the catalyst systems maintaining high yields and stereoinduction, exposing the potential for further elaboration and possible attachment to a solid support. In addition, the substrate scope of the reaction was expanded. The system was found to tolerate not only a wide range of chemically diverse dienophiles, but also cyclic and acyclic dienes, albeit in lower yield and stereoselectivity. Thus, the novel sulfinimine-based SIAM ligands were shown to be efficient in a chiral catalytic system for a broad range of substrates. Their modular design offers the potential for elaboration at a number of sites, hence widening their appeal. Their application in the asymmetric catalysis of a more complex real system was described by Murai, Ishihara and co-workers in the synthesis of the spirocyclic core of gymnodimine.[112]

Encouraged by the success of the sulfinimine-based SIAM ligands for Lewis-acid catalysis, Ellman et al. turned their focus to the synthesis of alternative novel ligands incorporating the chiral sulfinimines as asymmetric inducers. Building on the success of previous *P*,*N* ligands the use of sulfinimine-based *P*,*N* ligands **272** to introduce asymmetry in palladium-catalysed allylic alkylations was explored (Scheme 84).[113] The sulfinimine-based chiral scaffold was designed to incorporate a chelating phosphine and an sp^2 nitrogen in positions that are relative to the chiral centre and that are analogous to the phosphinooxazoline skeleton.



Scheme 84.

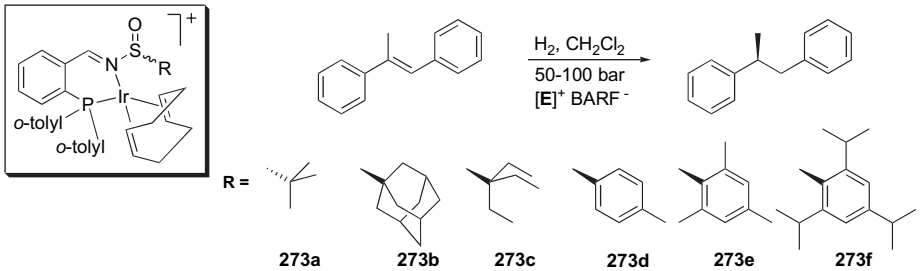
Initial investigations sought to optimise the conditions of the reaction and, for this purpose, ligand **272a** was employed. Gratifyingly high levels of conversion were observed, though with disappointing enantioselectivity (43–67% ee). Switching to a less polar solvent was found to result in a significant improvement in the stereoselectivity of the reaction. Thus, reaction in dichloromethane with $[Pd(allyl)Cl]_2$ was found to be optimal. While the transformation was now affording high yields and stereoselectivities (86–88% ee), it was deemed, however, to be inhibitively slow (>25 h).

The focus was then turned to the investigation of the effect of altering the substitution patterns on the ligand backbone. Substituting the sulfinyl *tert*-butyl with a *p*-tolyl group (**272b**) resulted not only in a slower transformation, but isolation of the product in a racemic form. Introduction of a methyl group onto the ligand scaffold (**272c**) provided a modest increase in the rate of reaction (5 h), though the stereoinduction was found to be unacceptably low (56% ee). From clues gained through further structural analysis, Ellman chose to investigate the effects of varying the phosphorous substituents. Incorporation of *ortho*-toluene groups into the structure (**272d**) was found to provide a series of significant improvements in the system. While reaction with ligand **272a** had required a loading of 5 mol % and low concentrations (0.07 M), in order to provide an effective transformation, reaction with **272d**, while still requiring low concentrations, provided high yields and high levels of stereoinduction (93–96% ee), and significantly shorter reaction times (<1 h). Thus, sulfinimine-based ligands had been shown to be applicable to asymmetric Pd-catalysed alkylations.

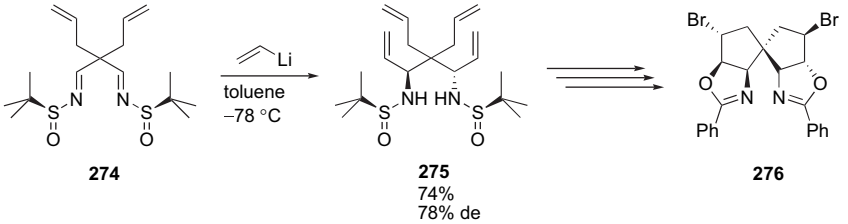
Prompted by the reports from Senanayake et al. on the facile synthesis of a variety of structurally diverse sulfinamides, Ellman et al. chose to expand the scope of their investigations on the effect of the sulfinyl substituent on the sulfinimine-based ligands activity; previously only the *tert*-butyl and *p*-tolyl groups had been considered. The system in which they chose to test the various ligands was a second transition-metal-catalysed reaction, the iridium-catalysed asymmetric hydrogenation of olefins (Scheme 85).[114]

Optimisation of the reaction was carried out using ligand **273a**. In line with previously established iridium catalysis systems, it was found that chlorinated solvents were required for efficient turnover, with dichloromethane providing complete conversion within 1 h and 94% ee. In addition, it was found that the counterion played a critical role, with the non-co-ordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate (BARF) providing the most efficient catalysis. With the optimum conditions established and the catalytic system working efficiently, the Ellman group turned their focus to examining the effect of the sulfur substituent on the reaction of the chiral ligands. It was expected that increasing the steric bulk of the sulfinamide component would correspond with an improvement in the enantioselectivity. Reaction with ligands **273b** and **273c**, however, resulted in a reduction in both the rate and selectivity. In line with their previous observations, reaction with the ligands derived from arenesulfinyl imines **273d–f** was significantly impaired. These results only highlighted the negative impact of incorporating an aryl group at this position, with almost no reaction and effectively no selectivity observed. Ligands **273a–c** provided constantly better transformations with higher yield (58–99%) and stereocontrol (84–94% ee), with **273d–f** providing generally lower yields (52–99%) and significantly lower stereocontrol (5–7% ee). While the scope of this reaction was not examined, the asymmetric iridium-catalysed hydrogenation was found to be highly efficient in the reduction of α,β-unsaturated esters and allylic alcohols.

Recently, Kato et al. disclosed a report on their synthesis of a novel spirocyclic bis(oxazoline) chiral ligand **276** (Scheme 86).[115] While sulfinimines are not incorporated into the final skeleton, the stereochemistry of the ligand is set up through exploiting the stereodirecting nature of *t*-BS-imines.



Scheme 85.



Scheme 86.

Addition of vinyllithium to **274** afforded the bis-sulfinamide **275** in good yield, deprotection and subsequent modification leading to the ring-closing metathesis substrate providing direct access to the novel ligand skeleton **276**.

7. Conclusions

In summary, Ellman et al. have developed a novel class of sulfinimine-based chiral ligands. In both the SIAM and *P*,*N*-sulfinyl imine ligands derive their stereochemical induction derives from the stereogenic sulfur atoms. Not only have these ligands been found to be efficient for a range of substrates, but in addition they have been applied in more complex systems, with little decrease in efficiency or stereoselectivity observed.

The recent widespread application of sulfinimines has helped to establish them as key chiral *N*-auxiliaries in the direct, asymmetric preparation of amines. They have proved to be efficient *N*-protecting groups, domesticating the capricious nature of the imine double bond, while providing suitable activation for the reaction with a diverse range of nucleophiles. Facile deprotection of the sulfinyl group provides access to substrates for further elaboration. Two classes of chiral sulfinimines have emerged as the reagents of choice, their application having been so extensive that the sulfinamides are now commercially available. Both *p*-TS-imines and *t*-BS-imines display characteristics peculiar to their chemical makeup. Between them, these two classes have been applied to a vast range of reactions and have demonstrated the high stereodirecting nature of these chiral sulfoxides. The difference in chemistry between the *p*-tolyl- and *tert*-butyl groups highlights the influence the *S*-substituent has on the reactivity of the sulfinimines. With new modular routes being developed for the preparation of a variety of *S*-substituted chiral sulfinamides, the potential for these highly efficient chiral *N*-auxiliaries is vast. Undoubtedly, the exploration and application of new and variously substituted sulfinimines will help to realise and expand the potential of chiral sulfinimines in asymmetric synthesis.

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Biographical sketch

Daniel Morton was born in Louth, UK (1979). He received his MChem in 2001 from the University of East Anglia (UK), where he remained and under the joint supervision of Dr. Robert Stockman and Professor Robert Field obtained his PhD in 2005 for work on the reaction of sulfur ylides with *tert*-butylsulfinimines for the synthesis of chiral aziridines. He is currently employed at Leeds University as a postdoctoral fellow in the group of Professor Adam Nelson, where he is involved in studies towards the total synthesis of the polycyclic ether, hemibrevetoxin B.

Robert Stockman was born in Castle Cary, Somerset, UK. He obtained his B.Sc. in Chemistry at the University of Bath in 1994, which incorporated a year spent in the Process Chemistry group at SmithKline Beecham in Great Burgh. He then moved to the University of Bristol to undertake a Ph.D. in the group of Professor Tim Gallagher, studying the utility of pyrrolidin-3-ones as building blocks for the synthesis of indolizidines and phakellin. In January 1998, he then moved to work as a postdoctoral fellow with Professor Philip Magnus, FRS, at the University of Texas at Austin, where he worked on the syntheses of nakadomarin and manzamine A. In July 1999, he was appointed as a Lecturer in Organic Chemistry at the University of East Anglia. His research interests encompass the development of new methods for the asymmetric synthesis of functionalised heterocycles and the use of combined two-directional synthesis/cascade approaches for target- and diversity-oriented synthesis.

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Chemical synthesis of ComX pheromone and related peptides containing isoprenoidal tryptophan residues

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Abstract—The ComX pheromone is a post-translationally modified oligopeptide that stimulates natural genetic competence controlled by quorum sensing in *Bacillus subtilis*. Recently, the structure of the $ComX_{RO\text{-}E\text{-}2}$ pheromone produced by strain RO-E-2 was determined. Based on the NMR analysis, a geranyl group is bound to the tryptophan residue, which results in the formation of a tricyclic ring structure. It was proposed that one of the four possible stereochemical isomers was based on a conformational search for model compounds and the assumption that amino acid residues in the natural pheromone have the L-configuration. All possible modified tryptophan residues and the corresponding $ComX_{RO\text{-}E\text{-}2}$ peptides were synthesized to confirm the precise stereochemistry. Here, the synthesis of the modified tryptophan derivatives was reported in detail. It was succeeded in synthesizing four optically active modified tryptophan methyl esters from which the four diastereomeric $ComX_{RO\text{-}E\text{-}2}$ peptides were prepared. Since only one of the four diastereomers was spectroscopically identical to the natural pheromone and exhibited biological activity, the absolute structure of the $ComX_{RO\text{-}E\text{-}2}$ pheromone was able to be established unambiguously. Furthermore, it was noticed that two other bioactive pheromones were present in the culture broth that were co-purified with $ComX_{RO\text{-}E\text{-}2}$ pheromone. These pheromones were presumed to be the N-terminal truncated peptides of $ComX_{RO\text{-}E\text{-}2}$ pheromone, i.e., [2-6]$ComX_{RO\text{-}E\text{-}2}$ and [3-6]$ComX_{RO\text{-}E\text{-}2}$, by LC-MS and NMR analyses. Using Fmoc solid-phase peptide synthesis, $ComX_{RO\text{-}E\text{-}2}$ pheromone and the [2-6]$ComX_{RO\text{-}E\text{-}2}$ and [3-6]$ComX_{RO\text{-}E\text{-}2}$ peptides were prepared. The synthetic peptides were identical to the natural pheromones and also showed significant biological activity.

1. Introduction

Bacteria constitutively secrete specific pheromones with the pheromone concentration increasing with cell density. When these concentrations reach threshold levels, bacteria respond to the pheromone by altering their gene expression. The regulation that depends on cell density is called 'quorum sensing'.[1–4] The quorum sensing pheromones are oligopeptides in Gram-positive bacteria, while Gram-negative pheromones are mainly *N*-acylhomoserine lactones. *Bacillus subtilis* and related bacilli produce a unique pheromone that stimulates natural genetic competence controlled by the quorum sensing.[5] This *B. subtilis* competent factor is a post-translationally modified oligopeptide known as ComX pheromone. The ComX pheromone is thought to activate the signal transduction cascade for natural genetic competence by binding to the membrane-embedded histidine autokinase ComP.[6,7]

The amino acid sequence of the ComX pheromone varies according to the *B. subtilis* strain, but each possesses a modified tryptophan residue.[8–11] This modification increases the hydrophobicity and molecular weight of the peptide encoded by *comX*.[5] ComX is biosynthesized as a pre-protein, which is then processed and modified by ComQ to become the active ComX pheromone.[12] ComQ contains an isoprenyl transferase domain, and this putative isoprenoid-binding site in ComQ is required for the expression of pheromone activity.[13] Furthermore, [^{3}H]-5-mevalonate, a precursor of isoprenoid, is incorporated into ComX pheromone.[10] These results

Keywords: *Bacillus subtilis*; ComX; Post-translational modification; Quorum sensing; Tryptophan.
Abbreviations: Clt, 2-chlorotrityl; [Dα]$ComX_{RO\text{-}E\text{-}2}$, $ComX_{RO\text{-}E\text{-}2}$ peptide containing the modified D-tryptophan residue with an α-geranyl group; [Dβ]$ComX_{RO\text{-}E\text{-}2}$, $ComX_{RO\text{-}E\text{-}2}$ peptide containing the modified D-tryptophan residue with a β-geranyl group; DIPEA, *N*,*N*′-diisopropylethylamine; HATU, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HBTU, *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; [Lα]$ComX_{RO\text{-}E\text{-}2}$, $ComX_{RO\text{-}E\text{-}2}$ peptide containing the modified L-tryptophan residue with an α-geranyl group; [Lβ]$ComX_{RO\text{-}E\text{-}2}$, $ComX_{RO\text{-}E\text{-}2}$ peptide containing the modified L-tryptophan residue with a β-geranyl group; Pp, 2-phenyl-2-propyl; Su, succinimidyl; TAS-F, tris(dimethylamino)sulfonium difluorotrimethylsilicate; Teoc, 2-(trimethylsilyl)-ethoxycarbonyl.

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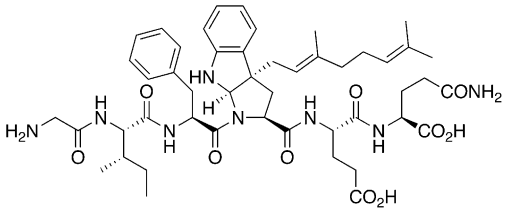
indicate that ComX pheromone is activated by isoprenylation from an inactive precursor. Isoprenylation of a tryptophan residue during post-translational modification has not been previously reported, although the modification of cysteine residues in proteins by farnesyl or geranylgeranyl groups is well known.[14]

We recently isolated the $ComX_{RO\text{-}E\text{-}2}$ pheromone using an *Escherichia coli* expression system. This required only *comQXP′*$_{RO\text{-}E\text{-}2}$ from *B. subtilis* strain RO-E-2, which was driven by a T7 phage promoter to produce biologically active $ComX_{RO\text{-}E\text{-}2}$ pheromone.[15] We determined the planar structure of the tryptophan residue by NMR analysis, which showed a tricyclic ring structure with a geranyl group attached to the 3-position of tryptophan. A conformational search was then carried out on the L-tryptophan derivative model compound using a Monte Carlo protocol to elucidate the stereochemistry of $ComX_{RO\text{-}E\text{-}2}$ pheromone. This search was based on the assumption that the pheromone was composed only of L-amino acids. We found that only one stereostructure could explain the NMR data. We thus proposed the absolute structure of the $ComX_{RO\text{-}E\text{-}2}$ pheromone **1** and its modified tryptophan residue to be [2*S*,3a*R*,8a*S*]-3α-geranyl-1,2,3,3α,8,8α-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid [L-Trp*(α-Ger)] (Fig. 1). To confirm the structure of the $ComX_{RO\text{-}E\text{-}2}$ pheromone, synthesis of all possible $ComX_{RO\text{-}E\text{-}2}$ peptides and investigation of their biological activities and physiological data were necessary. There are four possible structures **2**–**5** for the modified tryptophan residue (Fig. 2), i.e., [Lα]$ComX_{RO\text{-}E\text{-}2}$ **2** has the modified L-tryptophan residue with an α-geranyl group [L-Trp*(α-Ger)], [Lβ]$ComX_{RO\text{-}E\text{-}2}$ **3** has the modified L-tryptophan residue with a β-geranyl group [L-Trp*(β-Ger)], [Dα]$ComX_{RO\text{-}E\text{-}2}$ **4** has the modified D-tryptophan residue with an α-geranyl group [D-Trp*(α-Ger)], and [Dβ]$ComX_{RO\text{-}E\text{-}2}$ **5** has the modified D-tryptophan residue with a β-geranyl group [D-Trp*(β-Ger)]. We therefore synthesized four optically active geranyl tryptophan methyl esters, and prepared four diastereomeric $ComX_{RO\text{-}E\text{-}2}$ peptides to confirm our proposed structure for the $ComX_{RO\text{-}E\text{-}2}$ pheromone.

Two additional peptides were co-isolated with $ComX_{RO\text{-}E\text{-}2}$ pheromone from the culture broth of *E. coli* ED413. These were determined to be N-terminal truncated peptides of $ComX_{RO\text{-}E\text{-}2}$ pheromone. Using solid-phase peptide synthesis as described previously,[16] we synthesized these two peptides in addition to $ComX_{RO\text{-}E\text{-}2}$ pheromone and investigated their biological activity.



H-Gly-Ile-Phe-Trp*(Ger)-Glu-Gln-OH

$ComX_{RO\text{-}E\text{-}2}$ pheromone **1**

Figure 1. The proposed structure of $ComX_{RO\text{-}E\text{-}2}$ pheromone.

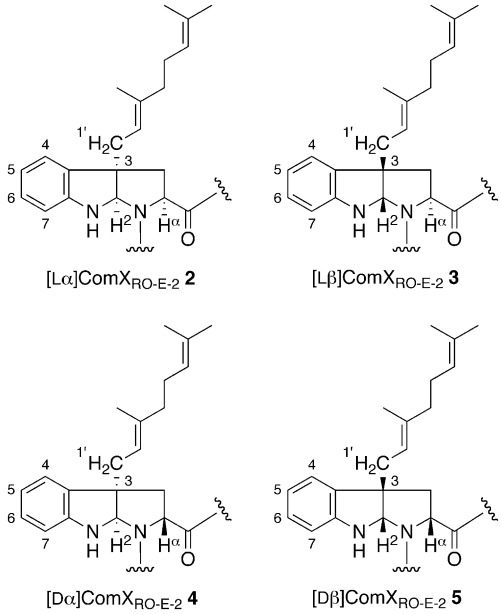


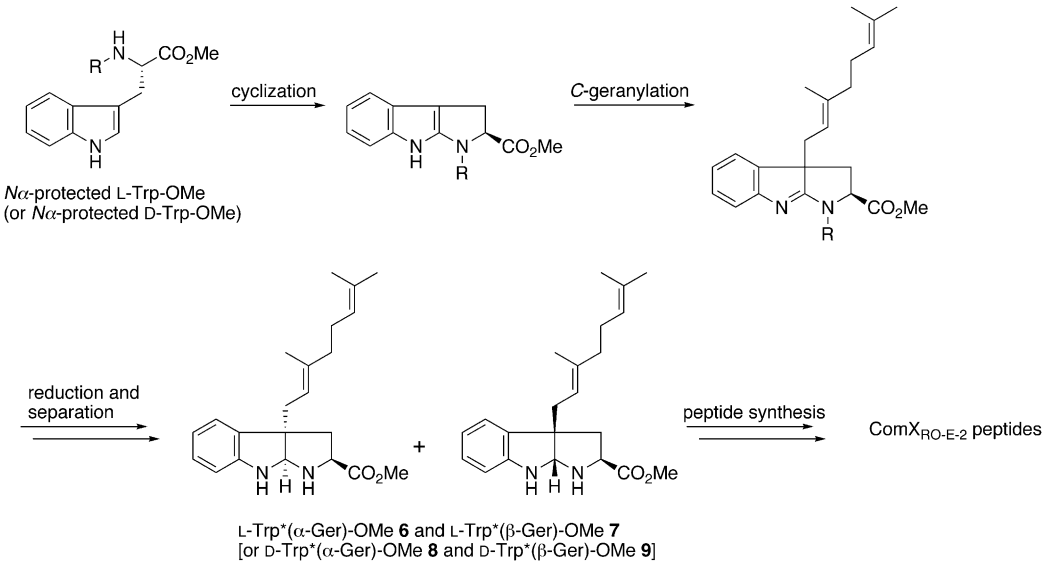
Figure 2. Four possible structures of the modified tryptophan residue in the $ComX_{RO\text{-}E\text{-}2}$ pheromone based on the NMR analysis.

2. Results

2.1. Synthesis of modified tryptophan and stereoisomers

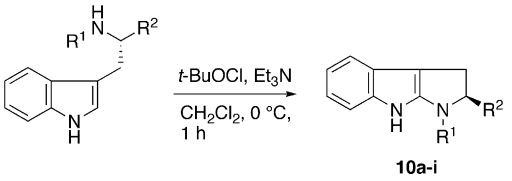
For efficient synthesis of the four stereoisomeric geranyl-modified tryptophan residues and the corresponding peptides composed of the $ComX_{RO\text{-}E\text{-}2}$ sequence, we selected L- or D-tryptophan methyl esters as chiral starting materials and geranyl bromide as the geranylating reagent. The optically active tricyclic tryptophan derivatives were synthesized by cyclization of tryptophan methyl ester derivatives, followed by geranylation at the C3 position. The resulting C3 diastereomers were separated, and each isomer was converted to the protected tryptophan derivatives **6**–**9** prior to peptide synthesis (Scheme 1).

The cyclization of *N*-acetyl L-tryptophan methyl ester was carried out with *t*-BuOCl (Table 1, entry 1).[17,18] The geranyl group was then introduced at the C3 position of the tricyclic compound **10a** with NaH and geranyl bromide in DMF (Table 2, entry 1).[18] Unfortunately, the acetyl deprotection of the C3-geranylated diastereomers did not proceed under the various conditions tried (data not shown). Thus, we screened for removable protecting groups and conditions for C3-geranylation. Using N-protected tryptophan derivatives, we synthesized nine tricyclic compounds **10a**–**i** that were purified by recrystallization (Table 1).[19] Using **10a**–**i**, we optimized the conditions for C3-geranylation (Table 2).[20] The usual quenching method with methanol or water resulted in product decomposition, and quenching with 5% aqueous $KHSO_4$ gave the C3-β-geranylated compound in poor yield in addition to the N1-geranylated compound. We found that immediate neutralization with a phosphate buffer prevented the decomposition of the C3-geranylated products. When carbamates were selected as the N-protecting group, C-geranylation of **10b**–**e** did not proceed at all (Table 2). We also found that the ester was important for the reaction because the geranylation of 2-chlorotrityl (Clt)



Scheme 1. Synthetic strategy toward four $ComX_{RO\text{-}E\text{-}2}$ peptides.

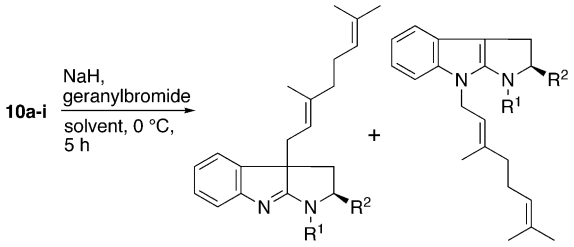
Table 1. Cyclization of various tryptophan derivatives



Entry	R^1	R^2	Yield, %[a] (product)
1	Ac	CO_2Me	92 (**10a**)
2	Boc	CO_2Me	42 (**10b**)
3	CO_2Bn	CO_2Me	49 (**10c**)
4	CO_2Me	CO_2Me	78 (**10d**)
5	CO_2Et	CO_2Me	69 (**10e**)
6	$COCCl_3$	CO_2Me	85 (**10f**)
7	$COCF_3$	CO_2Me	79 (**10g**)
8	Bz	CO_2Me	95 (**10h**)
9	Bz	CH_2OClt	62 (**10i**)

[a] Isolated yield with recrystallization.

Table 2. *C*- or *N*-selective geranylation under various conditions

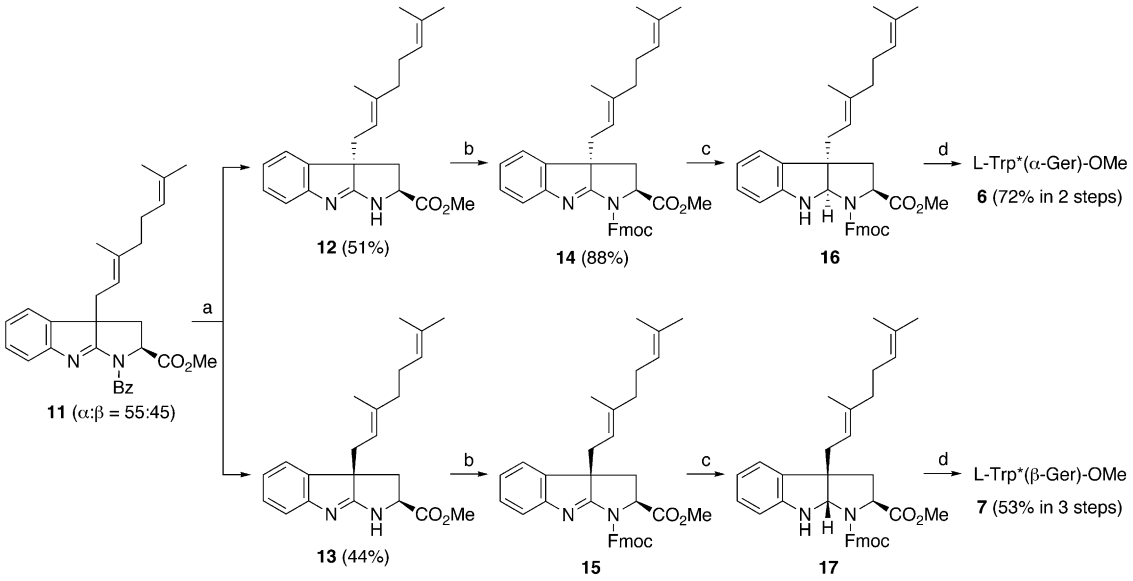


Substrate (R^1, R^2)	Solvent	Yield, %[a]	
		C-Ger (α:β)[b]	*N*-Ger
10a (Ac, CO_2Me)	DMF	63 (33:30)	9
10b (Boc, CO_2Me)	DMF	0	0
10c (CO_2Bn, CO_2Me)	DMF	0	0
10d (CO_2Me, CO_2Me)	DMF	0	14
10e (CO_2Et, CO_2Me)	DMF	0	8
10f ($COCCl_3$, CO_2Me)	DMF	0	0
10g ($COCF_3$, CO_2Me)	DMF	0	0
10h (Bz, CO_2Me)	DMF	81 (44:37)	15
10i (Bz, CH_2OClt)	DMF	0	72
10h (Bz, CO_2Me)	NMP	77 (32:45)	18
10h (Bz, CO_2Me)	THF	83 (47:36)	11

[a] Isolated yield.
[b] α/β ratios were determined by ^1H NMR, and the stereochemistries were determined by NOE.

ether **10i** gave only the N-geranylated compound. The Bz-protected substrate **10h** gave a better yield of C3-geranylated diastereomers when compared with **10a**. The solvent for geranylation also affected the yield and diastereomeric ratio of the geranylated products. THF increased the yield slightly and the ratio of the C3-α-geranyl product improved, but the reverse was true for NMP. The key intermediate **11** was obtained in high yield using the optimized conditions. Mixtures of the C3-geranyl isomers were acceptable for the purpose of synthesizing the four diastereomers. Since the C3-geranylated diastereomers could not be separated by column chromatography, the diastereomixture **11** was used directly as the starting material in the next step.

Next, deprotection, separation of diastereomers, and chemoselective reduction of the imine were attempted (Scheme 2). Treatment of **11** with DIBAL-H selectively cleaved the Bz group. The reductive diastereomeric products **12** and **13** were easily separated by column chromatography using a solvent system of chloroform and methanol to afford the optically active tryptophan derivatives **12** and **13**. We determined the α-geranyl configuration of **12** based on NOE analysis, however purified **13** was not sufficiently stable for direct determination of its stereochemistry. Because compound **13** was readily prepared from the β-geranyl isomer of **11** by treatment with DIBAL-H in nearly quantitative yield, and compound **13** was also determined to have the β-geranyl configuration. It was necessary to protect the unstable secondary amines **12** and **13** with an Fmoc group before the reduction of the imine. After Fmoc protection, the reduction of the imines **14** and **15** was carried out with catecholborane to give amines **16** and **17**, respectively. Fmoc was found to be the best protecting group for the reduction. Bz-protected **11** required prolonged reduction with catecholborane and was difficult to deprotect,[20] and the free amine **12** was

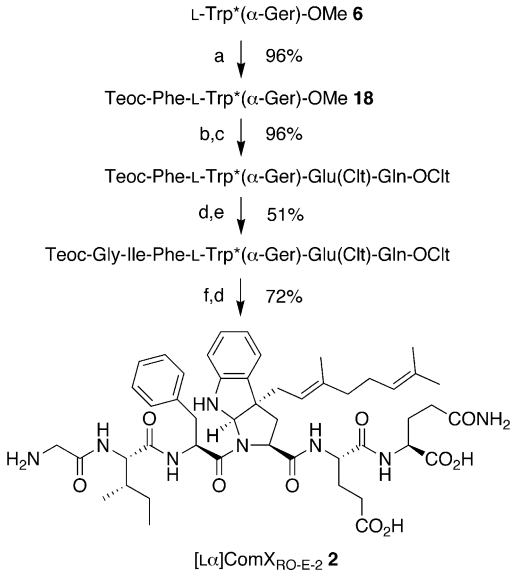


Scheme 2. Synthesis of L-Trp*(α-Ger)-OMe **6** and L-Trp*(β-Ger)-OMe **7**. Reaction conditions: (a) DIBAL-H, THF, –78 °C, 2 h; (b) Fmoc-OSu, 1.0 M aqueous $NaHCO_3$, dioxane, rt, 1.5 h; (c) catecholborane, THF, 0 °C, 2 h; (d) piperidine, CH_3CN, rt, 1.5 h.

decomposed by reduction. Cleavage of the Fmoc group gave L-Trp*(α-Ger)-OMe **6** for the synthesis of [Lα]$ComX_{RO-E-2}$ **2**, which has our proposed configuration for natural $ComX_{RO-E-2}$ pheromone. We confirmed that L-Trp*(α-Ger)-OMe **6** had a cis configuration based on the NOE between the H-2 proton and the geranyl group. We also synthesized L-Trp*(β-Ger)-OMe **7** from intermediate **13** using the same procedure (Scheme 2), and D-Trp*(α-Ger)-OMe **8** and D-Trp*(β-Ger)-OMe **9** from the corresponding *N*-benzoyl-D-tryptophan methyl esters.

2.2. Synthesis of $ComX_{RO-E-2}$ peptides

We synthesized peptides containing the same amino acid sequence as the $ComX_{RO-E-2}$ pheromone using each modified tryptophan methyl ester (Scheme 3). The $ComX_{RO-E-2}$ pheromone is very acid labile.[15,16] Therefore, we used Clt as a protecting group for the carboxy groups because it can be cleaved under mild acidic conditions. Methyl ester **6** was treated with 2-(trimethylsilyl)ethoxycarbonylphenylalanine (Teoc-Phe) to obtain dipeptide **18**. From the analysis of the HMBC spectrum, we found that L-Trp*(α-Ger)-OMe **6** reacts with amino acids only at the *N*α-position under common amino acid coupling conditions (data not shown). Dipeptide methyl ester **18** was hydrolyzed under alkaline conditions, followed by coupling with Glu(Clt)-Gln-OClt. Purification of the resulting tetrapeptide was carried out by silica gel column chromatography with 1% triethylamine so as not to cleave the Clt esters. After cleavage of the Teoc group of the purified tetrapeptide, the peptide was coupled to Teoc-Gly-Ile. Finally, the Clt esters were cleaved with 50% aqueous AcOH, followed by removal of the Teoc group with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F). The resultant compound was purified by HPLC to give the desired [Lα]$ComX_{RO-E-2}$ peptide **2**. The other three diastereomers, [Lβ]$ComX_{RO-E-2}$ peptide **3**, [Dα]$ComX_{RO-E-2}$ peptide **4**, and [Dβ]$ComX_{RO-E-2}$ peptide **5**, were synthesized using L-Trp*(β-Ger)-OMe **7**, D-Trp*(α-Ger)-OMe **8**, and D-Trp*(β-Ger)-OMe **9**, respectively, as shown in Figure 3.



Scheme 3. Synthesis of [Lα]$ComX_{RO-E-2}$ **2**. Reaction conditions: (a) Teoc-Phe, HATU, HOAt, Et_3N, CH_2Cl_2, 0 °C, 2 h; (b) LiOH, THF, MeOH, H_2O, rt, 1 h; (c) Glu(Clt)-Gln-OClt, HATU, HOAt, Et_3N, CH_2Cl_2, 0 °C, 2 h; (d) TAS-F, CH_2Cl_2, rt, 24 h; (e) Teoc-Gly-Ile, HATU, HOAt, Et_3N, CH_2Cl_2, 0 °C, 2 h; (f) 50% aqueous AcOH, 4 °C, 24 h.

2.3. Comparison of synthetic $ComX_{RO-E-2}$ peptides and natural pheromone

The ^1H NMR spectra of the four synthetic peptides were compared (Fig. 4). [Lα]$ComX_{RO-E-2}$ peptide **2** possessed the proposed stereostructure and exhibited the same ^1H NMR spectrum as the natural peptide pheromone. The spectra of the three other diastereomers **3**–**5** showed considerable differences, particularly in the region of the modified tryptophan residues.

We then investigated the biological activities of these peptides by β-galactosidase assay with *o*-nitrophenyl-β-D-

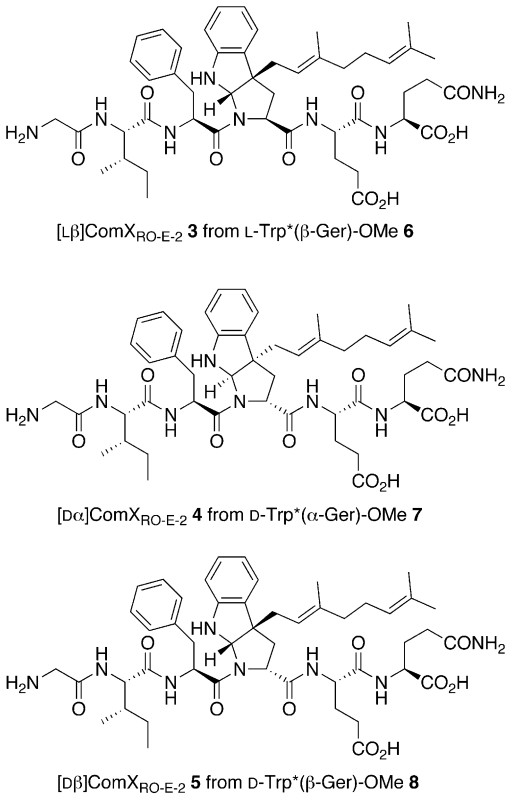


Figure 3. Other three ComX$_{RO-E-2}$ peptides.

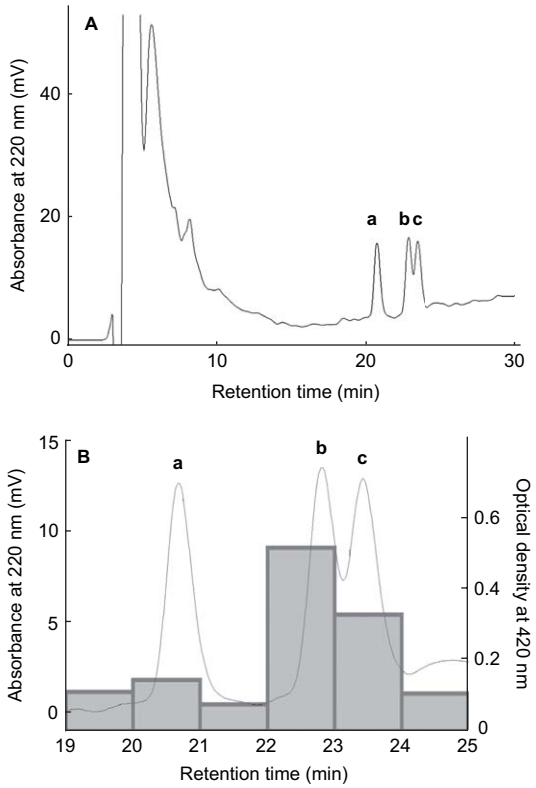


Figure 5. (a) HPLC of a ComX$_{RO-E-2}$ solution partially purified. (b) The effect of each fraction in bioassay and the corresponding HPLC. Gray bars represent optical density at 420 nm.

galactopyranoside using a *B. subtilis* tester strain (BD3020) as described previously.[9,10] In addition to the natural ComX$_{RO-E-2}$ pheromone, only one of the four synthetic peptides, [Lα]ComX$_{RO-E-2}$ **2**, showed obvious biological activity at 1.0 nM, while diastereomers **3–5** showed no biological activity up to 300 nM (Fig. 5).

2.4. Identification and solid-phase synthesis of N-terminal truncated natural pheromones

We analyzed the natural ComX$_{RO-E-2}$ pheromone solution from the culture broth using an *E. coli* expression system,

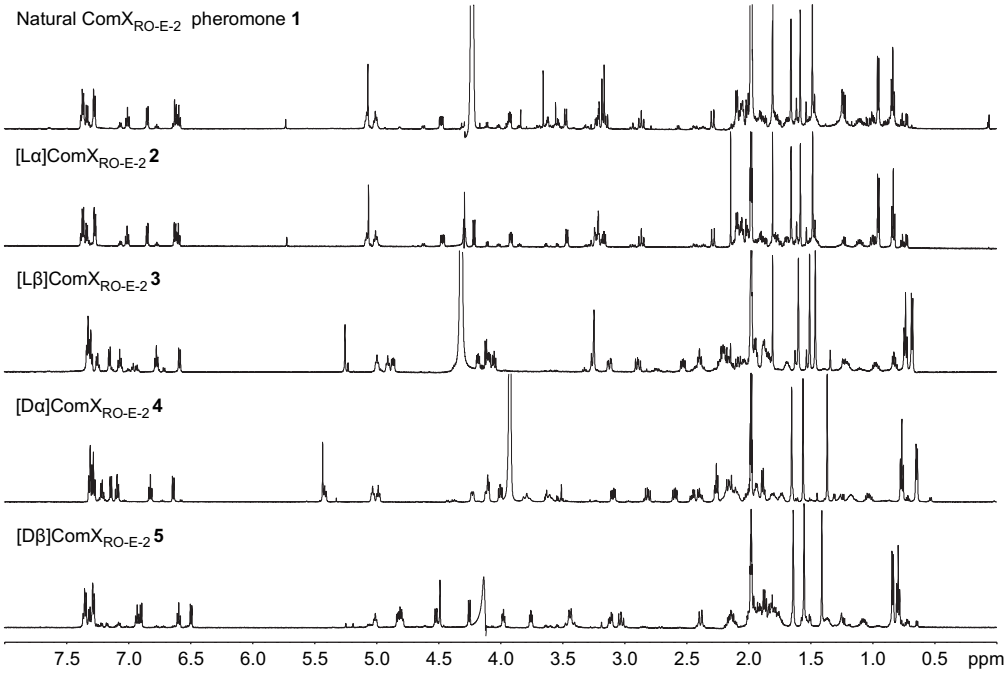


Figure 4. ^{1}H NMR spectra of the natural ComX$_{RO-E-2}$ pheromone and the synthetic peptides. Each DHO signal of [Lα]ComX$_{RO-E-2}$ **2** or [Dβ]ComX$_{RO-E-2}$ **5** was irradiated for suppression.

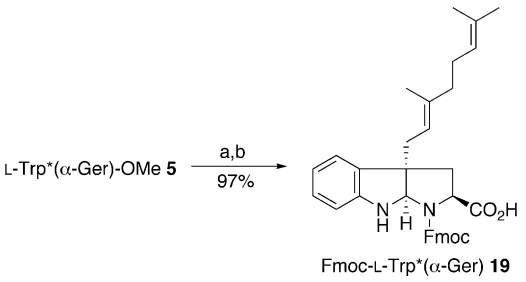
Table 3. HRMS of the $ComX_{RO\text{-}E\text{-}2}$ pheromone and its truncated peptides

Peak	HRMS $[M+H]^+$	Molecular composition (Δ ppm)	Amino acid sequence	Pheromone
a	745.39152	$C_{40}H_{53}N_6O_8$ (−0.56)	FW*EQ	[3-6]$ComX_{RO\text{-}E\text{-}2}$
b	915.49830	$C_{48}H_{67}N_8O_{10}$ (+0.91)	GIFW*EQ	$ComX_{RO\text{-}E\text{-}2}$
c	858.47591	$C_{46}H_{64}N_7O_9$ (−0.11)	IFW*EQ	[2-6]$ComX_{RO\text{-}E\text{-}2}$

W* represents the modified tryptophan residue with a geranyl group.

as reported previously.[9,10,15] Following the final purification step, we identified three biologically active fractions, including the $ComX_{RO\text{-}E\text{-}2}$ pheromone, as shown in Figure 5. Because the other two peptides in the active fractions showed $[M+H]^+$ molecular ions of 858.47591 and 745.39152 on HRMS analysis, and these peptides were assigned molecular formulas of $C_{46}H_{64}N_7O_9$ and $C_{40}H_{53}N_6O_8$, respectively (Table 3). These results suggest that the two peptides were N-terminal truncated peptides of $ComX_{RO\text{-}E\text{-}2}$ pheromone, i.e., [2-6]$ComX_{RO\text{-}E\text{-}2}$ and [3-6]$ComX_{RO\text{-}E\text{-}2}$.

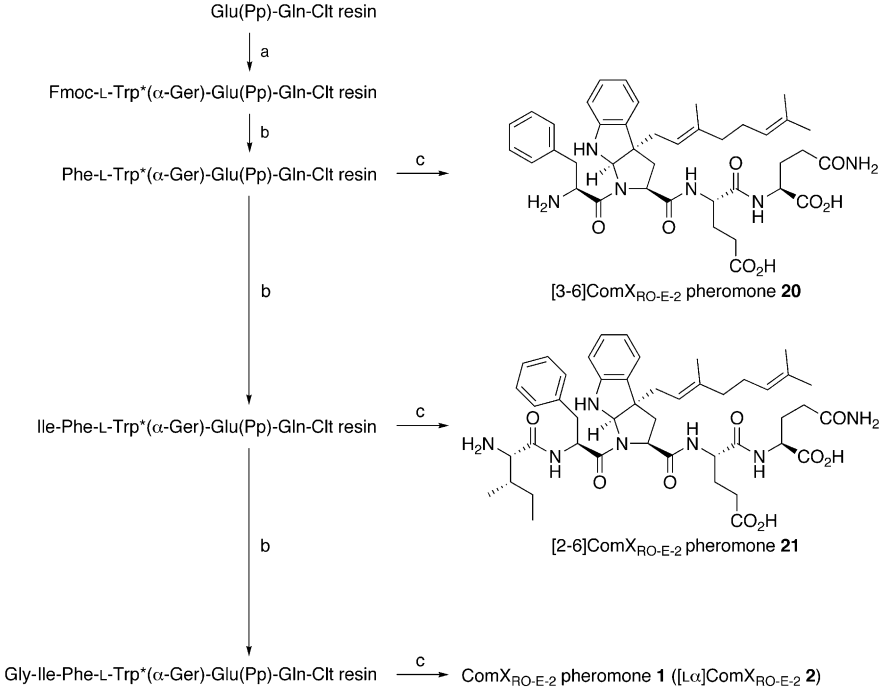
In order to confirm that these active compounds are N-terminal truncated pheromones, we attempted to synthesize



Scheme 4. Synthesis of Fmoc-L-Trp*(α-Ger) **19**. Reaction conditions: (a) LiOH, THF, CH_3OH, H_2O, rt, 1.5 h; (b) Fmoc-OSu, dioxane, 1.0 M aqueous $NaHCO_3$, rt, 1.5 h.

$ComX_{RO\text{-}E\text{-}2}$ pheromone and two N-terminal truncated $ComX_{RO\text{-}E\text{-}2}$ peptides, [3-6]$ComX_{RO\text{-}E\text{-}2}$ peptide **20** and [2-6]$ComX_{RO\text{-}E\text{-}2}$ peptide **21**, using solid-phase synthesis. We first synthesized the desired Fmoc-protected modified tryptophan for Fmoc solid-phase peptide synthesis. L-Trp*(α-Ger)-OMe **6** was hydrolyzed under alkaline conditions, followed by Fmoc protection to give Fmoc-L-Trp*(α-Ger) **19** (Scheme 4). Peptide bond formation was accomplished with a peptide synthesizer, although a previously reported manual synthesis procedure was also used (Scheme 5).[16] Both resin and protecting groups were smoothly cleaved under mild acidic conditions by treatment with 5% TFA at 4 °C for 20 h. The desired peptides were obtained after HPLC purification and analyzed by ^1H NMR spectroscopy and HRMS. The two synthetic N-terminal truncated peptides, [3-6]$ComX_{RO\text{-}E\text{-}2}$ peptides **20** and [2-6]$ComX_{RO\text{-}E\text{-}2}$ peptides **21**, were found to be identical to the natural truncated pheromones.

The biological activity of these peptides was investigated by β-galactosidase assay (Fig. 6). The two peptides showed strong activities, although these were approximately 10-fold weaker than that of the $ComX_{RO\text{-}E\text{-}2}$ (Fig. 7). The dose–response curve of [2-6]$ComX_{RO\text{-}E\text{-}2}$ (peptide **21**) was saturated at 100 nM with an EC_{50} value of 7 nM. [3-6]$ComX_{RO\text{-}E\text{-}2}$ (peptide **20**) showed an EC_{50} value of 8 nM, but its dose–response curve did not reach 100%, even at 1 μM.



Scheme 5. Solid-phase peptide synthesis of $ComX_{RO\text{-}E\text{-}2}$ peptides. Reaction conditions: (a) Fmoc-L-Trp*(α-Ger) **19**, HATU, HOAt, Et_3N, CH_2Cl_2, 0 °C, 2 h; (b) Stepwise solid-phase peptide synthesis with peptide synthesizer using HBTU/HOBt/DIPEA chemistry; (c) 5% TFA, 5% trifluoroethanol, CH_3CN, 4 °C, 20 h.

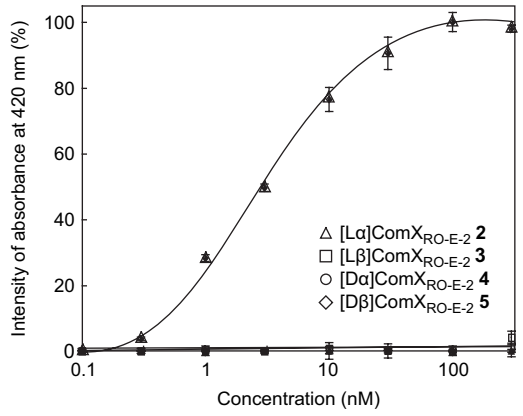


Figure 6. Dose–response curves obtained using the ComX$_{RO-E-2}$ peptide and its diastereomers. Error bars are SD of the means of triplicate samples.

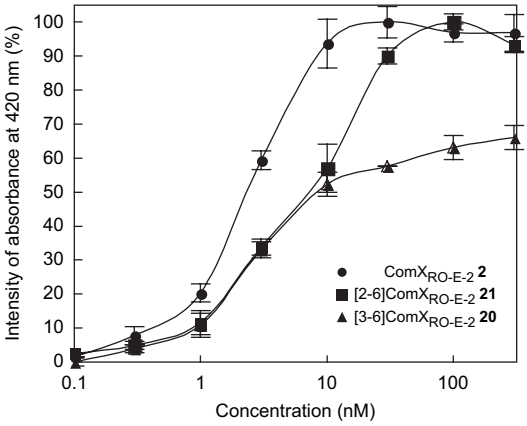


Figure 7. Dose–response curves obtained using the N-terminal truncated ComX$_{RO-E-2}$ peptides. Error bars are SD of the means of triplicate samples.

3. Discussion

The first key step in the synthesis of the modified tryptophan residue was C-geranylation. We screened a variety of conditions for C3-geranylation of the tricyclic N-protected tryptophan methyl esters. We found that Bz-Trp-OMe was the most suitable reactant for C-geranylation. Immediate neutralization with buffer was particularly important to prevent degradation of the C-geranylated products in the subsequent workup. The conditions established are also useful for synthesizing related compounds using other functional groups, such as prenyl, farnesyl, and geranylgeranyl.[21] Based on the hard–soft acid–base theory, we expected C3-geranylation to occur predominantly in THF, a relatively nonpolar solvent. However, THF gave little enhancement of C-geranylation when compared with relatively polar solvents such as DMF or NMP. C/N selectivity in the dimethylallylation of **10a** using alkylating methods involving quaternary ammonium salts was reported to be ineffective by Cardoso et al.[18] On the other hand, geranylation of ether **10i** gave only the N1-geranylated compound in good yield and we were thus able to preferentially synthesize either the N1- or C3-geranylated compound. The synthetic conditions were optimized to yield diastereomeric mixtures of C3-geranyl-modified tryptophans. Because we required both diastereomers for this synthesis, we did not investigate the α/β selectivity in the C3-geranylation in this work, although we observed that selectivity was affected by the choice of solvent. At present, we require only the α-diastereomer to synthesize the natural peptides. We are currently optimizing α-selectivity at the C3 position by investigating alternative solvents and various ester protecting groups for the effective synthesis of ComX pheromones and related peptides.

The second key step was chemoselective reduction to produce modified tryptophan methyl esters **6** and **7** (or **8** and **9**). Compounds **11**, **14**, and **15** contain various reactive functional groups such as olefin, methyl ester, imine, and benzamide (or carbamate). Reduction of **11** using an equivalent amount of DIBAL-H mediated the chemoselective cleavage of benzamide, rather than the reduction of other functional groups. Employment of $NaBH_3CN$, $NaBH_4$, excess DIBAL-H or $BH_3 \cdot SMe_2$ gave various reductive compounds non-chemoselectively. Employment of pinacholborane gave only L-Trp*(β-Ger)-OMe **7** in 51% yield (data not shown). Reduction of **14** (or **15**) with Lindlar's reagent[22] or Et_3SiH under acidic conditions did not facilitate imine reduction. By contrast, catecholborane was found to be the best reagent for the chemoselective reduction of the imine.[23]

Additionally, it was very important to obtain the modified tryptophans in optically pure form. We were able to separate diastereomers **12** and **13** by column chromatography easily, although we were not able to separate the diastereomers in other steps at preparative scale. However, a single isomer is afforded after cleavage of the Bz group, which allowed us to synthesize all four tryptophan residues. The ^1H NMR spectrum of Fmoc-Trp*(Ger)-OMe **16** indicated two different compounds in a 1:1 ratio, although both have the cis configuration as indicated by an NOE between the H-2 proton and the geranyl group. We believe that the two compounds are conformational isomers, since NMR and other analyses showed that cleavage of the Fmoc group gives only optically active esters **6**. We also observed similar phenomena on compounds **17** and **18**, although the ratio of conformers is different on **18** (10:1). Furthermore, the conformational search previously reported for the model study showed two stable conformers.[15] One of the conformers should have a similar three-dimensional structure to the modified tryptophan residue in ComX$_{RO-E-2}$ pheromone. The coupling constants between α and one of the β protons are nearly zero, indicating that the dihedral angle between α and one of the β protons is about 90°.[24] The conformational search clearly suggested this stereostructure, which is important for the expression of biological function. Subsequent investigation into the structure–activity relationships of ComX$_{RO-E-2}$ analogs will clarify the importance of this stereostructure for pheromone activity.

The four peptides were synthesized using a liquid-phase method instead of a solid-phase method for two reasons. First, we wanted to confirm the amino acid coupling reaction with the modified tryptophans at the Nα-position rather than the N1-position. L-Trp*(α-Ger)-OMe **6** was reacted with Teoc-Phe under typical coupling conditions, and HMBC analysis showed that the reaction occurred only at the Nα-position. Second, we were not able to obtain modified Fmoc-protected D-tryptophan with a free carboxyl group,

which is a requirement for solid-phase synthesis, nor was the compound sufficiently stable for this purpose.

Synthetic peptide **2** and natural $ComX_{RO\text{-}E\text{-}2}$ pheromone exhibited identical ^1H NMR spectra and showed very similar biological activity. Thus, the absolute structure of $ComX_{RO\text{-}E\text{-}2}$ pheromone was confirmed to be the same as our proposed structure [Lα]$ComX_{RO\text{-}E\text{-}2}$ **2**, and the structure of the modified tryptophan residue was determined to be [2*S*,3a*R*,8a*S*]-3α-geranyl-1,2,3,3α,8,8α-hexahydropyrrolo-[2,3-*b*]indole-2-carboxylic acid.

We had previously synthesized putative pheromones with 1-, 2-, 4-, 5-, 6- or 7-geranyl substituted tryptophan residues.[16] All of these peptides, including the three newly synthesized diastereomers reported here, had the same molecular formula and showed similar hydrophobicity to the natural $ComX_{RO\text{-}E\text{-}2}$ pheromone on LC analysis, but none exhibited its biological activity. These results suggest that the structure of the tryptophan residue, including its stereostructure, is essential both for the interaction of $ComX_{RO\text{-}E\text{-}2}$ pheromone with receptor ComP and for the signal transduction that results in the expression of genetic competence.

Furthermore, we identified two additional bioactive peptides in the *E. coli* ED413 culture broth. Their structures were predicted to be [2-6]$ComX_{RO\text{-}E\text{-}2}$ and [3-6]$ComX_{RO\text{-}E\text{-}2}$ based on their molecular weights. The Fmoc-modified L-Trp having a free carboxyl group was sufficiently stable to permit the synthesis of these two peptides and $ComX_{RO\text{-}E\text{-}2}$ pheromone itself by solid-phase methods. This method will be useful for future studies on structure–activity relationships and to synthesize probes for investigating ligand–receptor interactions.

The two synthetic N-terminal truncated peptides were identical to the natural peptides. Even the [3-6]$ComX_{RO\text{-}E\text{-}2}$, which has only four amino acid residues, showed low but apparent biological activity. This suggests that while the modified tryptophan residue is essential for biological activity, the two N-terminal amino acid residues are not absolutely required.

Several other ComX pheromones have been reported, and some of these are thought to possess farnesyl groups. The structure of the modified tryptophan residues in these pheromones may be similar to that of $ComX_{RO\text{-}E\text{-}2}$ pheromone. We are now able to synthesize these pheromones using a method similar to that described here. It will be interesting to determine whether these pheromones have the same stereostructures as $ComX_{RO\text{-}E\text{-}2}$ pheromone.

Numerous secondary metabolites of isoprenylated tryptophan derivatives are known;[25–27] however, only four examples of post-translational modification on tryptophan residues have been reported to date.[28–31] The structure of the geranyl-modified tryptophan residue described here is the fifth example of the post-translational modification of tryptophan. Post-translational isoprenylation, farnesyl or geranylgeranyl modification on the C-terminal cysteine residue is known to be quite common.[14] However, isoprenylation on a tryptophan residue is unprecedented, and geranylation is also unknown. The consensus sequence of cysteine isoprenylation is widely known, but we have not yet been able to confirm the consensus sequence for tryptophan isoprenylation among the ComX pheromones. We have no evidence that this novel modification occurs in any other peptide. However, the present tryptophan isoprenylation in a pheromone that governs genetic exchange in *B. subtilis* reminds us that cysteine isoprenylation was first discovered in the sex pheromones of basidiomycetous yeasts.[32–36]

4. Conclusion

We synthesized four diastereomers of unique tricyclic tryptophan residues modified with a geranyl group and their four corresponding peptides. We established the precise structure of $ComX_{RO\text{-}E\text{-}2}$ pheromone, including the modified tryptophan residue, as [2*S*,3a*R*,8a*S*]-3α-geranyl-1,2,3,3α,8,8α-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid by comparing NMR spectra and biological activities of the synthetic peptides with those of the natural pheromone.

We also identified other natural $ComX_{RO\text{-}E\text{-}2}$ pheromones. We found that these pheromones were N-terminal truncated peptides of $ComX_{RO\text{-}E\text{-}2}$ pheromone, i.e., [2-6]$ComX_{RO\text{-}E\text{-}2}$ and [3-6]$ComX_{RO\text{-}E\text{-}2}$. These pheromones were synthesized using the solid-phase method and were identical to the natural pheromones analytically and biologically.

5. Experimental

5.1. General methods

High-performance liquid chromatography was performed on a HPLC system equipped with Jasco LC-980 series. HRMS (ESI-TOF, positive) was recorded on a Mariner system (Applied Biosystems) using either an angiotensin/bradykinin/neurotensin mixture or a polypropylene glycol solution as a calibration standard. Optical densities were measured with an AE-15F photoelectric colorimeter (Erma). NMR spectra were recorded on a Bruker ARX-400 or a Bruker AMX-600 spectrometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Organic solvents were purchased as anhydrous grade except for the following solvents, which were freshly distilled prior to use: THF and diethyl ether were dried by distillation from Na and benzophenone ketyl. Moisture-sensitive reactions were carried out under a dry nitrogen atmosphere in well-dried equipment with a tightly fitted rubber septum. Open column chromatography was performed using silica gel BW-300 (Fuji silysia) or ODS Cosmosil 140C18-OPN (Nacalai Tesque). Solid-phase peptide synthesis was performed with a model 433A peptide synthesizer (Applied Biosystems). Fmoc-protected amino acid derivatives except modified tryptophan residues and Clt resin were purchased from commercial sources (Watanabe chemical, Nova biochem).

5.2. Bacterial strains, pheromone production, and biological activity

The *E. coli* $ComX_{RO\text{-}E\text{-}2}$ producer strain (ED413) and the *B. subtilis* tester strain (BD3020) were grown[4,5] and pheromone production was carried out as described previously.[4]

Biological activity was measured by a β-galactosidase assay using the *B. subtilis* tester strain (BD3020) employed the expression of a *srfA-lacZ* fusion, under control of the natural *srfA* promoter, which responds to add $ComX_{RO\text{-}E\text{-}2}$ pheromone. BD3020 was grown overnight to stationary phase and was then diluted 100-fold. The diluted culture (0.5 ml) was added to a sample solution (3 μl of 50% aqueous CH_3CN solution), and incubated at 37 °C for 5 h. After toluene (5 μl) was added to the mixture, biological activity was measured at 420 nm (%) with a standard method using *o*-nitrophenyl-β-D-galactopyranoside at 30 °C.

5.3. Purification of $ComX_{RO\text{-}E\text{-}2}$ derivatives

The pre-purification was as reported previously. The two active fractions were purified by HPLC on an ODS column (4.6×250 mm ID, Develosil ODS-HG-5, Nomura Chemical) at a flow rate of 1.0 ml/min, with CH_3CN and 0.1% aqueous ammonium acetate to give pure $ComX_{RO\text{-}E\text{-}2}$ derivatives. The solution was concentrated to remove CH_3CN, and freeze-dried several times to give pure $ComX_{RO\text{-}E\text{-}2}$ derivatives.

5.4. Synthesis of $ComX_{RO\text{-}E\text{-}2}$ pheromone

5.4.1. Typical cyclization. To a solution of N-protected tryptophan methyl ester (1.00 mmol) and Et_3N (4.0 equiv) in CH_2Cl_2 (10 ml) at 0 °C under nitrogen was slowly added *t*-BuOCl (1.00 mmol). The reaction mixture was stirred at 0 °C for 1 h, and warmed to room temperature for 12 h. Et_2O (200 ml) and H_2O (200 ml) were added to the mixture. The two layers were separated, and the organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated. The residue was recrystallized from CH_2Cl_2/Et_2O (or appropriate solvents) to give the tricyclic compound as a powder.

5.4.1.1. Tricyclic compound from Bz-L-Trp-OMe 10h. $[\alpha]_D^{23}$ −104 (*c* 1.0, $CHCl_3$); ^1H NMR (600 MHz, DMSO-d_6) δ 11.50 (br, 1H), 7.60 (d, 2H, *J*=7.1 Hz), 7.53–7.36 (m, 4H), 7.26 (dd, 1H, *J*=4.9, 8.6 Hz), 6.98–6.95 (m, 2H), 5.58 (d, 1H, *J*=8.2 Hz), 3.60 (dd, 1H, *J*=8.2, 9.2 Hz), 3.44 (s, 3H), 3.06 (d, 1H, *J*=9.2 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 171.5, 166.8, 143.1, 138.0, 135.2, 131.0, 128.8, 127.5, 122.9, 120.3, 119.5, 117.2, 112.9, 99.0, 67.1, 52.7, 29.4; Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.24; H, 4.92; N, 8.87.

5.4.1.2. D-Enantiomer of 10h. $[\alpha]_D^{28}$ +106 (*c* 1.0, $CHCl_3$).

5.4.2. Typical geranylation. To a solution of **2** (1.00 mmol) in THF (10 ml) at 0 °C under nitrogen was added NaH (1.3 equiv). After stirring at 0 °C for 1 h, geranyl bromide (1.1 eq) was added to the mixture. After stirring for 5 h at 0 °C, the reaction mixture was quenched and neutralized with 0.1 M phosphate buffer (pH 7). The reaction mixture was extracted with Et_2O (4×20 ml), washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography using appropriate solvents to give the C-geranylated diastereoisomeric mixtures and N-geranylated compound.

5.4.2.1. β-Geranyl compound of 11. ^1H NMR (600 MHz, $CDCl_3$) δ 1.57 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.98–2.05 (m, 4H), 2.37 (dd, 1H, *J*=10.9, 12.9 Hz), 2.56 (dd, 1H, *J*=7.8, 14.2 Hz), 2.57 (d, 1H, *J*=12.9 Hz), 2.77 (dd, 1H, *J*=6.7, 14.2 Hz), 3.86 (s, 3H), 4.86 (m, 1H), 5.05 (m, 1H), 5.60 (d, 1H, *J*=10.9 Hz), 7.03 (dt, 1H, *J*=1.8, 7.2 Hz), 7.18–7.26 (m, 3H), 7.43 (dd, 1H, *J*=7.5, 7.8 Hz), 7.56 (dt, 1H, *J*=1.1, 7.5 Hz), 7.61 (dd, 1H, *J*=1.1, 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.4, 17.6, 25.6, 26.4, 30.8, 34.8, 39.8, 52.8, 60.5, 65.0, 117.2, 119.9, 122.6, 123.7, 123.9, 128.1, 128.5, 129.5, 131.6, 132.5, 133.2, 139.5, 139.7, 158.2, 168.5, 171.4, 181.5; Anal. Calcd for $C_{29}H_{32}N_2O_3$: C, 76.29; H, 7.06; N, 6.14. Found: C, 76.31; H, 7.07; N, 6.24.

5.4.2.2. Secondary amines 12 and 13. To a solution of **11** (2.23 g, 4.89 mmol) in THF (49 ml) was slowly added DIBAL-H (1.01 M solution in hexane, 9.70 ml, 9.80 mmol) at –78 °C. After stirring for 2 h at –78 °C, the reaction mixture was poured into 0.1 M phosphate buffer (pH 7.0, 50 ml). It was extracted with EtOAc (4×50 ml). The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH$ 100/1 → 80/1) to give α-isomer **12** (871 mg, 2.47 mmol, 51%) as a colorless oil and β-isomer **13** (751 mg, 2.13 mmol, 44%) as a colorless oil.

5.4.2.3. α-Geranyl secondary amine 12. $[\alpha]_D^{26}$= +288 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 3H), 1.62 (s, 3H), 1.70 (s, 3H), 2.00–2.09 (m, 4H), 2.09 (dd, 1H, *J*=9.8, 11.9 Hz), 2.18 (dd, 1H, *J*=7.4, 13.9 Hz), 2.44 (dd, 1H, *J*=8.0, 13.9 Hz), 2.67 (dd, 1H, *J*=5.1, 11.9 Hz), 3.77 (s, 3H), 4.95 (dd, 1H, *J*=5.1, 9.8 Hz), 5.09 (m, 1H), 5.22 (m, 1H), 6.83 (ddd, 1H, *J*=1.0, 7.4, 7.5 Hz), 7.01 (dd, 1H, *J*=1.0, 7.7 Hz), 7.09 (dd, 1H, *J*=0.8, 7.4 Hz), 7.15 (ddd, 1H, *J*=0.8, 7.5, 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 17.7, 25.7, 26.5, 34.4, 39.4, 39.9, 52.1, 60.2, 71.0, 111.8, 118.6, 120.4, 123.9, 124.2, 128.1, 131.5, 133.2, 139.3, 149.5, 173.4, 184.6; Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.96; H, 7.87; N, 7.50.

5.4.2.4. D-Enantiomer of 12. $[\alpha]_D^{28}$=−279 (*c* 1.0, $CHCl_3$).

5.4.2.5. β-Geranyl secondary amine 13. ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.60 (s, 3H), 1.69 (s, 3H), 1.93–2.04 (m, 4H), 2.16 (dd, 1H, *J*=7.1, 13.9 Hz), 2.38–2.49 (m, 2H), 2.64 (d, 1H, *J*=12.8 Hz), 3.81 (s, 3H), 4.93 (d, 1H, *J*=9.6 Hz), 5.04–5.11 (m, 2H), 6.86 (dt, 1H, *J*=0.7, 7.6 Hz), 6.93 (dd, 1H, *J*=0.7, 7.6 Hz), 7.09 (dd, 1H, *J*=0.9, 7.6 Hz), 7.16 (dt, 1H, *J*=0.9, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 17.6, 25.6, 26.6, 37.4, 38.1, 39.9, 51.9, 53.2, 55.9, 117.2, 117.5, 121.1, 121.7, 124.2, 131.1, 137.5, 138.3, 139.1, 155.8, 172.5, 174.7; HRMS (ESI$^+$) *m/z*: calcd for $C_{22}H_{29}N_2O_2$ ($[M+H]^+$) 353.2224. Found 353.2228.

5.4.2.6. Fmoc-protected compound 14. To a solution of **12** (100 mg, 0.284 mmol) in dioxane (3.0 ml) and 1.0 M aqueous $NaHCO_3$ (3.0 ml) was added Fmoc-OSu (120 mg, 0.356 mmol) at room temperature. After stirring for 2 h, water (10 ml) was added to the reaction mixture and the mixture was extracted with EtOAc (4×10 ml). The organic layer was washed with saturated aqueous NaCl, dried over

Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 150/2→125/2) to give **14** (143 mg, 0.249 mmol, 88%) as a colorless oil.

$[\alpha]_D^{29}$ +317 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3COCD_3) δ 1.42 (s, 3H), 1.56 (s, 3H), 1.64 (s, 3H), 1.90–2.04 (m, 4H), 2.27 (dd, 1H, *J*=9.9, 12.0 Hz), 2.46 (d, 2H, *J*=7.9 Hz), 2.73 (dd, 1H, *J*=5.2, 12.0 Hz), 3.78 (s, 3H), 4.38 (dd, 1H, *J*=6.9, 8.1 Hz), 4.55 (dd, 1H, *J*=8.1, 10.4 Hz), 4.59 (dd, 1H, *J*=6.9, 10.4 Hz), 5.06 (m, 1H), 5.09 (m, 1H), 5.21 (dd, 1H, *J*=5.2, 9.9 Hz), 7.13 (dt, 1H, *J*=0.9, 7.5 Hz), 7.29 (ddd, 1H, *J*=1.2, 7.5, 7.9 Hz), 7.31–7.36 (m, 3H), 7.39–7.44 (m, 2H), 7.82–7.96 (m, 3H), 7.96 (dd, 1H, *J*=0.6, 7.5 Hz), 8.26 (dd, 1H, *J*=0.6, 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 17.8, 25.8, 27.3, 35.8, 39.9, 40.6, 47.4, 52.3, 60.8, 69.4, 74.1, 115.9, 118.3, 118.6, 120.6, 120.7, 124.8, 124.9, 125.0, 126.6, 127.4, 128.0, 128.2, 128.6, 128.7, 129.1, 131.9, 133.1, 140.6, 141.9, 142.2, 143.3, 143.4, 143.8, 151.6, 173.8, 176.4; HRMS (ESI+) *m/z*: calcd for $C_{37}H_{39}N_2O_4$ ([M+H]$^+$) 575.2904. Found 575.2922.

5.4.2.7. D-Enantiomer of 14. $[\alpha]_D^{28}$ –314 (*c* 0.50, $CHCl_3$).

5.4.2.8. L-Trp*(α-Ger)-OMe 6. To a solution of **14** (458 mg, 0.797 mmol) in THF (31 ml) was added catecholborane (1.01 M solution in THF, 1.0 ml, 1.00 mmol) at 0 °C. After stirring for 2 h, water (30 ml) was added to the reaction mixture, followed by extraction with EtOAc (4×30 ml). The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (hexane/acetone 10/1→8/1) to give a reductive compound. To a solution of the reductive compound in CH_3CN (2.7 ml) at room temperature was added piperidine (0.3 ml). After stirring for 1 h, the reaction mixture was quenched and neutralized with 0.1 M phosphate buffer (pH 7.0, 3.0 ml). The reaction mixture was extracted with EtOAc (4×5 ml). The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (hexane/acetone 6/1→5/1) to give **6** (202 mg, 0.570 mmol, 72%, in two steps) as a colorless oil.

$[\alpha]_D^{26}$=+52.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ 6.99 (t, 1H, *J*=7.6 Hz), 6.96 (d, 1H, *J*=7.6 Hz), 6.69 (t, 1H, *J*=7.6 Hz), 6.40 (d, 1H, *J*=7.6 Hz), 5.24 (m, 1H), 5.14 (m, 1H), 4.63 (s, 1H), 3.71 (dd, 1H, *J*=3.3, 7.8 Hz), 3.07 (s, 3H), 2.46 (dd, 1H, *J*=3.3, 12.6 Hz), 2.35 (dd, 1H, *J*=7.9, 14.5 Hz), 2.31 (dd, 1H, *J*=7.6, 14.5 Hz), 2.18 (dd, 1H, *J*=7.8, 12.6 Hz), 2.10–2.06 (m, 2H), 2.01–1.97 (m, 2H), 1.67 (s, 3H), 1.53 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 174.8, 151.2, 137.8, 131.7, 128.4, 125.1, 124.4, 121.4, 120.3, 118.3, 109.6, 83.5, 60.2, 58.1, 51.7, 41.9, 40.6, 37.2, 27.2, 25.8, 17.7, 16.4; Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.52; H, 8.49; N, 7.83.

5.4.2.9. D-Trp*(β-Ger)-OMe 9 (D-enantiomer of 6). $[\alpha]_D^{28}$ –52.1 (*c* 1.0, $CHCl_3$).

5.4.2.10. L-Trp*(β-Ger)-OMe 7. $[\alpha]_D^{29}$ –76.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ 7.01 (dd, 1H, *J*=7.5, 7.7 Hz), 6.94 (d, 1H, *J*=7.4 Hz), 6.73 (dd, 1H, *J*=7.4, 7.5 Hz), 6.38 (d, 1H, *J*=7.7 Hz), 5.19 (m, 1H), 5.13 (m, 1H), 4.59 (s, 1H), 3.65 (dd, 1H, *J*=5.8, 10.7 Hz), 3.24 (s, 3H), 2.35 (dd, 1H, *J*=7.8, 14.5 Hz), 2.31 (dd, 1H, *J*=7.1, 14.5 Hz), 2.27 (dd, 1H, *J*=5.8, 12.0 Hz), 2.09–2.05 (m, 2H), 2.01–1.96 (m, 2H), 1.89 (dd, 1H, *J*=10.7, 12.0 Hz), 1.68 (s, 3H), 1.53 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 173.6, 150.9, 136.8, 132.9, 130.6, 127.5, 124.1, 123.1, 120.3, 117.2, 107.8, 82.2, 59.1, 58.1, 50.9, 44.0, 39.5, 36.4, 26.2, 24.8, 16.7, 15.4; Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.52; H, 8.57; N, 7.99.

5.4.2.11. D-Trp*(α-Ger)-OMe 8 (D-enantiomer of 7). $[\alpha]_D^{28}$ +75.4 (*c* 1.0, $CHCl_3$).

5.4.3. Synthesis of the $ComX_{RO\text{-}E\text{-}2}$ peptides. We chose Teoc as the N-terminal protecting group, and Clt as the carboxy-protecting group. The Teoc group was cleaved under neutral condition using TAS-F, and the Clt group was cleaved under mild acidic conditions using 50% aqueous AcOH. All reactions were monitored with LC/MS and TLC. Peptides were purified by silica gel column chromatography containing 1% Et_3N so as not to cleave the Clt group. All Clt esters were unstable, so they were carried on to the next step immediately without further purification.

5.4.3.1. Teoc-Phe-L-Trp*(α-Ger)-OMe 18. To a solution of L-Trp*(α-Ger)-OMe **6** (80.5 mg, 0.227 mmol), Teoc-Phe (150 mg, 0.485 mmol), and Et_3N (94.6 mg, 0.935 mmol) in CH_2Cl_2 (5.0 ml) under nitrogen were added HOAt (66.0 mg, 0.485 mmol) and HATU (185 mg, 0.487 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was quenched and neutralized with 0.1 M phosphate buffer (10 ml). The reaction mixture was extracted with EtOAc (4×10 ml). The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 6/1→4/1) to give **18** (141 mg, 0.217 mmol, 96%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.27 (m, 3H), 7.23 (d, 2H, *J*=7.1 Hz), 6.96 (dd, 1H, *J*=7.3, 7.7 Hz), 6.86 (d, 1H, *J*=7.4 Hz), 6.59 (dd, 1H, *J*=7.3, 7.4 Hz), 6.11 (d, 1H, *J*=7.7 Hz), 5.59 (d, 1H, *J*=8.2 Hz), 5.10–5.04 (m, 2H), 5.04 (s, 1H), 4.39 (m, 1H), 4.16–4.05 (m, 2H), 3.57 (d, 1H, *J*=8.3 Hz), 3.14 (dd, 1H, *J*=4.7, 12.7 Hz), 3.10 (s, 3H), 2.85 (dd, 1H, *J*=10.6, 12.7 Hz), 2.34 (d, 1H, *J*=12.8 Hz), 2.24 (dd, 1H, *J*=7.5, 14.4 Hz), 2.19 (dd, 1H, *J*=7.6, 14.4 Hz), 2.08–2.00 (m, 4H), 1.70 (s, 3H), 1.68 (s, 3H), 1.52–1.47 (m, 4H), 0.96 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 170.4, 155.4, 149.5, 138.8, 136.2, 131.6, 130.0, 129.4, 128.7, 127.2, 124.1, 123.9, 118.5, 118.4, 109.0, 80.9, 63.1, 59.7, 55.1, 53.7, 52.3, 41.3, 40.0, 37.9, 35.3, 26.6, 25.7, 17.8, 17.7, 16.2, –1.53; HRMS (ESI$^+$) *m/z*: calcd for $C_{37}H_{52}N_3O_5Si$ ([M+H]$^+$) 646.3671. Found 646.3684.

5.4.3.2. [Lα]$ComX_{RO\text{-}E\text{-}2}$ 2 ($ComX_{RO\text{-}E\text{-}2}$ pheromone). ^{1}H NMR (600 MHz, CD_3CN/D_2O 6/4) δ 7.33–7.39 (m, 3H), 7.27 (d, 2H, *J*=7.2 Hz), 7.01 (dd, 1H, *J*=7.4, 7.8 Hz), 6.85 (d, 1H, *J*=7.3 Hz), 6.63 (d, 1H, *J*=7.8 Hz), 6.60 (dd, 1H, *J*=7.3, 7.4 Hz), 5.08 (m, 1H), 5.06 (s, 1H), 5.00 (m, 1H), 4.47 (dd, 1H, *J*=4.9, 11.8 Hz), 4.21 (d, 1H, *J*=8.3 Hz),

3.92 (dd, 1H, *J*=4.8, 8.3 Hz), 3.46 (d, 1H, *J*=8.7 Hz), 3.26 (d, 1H, *J*=16.7 Hz), 3.23–3.20 (m, 2H), 3.17 (dd, 1H, *J*=6.4, 8.5 Hz), 2.87 (dd, 1H, *J*=11.8, 12.2 Hz), 2.28 (d, 1H, *J*=12.7 Hz), 2.14–1.98 (m, 10H), 1.94–1.84 (m, 2H), 1.80–1.75 (m, 2H), 1.68 (m, 1H), 1.66 (s, 3H), 1.58 (s, 3H), 1.49 (m, 1H), 1.48 (s, 3H), 1.10 (m, 1H) 1.00 (dd, 1H, *J*=8.7, 12.8 Hz), 0.96 (d, 3H, *J*=6.8 Hz), 0.83 (dd, 3H, *J*=7.3, 7.4 Hz); HRMS (ESI$^+$) *m*/*z*: calcd for $C_{48}H_{68}N_8O_{10}$ ([M+2H]$^{2+}$) 458.2524. Found 458.2525.

5.4.3.3. [Lβ]ComX$_{RO\text{-}E\text{-}2}$ 3. ^{1}H NMR (600 MHz, CD_3CN/D_2O, 6/4) δ 7.34–7.28 (m, 4H), 7.25 (dd, 1H, *J*=7.2, 7.4 Hz), 7.15 (d, 1H, *J*=7.4 Hz), 7.07 (dd, 1H, *J*=7.3, 7.8 Hz), 6.78 (dd, 1H, *J*=7.3, 7.4 Hz), 6.59 (d, 1H, *J*=7.8 Hz), 5.25 (s, 1H), 5.00 (m, 1H), 4.91 (m, 1H), 4.87 (dd, 1H, *J*=4.8, 9.5 Hz), 4.18 (dd, 1H, *J*=5.3, 8.9 Hz), 4.12 (d, 1H, *J*=7.4 Hz), 4.09 (dd, 1H, *J*=4.9, 8.1 Hz), 4.05 (dd, 1H, *J*=7.5, 8.9 Hz), 3.25 (s, 2H), 3.12 (dd, 1H, *J*=4.8, 14.1 Hz), 2.89 (dd, 1H, *J*=9.5, 14.1 Hz), 2.53 (dd, 1H, *J*=7.5, 12.8 Hz), 2.40 (m, 2H), 2.25–2.11 (m, 5H,), 2.08 (dd, 1H, *J*=8.9, 12.8 Hz), 2.05–1.93 (m, 3H), 1.90–1.81 (m, 4H), 1.69 (m, 1H), 1.60 (s, 3H), 1.51 (s, 3H), 1.46 (s, 3H), 1.20 (m, 1H), 0.98 (m, 1H), 0.74 (dd, 3H, *J*=7.3, 7.4 Hz), 0.68 (d, 3H, *J*=6.8 Hz); HRMS (ESI$^+$) *m*/*z*: calcd for $C_{48}H_{68}N_8O_{10}$ ([M+2H]$^{2+}$) 458.2524. Found 458.2530.

5.4.3.4. [Dα]ComX$_{RO\text{-}E\text{-}2}$ 4. ^{1}H NMR (600 MHz, CD_3CN/D_2O, 6/4) δ 7.26–7.23 (m, 4H) 7.21 (dd, 1H, *J*=7.2, 7.4 Hz), 7.14 (d, 1H, *J*=6.8 Hz), 7.09 (dd, 1H, *J*=7.4, 7.9 Hz), 6.82 (dd, 1H, *J*=6.8, 7.4 Hz), 6.64 (d, 1H, *J*=7.9 Hz), 5.43 (s, 1H), 5.42 (dd, 1H, *J*=6.4, 8.8 Hz), 5.03 (m, 1H), 4.99 (m, 1H), 4.23 (dd, 1H, *J*=3.7, 9.8 Hz), 4.13–4.09 (m, 2H) 4.00 (dd, 1H, *J*=7.3, 9.4 Hz), 3.80 (d, 1H, *J*=15.8 Hz), 3.63 (d, 1H, *J*=15.8 Hz), 3.09 (dd, 2H, *J*=6.4, 13.9 Hz), 2.81 (dd, 1H, *J*=8.8, 13.9 Hz), 2.60 (dd, 1H, *J*=7.3, 13.0 Hz), 2.45 (dd, 1H, *J*=7.6, 14.0 Hz), 2.39 (dd, 1H, *J*=7.9, 14.0 Hz), 2.26 (dd, 2H, *J*=7.2, 8.5 Hz), 2.19–2.06 (m, 5H), 2.04–1.89 (m, 5H), 1.81 (m, 1H), 1.74 (m, 1H), 1.65 (s, 3H), 1.56 (s, 3H), 1.37 (s, 3H), 1.18 (m, 1H), 1.03 (m, 1H), 0.77 (dd, 3H, *J*=7.3, 7.4 Hz), 0.65 (d, 3H, *J*=6.8 Hz); HRMS (ESI$^+$) *m*/*z*: calcd for $C_{48}H_{68}N_8O_{10}$ ([M+2H]$^{2+}$) 458.2524. Found 458.2533.

5.4.3.5. [Dβ]ComX$_{RO\text{-}E\text{-}2}$ 5. ^{1}H NMR (600 MHz, CD_3CN/D_2O, 6/4) δ 7.37–7.27 (m, 5H), 6.94 (dd, 1H, *J*=7.5, 7.7 Hz), 6.90 (d, 1H, *J*=7.4 Hz), 6.60 (dd, 1H, *J*=7.4, 7.5 Hz), 6.49 (d, 1H, *J*=7.7 Hz), 5.01 (m, 1H), 4.84–4.79 (m, 2H), 4.53 (d, 1H, *J*=9.0 Hz), 4.49 (s, 1H), 4.28 (d, 1H, *J*=7.9 Hz), 3.98 (dd, 1H, *J*=6.4, 6.5 Hz), 3.76 (dd, 1H, *J*=5.7, 7.5 Hz), 3.46 (d, 1H, *J*=17.1 Hz), 3.42 (d, 1H, *J*=17.1 Hz), 3.11 (dd, 1H, *J*=5.6, 12.6 Hz), 3.05 (dd, 1H, *J*=12.6, 12.6 Hz), 2.39 (d, 1H, *J*=12.7 Hz), 2.18–2.09 (m, 2H), 1.98–1.71 (m, 13H), 1.64 (s, 3H), 1.55 (s, 3H), 1.54 (m, 1H), 1.41 (s, 3H), 1.37 (m, 1H), 1.08 (m, 1H), 0.84 (d, 3H, *J*=6.8 Hz), 0.79 (d, 3H, *J*=7.3, 7.4 Hz); HRMS (ESI$^+$) *m*/*z*: calcd for $C_{48}H_{68}N_8O_{10}$ ([M+2H]$^{2+}$) 458.2524. Found 458.2521.

5.4.4. Synthesis of Fmoc-protected tryptophan residue for solid-phase peptide synthesis.

5.4.4.1. Fmoc-L-Trp*(α-Ger) 19. To a solution of L-Trp*(α-Ger)-OMe **6** (312 mg, 0.880 mmol) in THF (3 ml) and CH_3OH (3.0 ml), 1 M aqueous LiOH (3.0 ml) was added dropwise at room temperature. After the reaction mixture had been stirred for 30 min, it was neutralized with 0.1 M phosphate buffer (10 ml). The reaction mixture was extracted with EtOAc (5×10 ml). The organic solvent was removed by evaporation. The residue was dissolved in dioxane (8.8 ml) and 1 M aqueous Na_2CO_3 (4.4 ml). To the solution was added Fmoc-OSu (386 mg, 1.16 mmol) at room temperature. After the reaction mixture had been stirred for 2 h, the reaction was neutralized with 0.1 M phosphate buffer (10 ml). The reaction mixture was extracted with EtOAc (4×30 ml). The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH$ 100/1→50/1) to give Fmoc-L-Trp*(α-Ger) **19** (482 mg, 0.857 mmol, 97% in two steps) as a colorless oil.

Anal. Calcd for $C_{36}H_{38}N_2O_4$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.95; H, 7.12; N, 5.08.

5.4.5. Syntheses of ComX$_{RO\text{-}E\text{-}2}$ pheromones with solid-phase peptide synthesis. Peptide bond formation was carried out according to the procedure for putative ComX$_{RO\text{-}E\text{-}2}$ peptides[16] except for the final cleavage and the deprotection procedures. Cleavage and deprotection of the resin was carried out as follows. To a suspension of the attached resin in CH_3CN was added 5% TFA and 5% trifluoroethanol at 0 °C. The reaction mixture was shaken in a rotary shaker for 20 h at 4 °C.

5.4.5.1. [3-6]ComX$_{RO\text{-}E\text{-}2}$ 20. ^{1}H NMR (600 MHz, CD_3CN/D_2O, 6/4) δ 7.42–7.34 (m, 3H), 7.28 (d, 2H, *J*=6.9 Hz), 7.02 (dd, 1H, *J*=7.5, 7.7 Hz), 6.88 (d, 1H, *J*=7.2 Hz), 6.63–6.60 (m, 2H), 5.09 (m, 1H), 5.07 (s, 1H), 5.02 (m, 1H), 4.28 (dd, 1H, *J*=4.8, 11.8 Hz), 3.96 (dd, 1H, *J*=4.8, 7.8 Hz), 3.38 (d, 1H, *J*=8.7 Hz), 3.27 (dd, 1H, *J*=4.8, 12.2 Hz), 3.21 (dd, 1H, *J*=5.2, 6.1 Hz), 2.99 (dd, 1H, *J*=11.8, 12.2 Hz), 2.28 (d, 1H, *J*=12.9 Hz), 2.19–2.12 (m, 2H), 2.11 (d, 1H, *J*=6.8 Hz), 2.17–1.90 (m, 12H), 1.76 (m, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.52 (m, 1H), 1.48 (s, 3H), 1.17 (dd, 1H, *J*=8.7, 12.9 Hz); HRMS (ESI$^+$) *m*/*z*: calcd for $C_{40}H_{53}N_6O_8$ ([M+H]$^+$) 745.3919. Found 745.3939.

5.4.5.2. [2-6]ComX$_{RO\text{-}E\text{-}2}$ 21. ^{1}H NMR (600 MHz, CD_3CN/D_2O, 6/4) δ 7.39–7.34 (m, 3H), 7.28 (d, 2H, *J*=7.2 Hz), 7.01 (dd, 1H, *J*=7.6, 7.7 Hz), 6.87 (d, 1H, *J*=7.5 Hz), 6.63–6.59 (m, 2H), 5.08 (s, 1H), 5.07 (m, 1H), 5.00 (m, 1H), 4.51 (dd, 1H, *J*=5.1, 11.2 Hz), 3.94 (dd, 1H, *J*=4.8, 7.9 Hz), 3.55 (d, 1H, *J*=8.8 Hz), 3.23–3.17 (m, 3H), 2.87 (dd, 1H, *J*=11.2, 12.2 Hz), 2.29 (d, 1H, *J*=12.8 Hz), 2.09 (d, 2H, *J*=7.2 Hz), 2.08–1.92 (m, 9H), 1.89–1.68 (m, 3H), 1.66 (s, 3H), 1.61 (m, 1H), 1.58 (s, 3H), 1.49 (s, 3H), 1.41 (m, 1H), 1.12–1.05 (m, 2H), 0.91 (d, 3H, *J*=6.8 Hz), 0.82 (dd, 3H, *J*=7.4, 7.5 Hz); HRMS (ESI$^+$) *m*/*z*: calcd for $C_{46}H_{64}N_7O_9$ ([M+H]$^+$) 858.4760. Found 858.4763.

Acknowledgements

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Triazolopeptides: chirospecific synthesis and *cis/trans* prolyl ratios of structural isomers

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Abstract—As *cis/trans* prolyl isomerization plays a crucial role in various biological processes, peptide mimics capable of modifying the *cis/trans* Xaa-Pro ratio are of particular interest. A practical approach toward proline derived triazolopeptides employing [3+2] azide–alkyne cycloadditions as the key reaction step and the analysis of their *cis/trans* prolyl ratios are reported. Structural investigations indicated the adjustability of both the cis-percentage and the conformational stability toward intramolecular H-bonding effects.

1. Introduction

Representing the only naturally occurring cyclic amino acid, proline displays properties distinct from those of open chain amino acids, when amide cis/trans isomerization deserves particular attention.[1,2] While engineering a number of mutant proteins to contain artificial proline analogs, Lummis et al. revealed very recently that cis/trans isomerization of a Pro in a hinge position of the 5-HT3 receptor elicits opening of an ion channel.[3] In fact, mutants bearing Pro mimetics with a high prevalence for the cis conformer proved constitutively active, while amino acids with very low cis/trans ratios rendered the receptor inactive. The importance of cis/trans isomerization for molecular recognition has also been shown by introduction of unnatural proline derivatives with an increased cis prevalence into a cyclic HIV-1 V3 loop analog. This loop has a common Gly-Pro-Gly-Arg motif, representing a type II β-turn, which is supposed to switch into a type VI β-turn, demanding a *cis*-proline peptide bond, as the key-step before getting the HIV-1 infective.[4] These findings underline the importance of molecular tools for a fine tuning of the *cis/trans* prolyl energy level ratio for the elucidation of biological systems.

Such an adjustment has been commonly accomplished by modifying the pyrrolidine moiety employing ring size variations,[5] sterically demanding substituents[6,7] as well as introduction of fluorine[8,9] or by introducing bridging elements to furnish Freidinger-type lactams.[10–13] Just few employing click chemistry, we herein report on the fine tuning of *cis/trans* prolyl ratios by bioisosteric replacement of the backbone amide group with a 1,2,3-triazole based moiety.[14,15]

In contrast to the established methods, this strategy leaves the geometric properties of the pyrrolidine moiety unmodified, which can be of particular interest if alterations on the sterical demand of the heterocyclic residue are considered unfavorable for the desired application.

[3+2] Azide–alkyne cycloadditions have been applied to various research areas, including drug discovery processes, bioconjugate chemistry, and solid phase organic synthesis.[16–19] Very recently, copper-promoted [3+2] cycloaddition reactions between amino acid derived building blocks gave rise to different '1,4' linked peptide mimetics that we call triazolopeptides. In principal, four types of triazolopeptides can be differentiated that we refer to as 1,4- and 1,5-triazolopeptides as well as 4,1- and 5,1-linked derivatives (Chart 1).

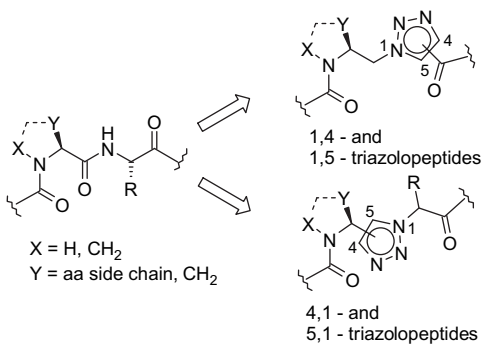

Chart 1.

Keywords: Triazolopeptide; *cis/trans* Prolyl isomerization; Click chemistry; Azide–alkyne cycloaddition.
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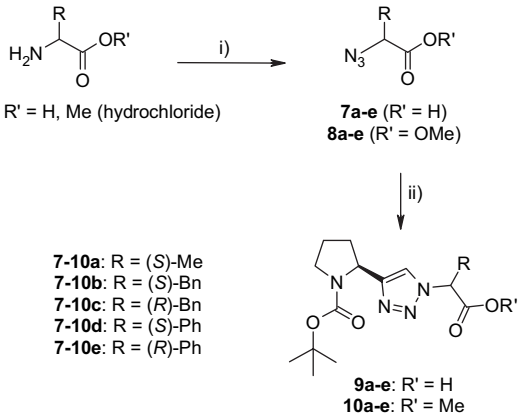
The sequence of the numbering that we use here corresponds to the substitution pattern of the triazole moiety, following the direction of the backbone (N to C terminal).[20–23]

2. Results and discussion

In this paper, we describe a divergent synthetic approach to all four subtypes and their impact on cis/trans isomerization when natural proline was employed as the common chiral building block. Taking advantage of previously described protocols,[24–27] commercially available *N*-Boc protected prolinol (**1**) was *O*-activated and subsequently reacted with sodium azide to give the azidomethylpyrrolidine **2** (Scheme 1). On the other hand, Swern oxidation of **1** with SO_3/pyridine and DMSO yielded the carbaldehyde **3** that could be transformed into the dibromo-substituted alkene **4** by Corey–Fuchs olefination. Subsequent treatment with 2 equiv of *n*-BuLi gave the pyrrolidinylacetylene **5**.

With the aim to understand the influence of the mode of triazole linkage on *cis*/*trans* prolyl ratios, we envisioned to transform the cyclization precursors **2** and **5** into the triazole-linked Pro-Gly mimetics **6a**,**b** and **6c**,**d**, respectively. In detail, azide **2** was reacted with ethyl propiolate when [3+2] azide–alkyne cycloadditions were carried out using both classical and Cu^I catalyzed conditions.[14,28] While Huisgen's 1,3-dipolar cycloaddition gave rise to an easily separable mixture of the 1,4- and 1,5-triazoles **6a** and **6b** in a 3:7 ratio, the copper assisted variant reported by Meldal and Sharpless exclusively yielded the protected 1,4-triazolopeptide **6a**. To approach to the 4,1- and 5,1-subtypes, the proline derived alkyne **5** was reacted with azidoacetic acid ethyl ester,[29] which was freshly prepared from ethyl bromoacetate and sodium azide. As expected, complete regiocontrol was observed under Cu^I catalysis resulting in the formation of the 4,1-substituted congener **6c** while heating in ethyl acetate afforded a 3:1 ratio of the regioisomers **6c** and **6d**.

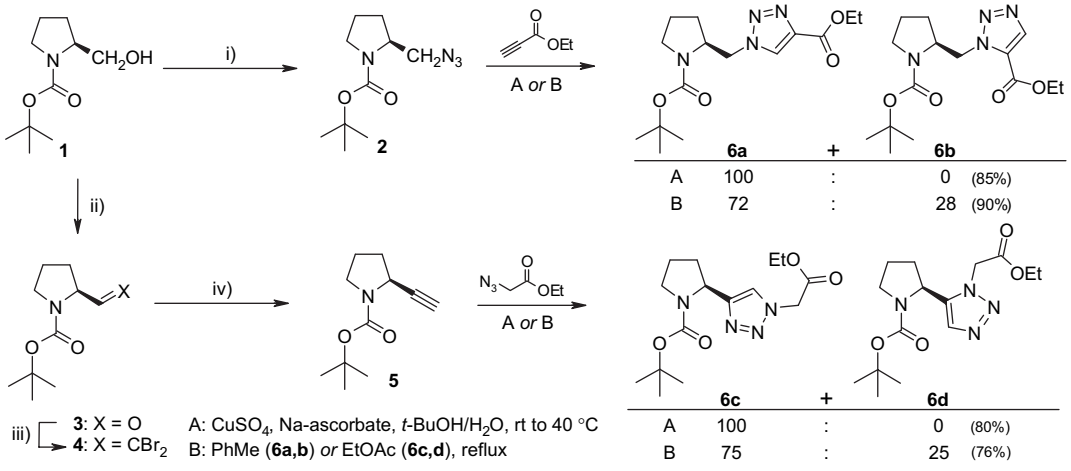
To evaluate a general access to triazole-linked Pro-Xaa mimetics, we intended an introduction of representative chiral α-amino acids into triazolopeptides of type 4,1. Therefore, (*S*)-alanine, (*S*)- and (*R*)-phenylalanine, and both enantiomers of phenylglycine as an amino acid, which is highly prone to racemization were reacted with trifluoromethylsulfonic azide and $CuSO_4$ to yield the respective azido acids **7a**–**e** (Scheme 2).[30] Employing analogous conditions, diazo transfer was also done starting from the corresponding methyl ester hydrochlorides to give rise to azido acid esters **8a**–**e**.



Scheme 2. (i) (1) **7a**–**e**: $CuSO_4 \cdot 5H_2O$, H_2O/MeOH, K_2CO_3, TfN_3, 12 h (62–86%); (2) **8a**–**e**:$CuSO_4 \cdot 5H_2O$, MeOH, DIPEA, TfN_3, 2.5–15 h, (71–91%); (ii) **5**, $CuSO_4 \cdot 5H_2O$, Na-ascorbate, *t*-BuOH/H_2O, rt or 40 °C, 1–3 d (36–92%).

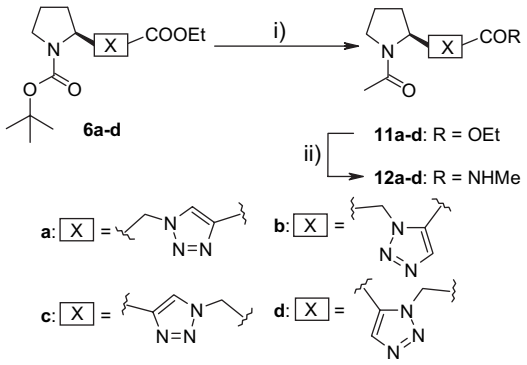
While the synthesis of building blocks **7a**–**e** and **8a**–**c** proceeded straightforward, the Phg derivatives **8d**,**e** displayed partial racemization, as detected by HPLC on a chiral column. However, pure enantiomers **8d** and **8e** could be prepared by esterification of **7d** and **7e**, respectively, using thionyl chloride in methanol.

Copper-promoted [3+2] azide–alkyne cycloaddition reactions of the azido acids **7a**–**e** and the azido esters **8a**–**e** with the central alkyne **5** proceeded smoothly resulting in the formation of the triazoles **9a**–**e** and **10a**–**e**, respectively. When starting from the phenylglycine derivatives **8d**,**e**, which are expectedly prone to epimerization,[31] room temperature proved to be necessary to diminish epimerization.



Scheme 1. (i) (1) MsCl, DIPEA, CH_2Cl_2, 0 °C to rt, 2.5 h (86%); (2) NaN_3, DMF, 70 °C, 24 h (83%); (ii) SO_3/pyridine, DIPEA, DMSO/CH_2Cl_2, −5 °C, 5 h (92% crude); (iii) PPh_3, CBr_4, CH_2Cl_2, −5 to 0 °C, 2 h (90%); (iv) *n*-BuLi, THF, −78 °C, 1 h 15 min (83%).

Exchange of the Boc protecting groups of the four isomeric triazolopeptides **6a–d** with acetyl groups gave rise to model Pro-Gly surrogates more ideally mimicking a *cis*/*trans* prolyl isomerization when treated with TFA and subsequent acetylation with acetyl chloride and DIPEA yielded *N*-acetyl analogs **11a–d** (Scheme 3).



Scheme 3. (i) (1) TFA, CH_2Cl_2, 0 °C, 35 min; (2) AcCl, DIPEA, CH_2Cl_2, rt, 19 h (23–88%; two steps); (ii) $MeNH_2$, EtOH, 0 °C, 2 h (18–86%).

To investigate the influence of intramolecular hydrogen bonding on the conformational behavior of our test set, the ethyl esters **11a–d** were converted to the *N*-methyl amides **12a–d** by treatment with methylamine.

The conformational properties of the model triazolopeptides **11a–d** and **12a–d** were examined by means of NMR spectroscopy in 2 mM $CDCl_3$ solution. The cis/trans ratios were determined on the basis of the triazole protons, which exhibited clearly separated signals for the two conformers in each case. NOESY experiments were done with the peptide mimetics **11a–d** and **12a** in order to unambiguously assign signal sets to particular isomers by comparing dipolar couplings of the acetyl methyl group with the C^2H or C^5H_2 protons of the pyrrolidine moiety. *N*-Acetylprolylglycine methyl ester and *N*-acetylprolylglycine *N*′-methyl amide were employed as reference peptides (Table 1).[32]

Table 1. NMR-derived *cis*/*trans* prolyl ratios of the model peptide surrogates **11a–d** and **12a–d** (2 mM, $CDCl_3$) compared to AcProGlyOMe and AcProGlyNHMe,[32] respectively (5% steps)

Cpd (type)	% cis	Cpd (type)	% cis
11a (1,4)	5	**12a** (1,4)	<1
11b (1,5)	30	**12b** (1,5)	15
11c (4,1)	30	**12c** (4,1)	30
11d (5,1)	10	**12d** (5,1)	5
AcProGlyOMe	10	AcProGlyNHMe	<1

NMR data indicated a 1:9 *cis*/*trans* prolyl ratio for the 5,1-triazolopeptide **11d**, which is very similar to *N*-acetylprolylglycine methyl ester.[32] Investigation of the 4,1-regioisomer **11c** showed a substantially higher cis-fraction of 30%. Thus, the homologization of the backbone led to an increase of the *cis*-isomer. Interestingly, the NMR spectra indicated an inverse behavior for the triazolopeptides **11a**,**b** when the 1,4-regioisomer with an elongated backbone displayed a low tendency to form a *cis* prolyl structure (**11a**: 5% cis) whereas the 1,5-isomer **11b** existed as 3:7 mixture of *cis*/*trans* isomers.

The additional amide NH function of *N*-acetylprolylglycine *N*′-methyl amide facilitates formation of an intramolecular hydrogen bond toward the acetyl carbonyl group. A β-turn can be adopted if the peptide bond between the amino acid in position *i* and proline in position *i*+1 displays trans geometry. As a consequence, almost exclusive formation of the *trans* prolyl isomer was observed.[32] Interestingly, substantial decrease of the cis-population was observed for the 1,5 and 5,1-triazolopeptides **12b**,**d** incorporating an NH that can form an intramolecular 10-membered ring. On the other hand the 1,4- and 4,1-linked isomers **12a**,**c** could only form an 11-membered ring, which is obviously less favored. As a consequence, introduction of an amide functionality did not significantly change the cis/trans ratio. FTIR spectroscopy of a 2 mM $CDCl_3$ solution clearly corroborated our observation revealing strong absorption bands at 3330–3350 cm^{-1} (besides absorptions at 3430–3455 cm^{-1}) for **12b**,**d** and the reference carboxamide clearly indicating an equilibrium between an intramolecular hydrogen bond and a non-associated conformation. Molecular origins for the distinct conformational behavior of our triazolopeptides might be attractive or repulsive dipolar interactions between the carbonyl group of the *N*-acetyl substituent and the triazole moiety.[33]

3. Conclusion

In conclusion, we applied [3+2] azide–alkyne cycloaddition reactions for the synthesis of four different types of triazolopeptides mimicking a Pro-Gly dipeptide. While 1,4- and 4,1-triazolopeptides were regioselectively accessible employing a Cu^I catalyzed protocol, the 1,5- and 5,1-linked subtypes resulted from separation of a mixture of regioisomers. A regiocontrolled approach toward 1,5- and 5,1-triazolopeptides employing ruthenium-catalyzed methodology appears very promising.[34] Structural studies indicated the adjustability of both the cis-percentage and the conformational stability toward intramolecular H-bonding effects. Investigations toward the application of triazolopeptides on the development of neurotensin analogs and TetR-based artificial transactivators are currently ongoing in our laboratory.

4. Experimental

4.1. General

Although we did not observe problems associated with a putatively explosive character of the used azides, the low weight azidoacetic acid ethyl ester was not distilled but used as a solution. Reagents and solvents were obtained from commercial sources unless stated otherwise, and were used as received. Unless otherwise noted, reactions were conducted without inert atmosphere. Evaporations of final product solutions were done under vacuo with a rotatory evaporator. Reaction temperatures were measured externally. Reactions were monitored by TLC on Merck silica gel plates (0.25 mm), visualized by UV light, iodine and/or ninhydrin solution. Flash chromatography was carried out with 230–400 mesh silica gel and 0.8–1.0 bar nitrogen pressure. EIMS was carried out using EI ionization (70 eV) with solid inlet on a Finnigan MAT TSQ 70 or

a Jeol GCmate II spectrometer. HRMS was carried out with a resolution of $M/\Delta M = 5000$ relative to PFK on a Jeol GCmate II spectrometer. Standard NMR spectra were recorded at 300 K on a Bruker Avance 600 (^{1}H at 600 MHz, ^{13}C at 150 MHz) or a Bruker Avance 360 (^{1}H at 360 MHz, ^{13}C at 90 MHz). Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: 7.26, $CDCl_3$: 77.0). Elemental analyses were performed at the Institute of Organic Chemistry (Analytical Departments) of the Friedrich Alexander University, Erlangen-Nürnberg. Melting points were determined with a Büchi 510 apparatus and are uncorrected. HPLC analysis were run on a Agilent 1100 Series with a Diode Array Detector at 190, 230 and 250 nm. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. IR spectra were measured on a Jasco 410 FTIR spectrometer.

4.2. Azidoacetic acid ethyl ester

Bromoacetic acid ethyl ester (3.34 g, 2.22 mL, 20.0 mmol) and NaN_3 (2.60 g, 40.0 mmol) were dissolved in DMF (15 mL), heated to 60 °C, and stirred for 2 h. After cooling to room temperature, the solution was diluted with water (100 mL), extracted with ethyl acetate (4×10 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL). This layer was re-extracted with ethyl acetate (2×10 mL). The combined organic layers were washed with brine (50 mL), and the aqueous layer was re-extracted with ethyl acetate (2×10 mL). The combined organic layers were dried with Na_2SO_4, and the resulting solution was diluted to 100 mL, stored over molecular sieves under nitrogen, and was used for cycloaddition reactions without further purification.

4.3. General procedure for the diazo transfer on amino acid methyl ester hydrochlorides

The hydrochlorides of the amino acid methyl esters (approx. 16.0 mmol) were dissolved in methanol (12 mL). An aqueous solution of $CuSO_4 \cdot 5H_2O$ (10 g/L, approx. 0.01 equiv) and diisopropylethylamine (1.5 equiv) were added at room temperature, whereupon the color of the solution changed from turquoise to deep blue. Subsequently, a freshly prepared trifluoromethane sulfonic azide solution (1 M in CH_2Cl_2, 1.8 equiv) was added. After stirring for 15 h, the solvent was removed, and the crude product was purified either by Kugelrohr distillation under reduced pressure (**8a**) or by flash column chromatography (**8b**,**c**). TLC detection was done with a PPh_3/hexanes solution (1% m/v) followed by ninhydrin.

4.3.1. (*S*)-2-Azidopropionic acid methyl ester (8a). Following the general procedure, alanine methyl ester hydrochloride was converted to **8a** (90%) as a colorless oil. R_f 0.46 (hexanes/ethyl acetate 4:1); $[\alpha]_D^{25}$ 12.2 (*c* 1.0, $CHCl_3$); IR (Neat) 2958, 2138, 2108, 1748 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.49 (d, 3H, *J*=7.7 Hz, CH*CH*$_3$), 3.80 (s, 3H, OCH_3), 3.96 (q, 1H, *J*=7.7 Hz, *CH*CH$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 16.8 (CH_3), 52.6 (OCH_3), 57.3 (CH), 171.4 (C=O).

4.3.2. (*S*)-2-Azido-3-phenylpropionic acid methyl ester (8b). Following the general procedure, (*S*)-phenylalanine methyl ester hydrochloride was converted to **8b** (91%) as a colorless oil. R_f 0.63 (CH_2Cl_2); $[\alpha]_D^{28}$ −47.8 (*c* 1.0, $CHCl_3$); IR (Neat) 3030, 2954, 2109, 1746 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.01 (dd, 1H, *J*=14.0, 8.7 Hz, CH_2), 3.18 (dd, 1H, *J*=14.0, 5.4 Hz, CH_2), 3.77 (s, 3H, OCH_3), 4.07 (dd, 1H, *J*=8.7, 5.4 Hz, CH), 7.19–7.36 (m, 5H, Ar–H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 37.6 (CH_2), 52.6 (OCH_3), 63.3 (CH), 127.3+128.7+129.2 (aryl CH), 135.9 (aryl *C*–C), 170.4 (C=O); EIMS 162 (M−HN_3), 118 (M−N_2−COOMe), 91 (Bn^+); M^+ not detected.

4.3.3. (*R*)-2-Azido-3-phenylpropionic acid methyl ester (8c). *Following the general procedure*, (*R*)-phenylalanine methyl ester hydrochloride was converted to **8c** (85%). $[\alpha]_D^{28}$ 48.5 (*c* 1.0, $CHCl_3$).

4.4. Esterification of phenylglycine derivates

4.4.1. (*S*)-2-Azido-2-phenylacetic acid methyl ester (8d). Methanol (10.0 mL) was cooled to −10 °C, whereupon thionyl chloride (1.09 mL, 15.0 mmol) was added dropwise over 5 min while stirring vigorously. Subsequently, a solution of **7d** (895 mg, 5.05 mmol) in methanol (10 mL) was added over 2 min and the mixture was allowed to warm to room temperature. After 6 h 50 min, ice (30 g) and water (80 mL) were added and the pH was adjusted to 8 with a NaH_2PO_4 buffer. The mixture was extracted with ether (4×20 mL), the combined organic layers were dried with $MgSO_4$, concentrated, and the crude product (862 mg, 89%) was used without further purification, as a HPLC analysis indicated sufficient purity. Colorless oil; R_f 0.46 (hexanes/ethyl acetate 4:1); TLC detection was done with a PPh_3/hexanes solution (1% m/v) followed by ninhydrin; HPLC: t_R 19.5 min, >99% ee (Chiralcel® OD, 4.6× 250 mm, hexanes/isopropanol 99:1, 0.5 mL/min, 254 nm detection); $[\alpha]_D^{22}$ 157.5 (*c* 1.0, $CHCl_3$); IR (Neat) 2955, 2844, 2105, 1746 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.78 (s, 3H, OCH_3), 4.98 (s, 1H, CH), 7.33–7.49 (m, 5H, ArH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 52.9 (OCH_3), 65.3 (CH), 127.6+129.1+129.3 (aryl CH), 133.8 (aryl C–C), 196.6 (C=O); EIMS 191 (M^+).

4.4.2. (*R*)-2-Azido-2-phenylacetic acid methyl ester (8e). Compound **7e** was reacted under the conditions described above, furnishing **8e** (88%) as a colorless oil. HPLC: t_R 17.9 min, >99% ee (Chiralcel® OD, 4.6×250 mm, hexanes/isopropanol 99:1, 0.5 mL/min, 254 nm detection); $[\alpha]_D^{22}$ −159.2 (*c* 1.0, $CHCl_3$).

4.5. (*S*)-1-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl-methyl)-(1,2,3)-triazole-4-carboxylic acid ethyl ester (6a) and (*S*)-1-(1-*tert*-Butoxycarbonylpyrrolidin-2-ylmethyl)-(1,2,3)-triazole-5-carboxylic acid ethyl ester (6b)

To a solution of **2** (3.92 g, 17.3 mmol) in toluene (60 mL) was added ethyl propiolate (5.26 mL, 51.9 mmol). The mixture was heated to reflux for 19 h, whereupon another portion of ethyl propiolate (1.75 mL, 17.3 mmol) was added and refluxing was continued for 5 h. After cooling to room temperature, the solvent was removed and the residue was purified by flash column chromatography (hexanes/ethyl acetate 9:1 increasing to 1:1), furnishing 3.68 g (66%) of **6a** and 1.40 g (25%) of **6b** as a waxy solid and viscous oil, respectively.

4.5.1. Compound 6a. Mp 86–88 °C, R_f 0.20 (hexanes/ethyl acetate 1:1); $[\alpha]_D^{22}$ −68.6 (*c* 1.0, $CHCl_3$); IR (Neat) 3132, 2978, 1739, 1723, 1693 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.410+1.415 (2×t, 3H, *J*=7.1 Hz, CH_2CH_3), 1.50 (s, 9H, Boc CH_3), 1.59–2.10 (br m, 4H, CH_2), 3.00–3.53+3.29 (br m+dd, 2H, *J*=14.2, 6.0 Hz, NCH_2), 4.12 (br s, 1H, CH), 4.36–4.85+4.42+4.52 +4.75 (br m+q+q+dd, 4H, *J*=7.1 Hz+7.1 Hz+12.8, 5.4 Hz, OCH_2+$CHCH_2$-triazole), 8.00+8.04 (br s+s, 1H, triazole H); EIMS 324 (M^+).

4.5.2. Compound 6b. R_f 0.36 (hexanes/ethyl acetate 1:1); $[\alpha]_D^{22}$ −8.8 (*c* 1.0, $CHCl_3$); IR (Neat) 3132, 2977, 1731, 1696 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.3–1.43+1.38 (br s+t, 12H, *J*=6.9 Hz, Boc CH_3+CH_2CH_3), 1.61–1.98 (br m, 4H, CH_2), 3.22–3.49 (br m, 2H, NCH_2), 4.28–4.57+4.38 (m+br q, 3H, *J*=6.9 Hz, CH+CH_2CH_3), 4.67–4.90+4.74 (m+dd, 2H, *J*=13.5, 5.6 Hz, $CHCH_2$-triazole), 8.09 (s, 1H, triazole H); EIMS 324 (M^+).

4.6. (*S*)-1-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl-methyl)-(1,2,3)-triazole-4-carboxylic acid ethyl ester (6a)

Compound **2** (226 mg, 1.00 mmol) and ethyl propiolate (122 μL, 1.20 mmol) were dissolved in *tert*-butanol. Aqueous solutions of $CuSO_4 \cdot 5H_2O$ (1 M, 20 μL) and sodium ascorbate (1 M, 100 μL) were added. After stirring at room temperature for 1 d, water (50 mL) was added and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, concentrated, and the residue was purified by flash column chromatography (hexanes/ethyl acetate 4:1), furnishing 276 mg (85%) of **6a**.

4.7. (*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]acetic acid ethyl ester (6c) and (*S*)-2-[5-(1-*tert*-butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]acetic acid ethyl ester (6d)

Compound **5** (195 mg, 1.00 mmol) was dissolved in a solution of azidoacetic acid ethyl ester (approx. 0.2 M in ethyl acetate, 7.5 mL, approx. 1.50 mmol) and heated to reflux for 48 h. After cooling to room temperature, the solvent was removed and the mixture of regioisomers was obtained by flash column chromatography (hexanes/ethyl acetate 4:1), furnishing 248 mg (76%) of a colorless oil that was used in the next step without further separation. R_f 0.15 (hexanes/ethyl acetate 1:1).

4.8. General procedure for cycloaddition reactions with 5 under catalytic conditions (6c, 9a–e, 10a–e)

Compound **5** (50–200 mg) and the corresponding azide (1.0–1.2 equiv; slight excesses with respect to **5** resulted in higher yields) were dissolved in *tert*-butanol (1–2 mL). After addition of aqueous solutions of $CuSO_4 \cdot 5H_2O$ (1 M, 0.02 equiv) and sodium ascorbate (1 M, 0.1 equiv), water (0.5–1 mL) was added. In cases where addition of water caused solubility issues, the latter was replaced by methanol. The mixture was stirred either at room temperature or at 40 °C until TLC indicated either stagnation or completion of the reaction, which was the case after 1–4 d. In case of **10d** and **10e**, maintaining room temperature and interrupting the reaction after 20 h were crucial for suppression of the epimerization rate. The mixtures were diluted with water (50 mL). In case of **9a–e**, the pH was adjusted to 2–3 by addition of aqueous HCl. The compounds were isolated by extraction with CH_2Cl_2 or ethyl acetate (4×20 mL), washed with brine (20 mL), re-extraction of the washing liquid (20 mL), drying of the combined organic layers with $NaSO_4$ or $MgSO_4$, evaporation, and flash column chromatography.

4.8.1. (*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]acetic acid ethyl ester (6c). Compound **5** and azidoacetic acid ethyl ester in ethyl acetate were reacted at 40 °C following the general procedure (reaction time: 38 h). Flash column chromatography (hexanes/ethyl acetate 3:2) furnished **6c** (79%) as a colorless solid. Mp 75–76 °C; R_f 0.21 (hexanes/ethyl acetate 3:2); $[\alpha]_D^{29}$ −59.3 (*c* 1.0, methanol); IR (Neat) 3141, 2977, 2270, 1756, 1691 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.29 (t, 3H, *J*=7.1 Hz, CH_2CH_3), 1.36+1.43 (2×br s, 9H, Boc CH_3), 1.83–2.56 (br m, 4H, CH_2), 3.30–3.63 (br m, 2H, NCH_2), 4.25 (q, 2H, *J*=7.1 Hz, CH_2CH3), 4.95–5.19 (br m, 3H, CH_2CO+NCH), 7.45+7.61 (br s+br s, 1H, triazole H); EIMS 324 (M^+).

4.8.2. (2*S*,2′*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]propionic acid (9a). Compounds **5** and **7a** were reacted at 40 °C following the general procedure (reaction time: 48 h). Flash column chromatography (CH_2Cl_2/methanol/HCOOH 97:3:0.5) furnished **9a** (76%) as a colorless solid. Mp 58–62 °C; R_f 0.13 (CH_2Cl_2/methanol/HCOOH 95:5:0.5); $[\alpha]_D^{26}$ −47.5 (*c* 1.0, methanol); IR (Neat) 3481, 3142, 2977, 2881, 2484, 2249, 1743, 1687 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; rotamers and broadened signals were observed) δ 1.16–1.56 (2×br s, 9H, Boc CH_3), 1.72–2.48+1.82 (br m+d, 7H, *J*=6.6 Hz, CH_2+$CHCH_3$), 3.35–3.63 (br m, 2H, NCH_2), 5.05 (dd, 1H, *J*=7.4, 2.4 Hz, NCH), 5.42 (br s, 1H, CH_3CH), 6.00 (br s, 1H, OH), 7.67 (br s, 1H, triazole H); ^{13}C NMR (90 MHz, $CDCl_3$; rotamers and broadened signals were observed) δ 18.3+18.6 (CH_3), 23.4+24.4 (CH_2), 28.5 (Boc CH_3), 31.4+33.3 (CH_2), 46.5+47.0, 53.0+54.0, 58.4 (2×CH+CH_2), 80.5 (Boc C^q), 120.8+121.9, 149.1+150.9, 155.1 (2×triazole C+Boc C=O), 171.2 (COOH); EIMS 310 (M^+); Anal. Calcd for $C_{14}H_{22}N_4O_4 \cdot 0.25H_2O$: C, 53.41; H, 7.20; N, 17.79. Found: C, 53.41; H, 7.06; N, 17.89 (the percentage of H_2O was corroborated by ^1H NMR spectroscopy).

4.8.3. (2*S*,2′*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]-3-phenylpropionic acid (9b). Compounds **5** and **7b** were reacted at 40 °C following the general procedure (reaction time: 48 h). Flash column chromatography (CH_2Cl_2/methanol/HCOOH 97:3:0.5) furnished **9b** (73%) as a colorless solid. Mp 75–78 °C; R_f 0.18 (CH_2Cl_2/methanol/HCOOH 95:5:0.5); $[\alpha]_D^{26}$ −139.0 (*c* 1.0, methanol); IR (Neat) 3469, 3148, 2977, 2880, 2511, 2250, 1740, 1689, 1640 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.13–1.56 (2×br s, 9H, Boc CH_3), 1.72–2.40 (br m, 4H, CH_2), 3.30–3.59+3.53 (br m+dd, 2H, *J*=13.5, 5.6 Hz, NCH_2+$PhCH_2$), 5.01 (br d, 1H, *J*=5.5 Hz, NCH), 5.41–6.00 (br m, 2H, NCHCO+OH), 7.02 (br s, 2H, ArH), 7.15–7.23 (m, 3H, ArH), 7.58+7.69

(br s+br s, 1H, triazole H); ^{13}C NMR (150 MHz, $CDCl_3$; rotamers and broadened signals were observed) δ 23.1+24.5 (CH_2), 28.4+28.6 (Boc CH_3), 31.0+33.4, 39.0+39.1 (CH_2), 46.3+46.9, 52.8+54.1, 64.0+64.2 (NCH_2+2×NCH), 80.4+80.8 (Boc C^q), 121.6+122.9, 127.4+127.6, 128.8, 129.1, 135.2+135.3 (5×aryl C), 148.6+150.6, 154.9+155.3 (aryl C+Boc C=O), 169.7 (COOH); EIMS 386 (M^+); Anal. Calcd for $C_{20}H_{26}N_4O_4$: C, 62.16; H, 6.78; N, 14.50. Found: C, 61.93; H, 6.60; N, 14.40.

4.8.4. (2*R*,2′*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]-3-phenylpropionic acid (9c). Compounds **5** and **7c** were reacted at 40 °C following the general procedure (reaction time: 48 h). Flash column chromatography (CH_2Cl_2/methanol/HCOOH 97:3:0.5) furnished **9c** (87%) as a colorless solid. Mp 72–75 °C; R_f 0.15 (CH_2Cl_2/methanol/HCOOH 95:5:0.5); $[\alpha]_D^{26}$ 14.7 (*c* 1.0, methanol); IR (Neat) 3474, 3138, 2978, 2880, 2512, 2249, 1740, 1689, 1640 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.23–1.48 (2×br s, 9H, Boc CH_3), 1.61–2.27 (br m, 4H, CH_2), 3.23–3.61+3.47+3.54 (br m+dd+dd, 4H, *J*=14.2, 8.3 Hz+14.2, 5.9 Hz, NCH_2+$PhCH_2$), 5.06 (dd, 1H, *J*=5.7, 3.9 Hz, NCH), 5.44–5.99 (br m, 2H, NCHCO+OH), 6.92–7.02 (br m, 2H, ArH), 7.12–7.26 (m, 3H, ArH), 7.48 (br s, 0.4H, triazole H), 7.93 (br s, 0.6H, triazole H); H/D exchange: 5.55 (br m, 1H, NCHCO); ^{13}C NMR (150 MHz, $CDCl_3$; rotamers and broadened signals were observed) δ 22.7+24.0 (CH_2), 28.6 (Boc CH_3), 32.2+33.3, 39.3+39.5 (CH_2), 46.3+47.0, 53.0+54.4, 64.1+64.3 (NCH_2+2×NCH), 80.7+80.9 (Boc C^q), 121.3+122.7, 127.5 (s), 128.7 (w), 128.9 (s), 129.2 (w), 135.3+135.3 (5×aryl C), 148.9+150.7, 155.0+155.8 (aryl C+Boc C=O), 169.9+170.0 (COOH); EIMS 386 (M^+); Anal. Calcd for $C_{20}H_{26}N_4O_4\cdot0.25H_2O$: C, 61.44; H, 6.83; N, 14.33. Found: C, 61.57; H, 6.62; N, 14.48 (the percentage of H_2O was corroborated by ^{1}H NMR spectroscopy).

4.8.5. (2*S*,2′*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]-2-phenylacetic acid (9d). Compounds **5** and **7d** were reacted at 40 °C following the general procedure (reaction time: 48 h). Flash column chromatography (CH_2Cl_2/methanol/HCOOH 97:3:0.5) furnished **9d** (92%) as a colorless solid. Mp 77–78 °C; R_f 0.21 (CH_2Cl_2/methanol/HCOOH 95:5:0.5); $[\alpha]_D^{26}$ 35.6 (*c* 1.0, methanol); IR (Neat) 3469, 3155, 2977, 2880, 2555, 2501, 2250, 1742, 1687, 1638 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$; rotamers were observed) δ 1.14–1.49 (2×br s, 9H, Boc CH_3), 1.68–1.95 (br m, 1.7H, CH_2), 2.01–2.29 (br m, 2H, CH_2), 2.34–2.49 (br m, 0.3H, CH_2), 3.36+3.38 (dd+dd, 2H, *J*=16.6, 5.5 Hz+16.6, 10.0 Hz, NCH_2), 4.99 (br d, 1H, *J*=5.7 Hz, NCH), 5.50–6.46 (br s, 1H, OH), 6.47–6.60 (br m, 1H, NCHCO), 7.32–7.48 (m, 5H, ArH), 7.79+7.86 (br s+br s, 1H, triazole H); ^{13}C NMR (150 MHz, $CDCl_3$; rotamers and broadened signals were observed) δ 23.4+24.5 (CH_2), 28.3+28.4 (Boc CH_3), 30.8+33.2, 46.4+46.8, 52.9+53.9, 66.3+66.4 (2×CH_2+2×NCH), 80.5+80.9 (Boc C^q), 121.5+122.4, 123.2, 128.1–128.4, 129.3–129.7, 133.8+134.0, 150.5, 154.9+155.4 (6×aryl C+Boc C=O), 169.0 (COOH); EIMS 372 (M^+); Anal. Calcd for $C_{19}H_{24}N_4O_4\cdot0.25H_2O$: C, 60.54; H, 6.55; N, 14.86; Found: C, 60.44; H, 6.40; N, 14.73 (the percentage of H_2O was corroborated by ^{1}H NMR spectroscopy).

4.8.6. (2*R*,2′*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]-2-phenylacetic acid (9e). Compounds **5** and **7e** were reacted at 40 °C following the general procedure (reaction time: 48 h). Flash column chromatography (CH_2Cl_2/methanol/HCOOH 97:3:0.5) furnished **9e** (81%) as a colorless solid. Mp 74–76 °C; R_f 0.10 (CH_2Cl_2/methanol/HCOOH 95:5:0.5); $[\alpha]_D^{26}$ −117 (*c* 1.0, methanol); IR (Neat) 3155, 2977, 2880, 2555, 2487, 2249, 1738, 1690, 1642 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 0.93–1.50 (2×br s, 9H, Boc CH_3), 1.72–1.96 (br m, 1.8H, CH_2), 2.00–2.38 (br m, 2.2H, CH_2), 3.25–3.71+3.40 (br m+ddd, 2H, *J*=10.5, 8.0, 7.8 Hz, NCH_2), 5.03 (ddd, 1H, *J*=7.4, 2.8, 0.6 Hz, NCH), 5.96 (br s, 1H, OH), 5.55+6.62 (br s+br s, 1H, NCHCO), 7.23–7.49 (br m, 5H, ArH), 8.06 (s, 0.1H, triazole H), 8.25 (br s, 0.9H, triazole H); ^{13}C NMR (90 MHz, $CDCl_3$; rotamers and broadened signals were observed) δ 23.1 (CH_2), 28.2+28.5 (Boc CH_3), 33.6, 46.7, 54.7, 64.2+66.0 (2×CH_2+2×NCH), 81.0 (Boc C^q), 121.8, 127.5, 129.3, 129.4, 135.0, 151.0, 156.0 (6×aryl C+Boc C=O), 169.0 (COOH); EIMS 372 (M^+); Anal. Calcd for $C_{19}H_{24}N_4O_4\cdot0.25H_2O$: C, 60.54; H, 6.55; N, 14.86. Found: C, 60.74; H, 6.45; N, 14.95 (the percentage of H_2O was corroborated by ^{1}H NMR spectroscopy).

4.8.7. (2*S*,2′*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]propionic acid methyl ester (10a). Compounds **5** and **8a** were reacted at room temperature following the general procedure (reaction time: 4 d). Flash column chromatography (hexanes/ethyl acetate 8:2) furnished **10a** (36%) as a colorless resin. R_f 0.11 (hexanes/ethyl acetate 1:1); $[\alpha]_D^{27}$ −50.6 (*c* 1.0, methanol); IR (Neat) 3136, 2975, 2877, 1753, 1692 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.27–1.50 (2×br s, 9H, Boc CH_3), 1.72–2.60+1.81 (br m+d, 7H, *J*=7.3 Hz, CH_2+$CHCH_3$), 3.32–3.63 (br m, 2H, NCH_2), 3.75 (s, 3H, OCH_3), 5.03 (br s, 1H, NCH), 5.45 (br s, 1H, CH_3CH), 7.49+7.67 (br s+br s, 1H, triazole H); EIMS 324 (M^+); HRMS calculated for $C_{15}H_{24}N_4O_4$: 324.1798, found: 324.1798.

4.8.8. (2*S*,2′*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]-3-phenylpropionic acid methyl ester (10b). Compounds **5** and **8b** were reacted at room temperature following the general procedure (reaction time: 4 d). Flash column chromatography (hexanes/ethyl acetate 8:2) furnished **10b** (49%) as a colorless solid. Mp 69–72 °C; R_f 0.26 (hexanes/ethyl acetate 1:1); HPLC: t_R 32.8 min (silica gel 5 μm, 4.6×250 mm, diisopropyl ether/acetonitrile 94:6, 0.5 mL/min, 254 nm detection); $[\alpha]_D^{24}$ −112 (*c* 1.0, methanol); IR (Neat) 3136, 2976, 2876, 2246,1750, 1693 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.26–1.56 (2×br s, 9H, Boc CH_3),1.79–2.50 (br m, 4H, CH_2), 3.31–3.56+3.49 (br m+dd, 4H, *J*=14.1, 6.6 Hz, NCH_2+$PhCH_2$), 3.73 (s, 3H, OCH_3), 4.99 (br s, 1H, NCH), 5.54 (br s, 1H, NCHCO), 6.98–7.07 (m, 2H, ArH), 7.17–7.29 (m, 3H, ArH), 7.36 (br s, 0.6H, triazole H), 7.64 (br s, 0.4H, triazole H); EIMS 400 (M^+); Anal. Calcd for $C_{21}H_{28}N_4O_4$: C, 62.98; H, 7.05; N, 13.99. Found: C, 62.75; H, 7.06; N, 13.96.

4.8.9. (2*R*,2′*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]-3-phenylpropionic acid methyl ester (10c). Compounds **5** and **8c** were reacted at room temperature following the general procedure (reaction time:

4 d). Flash column chromatography (hexanes/ethyl acetate 8:2) furnished **10c** (81%) as a colorless solid. Mp 97–99 °C; R_f 0.28 (hexanes/ethyl acetate 1:1); HPLC: t_R 34.4 min (silica gel 5 μm, 4.6×250 mm, diisopropyl ether/acetonitrile 94:6, 0.5 mL/min, 254 nm detection); $[\alpha]_D^{24}$ 10.8 (*c* 1.0, methanol); IR (Neat) 3138, 2975, 2877, 2251, 1751, 1692 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.18–1.58 (2×br s, 9H, Boc CH_3), 1.81–2.51 (br m, 4H, CH_2), 3.31–3.56+3.42+3.50 (br m+dd+dd, 4H, *J*=14.1, 8.9 Hz+14.1, 6.6 Hz, NCH_2+PhH_2), 3.72 (s, 3H, OCH_3), 4.99 (br s, 1H, NCH), 5.45 (br s, 1H, NCHCO), 6.99–7.07 (m, 2H, ArH), 7.17–7.28 (m, 3H, ArH), 7.40+7.54 (br s+br s, 1H, triazole H); EIMS 400 (M^+); Anal. Calcd for $C_{21}H_{28}N_4O_4$: C, 62.98; H, 7.05; N, 13.99. Found: C, 62.99; H, 7.07; N, 13.91.

4.8.10. (2*S*,2′*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]-2-phenylacetic acid methyl ester (10d). Compounds **5** and **8d** were reacted at room temperature following the general procedure (reaction interrupted after 20 h). Flash column chromatography (hexanes/ethyl acetate 7:3) furnished **10d** (26%) as a colorless resin. R_f 0.26 (hexanes/ethyl acetate 1:1); HPLC: t_R 67.6 min, 56% de (silica gel 5 μm, 4.6×250 mm, diisopropyl ether/acetonitrile 99:1, 1.0 mL/min, 254 nm detection); $[\alpha]_D^{22}$ 19.5 (*c* 1.0, methanol); IR (Neat) 3144, 2976, 2875, 1754, 1692 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.02–1.51 (m, 9H, Boc CH_3), 1.80–2.53 (br m, 4H, CH_2), 3.27–3.60 (br m, 2H, NCH_2), 3.83 (s, 3H, OCH_3), 4.85–5.08 (br m, 1H, NCH), 6.53+6.56 (br s+br s, 1H, NCHCO), 7.29–7.76+7.58+7.67 (m+br s+br s, 6H, Ar–H+2×triazole H).

4.8.11. (2*R*,2′*S*)-2-[4-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]-2-phenylacetic acid methyl ester (10e). Compounds **5** and **8e** were reacted at room temperature following the general procedure (reaction interrupted after 20 h). Flash column chromatography (hexanes/ethyl acetate 7:3) furnished **10e** (26%) as a colorless resin. R_f 0.26 (hexanes/ethyl acetate 1:1); HPLC: t_R 75.3 min, >98% de (silica gel 5 μm, 4.6×250 mm, diisopropyl ether/acetonitrile 99:1, 1.0 mL/min, 254 nm detection); $[\alpha]_D^{22}$ −108 (*c* 1.0, methanol); IR (Neat) 3144, 2976, 2877, 1754, 1692 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.02–1.51 (m, 9H, Boc CH_3), 1.80–2.53 (br m, 4H, CH_2), 3.27–3.60 (br m, 2H, NCH_2), 3.82+3.83 (2×s, 3H, OCH_3), 4.85–5.08 (br m, 1H, NCH), 6.53+6.56 (br s+br s, 1H, NCHCO), 7.29–7.76+7.58+7.67 (m+br s+br s, 6H, Ar–H+2×triazole H).

4.9. Exchange of the *N*-Boc group by an *N*-acetyl group

4.9.1. (*S*)-2-[4-(1-Acetylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]acetic acid ethyl ester (11c). Compound **6c** (26.2 mg, 0.081 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and treated with TFA in CH_2Cl_2 (1:1, 1.0 mL) while stirring on an ice bath. After 35 min the mixture was evaporated to dryness. After addition of CH_2Cl_2 (2 mL), the evaporation was repeated and the residue was dried thoroughly. Then CH_2Cl_2 (1.0 mL) and DIPEA (30.0 μL, 0.181 mmol) were added and the mixture was cooled to 0 °C. After addition of acetyl chloride (10.0 μL, 0.123 mmol), the temperature was maintained for 12 min, whereupon the ice bath was removed and the mixture was stirred at room temperature for 17 h. Additional amounts of DIPEA (15.0 μL, 0.090 mmol) and acetyl chloride (15.0 μL, 0.185 mmol) were added. After 1 h 45 min, TLC indicated complete conversion. Aqueous HCl (2 N, 5 mL) was added and the mixture was extracted with CH_2Cl_2 (4×5 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, evaporated, and the residue was purified by flash column chromatography (CH_2Cl_2/methanol 95:5), furnishing 18.9 mg (88%) of **11c** as a colorless solid. TLC detection: ninhydrin, 150 °C, 15 min. Mp 80–81 °C; R_f 0.27 (CH_2Cl_2/methanol 95:5); $[\alpha]_D^{26}$ −73.1 (*c* 2.0, $CHCl_3$); IR (Neat) 3137, 2270, 1751, 1636 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$; *cis*/*trans* rotamers were observed) δ 1.29+1.30 (t+t, 3H, *J*=7.2 Hz, CH_2CH_3), 1.83–1.93 (m, 0.33H, $CH_{2,cis}$), 1.93–2.00+1.97 (m+s, 1.33H, $CH_{2,cis}$+acetyl $CH_{3,cis}$), 2.03–2.10+2.04 (m+s, 2.67H, $CH_{2,trans}$+acetyl $CH_{3,trans}$), 2.12–2.22 (m, 1H, CH_2), 2.39–2.42 (m, 1H, CH_2), 2.56–2.62 (m, 0.67H, $CH_{2,trans}$), 3.50 (ddd, 0.67H, *J*=9.5, 9.5, 7.1 Hz, $NCH_{2,trans}$), 3.57 (ddd, 0.33H, *J*=11.8, 10.0, 7.4 Hz, $NCH_{2,cis}$), 3.63 (ddd, 0.67H, *J*=9.5, 8.5, 2.9 Hz, $NCH_{2,trans}$), 3.68 (ddd, 0.33H, *J*=11.8, 8.6, 2.7 Hz, $NCH_{2,cis}$), 4.25+4.26 (q+q, 2H, *J*=7.2 Hz, CH_2CH_3), 5.04 (d, 0.67H, *J*=17.5 Hz, NCH_2CO_{trans}), 5.11 (d, 0.67H, *J*=17.5 Hz, NCH_2CO_{trans}), 5.13 (s, 0.67H, NCH_2CO_{cis}), 5.15 (dd, 0.33H, *J*=7.9, 1.3 Hz, NCH_{cis}), 5.28 (dd, 0.33H, *J*=7.9, 1.6 Hz, NCH_{cis}), 7.42 (s, 0.33H, triazole H_{cis}), 7.69 (s, 0.67H, triazole H_{trans}); ^{13}C NMR (90 MHz, $CHCl_3$; *cis*/*trans* rotamers were observed) δ 14.2 (CH_2CH_3), 22.3+25.1 (acetyl CH_3), 22.6+22.9, 30.2+34.2, 46.2+48.1 (3×CH_2), 50.9+51.1, 52.4+55.4, 62.4+62.7 (2×CH_2+CH), 122.2+124.6, 148.8+150.8 (2×triazole C), 166.2+166.5, 169.4+169.9 (2×C=O); EIMS 266 (M^+); HRMS: calculated for $C_{12}H_{18}N_4O_3$: 266.1379, found: 266.1378.

Starting from **6a**,**b**,**d**, **11a**,**b**,**d**, respectively, were prepared analogously (direct column chromatography, no extraction steps):

4.9.2. (*S*)-1-(1-Acetylpyrrolidin-2-ylmethyl)-(1,2,3)-triazole-4-carboxylic acid ethyl ester (11a). Reaction time: 3.5 h. Flash column chromatography (CH_2Cl_2/methanol 98:2) furnished **11a** (56%) as a colorless solid. TLC detection: ninhydrin, 150 °C, 15 min. Mp 71–72 °C; R_f 0.29 (CH_2Cl_2/methanol 95:5); $[\alpha]_D^{27}$ −64.4 (*c* 1.0, $CHCl_3$); IR (Neat) 2975, 1735, 1641 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; approx. 3% of a *cis* rotamer were visible; the *trans* rotamer is described) δ 1.40 (t, 3H, *J*=7.2 Hz, CH_2CH_3), 1.46–1.62 (m, 1H, CH_2), 1.76–1.90 (m, 1H, CH_2), 1.91–2.04 (m, 2H, CH_2), 2.09 (s, 3H, acetyl CH_3), 3.25 (ddd, 1H, *J*=9.9, 7.8, 4.4 Hz, NCH_2), 3.38 (ddd, 1H, *J*=9.9, 7.6, 7.6 Hz, NCH_2), 4.30–4.47+4.42 (m+s, 3H, *J*=7.2 Hz, NCH+CH_2CH_3), 4.63 (dd, 1H, *J*=13.7, 2.8 Hz, NCHCH_2-triazole), 4.75 (dd, 1H, *J*=13.7, 6.6 Hz, NCHCH_2-triazole), 8.07 (s, 1H, triazole H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.5 (CH_2CH_3), 23.1+23.9 (acetyl CH_3+CH_2), 28.1 (CH_2), 48.4, 51.4, 57.1, 61.5 (3×NCH_2+OCH_2), 128.4, 140.6 (2×triazole C), 160.8 (ester C=O), 170.5 (amide C=O); EIMS 266 (M^+); HRMS calculated for $C_{12}H_{18}N_4O_3$: 266.1379, found: 266.1379.

4.9.3. (*S*)-1-(1-Acetylpyrrolidin-2-ylmethyl)-(1,2,3)-triazole-5-carboxylic acid ethyl ester (11b). Reaction time:

1.5 h. Flash column chromatography (CH_2Cl_2/methanol 95:5) furnished **11b** (76%) as a colorless resin. TLC detection: ninhydrin, 150 °C, 15 min. R_f 0.56 (CH_2Cl_2/methanol 9:1); $[\alpha]_D^{27}$ −13.6 (*c* 1.0, $CHCl_3$); IR (Neat) 3122, 2976, 1728, 1648, 1639 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; *cis*/*trans* rotamers were observed) δ 1.40 (t, 3H, *J*=7.2 Hz, CH_2CH_3), 1.58–2.07+1.97+1.99 (m+s+s, 7H, CH_2+acetyl $CH_{3,cis}$+acetyl $CH_{3,trans}$), 3.33–3.63+3.38+3.44 (m+ddd+ddd, 2H, *J*=9.8, 9.1, 7.0 Hz+9.8, 8.5, 3.1 Hz), NCH_2CH_2), 4.39+4.40 (q+q, 2H, *J*=7.2 Hz, CH_2CH_3), 4.68–4.76 (m, 1H, NCH), 4.86+4.90 (dd+dd, 2H, *J*=13.7, 5.7 Hz+13.7, 6.4 Hz, $NCHCH_2$-triazole), 8.09 (s, 0.74H, triazole H_{trans}), 8.12 (s, 0.26H, triazole H_{cis}); ^{13}C NMR (150 MHz, $CDCl_3$; *cis*/*trans* rotamers were observed) δ 14.3 (CH_2CH_3), 21.7 (w), 21.75 (w), 22.8 (s), 23.9 (s) (acetyl CH_3+CH_2), 27.6+28.7 (CH_2), 45.8+47.8, 51.2+51.3, 55.8+58.1, 62.0+62.3 (3×NCH_2+OCH_2), 128.5+129.0, 137.9+138.0 (2×triazole C), 158.7+158.8 (ester C═O), 169.9+170.1 (amide C═O); EIMS 266 (M^+); HRMS calculated for $C_{12}H_{18}N_4O_3$: 266.1379, found: 266.1379.

4.9.4. (*S*)-2-[5-(1-Acetylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]acetic acid ethyl ester (11d). The title compound was obtained from a mixture of **6c** and **6d** as obtained from thermal cycloaddition and was separated from **11c** by flash column chromatography (CH_2Cl_2/acetone 7:3) furnishing **11d** (31%) as a colorless resin. TLC detection: ninhydrin, 150 °C, 20 min. R_f 0.27 (CH_2Cl_2/acetone 1:1); $[\alpha]_D^{24}$ 37.2 (*c* 1.0, $CHCl_3$); IR (Neat) 3125, 1748, 1644 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; *cis*/*trans* rotamers were observed) δ 1.291+1.297 (t+t, 3H, *J*=7.2 Hz, CH_2CH_3), 1.84–2.44+1.94+2.01 (m+s+s, 7H, CH_2+acetyl $CH_{3,cis}$+acetyl $CH_{3,trans}$), 3.56 (ddd, 1H, *J*=10.0, 7.4, 7.4 Hz, NCH_2), 3.65 (ddd, 1H, *J*=10.0, 7.3, 4.3 Hz, NCH_2), 4.21+4.26 (dq+dq, 2H, *J*=11.0, 7.2 Hz, CH_2CH_3), 4.96 (d, 0.12H, *J*=17.6 Hz, NCH_2CO_{cis}), 5.03 (dd, 1H, *J*=7.4, 3.1 Hz, NCH), 5.29 (d, 0.12H, *J*=17.6 Hz, NCH_2CO_{cis}), 5.42 (d, 0.88H, *J*=17.7 Hz, NCH_2CO_{trans}), 5.69 (d, 0.88H, *J*=17.7 Hz, NCH_2CO_{trans}), 7.48 (s, 0.12H, triazole H_{cis}), 7.54 (s, 0.88H, triazole H_{trans}); ^{13}C NMR (90 MHz, $CDCl_3$; *cis*/*trans* rotamers were observed) δ 14.2 (CH_2CH_3), 22.2 (w), 22.4 (w), 22.6 (s), 25.2 (s) (acetyl CH_3+CH_2), 32.3+33.3, 46.2+47.6, 49.4+49.8, 50.2+53.2, 62.3+62.9 (4×CH_2+CH), 131.0+132.6, 140.3 (2×triazole C), 167.5, 169.8 (2×C═O); EIMS 266 (M^+); HRMS: calculated for $C_{12}H_{18}N_4O_3$: 266.1379, found: 266.1379.

4.10. Methylaminolysis of ethyl esters 11a–d

4.10.1. (*S*)-2-[4-(1-Acetylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]acetic acid *N*-methyl amide (12c). Compound **11c** (31.7 mg, 0.119 mmol) was dissolved in ethanol (1.0 mL) and cooled to 0 °C. After addition of methylamine solution (8 M in ethanol, 0.5 mL), the mixture was stirred for 2 h, whereupon TLC indicated complete conversion. The solvent was removed under reduced pressure, CH_2Cl_2 (2 mL) was added, evaporated to dryness and the residue was purified by flash column chromatography (CH_2Cl_2/methanol 95:5), furnishing 23.0 mg (77%) of **12c** as a colorless solid. TLC detection: ninhydrin, 150 °C, 25 min. Mp 109–112 °C; R_f 0.30 (CH_2Cl_2/methanol 95:5); $[\alpha]_D^{26}$ −68.5 (*c* 1.0, $CHCl_3$); IR (Neat) 3293, 3247, 3127, 3085, 1679, 1627 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; *cis*/*trans* rotamers were observed) δ 1.87–2.52+1.99+2.07 (m+s+s, 7H, CH_2+acetyl $CH_{3,cis}$+acetyl $CH_{3,trans}$), 2.79 (d, 2.25H, *J*=4.8 Hz, $NCH_{3,trans}$), 2.82 (d, 0.75H, *J*=4.8 Hz, $NCH_{3,cis}$), 3.52 (ddd, 1H, *J*=9.7, 9.4, 6.9 Hz, NCH_2), 3.66 (ddd, 1H, *J*=9.7, 8.0, 3.2 Hz, NCH_2), 4.90 (d, 0.75H, *J*=16.3 Hz, $NCH_2C{=}O_{trans}$), 4.96 (d, 0.75H, *J*=16.3 Hz, $NCH_2C{=}O_{trans}$), 4.90 (d, 0.50H, *J*=0.90 Hz, $NCH_2C{=}O_{cis}$), 5.14 (dd, 0.25H, *J*=7.7, 1.8 Hz, NCH_{cis}), 5.26 (dd, 0.75H, *J*=7.7, 2.4 Hz, NCH_{trans}), 6.34+6.46 (br s+br s, 1H, NH), 7.58 (s, 0.25H, triazole H_{cis}), 7.65 (s, 0.75H, triazole H_{trans}); ^{13}C NMR (150 MHz, $CDCl_3$; *cis*/*trans* rotamers were observed) δ 22.4 (w), 22.8 (w), 22.9 (s), 24.9 (s), 26.5+26.6, 30.8+34.1 (2×CH_3+2×CH_2), 46.2+48.1, 52.6 (s), 53.0 (s), 53.1 (w), 55.1 (w) (2×NCH_2+NCH), 122.6+124.5, 149.3+150.5 (2×triazole C), 165.5+165.9, 169.7+170.0 (2×C═O); EIMS 251 (M^+); HRMS calculated for $C_{11}H_{17}N_5O_2$: 251.1382, found: 251.1382.

Starting from **11a**,**b**,**d**, **12a**,**b**,**d**, respectively, were prepared analogously:

4.10.2. (*S*)-1-(1-Acetylpyrrolidin-2-ylmethyl)-(1,2,3)-triazole-4-carboxylic acid *N*-methyl amide (12a). Reaction interrupted after 2 h 25 min. Flash column chromatography (CH_2Cl_2/methanol 95:5) furnished **12a** (19%; 54% of the starting material were recovered) as a colorless solid. TLC detection: ninhydrin, 150 °C, 25 min. Mp 150–151 °C; R_f 0.08 (CH_2Cl_2/methanol 95:5); $[\alpha]_D^{26}$ −88.4 (*c* 0.25, $CHCl_3$); IR (Neat) 3330, 2241, 1649, 1578 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.32–1.45 (m, 1H, CH_2), 1.74–2.07 (m, 4H, CH_2), 2.10 (s, 3H, acetyl CH_3), 3.01 (d, 3H, *J*=5.0 Hz, NCH_3), 3.24 (ddd, 1H, *J*=10.0, 7.9, 4.3 Hz, NCH_2), 3.37 (ddd, 1H, *J*=10.0, 7.8, 7.6 Hz, NCH_2), 4.31–4.44 (m, 1H, NCH), 4.61 (dd, 1H, *J*=13.9, 3.0 Hz, $CHCH_2$-triazole), 4.77 (dd, 1H, *J*=13.9, 6.1 Hz, $CHCH_2$-triazole), 7.11 (q, 1H, *J*=5.0 Hz, NH), 8.01 (s, 1H, triazole H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 23.1, 23.9, 25.9, 27.9 (2×CH_3+2×CH_2), 48.4, 51.5, 56.9 (2×NCH_2+NCH), 126.1, 143.7 (2×triazole C), 160.7, 170.5 (2×amide C═O); EIMS 251 (M^+); HRMS calculated for $C_{11}H_{17}N_5O_2$: 251.1382, found: 251.1382.

4.10.3. (*S*)-1-(1-Acetylpyrrolidin-2-ylmethyl)-(1,2,3)-triazole-5-carboxylic acid *N*-methyl amide (12b). Reaction time: 2.5 h. Flash column chromatography (CH_2Cl_2/methanol 95:5) furnished **12b** (64%) as a colorless solid. TLC detection: ninhydrin, 150 °C, 30 min. Mp 176–177 °C; R_f 0.04 (CH_2Cl_2/methanol 95:5); $[\alpha]_D^{26}$ 11.9 (*c* 1.0, $CHCl_3$); IR (Neat) 3282, 3120, 2970, 2242, 1670, 1652, 1626, 1627 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; *cis*/*trans* rotamers were observed) δ 1.79 (s, 0.66H, acetyl $CH_{3,cis}$), 1.92–2.06+1.98 (m+s, 6.34H, CH_2+acetyl $CH_{3,trans}$), 2.95+2.96 (d+d, 3H, *J*=4.6 Hz, NCH_3), 3.35–3.66 (m, 2H, NCH_2), 4.37–4.47 (m, 0.22H, NCH_{cis}), 4.59–4.81+4.73 (m+dd, 1.78H, *J*=13.3, 7.0 Hz, NCH_{trans}+$CHCH_2$-triazole), 4.87+4.91 (dd+dd, 1H, *J*=13.3, 5.7 Hz+13.3, 6.8 Hz, NCH_{trans}+NCH_{cis}), 7.06 (q, 0.22H, *J*=4.6 Hz, NH_{cis}), 7.54 (q, 0.78H, *J*=4.6 Hz, NH_{trans}), 7.99 (s, 0.22H, triazole H_{cis}), 8.03 (s, 0.78H, triazole H_{trans}); ^{13}C NMR (150 MHz, $CDCl_3$; *cis*/*trans* rotamers were observed) δ 21.4 (w), 21.8 (w), 22.6 (s), 23.8 (s), 26.5+26.6, 28.0+28.8 (2×CH_3+2×CH_2), 45.8+47.7, 51.1+51.4, 56.3+58.4 (2×NCH_2+NCH), 131.7+132.2, 133.8+134.6 (2×triazole

C), 158.5+158.7, 170.1+170.5 (2×C=O); EIMS 251 (M^+); HRMS calculated for $C_{11}H_{17}N_5O_2$: 251.1382, found: 251.1383.

4.10.4. (*S*)-2-[5-(1-Acetylpyrrolidin-2-yl)-(1,2,3)-triazol-1-yl]acetic acid *N*-methyl amide (12d). Reaction time: 3.5 h. Flash column chromatography (CH_2Cl_2/methanol 9:1) furnished **12d** (86%) as a colorless solid. TLC detection: ninhydrin, 150 °C, 30 min. Mp 142–144 °C; R_f 0.33 (CH_2Cl_2/methanol 9:1); $[\alpha]_D^{22}$ −50.0 (*c* 0.5, $CHCl_3$); IR (Neat) 3294, 3119, 3086, 2951, 2881, 1684, 1627 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; *cis*/*trans* rotamers were observed) δ 1.90–2.42+1.92+2.06 (m+s+s, 7H, CH_2+acetyl $CH_{3,cis}$+acetyl $CH_{3,trans}$), 2.81+2.82 (d+d, 3H, J=4.8 Hz, NCH_3), 3.60 (ddd, 1H, J=10.0, 7.4, 7.4 Hz, NCH_2), 3.73 (ddd, 1H, J=10.0, 7.3, 4.8 Hz, NCH_2), 4.91 (d, 0.09H, J=16.5 Hz, $NCH_2C{=}O_{cis}$), 5.04 (d, 0.91H, J=16.5 Hz, $NCH_2C{=}O_{trans}$), 5.09 (dd, 1H, J=8.2, 3.6 Hz, NCH), 5.18 (d, 0.09H, J=16.5 Hz, $NCH_2C{=}O_{cis}$), 5.37 (d, 0.91H, J=16.5 Hz, $NCH_2C{=}O_{trans}$), 6.58 (br s, 0.09H, NH_{cis}), 6.75 (br s, 0.91H, NH_{trans}), 7.47+7.58 (s+s, 1H, triazole H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.7, 24.8, 26.6, 32.4 (2×CH_3+2×CH_2), 47.9, 51.0, 51.5 (2×NCH_2+NCH), 131.2, 140.5 (2×triazole C), 165.9, 169.9 (2×C=O); EIMS 251 (M^+); HRMS calculated for $C_{11}H_{17}N_5O_2$: 251.1382, found: 251.1382.

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra of the target compounds **11a–d** and **12a–d**; copies of NOESY spectra of **11a–d** and **12a**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.007.

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Mild and selective oxidation of alcohols to aldehydes and ketones using $NaIO_4$/TEMPO/NaBr system under acidic conditions

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Abstract—A TEMPO-catalyzed selective oxidation of alcohols to the corresponding aldehydes and ketones using $NaIO_4$ as the terminal oxidant is reported. The $NaIO_4$/TEMPO/NaBr system provides a mild and efficient method for the oxidation of alcohols that are sensitive to basic conditions. Furthermore, the recoverable ionic liquid immobilized TEMPO-catalyzed oxidation of benzyl alcohol in ionic liquid–H_2O medium is also developed.

1. Introduction

Oxidation of alcohols to carbonyl compounds is among the most important functional group transformations available to the synthetic chemists.[1] In recent years, nitroxyl radical TEMPO (2,2,6,6-tetramethylpiperdine-1-oxyl) has been extensively used as a catalyst for the catalytic oxidation of alcohols to corresponding carbonyl compounds. Typically, such oxidations are carried out in the presence of a catalytic amount of TEMPO and a stoichiometric amount of a terminal oxidant such as bleach (NaClO),[2] sodium chlorite,[3] sodium bromite,[4] sodium or calcium hypochlorite,[5] *N*-chlorosuccinimide (NCS),[6] *m*-chloroperbenzoic acid (*m*-CPBA),[7] trichloroisocyanuric acid,[8] *tert*-butyl hypochlorite,[9] [bis(acetoxy)iodo] benzene (BAIB),[10] Oxone,[11] iodine,[12] oxygen or air.[13] To the best of our knowledge, sodium periodide ($NaIO_4$), a stable and conventional inorganic nonmetal oxidant, has not been used for these transformations. Herein, we describe a TEMPO-mediated oxidation method using $NaIO_4$ as the terminal oxidant and NaBr as co-catalyst. Compared with the systems that performed under basic conditions, especially the extensively used NaClO/TEMPO/NaBr system that works at 0 °C and pH 8.6–9.5,[2a] the present $NaIO_4$/TEMPO/NaBr system could work at room temperature without generation of over-oxidized product. Also this buffer-free system provides an alternative method for the oxidation of alcohols that are sensitive to basic conditions.

Keywords: Oxidation; Alcohols; Aldehydes; Ketones; Sodium periodide; TEMPO; Ionic liquids.
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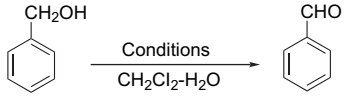
2. Results and discussion

2.1. $NaIO_4$/TEMPO/NaBr system for the selective oxidation of alcohols to aldehydes and ketones under two-phase conditions (CH_2Cl_2–H_2O)

Initially, we attempted the $NaIO_4$/TEMPO/CH_2Cl_2–H_2O (1:1) system for the oxidation of benzyl alcohol, and the results are summarized in Table 1. We found that benzyl

Table 1. Oxidation of benzyl alcohol under different conditions



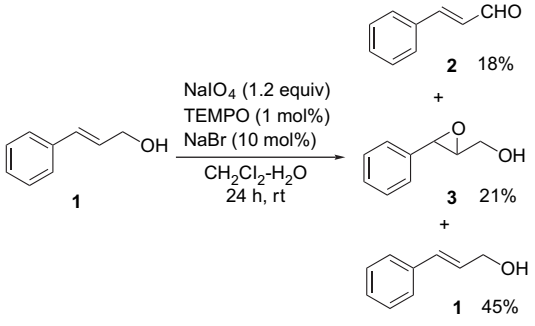
Entry	Conditions	Time (h)	Yield[d] (%)
1	1.2 equiv $NaIO_4$, 1 mol % TEMPO[a]	28	90
2	1.2 equiv $NaIO_4$, 1 mol % TEMPO, 10 mol % NaBr[a]	10	96
3	1.2 equiv $NaIO_4$, 1 mol % TEMPO, 10 mol % NaCl	16	96
4	1.2 equiv $NaIO_4$, 1 mol % TEMPO, 10 mol % NaBr, pH 2.0[b]	10	95
5	3 equiv $NaIO_4$, 1 mol % TEMPO, 10 mol % NaBr	10	96
6	1.2 equiv $NaIO_4$, 1 mol % TEMPO, 10 mol % $(n\text{-Bu})_4NBr$, 10 mol % NaBr	10	96
7	1.2 equiv $NaIO_4$, 1 mol % TEMPO, 10 mol % NaBr, reflux	8	96
8	1 equiv $NaIO_4$	48	10
9	1.2 equiv $NaIO_4$, 1 mol % TEMPO, 10 mol % NaBr, pH 8.6[c]	24	5

[a] Aqueous layer pH 4.0.
[b] Aqueous layer pH was adjusted with 0.5 M H_2SO_4.
[c] Aqueous layer pH was adjusted with $NaHCO_3$.
[d] Isolated yield.

alcohol was completely oxidized to benzaldehyde by $NaIO_4$ (1.2 equiv) and TEMPO (0.01 equiv) in CH_2Cl_2–H_2O (1:1) two-phase system at room temperature (Table 1, entry 1). Furthermore, NaBr and NaCl (10 mol %) could significantly promote the transformation (Table 1, entries 2 and 3) without generation of overoxidized product. In the $NaIO_4$/TEMPO/NaBr system, the aqueous layer was maintained at pH 4.0 during the reaction. When the aqueous layer was adjusted at pH 2.0 with 0.5 M H_2SO_4 (Table 1, entry 4), the reaction gave a similar yield (Table 1, entry 2). Increasing the amount of $NaIO_4$ (Table 1, entry 5) or adding phase transfer catalyst (Table 1, entry 6) did not improve the yield, but refluxing could accelerate the reaction somewhat (Table 1, entry 7). In all cases, TEMPO was necessary. Otherwise, the reaction proceeded very slowly and gave poor yield (Table 1, entry 8). It is noteworthy that when the aqueous layer was buffered at pH 8.6 (Table 1, entry 9), only 5% yield was obtained.

As the next step, we used the $NaIO_4$/TEMPO/NaBr system to oxidize various alcohols under the optimized reaction conditions (Table 2). It was found that primary benzylic alcohols could be oxidized to the corresponding aldehydes in excellent yields. The electron-withdrawing group substituted benzylic alcohols (Table 2, entry 2) reacted faster than the electron-donating group substituted benzylic alcohols (Table 2, entries 3–5). The chloro-substituted benzylic alcohols (Table 2, entries 6 and 7) exhibited a similar reactivity with benzylic alcohol (Table 2, entry 1). Refluxing could promote the reactions (Table 2, entries 2′ and 7′). Primary aliphatic alcohols (Table 2, entries 8 and 9) as well as secondary aliphatic and benzylic alcohols (Table 2, entries 10 and 11) could also be oxidized to the corresponding aldehydes and ketones in excellent yields after a prolonged reaction time (20–28 h).

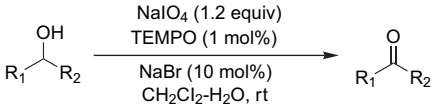
We also examined the unsaturated alcohol, cinnamic alcohol (**1**) (Scheme 1). It was found that besides cinnamaldehyde (**2**, 18%) and unreacted cinnamic alcohol (**1**, 45%), an epoxide 3-phenyl oxiranemethanol (**3**) was also obtained in 21% yield (determined by GC–MS). Taking into account the $NaIO_4$-mediated selective halogenation of alkenes and aromatics using alkali metal halides,[14] we attributed the formation of the epoxide to the electrophilic addition of hypohalogenous acid to the double bond of cinnamic alcohol, which was followed by an intramolecular nucleophilic substitution in one-pot procedure.

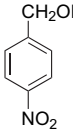
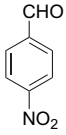
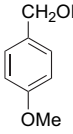
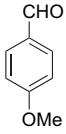
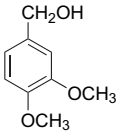
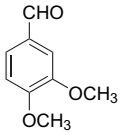
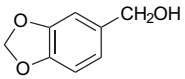
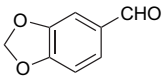
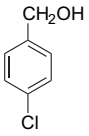
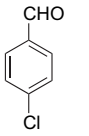
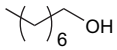
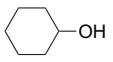
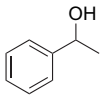
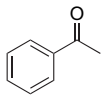


Scheme 1. Oxidation of cinnamic alcohol.

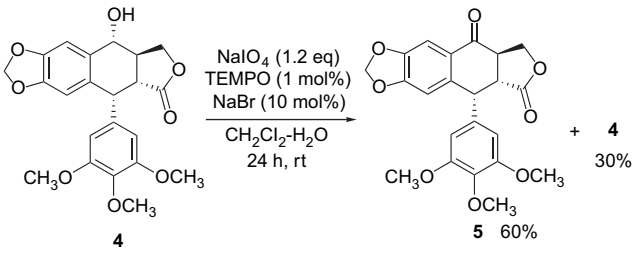
Compared with the extensively used and more active NaOCl/TEMPO/KBr system,[2a,15] which must be buffered at pH 8.6–9.5 and requires 0 °C reaction temperature, our $NaIO_4$/TEMPO/NaBr system works efficiently under slightly acidic conditions (pH~4.0). Therefore, our procedure provides an alternative methodology for the oxidation of alcohols that are sensitive to basic conditions. Using the $NaIO_4$/TEMPO/NaBr system, natural product podophyllotoxin (**4**), which is unstable under basic conditions, was oxidized to ketone **5** in 60% isolated yield (not optimized) with a 30% recovery of substrate **4** (Scheme 2). Under the reaction conditions, both the lactone ring opened and C-2 isomerized products were not observed.

Table 2. Oxidation of various primary and secondary alcohols



Entry	Alcohols[a]	Products	Time (h)	Yield (%)[c]
1	$C_6H_5CH_2OH$	C_6H_5CHO	10	96
2			8	96
2′			6[b]	95
3			15	95
4			15	96
5			15	95
6			12	95
7			12	95
7′			10[b]	96
8	$C_6H_5CH_2CH_2OH$	$C_6H_5CH_2CHO$	20	95
9			28	96[d]
10			28	95[d]
11			18	95

[a] Reaction conditions: alcohol (50 mmol), TEMPO (0.5 mmol), $NaIO_4$ (60 mmol), NaBr (5 mmol), DCM (100 ml), water (120 ml), rt.
[b] Under reflux conditions.
[c] Isolated yield.
[d] Determined by GC.



Scheme 2. Oxidation of podophyllotoxin (**4**) to ketone **5**.

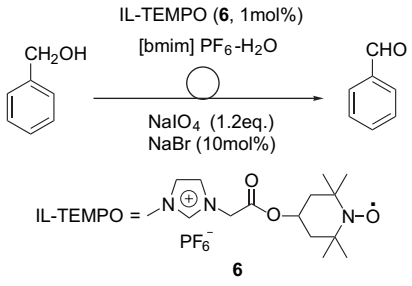
2.2. Recoverable ionic liquid immobilized TEMPO-catalyzed oxidation of benzyl alcohol using $NaIO_4$ in ionic liquid–H_2O two-phase condition

Although low catalyst concentrations are required for an efficient transformation, product separation and TEMPO recovery remain key issues in TEMPO-catalyzed oxidation. Consequently, several solid-supported TEMPO moieties have been developed, which include silica-supported TEMPO,[16] sol–gel entrapped TEMPO[17] and polyamine immobilized piperidinyl oxyl (PIPO).[18] These catalysts are heterogeneous in nature and are readily recovered by simple filtration from the reaction medium. Recently, it was reported that soluble polymer poly(ethylene glycol)-supported TEMPO catalysts (PEG-TEMPOs) exhibited high activity for the chemoselective oxidation of alcohols.[19] This class of catalysts could be readily recovered via precipitation with diethyl ether.

In the last decade, room temperature ionic liquids (RTILs) have become promising candidates to replace traditional solvents used in organic chemistry for their interesting properties such as high thermal stability, nonvolatility, high loading capacity, easy recyclability and tunable polarity. A number of chemical reactions can be performed in ionic liquids.[20] Recently, the so-called 'task-specific ionic liquids' immobilized catalysts have been demonstrated to be an effective strategy for facilitating product separation and catalyst recovery.[21] More recently, a TEMPO-derived task-specific ionic liquid (IL-TEMPO) (**6**) for oxidation of alcohols by the Anelli protocol has been reported.[22]

In order to develop a recoverable TEMPO-catalyzed and environmentally friendly oxidation process, we investigated IL-TEMPO-catalyzed $NaIO_4$ oxidation of benzyl alcohol in [bmim]PF_6–H_2O medium (Table 3). Compared with the CH_2Cl_2–H_2O medium version, the IL-TEMPO-catalyzed oxidation in water–IL two-phase conditions showed similar activity and selectivity. The crude product could easily be separated from the IL medium by simple extraction with diethyl ether. The IL solution containing the catalyst **6** could be reused up to six times without significant decrease of catalytic activity and selectivity.

Table 3. Oxidation of benzyl alcohol to benzaldehyde using $NaIO_4$ in the recovered IL immobilized TEMPO-IL solution[a]



Run	1	2	3	4	5	6
Time (h)	15	15	16	16	16	16
Isolated yield (%)	98	95	95	94	93	93

[a] In 20 mmol scale.

3. Conclusion

In summary, we have developed a novel and efficient TEMPO-catalyzed oxidation of alcohols to the corresponding aldehydes and ketones using $NaIO_4$ as the terminal oxidant. The reaction could be performed at room temperature under two-phase conditions. The procedure provides an alternative method for the oxidation of alcohols that are sensitive to basic conditions. Furthermore, the $NaIO_4$/IL immobilized TEMPO/RTIL system was also developed and could be recycled up to six times without remarkable deactivation.

4. Experimental

4.1. General

All chemicals were of reagent grade and used as purchased. ^{1}H NMR spectra were recorded in deuterated solvent on Bruker Avance-500 spectrometer operating at 500 MHz or on Bruker Avance-300 spectrometer operating at 300 MHz. ^{13}C NMR spectra were recorded in deuterated solvent on Bruker Avance-500 spectrometer operating at 125 MHz. Infrared spectra were recorded on a Nicolet Nexus 470 FT-IR spectrometer and measured as thin film or in KBr. Melting points were measured on WRS-1B digital melting point apparatus. Capillary gas chromatography was performed on a Hewlett–Packard HP 6890 gas chromatograph/mass spectra instrument (GC–MS). Mass spectra (EI, 70 eV) were recorded on an HP5989B mass spectrometer. ESI-MS spectra were recorded on a Bruker Daltonics Esquire 3000 plus instrument. HRMS data were obtained on a Bruker FT-ICR-MS Apex III apparatus.

4.2. Typical experimental procedure for oxidation of alcohols using $NaIO_4$/NaBr/TEMPO system

4-Nitrobenzyl alcohol (7.65 g, 50 mmol) and TEMPO (78 mg, 0.5 mmol) were dissolved in DCM (100 ml). Then the aqueous $NaIO_4$ (12.84 g, 60 mmol) and NaBr (0.51 g, 5 mmol) solution (120 ml) were added. The reaction mixture was vigorously stirred at room temperature and monitored by TLC. For 10 h, after completion, the organic layer was washed by NaS_2O_3 aqueous solution and then dried over anhydrous sodium sulfate and concentrated in vacuum. The residue was purified by silica gel chromatography eluting with EtOAc–hexane (1:3) to give 4-nitrobenzyl aldehyde (7.25 g, 96% yield).

4.2.1. Benzaldehyde. Colourless liquid; IR (neat): ν= 1700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=7.48–7.52 (m, 2H), 7.60–7.65 (m, 1H), 7.85–7.90 (m, 2H), 9.95 (s, 1H); MS (EI): *m*/*z* 106 (M^+).

4.2.2. 4-Nitrobenzaldehyde. Light yellow solid; mp 104–106 °C; IR (KBr): ν=1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=8.10 (d, J=8.6 Hz, 2H), 8.40 (d, J=8.6 Hz, 2H), 9.90 (s, 1H); MS (EI): m/z 151 (M^+).

4.2.3. 4-Methoxybenzaldehyde. Colourless liquid; IR (neat): ν=1688 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=3.85 (s, 3H), 7.00 (d, J=8.2 Hz, 2H), 7.85 (d, J=8.2 Hz, 2H), 9.80 (s, 1H); MS (EI): m/z 136 (M^+).

4.2.4. 3,4-Dimethoxybenzaldehyde. Colourless liquid; IR (neat): ν=1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=3.80 (s, 3H), 3.85 (s, 3H), 7.20–7.30 (m, 3H), 9.85 (s, 1H); MS (EI): m/z 166 (M^+).

4.2.5. 4-Chlorobenzaldehyde. White solid; mp 45–46 °C; IR (KBr): ν=1703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=7.55 (d, J=7.8 Hz, 2H), 7.85 (d, J=7.8 Hz, 2H), 9.95 (s, 1H); MS (EI): m/z 141 (M^+).

4.2.6. 2-Chlorobenzaldehyde. Colourless liquid; IR (neat): ν=1705 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=7.33–7.48 (m, 3H), 7.75 (d, J=8.0 Hz, 1H), 10.25 (s, 1H); MS (EI): m/z 141 (M^+).

4.2.7. 3,4-Methylenedioxybenzaldehyde. White solid; mp 83–84 °C; IR (KBr): ν=1682 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.00 (s, 2H), 6.95–7.35 (m, 3H), 9.82 (s, 1H); MS (EI): m/z 150 (M^+).

4.2.8. Phenylacetaldehyde. Colourless liquid; IR (neat): ν=1710 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=3.25 (d, J=2 Hz, 2H), 7.05–7.10 (m, 2H), 7.25–7.30 (m, 3H), 9.75 (t, J=2 Hz, 1H); MS (EI): m/z 120 (M^+).

4.2.9. Acetophenone. Colourless liquid; IR (neat): ν=1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.58 (s, 3H), 7.45–7.48 (m, 2H), 7.53–7.55 (m, 1H), 7.90 (d, J=8.5 Hz, 2H); MS (EI): m/z 120 (M^+).

4.2.10. Cyclohexanone. Colourless liquid; IR (neat): ν=1700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=1.70–1.78 (m, 2H), 1.85–1.92 (m, 4H), 2.40 (t, J=6.8 Hz, 4H); MS (EI): m/z 98 (M^+).

4.2.11. Octanal. Colourless liquid; IR (neat): ν=1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=0.96 (t, J=7.2 Hz, 3H), 1.20–1.35 (m, 8H), 1.60–1.70 (m, 2H), 2.43 (t, J=7.2 Hz, 2H), 9.75 (s, 1H); MS (EI): m/z 128 (M^+).

4.3. Oxidation of podophyllotoxin (4) to picropodophyllone (5)

The procedure was similar to the oxidation of 4-nitrobenzyl alcohol above. White solid; mp 155–160 °C; IR (KBr): ν=2920, 1778, 1668, 1475, 1245, 1126, 938 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ=3.25 (d, J=1.55 Hz, 1H), 3.51 (s, 1H), 3.75 (s, 6H), 3.82 (s, 3H), 4.37 (ddd, J=9.0, 4.5, 1.5 Hz, 1H), 4.55 (s, 1H), 4.85 (d, J=9.2 Hz, 1H), 6.00 (s, 1H), 6.06 (s, 1H), 6.39 (s, 2H), 6.70 (s, 1H), 7.55 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ=43.5, 43.8, 46.6, 56.5, 60.8, 70.5, 102.5, 104.7, 107.1, 109.5, 127.5, 137.8, 138.6, 139.9, 149.2, 154.7, 155.2, 175.8, 193.5; ESI-MS: m/z 435 ([M+Na]$^+$).

4.4. Synthesis of IL immobilized TEMPO (6)

Compound **6** was synthesized according to the literature procedures.[22] Red solid; mp 53–54 °C; IR (KBr): ν=3055, 2977, 2933, 1736, 1567, 1266, 1173 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{25}N_3O_3$ (M−PF_6): 295.1890, found: 295.1898.

4.5. Experimental procedure for oxidation of benzyl alcohol to benzaldehyde using $NaIO_4$ in the recoverable IL immobilized TEMPO-IL solution

To a solution of benzyl alcohol (2.16 g, 20 mmol) and IL-TEMPO (90 mg, 0.2 mmol) in [bmim]PF_6 (20 ml) was added the solution of $NaIO_4$ (5.14 g, 24 mmol) and NaBr (0.21 g, 2 mmol) in water (20 ml). The mixture was vigorously stirred at room temperature. After the oxidation (TLC monitoring) was completed, the product was separated from the IL medium by extraction with ether (3×30 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The product was purified by flash silica gel chromatography eluting with EtOAc–hexane (1:5). The recovered IL containing the IL-TEMPO could be reused for consecutive recycling experiments.

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Ti(III)-promoted cyclizations. Application to the synthesis of (*E*)-*endo*-bergamoten-12-oic acids. Moth oviposition stimulants isolated from *Lycopersicon hirsutum*

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Abstract—The Ti(III)-promoted radical cyclization of epoxyenone **8** is described as the key step to access the diol **10** as a convenient starting material of the target molecules. The synthesis of β-(*E*)-*endo*-bergamoten-12-oic acid **2a** from (+)-8,9-epoxycarvone **8** was successfully achieved by Suzuki–Miyaura coupling of the terminal alkene **20** with β-iodomethacrylate **21c**, followed by deprotection and dehydration processes. Moreover, synthesis of the α-(*E*)-*endo*-1-hydroxy-bergamoten-12-oic acid derivative **34** was achieved by iterative elongation processes of the diol **10** lateral chain.

1. Introduction

The isolation of the α and β forms of (*E*)-*endo*-bergamoten-12-oic acids **1a** and **2a** (Fig. 1) from the leaves of *Lycopersicon hirsutum* by Coates et al. in 1988[1] opened the door to synthetic work, which was successfully achieved by Mori and Matsushima in 1994.[2] These two sesquiterpenoids seem to influence the oviposition behavior of *Heliothis zea* (Boddie) whose larvae are major agricultural pests of tomatoes, corn and cotton.[3] The synthesis of these *H. zea* oviposition stimulants may have potential application in agriculture since these sesquiterpenoids might prove effective when combined with pesticide baits for current pest control.

The starting material chosen by Mori et al. to construct the pinane-type carbon skeleton of bergamotenoic acids was the tricyclic lactone **6**.[4] Starting from **6**, construction of the side chain of both sesquiterpenes required the application of a preparatively demanding 13-step sequence that included the chromatographic separation of an almost equimolecular mixture of alkenes. Additionally, the stereocontrolled synthesis of **6** from *R*-(−)-carvone **7** was reported by our group in 1998 in a parallel synthetic study aimed at the synthesis of (+)-ampullicin **4** and (+)-isoampullicin **5**.[5]

The use of titanocene(III) chloride in cyclization processes on functionalized epoxides has offered a plausible alternative for accessing polycyclic structures since the time that Nugent and RajanBabu first reported the Ti(III)-promoted epoxide opening reactions and subsequent reactivity of the radical intermediates.[6] Based on the experience gained in the reactivity of Ti(III) against epoxy ketones we considered the possibility of preparing the tricyclic core present in the bergamotene series by using this cyclization method, starting from (+)-8,9-epoxycarvone **8**. If our assumption is correct then this may help to open new strategies for the synthesis of biologically active natural products such as those represented in Figure 1 (**1**–**6**).[7]

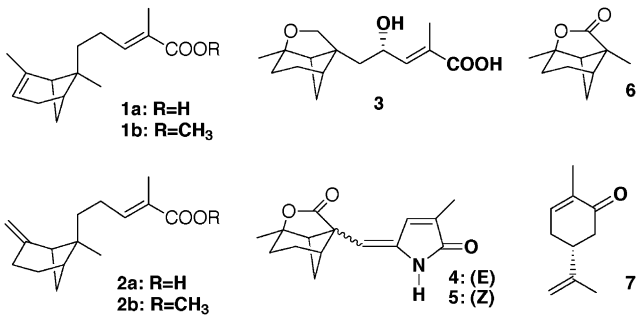

Figure 1.

Keywords: Sesquiterpenoids; β-Halomethacrylates; (*E*)-β-*endo*-Bergamoten-12-oic acids; (*S*)-(+)-Carvone.
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2. Results and discussion

We now wish to describe the synthesis of **6** through a novel route based on the titanium-promoted intramolecular cyclization of (+)-8,9-epoxycarvone **8**, which is easily obtained by epoxidation of (*S*)-(+)-carvone as a mixture of diastereomers.[8]

Addition of the reagent Cp_2TiCl to the epoxide **8** solution (Method A) afforded a mixture of two diastereomeric primary alcohols **9**:**10** in a 3:2 ratio (68% yield) together with a small amount of the β-hydrogen elimination product: (*S*)-(+)-5-[1-(hydroxymethyl)vinyl]-2-methyl-cyclohex-2-enone **11**[9] (10%). No change in the diastereoselectivity was observed by reverse addition (Method B), although a small increase in the elimination product **11** was observed (15%).[10] The reaction, which affords the diols **9** and **10**, is a chemo- and regioselective radical 4-*exo* cyclization process onto a carbonyl based on a seminal work of our group with epoxyenones and Ti(III).[11]

We assume that the outcome of **9** as the major diastereomer in the reaction mixture must be ascribed to the greater stability of one of the two complexes obtained by chelation of titanium within the two diastereomers (see Fig. 2). The equatorial orientation of the hydroxymethyl group in complex **A** led to the major isomer **9** through a more stable titanium complex than the one developed through the axially oriented hydroxymethyl group in complex **B**, which afforded the minor diastereomer **10**.[12]

Treatment of **10** with PPTS in dichloromethane at room temperature led to the tricyclic tertiary alcohol **12** in a 72% yield. Structural assignment of **12** was based on complete spectroscopic analysis, including bidimensional ^1H–^1H and ^1H–^{13}C correlations. The use of *p*-toluenesulfonic acid under the same reaction conditions led to the decomposition of the product.

Deoxygenation of the tertiary hydroxy function of **12** to **14** was achieved in two different ways: first by conversion into thiocarbonylimidazole **13**, followed by treatment with tri-*n*-butyltin hydride in refluxing toluene (60% overall yield for the two-step sequence), and second by direct reduction of alcohol **12**, by using chlorodiphenylsilane as a hydride source in the presence of a catalytic amount of indium trichloride (80% isolated yield) following the procedure recently reported by Baba et al.[13] Deoxygenation methods based on dissolving-metal reductions (Li, HMPA or ethylene diamine) of other functionalities (acetate, mesylate, tosylate) failed repeatedly due to competitive Grob fragmentation processes, activated when the tertiary alcohol was made to react under strong basic conditions.[14] The ether **14** exhibits the tricyclic core of massarinolin B (**3**), a bioactive sesquiterpenic acid isolated from *Massarina tunicata* by Shearer et al. (A-25-1; Lophiostomataceae).[15]

The tricyclic ether **14** was oxidized under treatment with chromium trioxide in acetic anhydride to afford the tricyclic lactone **6** following procedures reported by Magnus and Erman.[4] Transformation of **6** into the terminal olefin **20** was based on a modification of a procedure reported by Mori and Matsushima,[16] which included selective deprotection of the pyvaloate **17** to the primary alcohol **18** by treatment with diisobutylaluminium hydride in a mixture of toluene and dichloromethane at −78 °C (89% yield), followed by Dess–Martin periodinane oxidation[17] to aldehyde **19** and Wittig olefination with methylenetriphenylphosphorane (40% yield for the last two steps) (Scheme 1).

Elongation of olefin **20** was achieved by means of an efficient Pd-catalyzed Suzuki–Miyaura coupling[18] between **20** and the (*E*)-β-halomethacrylates **21a**–**d**.[19] Optimized reaction conditions for the coupling process between the olefinic product and (*E*)-β-halomethacrylates **21a**–**d** were found using (−)-β-pinene **22** as starting material under different reaction conditions (Table 1).

The best yields of the coupling product **23** were obtained by reaction of (−)-β-pinene with 9-BBN and further treatment with β-bromomethacrylate **21a**, using palladium tetrakistriphenylphosphine as the catalyst, potassium carbonate as the base, and a mixture of dimethylformamide and water (20:1) as the solvent at 50 °C for 48 h (Table 1, entry 9).

By applying the optimized conditions to the coupling of the olefin **20** with (*E*)-β-iodomethacrylate **21c** we were able to isolate the coupling product **24a** with 87% isolated yield (Table 1, entry 11).

Deprotection of the silyl groups by treatment of **24a** with tetra-*n*-butylammonium fluoride and further treatment with an ethereal solution of diazomethane led to the isolation of the methyl ester **24c** in quantitative yields.

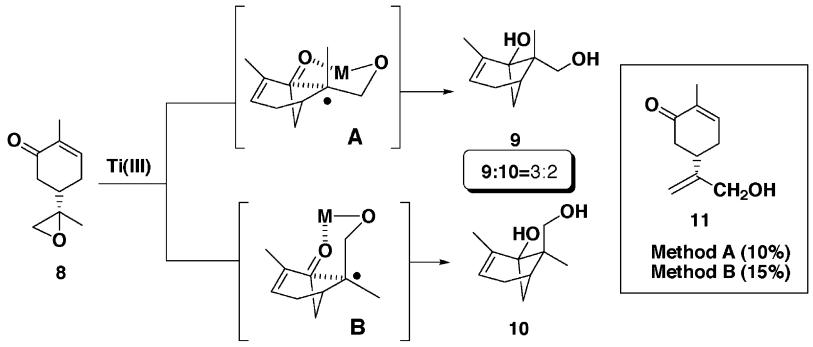
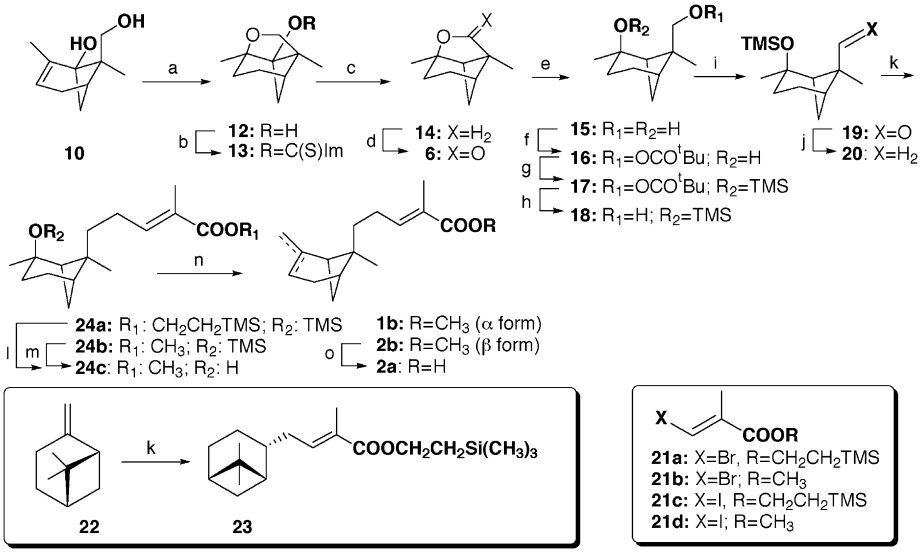
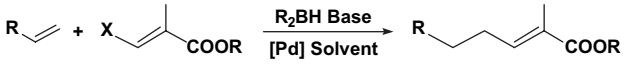


Figure 2.



Scheme 1. (a) PPTS, THF, reflux, 4 h (72%); (b) thiocarbonyldiimidazole, CH_2Cl_2, rt, 24 h (75%); (c) (from **13**) nBu$_3$SnH, AIBN, toluene, reflux, 5 h (80%); (from **12**) $InCl_3$, Ph_2SiHCl, $ClCH_2CH_2Cl$, 80 °C, 3 h (80%); (d) see Ref. 4; (e–g): see Ref. 2; (h) DIBAL-H, CH_2Cl_2–toluene (1:1), 0 °C, 20 min (90%); (i) Dess–Martin, CH_2Cl_2, 0 °C (73%); (j) $(Ph_3P)_3P{=}CH_2$, DME, rt, 15 h (56%); (k) **20**, 9-BBN, THF, rt, 15 h, **21**, DMF–H_2O (20:1), $Pd(PPh_3)_4$, 50 °C, 48 h (see Table 1); (l) (i) nBu$_4$NF, THF, rt; (ii) CH_2N_2, ether (70% two steps); (m) nBu$_4$NF, THF, rt, 48 h (75%); (n) Tf_2O, DMAP, CH_2Cl_2, rt, four days (83%); (o) 2 N KOH, MeOH, rt, 24 h (75%).

Table 1. Pd-catalyzed Suzuki–Miyaura couplings[a]

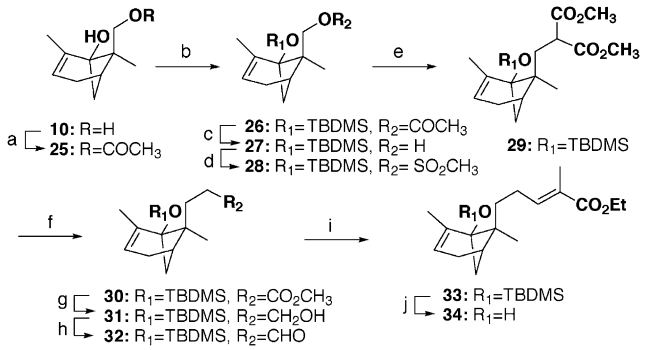


Entry	Alkene	R_2BH	Catalyst	HMA[c]	Base	Solvent	Product yield (%)[d]
1	**22**	$(RO)_2BH$[b]	$PdCl_2$(dppf)	**21a**	K_3PO_4	DMF	**23** (10)
2	**22**	9-BBN	$PdCl_2$(dppf)	**21a**	K_3PO_4	DMF	**23** (15)
3	**22**	$(RO)_2BH$[b]	$PdCl_2(CH_3CN)_2$	**21a**	K_3PO_4	DMF	**23** (15)
4	**22**	9-BBN	$PdCl_2(CH_3CN)_2$	**21a**	K_3PO_4	DMF	**23** (17)
5	**22**	9-BBN	$PdCl_2(CH_3CN)_2$	**21a**	K_2CO_3	DMF	**23** (20)
6	**22**	9-BBN	$PdCl_2(CH_3CN)_2$	**21a**	K_2CO_3	DMF/H_2O[e]	**23** (27)
7	**22**	$(RO)_2BH$[b]	$Pd(Ph_3P)_4$	**21a**	K_2CO_3	DMF/H_2O[e]	**23** (60)
8	**22**	9-BBN	$Pd(Ph_3P)_4$	**21a**	K_3PO_4	DMF/H_2O[e]	**23** (65)
9	**22**	9-BBN	$Pd(Ph_3P)_4$	**21a**	K_2CO_3	DMF/H_2O[e]	**23** (72)
10	**20**	9-BBN	$Pd(Ph_3P)_4$	**21a**	K_2CO_3	DMF/H_2O[e]	**24a** (85)
11	**20**	9-BBN	$Pd(Ph_3P)_4$	**21c**	K_2CO_3	DMF/H_2O[e]	**24a** (87)
12	**20**	9-BBN	$Pd(Ph_3P)_4$	**21b**	K_2CO_3	DMF/H_2O[e]	**24b** (70)
13	**20**	9-BBN	$Pd(Ph_3P)_4$	**21d**	K_2CO_3	DMF/H_2O[e]	**24b** (78)

[a] All reactions were run at 50 °C.
[b] $(RO)_2BH$–catecholborane.
[c] HMA–halomethacrylate.
[d] Isolated yields.
[e] DMF–H_2O (20:1).

Dehydration of **24c** by treatment with trifluoromethylsulfonic anhydride in the presence of excess of DMAP led to a reaction mixture with the β-form **2b** as the major dehydration product (83% isolated yield). Unfortunately, we were not able to isolate the α-form **1b** by chromatography on silica gel impregnated with silver nitrate, although we were able to detect its presence by ^{1}H NMR in the reaction mixture (8% yield). Saponification of the methyl ester **2b** led to the isolation of (+)-**2a** quantitatively.

Additionally, conversion of diol **10** into **27** required a three-step sequence of the protection–deprotection protocol: selective acetylation of the primary alcohol, silylation of the tertiary hydroxy function, and saponification of the acetate with ethanolic potassium hydroxide, to yield the primary alcohol **27** with 92% yield. Previous attempts to elongate the side chain without protection of the tertiary hydroxyl group resulted in a Grob fragmentation to afford the starting carvone. Something similar happened when we attempted a Horner–Wittig reaction with the hydroxyaldehyde obtained by selective oxidation of the diol **10**. Elongation of the lateral chain was first achieved with malonate displacement on the mesylate **28**, followed by decarboxylation to yield the methyl ester **30** with 68% yield (Scheme 2).



Scheme 2. (a) Ac_2O, pyr (100%); (b) TBDMSCl, imidazole, DMF (95%); (c) KOH, EtOH (97%); (d) MsCl, pyr (96%); (e) $NaCH(CO_2CH_3)_2$, toluene (85%); (f) NaCl, H_2O, DMSO (80%); (g) LAH, ether (88%); (h) $(ClCO)_2$, (DMSO), Et_3N, CH_2Cl_2 (98%); (i) NaH, $(EtO)_2POCH(CH_3)COOEt$, toluene (86%); (j) nBu$_4$NF, THF (90%).

Transformation of the methyl ester **30** into α-(*E*)-*endo*-1-hydroxy-bergamoten-12-oic ethyl ester **34** was achieved by LAH reduction to the primary alcohol **31**, followed by Swern oxidation and Wittig olefination of the aldehyde **32** to afford the ethyl ester **33** with 75% overall yield. Finally, deprotection of the silyl ether led us to isolate the ethyl ester **34** analog with 90% yield.

3. Conclusion

The Ti(III)-promoted cyclization of (+)-8,9-epoxycarvone **8** led to an equimolecular mixture of diastereomers, from which the diol **10** was isolated and further used as starting material for the synthesis of β-(*E*)-*endo*-bergamoten-12-oic acid **2a**. The key step in the synthesis proved to be a Suzuki–Miyaura coupling between the terminal alkene **20** and the β-iodomethacrylate **21c**. The synthesis of the α-(*E*)-*endo*-1-hydroxy-bergamoten-12-oic acid derivative **34** starting from **10** was achieved by iterative elongation sequences of the lateral chain.

4. Experimental

4.1. General methods

Melting points are uncorrected. ^{1}H NMR spectra were measured at either 200 or 400 MHz and ^{13}C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS (^{1}H) or solvent (^{13}C), except where indicated otherwise. IR spectra were recorded for neat samples on NaCl plates, unless otherwise noted. Standard mass spectrometry data were acquired by using GC–MS system in EI mode with a maximum *m*/*z* range of 600. Optical rotations were determined on a digital Perkin–Elmer 241 polarimeter in a 1 dm cell. When required, all solvents and reagents were purified by standard techniques: tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone ketyl and degassed before use. Dimethylformamide (DMF) was dried over CaH_2, distilled under reduced pressure, and degassed before use. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for the handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel using flash column techniques[20] on Merck silica gel 60 (0.040–0.063 mm). R_f values refer to TLC carried out on 0.25 mm Merck 60 F_{254} silica gel plates, with the same eluant as that indicated for the column chromatography unless otherwise indicated. Yields reported are for chromatographically pure isolated products unless otherwise mentioned.

4.2. Reductive opening of (+)-8,9-epoxycarvone 8: preparation of 9 and 10

Solution a: titanocene dichloride Cp_2TiCl_2 (3.3 g, 13.5 mmol) and powdered Zn (2.6 g, 40.5 mmol) were placed in a two-necked 50 mL round-bottomed flask under an argon atmosphere. Anhydrous freshly distilled and deoxygenated THF (25 mL) was added, and stirring was maintained for 1 h at room temperature (a deep green color appeared after 15 min).

Solution b: (+)-8,9-epoxycarvone **8**[6] (1 g, 6.1 mmol) was placed in a two-necked round-bottomed flask and anhydrous freshly distilled and deoxygenated THF (60 mL) was added under an argon atmosphere.

Method A: *solution a* was added dropwise via cannula to *solution b* under an argon atmosphere. The reaction mixture was stirred for 3–5 h at room temperature.

Method B: *solution b* was added dropwise via cannula to *solution a* under an argon atmosphere. The reaction mixture was stirred for 3–5 h at room temperature.

Work up: when the reaction mixture turned from deep green to red, saturated solutions of NaH_2PO_4 (75 mL) and NaCl (75 mL) were added. Stirring was maintained overnight and the reaction mixture was filtered. The filtrate was extracted with ether (3×25 mL), and the combined organic layers were washed with a saturated NaCl solution and dried over Na_2SO_4. Evaporation of the solvent at reduced pressure led to the isolation of the crude reaction product. Fractionation was successfully achieved by flash chromatography on silica gel. Elution with hexane–ethyl acetate (1:1) afforded diols **9** (413 mg, 41%) and **10** (275 mg, 27%) and (*S*)-(+)-5-[1-(hydroxymethyl)vinyl]-2-methyl-cyclohex-2-enone **11**[7] (150 mg, 15%).

4.2.1. (1*R*,5*S*,6*S*)-2,6-Dimethyl-6-hydroxymethylbicyclo[3.1.1]hept-2-en-1-ol 9. $[\alpha]_D^{20}$ +38 (*c* 1.8, $CHCl_3$); R_f 0.15 (hexane–ethyl acetate 4:6); IR ν 3385, 2930, 1653, 1456, 1375, 1339, 1240, 1152, 1107, 995, 781 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 3H), 1.6–2.4 (m, 5H), 1.73 (s, 3H), 3.67 (d, J=11 Hz, 1H), 4.26 (d, J=11 Hz, 1H), 5.2 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 17.0 (CH_3), 30.5 (CH_2), 31.2 (CH), 39.8 (CH_2), 46.7 (C), 69.5 (CH_2), 79.0 (C), 117.3 (CH), 146.1 (C) ppm; EIMS *m*/*z* (%) 168 (M^+, 6), 150 (13), 135 (11), 108 (52), 93 (24), 82 (100), 67 (17). HRMS (EI): calcd for $C_{10}H_{17}O_2$ (M^++H^+) 169.1228, found 169.1233.

4.2.2. (1*R*,5*S*,6*R*)-2,6-Dimethyl-6-hydroxymethylbicyclo[3.1.1]hept-2-en-1-ol 10. $[\alpha]_D^{20}$ −18.4 (*c* 1.2, $CHCl_3$); R_f 0.23 (hexane–ethyl acetate 4:6); IR ν 3338, 2925, 1654, 1597, 1421, 1263, 1164, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.8 (s, 3H), 1.6–2.3 (m, 5H), 3.4 (d, J=10.3 Hz, 1H), 3.75 (d, J=10.3 Hz, 1H), 5.27 (s, 1H)

ppm; ^{13}C NMR ($CDCl_3$) δ 16.7 (CH_3), 17.0 (CH_3), 30.9 (CH_2), 34.2 (CH), 39.4 (CH_2), 46.3 (C), 65.6 (CH_2), 77.6 (C), 117.5 (CH), 145.2 (C) ppm; EIMS *m/z* (%) 168 (M^+, 2.5), 150 (12), 135 (8), 108 (38), 93 (19), 82 (100), 67 (11). HRMS (EI): calcd for $C_{10}H_{17}O_2$ (M^++H^+) 169.1228, found 169.1235.

4.3. Cyclization of diol 10 catalyzed by PPTS: (1*R*,4*S*,6*S*,1*R*)-1,7-dimethyl-6-hydroxy-9-oxa-tricyclo[4.3.0.0.^{4,7}]nonane 12

PPTS (0.38 g, 1.5 mmol) was added to a solution of **9** (0.25 g, 1.5 mmol) in freshly distilled THF (45 mL). The reaction mixture was refluxed for 48 h. The solvent was evaporated at reduced pressure, water (25 mL) was added, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ (3×25 mL), dried (Na_2SO_4), filtered, and concentrated to give a residue (0.18 g), which was fractionated by flash chromatography over silica gel. Elution with hexane–ethyl acetate (7:3) afforded **12** (0.18 g, 72%); $[\alpha]_D^{20}$ +6 (*c* 0.2, $CHCl_3$); R_f 0.25 (hexane–ethyl acetate 7:3); IR ν 3447, 2926, 1724, 1674, 1462, 1365, 1171, 1035, 917 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 3H), 1.24 (s, 3H), 1.5–2.6 (m, 7H), 3.46 (d, *J*=9 Hz, 1H), 3.81 (d, *J*=9 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 20.0 (CH_3), 22.6 (CH_2), 30.4 (CH_2), 34.8 (CH_2), 35.8 (CH), 54.1 (C), 71.6 (CH_2), 81.4 (C), 89.2 (C) ppm; EIMS *m/z* (%), 168 (M^+, 10), 153 (12), 125 (100), 95 (46), 69 (62). HRMS (EI): calcd for $C_{10}H_{17}O_2$ (M^++H^+) 169.1228, found 169.1223.

4.4. (1*R*,4*S*,6*S*,1*R*)-1,7-Dimethyl-6-[1′-(imidazolyl)thiocarbonyloxy]-9-oxa-tricyclo[4.3.0.0.^{4,7}]nonane 13

To a solution of **12** (0.112 g, 0.66 mmol) in freshly distilled dichloromethane (5 mL) thiocarbonyldiimidazole (0.142 g, 0.80 mmol) was added. The reaction mixture was stirred under an argon atmosphere at room temperature for 24 h. Evaporation of the solvent gave a crude product (0.26 g), which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (1:1) afforded **13** (0.139 g, 75%); R_f 0.4 (ethyl acetate); $[\alpha]_D^{20}$ +71.19 (*c* 0.55, $CHCl_3$); IR ν 3133, 2924, 2853, 1678, 1525, 1474, 1462, 1367, 1286, 1235, 1092, 1035, 1021, 895, 886, 823, 761, 667, 645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.68 (t, *J*=5.2 Hz, 1H), 1.08 (dd, J_1=6 Hz, J_2=3 Hz, 1H), 1.34 (s, 3H), 1.49 (s, 3H), 1.61 (m, 2H), 2.10 (m, 3H), 4.22 (d, *J*=10.6 Hz, 1H), 4.66 (d, *J*=10.6 Hz, 1H), 7.07 (s, 1H), 7.42 (s, 1H), 8.15 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 12.6 (CH_2), 21.3 (CH_3), 23.5 (CH_3), 24.8 (CH), 26.0 (CH_2), 38.8 (CH_2), 46.9 (C), 58.4 (C), 79.4 (CH_2), 91.8 (C), 115.8 (CH), 130.8 (CH), 135.3 (CH), 166.0 (C) ppm; HRMS (EI): calcd for $C_{14}H_{19}O_2N_2S$ (M^++H^+) 279.1162, found 279.1173.

4.5. Preparation of (1*R*,4*S*,6*R*,7*S*)-1,7-dimethyl-9-oxa-tricyclo[4.3.0.0^{4,7}]nonane 14

4.5.1. Compound 14 (from 13). A solution of **13** (0.134 g, 0.53 mmol) and AIBN (20 mg) in toluene (2.5 mL) was heated to reflux and tri-*n*-butyltin hydride (0.12 mL, 1.2 mmol) was added dropwise. The reaction was stirred at the same temperature for 5 h. Then, the solvent was evaporated off and a saturated NaF solution (10 mL) was added and the mixture was stirred overnight at room temperature. The reaction product was extracted with ether (25 mL). The organic layers were dried over Na_2SO_4, and the solvent was evaporated off to afford **14**[4] (0.059 g, 80%); $[\alpha]_D^{20}$ +26.52 (*c* 1.64, $CHCl_3$); R_f 0.5 (hexane–ethyl acetate 8:2); IR ν 2965, 2924, 2866, 1452, 1375, 1229, 1173, 1134, 1032, 905 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 6H), 1.43 (d, *J*=9.2 Hz, 1H), 1.58–2.03 (m, 7H), 3.36 (d, *J*=8.7 Hz, 1H), 3.81 (d, *J*=8.7 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 19.7 (CH_3), 22.7 (CH_2), 22.9 (CH_2), 25.3 (CH_3), 32.5 (CH_2), 41.4 (CH), 51.9 (C), 52.3 (CH), 72.6 (CH_2), 86.9 (C) ppm; EIMS *m/z* (%): 152 (M^+, 3.2), 137 (8), 123 (10), 109 (19), 97 (100), 79 (46), 69 (51), 55 (30).

4.5.2. Compound 14 (from 12). To a mixture of $InCl_3$ (11 mg, 0.05 mmol) and **12** (170 mg, 1 mmol) in dry 1,2-dichloroethane (1 mL), chlorodiphenylsilane (0.43 g, 2 mmol) was added under an argon atmosphere. The reaction mixture was stirred at 80 °C for 3 h. The resulting mixture was poured into Et_2O (25 mL) and water (20 mL). The reaction mixture was extracted with Et_2O, and the organic layer was dried over $MgSO_4$. The evaporation of the ether solution gave the crude product, which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (1:1) afforded **14** (0.12 g, 80%), which exhibited the spectroscopic properties described above for **14**.

4.6. (1′*R*,2′*R*,5′*S*,6′*S*)-(2,6-Dimethyl-2-trimethylsilyloxy-bicyclo[3.1.1]-hept-6-yl)-methanol 18

To a solution of **17**[2] (0.74 g, 2.26 mmol) in dichloromethane (8 mL) and toluene (8 mL) at −78 °C, was added dropwise a solution of DIBAL-H (1.5 M in toluene, 23 mL, 33.6 mmol) under inert atmosphere. The reaction mixture was stirred for 30 min and then allowed to settle at −5 °C for 5 h. Ethyl acetate (70 mL) and an aqueous solution of potassium tartrate (5.0 M) were added and the reaction mixture was stirred overnight at room temperature. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (95:5) afforded **18** (0.49 g, 89.5%); $[\alpha]_D^{20}$ −31.8 (*c* 16.7, $CHCl_3$); R_f 0.4 (hexane–ethyl acetate 98:2); IR ν 3157, 2961, 2922, 2874, 1373, 1252, 1040, 839 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H), 0.98 (d, *J*=10.9 Hz, 1H), 1.31 (s, 3H), 1.34 (s, 3H), 1.62–2.02 (m, 7H), 2.70 (dd, J_1=3.0 Hz, J_2=10.7 Hz, 1H), 3.15 (dd, J_1=10.7 Hz, J_2=10.7 Hz, 1H), 3.95 (dd, J_1=3.0 Hz, J_2=10.7 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 2.5 (CH_3), 22.8 (CH_3), 24.2 (CH_2), 27.7 (CH_2), 30.6 (CH_3), 32.7 (CH_2), 39.3 (CH), 42.0 (C), 53.5 (CH), 66.7 (CH_2), 79.8 (C) ppm; HRMS (EI): calcd for $C_{13}H_{25}O_2NaSi$ (M^++Na^+) 265.1594, found 265.1587.

4.7. (1′*R*,2′*R*,5′*S*,6′*S*)-(2,6-Dimethyl-2-trimethylsilyloxy-bicyclo[3.1.1]-hept-6-yl)-carboxaldehyde 19

To a solution of Dess–Martin periodinane[14] (4.0 g, 9.5 mmol) in dichloromethane (40 mL), at 0 °C under an argon atmosphere, a solution of **18** (1.4 g, 6 mmol) in dichloromethane (20 mL) was added dropwise. The reaction mixture was stirred for 20 min. Then, the reaction mixture

was diluted with ether (50 mL) and aqueous 1.5 M NaOH solution (75 mL) was added. The reaction mixture was stirred for 15 min. The organic layer was washed with 1.5 M NaOH, water, and brine, dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (99.5:5) afforded **19** (0.93 g, 72.5%); $[\alpha]_D^{20}$ −5.13 (*c* 15.8, $CHCl_3$); R_f 0.5 (hexane–ethyl acetate 99:1); IR ν 2957, 2930, 1716, 1251, 1132, 1046, 1007, 859, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 9H), 1.13 (d, J=10 Hz, 1H), 1.27 (s, 6H), 1.6–2.6 (m, 7H), 9.66 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 2.3 (CH_3), 16.5 (CH_3), 23.0 (CH_2), 26.1 (CH_2), 29.2 (CH_3), 33.1 (CH_2), 39.9 (CH), 50.2 (C), 57.9 (CH), 76.6 (C), 203.9 (C) ppm; HRMS (EI): calcd for $C_{13}H_{24}O_2NaSi$ (M^++Na^+) 263.1438, found 263.1426.

4.8. (1′*R*,2′*R*,5′*S*,6′*S*)-(2,6-Dimethyl-6-vinylbicyclo-[3.1.1]hept-2-yloxy)-trimethylsilane 20

To a solution of aldehyde **19**[2] (0.88 g, 14.16 mmol) in dry DME (5 mL), a solution of methylenetriphenylphosphorane (4.7 g, 17 mmol) in DME (25 mL) was added dropwise. A white precipitate was formed immediately. The reaction mixture was stirred at room temperature overnight. Then, a saturated $NaHCO_3$ solution (25 mL) was added and the volatiles were removed in vacuo. The reaction product was then extracted with dichloromethane. The combined layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane afforded **20** (0.49 g, 56%); $[\alpha]_D^{20}$ +31.20 (*c* 1.5, $CHCl_3$); R_f 0.5 (hexane); IR ν 3075, 2961, 2919, 2868, 1629, 1451, 1411, 1370, 1343, 1249, 1167, 1128, 1047, 1020, 1001, 903, 858, 838, 753, 679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 9H), 0.99 (d, J=10.1 Hz, 1H), 1.29 (s, 3H), 1.31 (s, 3H), 1.5–2.4 (m, 7H), 4.80 (dd, J_1=1.2 Hz, J_2=2.2 Hz, 1H), 4.87 (dd, J_1=2.0 Hz, J_2=10.4 Hz, 1H), 6.48 (dd, J_1=11.2 Hz, J_2=17.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 2.7 ($3CH_3$), 24.8 (CH_3), 25.8 (CH_2), 29.4 (CH_2), 30.6 (CH_3), 34.1 (CH_2), 41.6 (CH), 43.5 (C), 55.7 (CH), 78.6 (C), 109.6 (CH_2), 145.9 (CH) ppm; HRMS (EI): calcd for $C_{14}H_{26}ONaSi$ (M^++Na^+) 261.1645, found 261.1671.

4.9. (−)-(1*S*,2*R*,5*S*)-5-(6,6-Dimethylbicyclo[3.1.1]hept-2-yl)-2-methyl-pent-2-enoic acid 2-(trimethyl-silanyl)-ethyl ester 23

4.9.1. Suzuki–Miyaura couplings. General procedure.

Solution a: (–)-β-pinene **22** (0.26 g, 1.9 mmol) was placed in a two-necked round-bottomed flask and anhydrous freshly distilled and deoxygenated THF (1 mL) was added under an argon atmosphere. Hydroborane (catecholborane, 9-BBN) (2.3 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred overnight at room temperature.

Solution b: to a solution of β-bromomethacrylate **21a** (0.65 g, 2.25 mmol) in a exhaustively degasified mixture of DMF–H_2O (20 mL, 20:1) the catalyst [$Pd(Ph_3P)_4$, $PdCl_2$(dppf), $PdCl_2(CH_3CN)_2$] (0.08 mmol) and the base (K_3PO_4 or K_2CO_3) (9 mmol) were added.

Solution a was added via syringe to *solution b* and the reaction mixture was stirred at 50 °C for 48 h. Then, the mixture was allowed to reach room temperature, water (50 mL) was added, and the reaction mixture was extracted with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on silica gel. Elution with hexane–ethyl acetate (95:5) afforded **23** (see yields Table 1). $[\alpha]_D^{20}$ −5.11 (*c* 1.27, $CHCl_3$); R_f 0.5 (hexane–ethyl acetate 9:1); IR ν 2921, 1711, 1648, 1383, 1250, 1153, 1116, 1066, 938, 838, 748, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H), 0.84 (d, J=10 Hz, 1H), 1.04 (s, 3H), 0.9–2.4 (m, 12H), 1.16 (s, 3H), 1.80 (s, 3H), 4.21 (t, J=10 Hz, 2H), 6.72 (t, J=6Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −1.5 ($3CH_3$), 12.5 (CH_3), 17.4 (CH_2), 22.3 (CH_2), 23.2 (CH_3), 27.0 (CH_2), 28.2 (CH_3), 33.8 (CH_2), 36.3 (CH_2), 38.7 (C), 41.1 (CH), 41.4 (CH), 45.8 (CH), 62.4 (CH_2), 127.5 (C), 141.6 (CH), 168.4 (C) ppm; HRMS (EI): calcd for $C_{19}H_{34}O_2NaSi$ (M^++Na^+) 345.2220, found 345.2210.

4.10. (+)-(1′*R*,2′*R*,5′*R*,6′*S*)-(*E*)-5-[2,6-Dimethyl-2-(trimethyl-silanyloxy)bicyclo[3.1.1]hept-6-yl]-2-methyl-pent-2-enoic acid trimethyl-silanylmethyl ester 24a

Solution a: (2,6-dimethyl-6-vinylbicyclo[3.1.1]hept-2-yloxy)-trimethylsilane **20** (0.15 g, 0.63 mmol) was placed in a two-necked round-bottomed flask and anhydrous freshly distilled and deoxygenated THF (1 mL) was added under an argon atmosphere. 9-BBN (0.5 M in THF, 1.9 mL, 0.95 mmol) was added dropwise and the reaction mixture was stirred overnight at room temperature.

Solution b: to a solution of halomethacrylate **21c** (0.26 g, 0.82 mmol) in a exhaustively degasified mixture of DMF–H_2O (7.5 mL, 20:1), $Pd(Ph_3P)_4$ (40 mg, 0.04 mmol) and powdered K_2CO_3 (0.46 g, 3.34 mmol) were added.

Solution a was added via syringe to *solution b* and the reaction mixture was stirred at 50 °C for 48 h. Then, the mixture was allowed to reach room temperature, water (25 mL) was added, and the reaction mixture was extracted with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on silica gel. Elution with hexane–ethyl acetate (95:5) afforded **24a** (0.39 g, 87%); $[\alpha]_D^{20}$ +6.28 (*c* 1.36, $CHCl_3$); R_f 0.5 (hexane–ethyl acetate 9:1); IR ν 2955, 2916, 1711, 1651, 1463, 1365, 1250, 1139, 1054, 1002, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 9H), 0.08 (s, 9H), 1.02 (t, J=8.0 Hz, 2H), 1.21 (s, 3H), 1.26 (s, 3H), 1.82 (s, 3H), 1.4–2.4 (m, 12H), 4.22 (t, J=8.0 Hz, 2H), 6.78 (t, J=7.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −1.5 ($3CH_3$), 2.7 ($3CH_3$), 12.3 (CH_3), 17.3 (CH_2), 23.9 (CH_3), 24.1 (CH_2), 27.9 (CH_2), 29.6 (CH_2), 31.3 (CH_3), 33.2 (CH_2), 35.0 (CH_2), 39.8 (CH), 40.7 (C), 54.9 (CH), 62.4 (CH_2), 78.7 (C), 127.0 (C), 143.7 (CH), 168.5 (C) ppm; HRMS (EI): calcd for $C_{23}H_{44}O_3NaSi_2$ (M^++Na^+) 447.2721, found 447.2719.

4.11. (+)-(1′*R*,2′*R*,5′*R*,6′*S*)-(*E*)-5-[2,6-Dimethyl-2-(trimethyl-silanyloxy)bicyclo[3.1.1]hept-6-yl]-2-methyl-pent-2-enoic acid methyl ester 24b

Solution a: (2,6-dimethyl-6-vinylbicyclo[3.1.1]hept-2-yloxy)-trimethylsilane **20** (0.12 g, 0.52 mmol) was placed in a two-necked round-bottomed flask and anhydrous freshly

distilled and deoxygenated THF (1 mL) was added under an argon atmosphere. 9-BBN (0.5 M in THF, 1.6 mL, 0.78 mmol) was added dropwise and the reaction mixture was stirred overnight at room temperature.

Solution b: to a solution of halomethacrylate **21d** (0.13 g, 0.57 mmol) in a exhaustively degasified mixture of DMF–H_2O (7.5 mL, 20:1), $Pd(Ph_3P)_4$ (40 mg, 0.04 mmol) and powdered K_2CO_3 (0.38 g, 2.76 mmol) were added.

Solution a was added via syringe to *solution b* and the reaction mixture was stirred at 50 °C for 48 h. Then, the mixture was allowed to reach room temperature, water (25 mL) was added, and the reaction mixture was extracted with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on silica gel. Elution with hexane–ethyl acetate (95:5) afforded **24b** (0.14 g, 79.9%); $[\alpha]_D^{20}$ +10.62 (*c* 1.97, $CHCl_3$); R_f 0.5 (hexane–ethyl acetate 9:1); IR ν 2955, 2917, 1717, 1645, 1437, 1249, 1128, 1045, 1005, 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 9H), 0.98 (d, J=10.0 Hz, 1H), 1.20 (s, 3H), 1.25 (s, 3H), 1.75 (s, 3H), 1.4–2.4 (m, 11H), 3.70 (s, 3H), 6.78 (t, J=7.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 2.7 ($3CH_3$), 12.2 (CH_3), 23.9 (CH_3), 24.1 ($2CH_2$), 27.9 (CH_2), 31.3 (CH_3), 33.2 (CH_2), 35.0 (CH_2), 39.8 (CH), 40.7 (C), 51.5 (CH_3), 54.9 (CH), 78.7 (C), 126.6 (C), 144.1 (CH), 168.8 (C) ppm; HRMS (EI): calcd for $C_{19}H_{34}O_3NaSi$ (M^++Na^+) 361.2169, found 361.2153.

4.12. Preparation of (+)-(1′*R*,2′*R*,5′*R*,6′*S*)-(*E*)-5-[2-hydroxy-2,6-dimethylbicyclo[3.1.1]hept-6-yl]-2-methylpent-2-enoic acid methyl ester 24c

4.12.1. Compound 24c (from 24a). Tetrabutylammonium fluoride (0.2 g, 0.63 mmol) was added to a solution of **24a** (0.16 g, 0.39 mmol) in dry THF (1 mL) at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 24 h. The solvent was evaporated in vacuo and a solution of 5% $NaHCO_3$ was added. The aqueous solution was extracted with ether at basic pH and then acidified with 6 N HCl to pH 4–5. The reaction mixture was then extracted with ether, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was treated with an ethereal diazomethane solution to afford a crude methyl ester (0.110 g). The crude product was chromatographed on silica gel. Elution with hexane–ethyl acetate (1:1) gave **24c** (0.072 g, 70%); $[\alpha]_D^{20}$ +8.0 (*c* 1.5, $CHCl_3$); R_f 0.3 (hexane–ethyl acetate 1:1); IR ν 3507, 2953, 2919, 1712, 1651, 1444, 1282, 1126, 924, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, J=10.0 Hz, 1H), 1.23 (s, 3H), 1.25 (s, 3H), 1.82 (s, 3H), 1.4–2.4 (m, 12H), 3.71 (s, 3H), 6.78 (t, J=7.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 12.2 (CH_3), 23.8 (CH_3), 23.9 (CH_2), 24.2 (CH_2), 28.3 (CH_2), 32.1 (CH_2), 35.1 (CH_2), 40.2 (CH), 40.9 (C), 51.5 (CH_3), 54.0 (CH), 75.9 (C), 126.7 (C), 143.7 (CH), 168.8 (C) ppm; HRMS (EI): calcd for $C_{16}H_{26}O_3NaSi$ (M^++Na^+) 289.1774, found 289.1766.

4.12.2. Compound 24c from 24b. Tetrabutylammonium fluoride (0.29 g, 0.92 mmol) was added to a solution of **24b** (0.28 g, 0.84 mmol) in THF (2 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 48 h at room temperature. Then, the solvent was evaporated off, the residue was dissolved in ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on silica gel. Elution with hexane–ethyl acetate (1:1) afforded **24c** (0.16 g, 74.4%).

4.13. (+)-(6′*S*,1′*S*,5′*S*)-2-Methyl-5-(6-methyl-2-methylenebicyclo[3.1.1]hept-6-yl)-pent-2-enoic acid methyl ester: β-(*E*)-*endo*-bergamoten-12-oic acid methyl ester 2b

Trifluoromethanesulfonic anhydride (0.91 g, 3.24 mmol) was added to a solution of **24c** (0.17 g, 0.65 mmol) and dimethylaminopyridine (0.95 g, 7.76 mmol) in dry dichloromethane (30 mL). The reaction mixture was stirred for four days at room temperature. Then, the reaction mixture was poured over a 5% aqueous $NaHCO_3$ solution (50 mL) and extracted with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (9:1) afforded **2b** (0.132 g, 83%); R_f 0.25 (hexane–ethyl acetate 9:1); $[\alpha]_D^{20}$ +20.0 (*c* 2.1, $CHCl_3$); IR ν 2949, 1717, 1443, 1272, 878, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.88 (s, 3H), 0.8–2.8 (m, 12H), 3.73 (s, 3H), 4.62 (m, 1H), 4.82 (m, 1H), 6.77 (t, J=8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 12.1 (CH_3), 18.0 (CH_3), 24.8 (CH_2), 28.3 (CH_2), 28.5 (CH_2), 32.5 (CH_2), 37.0 (CH_2), 42.7 (C), 43.1 (CH), 51.5 (CH_3), 52.3 (C), 103.3 (CH_2), 127.1 (C), 142.8 (CH), 155.6 (C), 168.5 (C) ppm; EIMS *m/z* (%): 248 (M^+, 6), 217 (6), 189 (3), 173 (3), 158 (16), 135 (10), 122 (54), 119 (100), 93 (82), 79 (64), 77 (41), 55 (43). HRMS (EI): calcd for $C_{16}H_{25}O_2$ (M^++H^+) 249.1856, found 249.1862.

4.14. (+)-(6′*S*,1′*S*,5′*S*)-2-Methyl-5-(6-methyl-2-methylenebicyclo[3.1.1]hept-6-yl)-pent-2-enoic acid methyl ester: β-(*E*)-*endo*-bergamoten-12-oic acid 2a

To a stirred solution of **2b** (0.094 g, 0.38 mmol) in MeOH (2 mL), 2 N KOH (2 mL, 4 mmol) was added at room temperature. The mixture was stirred for 24 h at that temperature. MeOH was removed in vacuo and the residual aqueous solution was acidified to pH 3 with 2 N HCl. The aqueous phase was extracted with ether (3×15 mL), the combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (8:2) afforded **2a** (0.067 g, 75%); R_f 0.40 (hexane–ethyl acetate 8:2); $[\alpha]_D^{20}$ +30 (*c* 2.1, $CHCl_3$); IR ν 3072, 2962, 2955, 1687, 1640, 1421, 1384, 1287, 930, 878 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.10–1.36 (m, 2H), 1.45 (d, J=10 Hz, 1H), 1.65–1.90 (m, 2H), 1.84 (s, 3H), 1.95–2.17 (m, 3H), 2.20–2.35 (m, 1H), 2.30 (dt, J_1=5.6 Hz, J_2=10 Hz, 1H), 2.57 (t, J=5.6 Hz, 2H), 4.62 (s, 1H), 4.82 (s, 1H), 6.93 (t, J=8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 11.8 (CH_3), 18.1 (CH_3), 25.1 ($2CH_2$), 28.3 (CH_2), 28.6 (CH_2), 32.4 (CH_2), 37.1 (CH_2), 43.2 (CH), 49.2 (C), 52.4 (CH), 103.4 (CH_2), 126.7 (C), 145.6 (CH), 155.7 (C), 173.6 (C) ppm; HRMS (EI): calcd for $C_{15}H_{22}O_2Na$ (M^++Na^+) 257.1512, found 257.1508.

4.15. (1*RS*,5*SR*,6*RS*)-(1-Hydroxy-2,6-dimethylbicyclo-[3.1.1]hept-2-en-6-yl)-methyl acetate 25

To a solution of diol **10** (594 mg, 3.54 mmol) in pyridine (0.30 mL, 3.89 mmol), acetic anhydride (0.33 mL,

3.54 mmol) was added. The reaction mixture was stirred at 0 °C under an argon atmosphere for 9 h and then diluted with Et_2O, and poured into ice water. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with $NaHCO_3$ (5%), brine, and dried with Na_2SO_4. Removal of the solvent afforded acetate **25** (742 mg, 100%), as a colorless oil; R_f 0.60 hexane–ethyl acetate (1:1); IR ν 3480, 2940, 1726, 1452, 1383, 1171, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.51 (d, J=8.1 Hz, 1H), 1.67 (s, 3H), 1.94 (s, 3H), 2.0–2.2 (m, 3H), 2.21 (t, J=7.0 Hz, 1H), 3.80 (d, J=11.0 Hz, 1H), 4.02 (d, J=11.0 Hz, 1H), 5.16 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.3 (CH_3), 16.6 (CH_3), 20.6 (CH_3), 30.6 (CH_2), 34.3 (CH), 38.9 (CH_2), 44.3 (C), 67.3 (CH_2), 76.9 (C), 117.3 (CH), 145.4 (C) 171.4 (C) ppm; HRMS (EI): calcd for $C_{12}H_{18}O_3Na$ (M^++Na^+) 233.1148, found 233.1136.

4.16. (1*RS*,5*SR*,6*RS*)-[1-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]methyl acetate 26

A mixture of the hydroxy ester **25** (581 mg, 2.77 mmol), *tert*-butyldimethylsilyl chloride (1.04 g, 6.91 mmol) and imidazole (573 mg, 8.42 mmol) in dry DMF (14 mL) was stirred for five days under an argon atmosphere at 40 °C, poured into ice water, and extracted with hexane. The extract was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was filtered through a small pad of silica gel, and concentrated to yield the silyl ether **26** as a colorless oil (0.82 g, 95%); R_f 0.80 (hexane–ethyl acetate 1:1); IR ν 2955, 2859, 1744, 1470, 1252, 1175, 1063, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 3H), 0.15 (s, 3H), 0.90 (s, 9H), 1.22 (s, 3H), 1.64 (d, J=8.1 Hz, 1H), 1.70 (s, 3H), 2.0–2.2 (m, 3H), 2.01 (s, 3H), 2.48 (t, J=7.2 Hz, 1H), 3.96 (d, J=10.8 Hz, 1H), 4.02 (d, J=10.8 Hz, 1H), 5.24 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −2.9 (CH_3), −1.9 (CH_3), 17.7 (CH_3), 18.3 (C), 18.8 (CH_3), 20.8 (CH_3), 25.9 ($3CH_3$), 30.8 (CH_2), 34.6 (CH), 39.1 (CH_2), 45.2 (C), 67.1 (CH_2), 78.5 (C), 117.3 (CH), 147.2 (C), 171.4 (C) ppm. HRMS (EI): calcd for $C_{18}H_{33}O_3Si$ (M^++H^+) 325.2193, found 325.2196.

4.17. (1*RS*,5*SR*,6*RS*)-[1-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]methanol 27

To a stirred solution of **26** (545 mg, 1.68 mmol) in EtOH (5.3 mL), 5 M KOH (0.8 mL) was added. The reaction mixture was stirred at room temperature under an argon atmosphere for 80 min and then concentrated to afford a residue, which was dissolved in H_2O and extracted with Et_2O. The combined organic extracts were washed with brine and dried with Na_2SO_4. Removal of the solvent afforded **27** (0.46 g, 97%) as a colorless oil; R_f 0.40 (hexane–ethyl acetate 1:1); IR ν 3403, 2955, 2859, 1462, 1238, 1169, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.15 (s, 3H), 0.87 (s, 9H), 1.25 (s, 3H), 1.60 (d, J=8.2 Hz, 1H), 1.72 (br s, 3H), 2.0–2.2 (m, 3H), 2.48 (t, J=5.2 Hz, 1H), 3.37 (d, J=10.3 Hz, 1H), 3.58 (d, J=10.3 Hz, 1H), 5.25 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −3.0 ($3CH_3$), −2.0 (CH_3), 17.6 (CH_3), 18.2 (C), 18.8 (CH_3), 25.9 ($3CH_3$), 30.6 (CH_2), 34.7 (CH), 39.1 (CH_2), 47.0 (C), 65.7 (CH_2), 79.1 (C), 117.6 (CH), 146.7 (C) ppm; HRMS (EI): calcd for $C_{16}H_{31}O_2Si$ (M^++H^+) 283.2088, found 283.2080.

4.18. (1*RS*,5*SR*,6*RS*)-[1-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]methyl methanesulfonate 28

To a stirred solution of the alcohol **27** (300 mg, 1.06 mmol) in dichloromethane (7 mL) and pyridine (0.17 mL, 2.12 mmol), at 0 °C methanesulfonyl chloride (0.12 mL, 1.6 mmol) was added. After 25 h at 25 °C, the mixture was poured into ice water and stirred for additional 2 h at room temperature. The two-phase system was extracted with ether. The combined ethereal extracts were washed with water and brine, dried (Na_2SO_4) and, concentrated under reduced pressure to give the mesylate **28** (0.37 g, 96%); R_f 0.50 (hexane–diethyl ether 1:1); IR ν 2474, 1464, 1358, 1250, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.14 (s, 3H), 0.87 (s, 9H), 1.26 (s, 3H), 1.64 (d, J=8.1 Hz, 1H), 1.70 (q, J=1.5 Hz, 3H), 2.1–2.25 (m, 3H), 2.48 (t, J=6.1 Hz, 1H), 2.94 (s, 3H), 4.06 (d, J=9.2 Hz, 1H), 4.20 (d, J=9.2 Hz, 1H), 5.29 (br s, 1H) ppm.

4.19. (1*SR*,5*SR*,6*SR*)-Dimethyl-2-[1-(*tert*-butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]-methyl malonate 29

To a solution of sodium dimethylmalonate, prepared from sodium (25.5 mg, 1.11 mmol) and dimethylmalonate (201.3 mg, 1.52 mmol) in toluene (1 mL), a solution of the mesyl compound **28** (366 mg, 1.01 mmol) in toluene (3.5 mL) was added. After three days at reflux the mixture was cooled, and then poured into ice water, and extracted with diethyl ether. The combined organic extracts were washed with brine and dried with Na_2SO_4. The solvent was evaporated at reduced pressure to afford a crude product, which was chromatographed on silica gel. Elution with hexane–ether (80:20) gave the diester **29** (0.34 g, 85%); R_f 0.40 (hexane–diethyl ether 1:1); IR ν 2953, 2859, 1740, 1435, 1236, 1165, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.08 (s, 3H), 1.06 (d, J=8.2 Hz, 1H), 1.8–2.2 (m, 5H), 1.70 (q, J=1.5 Hz, 3H), 2.42 (t, J=6.0 Hz, 1H), 3.39 (dd, J_1=3.0 Hz, J_2=5.9 Hz, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 5.25 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −3.0 (CH_3), −2.0 (CH_3), 18.2 (C), 18.8 ($2CH_3$), 25.8 ($3CH_3$), 30.6 (CH_2), 31.8 (CH_2), 36.0 (CH), 39.0 (CH_2), 45.3 (C), 48.3 (CH), 52.1 ($2CH_3$), 79.8 (C), 117.6 (CH), 147.0 (C), 170.4 (C), 170.7 (C) ppm; HRMS (EI): calcd for C_{21} $H_{37}O_5Si$ (M^++H^+) 397.2404, found 397.2397.

4.20. Methyl (1*SR*,5*SR*,6*SR*)-3-[1-(*tert*-butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]-propanoate 30

To a solution of the diester **29** (206 mg, 0.52 mmol) in DMSO (0.6 mL), water (18 mg, 1 mmol) and sodium chloride (61 mg, 1.04 mmol) were added. The suspension was refluxed for 7 h under an argon atmosphere, after which it was diluted with ethyl acetate. The solution was washed with water, and brine, dried (Na_2SO_4), and evaporated to afford the ester **30** (0.14 g, 80%) as a colorless oil; R_f 0.50 (hexane–diethyl ether 7:3); IR ν 2930, 2857, 1742, 1462, 1236, 1167, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 1.14 (s, 3H), 1.60 (d, J=8.0 Hz, 1H), 1.72 (br s, 3H), 1.8–2.3 (m, 7H), 2.24 (t, J=6.1 Hz, 1H), 3.62 (s, 3H), 5.23 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$)

δ −3.0 (CH_3), −2.0 (CH_3), 18.2 (C), 19.0 (CH_3), 19.1 (CH_3), 25.9 ($3CH_3$), 28.5 (CH_2), 29.5 (CH_2), 30.6 (CH_2), 35.8 (CH), 39.1 (CH_2), 45.3 (C), 51.1 (CH_3), 79.5 (C), 117.5 (CH), 147.0 (C), 174.7 (C) ppm; HRMS (EI): calcd for $C_{19}H_{35}O_3Si$ (M^++H^+) 339.2350, found 339.2338.

4.21. (1*SR*,5*SR*,6*SR*)-3-[1-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]propan-1-ol 31

$LiAlH_4$ (29.64 mg, 0.78 mmol) was added to a solution of the ester **30** (133 mg, 0.39 mmol) in diethyl ether (0.7 mL). The reaction mixture was stirred vigorously at room temperature under an argon atmosphere for 2 h, after which it was quenched with $Na_2SO_4 \cdot 10H_2O$. The resulting mixture was filtered, and the filtrate was then evaporated off under reduced pressure to afford unsaturated alcohol **31** (0.10 g, 88%); R_f 0.40 (hexane–diethyl ether 1:1); IR ν 3356, 2951, 2857, 1462, 1236, 1167, 1063, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.12 (s, 3H), 0.89 (s, 9H), 1.18 (s, 3H), 1.1–2.1 (m, 7H), 1.58 (d, J=8.1 Hz, 1H), 1.72 (br s, 3H), 2.43 (t, J=6.2 Hz, 1H), 3.53 (t, J=6.0 Hz, 2H), 5.19 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −2.9 (CH_3), −2.0 (CH_3), 18.2 (C), 19.0 (CH_3), 19.4 (CH_3), 25.9 ($3CH_3$), 28.1 (CH_2), 29.3 (CH_2), 30.6 (CH_2), 35.9 (CH), 39.0 (CH_2), 45.6 (C), 63.8 (CH_3), 79.9 (C), 117.3 (CH), 147.3 (C) ppm; HRMS (EI): calcd for $C_{18}H_{35}O_2Si$ (M^++H^+) 311.2400, found 311.2401.

4.22. (1*SR*,5*SR*,6*SR*)-3-[1-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]propanal 32

A solution of DMSO (0.04 mL) in dichloromethane (0.18 mL) was added dropwise to a stirred solution of oxalyl chloride (0.03 mL, 0.35 mmol) in dichloromethane (1.5 mL) under an argon atmosphere at −60 °C. After 5 min, a solution of the alcohol **31** (100 mg, 0.32 mmol) in CH_2Cl_2–DMSO (3:1, 2 mL) was added dropwise. The reaction mixture was stirred for 20 min, triethylamine (0.22 mL, 1.6 mmol) was added at −60 °C, and stirring was continued for 10 min. Then, the mixture was allowed to warm to room temperature and stirred for 4 h, after which water was added. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined extracts were washed with water, dried (Na_2SO_4), and filtered. The solvent was removed to afford the aldehyde **32** (71 mg, 100%) as a colorless oil; R_f 0.60 (hexane–diethyl ether 1:1); IR ν 2961, 2857, 1726, 1462, 1258, 1236, 1165, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.14 (s, 3H), 0.90 (s, 9H), 1.17 (s, 3H), 1.1–2.3 (m, 7H), 1.59 (d, J=8.0 Hz, 1H), 1.72 (s, 3H), 2.44 (t, J=7.4 Hz, 1H), 5.22 (br s, 1H), 9.71 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −2.9 (CH_3), −1.9 (CH_3), 18.3 (C), 19.1 (CH_3), 19.4 (CH_3), 25.4 (CH_2), 25.9 ($3CH_3$), 30.6 (CH_2), 35.9 (CH), 39.1 (CH_2), 39.8 (CH_2), 45.1 (C), 79.5 (C), 117.7 (CH), 147.0 (C), 203.1 (C) ppm; HRMS (EI): calcd for $C_{18}H_{33}O_2Si$ (M^++H^+) 309.2245, found 309.2240.

4.23. Ethyl (1*SR*,5*SR*,6*SR*)-(*Z*)-5-[1-(*tert*-butyldimethylsilyloxy)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl]-2-methylpent-2-enoate 33

A dry three-necked flask equipped with stirrer, condenser, and a dropping funnel was purged with argon and charged with a 65% dispersion oil of sodium hydride in mineral oil (10.2 mg, 0.27 mmol) and dry toluene (0.6 mL). To this stirred mixture at 0 °C triethyl 2-phosphonopropionate (76 mg, 0.32 mmol) was added dropwise, and the mixture was stirred for 30 min at room temperature to ensure a complete reaction. To this nearly clear solution the aldehyde **32** (90 mg, 0.29 mmol) in toluene (0.6 mL) was added dropwise. The mixture was stirred for an additional 3 h and diluted with ether, and water was then added dropwise. The organic layer was separated and the aqueous phase was extracted with ether. The combined extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded the unsaturated ester **33** as a colorless oil (98 mg, 86%); R_f 0.50 (hexane–diethyl ether 7:3); IR ν 2930, 2857, 1718, 1620, 1452, 1252, 1167, 1098, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.15 (s, 3H), 0.89 (s, 9H), 1.19 (s, 3H), 0.8–2.15 (m, 7H), 1.27 (t, J=7 Hz, 3H), 1.60 (d, J=8.1 Hz, 1H), 1.74 (s, 3H), 1.79 (s, 3H), 2.42 (t, J=6.0 Hz, 1H), 4.15 (q, J=7.0 Hz, 2H), 5.20 (br s, 1H), 6.69 (t, J=7.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ −2.9 (CH_3), −1.9 (CH_3), 11.9 (CH_3), 14.1 (CH_3), 18.2 (C), 19.0 (CH_3), 19.4 (CH_3), 24.2 (CH_2), 25.9 ($3CH_3$), 30.6 (CH_2), 32.1 (CH_2), 36.0 (CH), 39.1 (CH_2), 45.7 (C), 60.1 (CH_2), 79.7 (C), 117.4 (CH), 127.0 (C), 143.0 (CH), 147.2 (C), 168.1 (C) ppm; HRMS (EI): calcd for $C_{23}H_{41}O_3Si$ (M^++H^+) 393.2819, found. 393.2804.

4.24. Ethyl (1*SR*,5*SR*,6*SR*)-(*Z*)-5-[1-hydroxy-2,6-dimethylbicyclo[3.1.1]hept-2en-6-yl]-2-methylpent-2-enoate 34

A solution of the ester **33** (66 mg, 0.16 mmol) and $n$$Bu_4NF$ (159 mg, 0.5 mmol) in THF (1.1 mL) was stirred at room temperature for 19 h. A saturated aqueous NH_4Cl solution was added, and the resulting mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), and filtered. The solvent was removed to give the alcohol **34** (40 mg, 90%); R_f 0.20 (hexane–diethyl ether 7:3); IR ν 3489, 2932, 1693, 1647, 1449, 1370, 1279, 1235, 1161, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–2.15 (m, 7H), 1.26 (s, 3H), 1.31 (t, J=7.2 Hz, 3H), 1.62 (d, J=8.4 Hz, 1H), 1.81 (s, 3H), 1.83 (s, 3H), 2.25 (t, J=6.8 Hz, 1H), 4.20 (t, J=7.2 Hz, 2H), 5.25 (br s, 1H), 6.71 (t, J=6.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 12.1 (CH_3), 14.2 (CH_3), 17.3 (CH_3), 18.0 (CH_3), 24.3 (CH_2), 30.8 (CH_2), 31.5 (CH_2), 34.9 (CH), 39.9 (CH_2), 45.3 (C), 60.4 (CH_2), 78.3 (C), 117.9 (CH), 127.3 (C), 142.7 (CH), 144.7 (C), 168.3 (C) ppm; HRMS (EI): calcd for $C_{17}H_{27}O_3$ (M^++H^+) 279.1954, found 279.1947.

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Supplementary data

Spectroscopic data for compounds described in Schemes 1 and 2 and Table 1 can be found in the online version.

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.020.

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2-(2-Hydroxyaryl)cinnamic amides: a new class of axially chiral molecules

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Abstract—The syntheses of several differently substituted amides formally derived from a chiral amine, either *E*-2-(2-hydroxyphenyl)-cinnamic acid or both *E*- and *Z*-2-(2-hydroxynaphthyl)cinnamic acid, are reported. These molecules display a restricted rotation about the C_2–C_{aryl} bond. The barriers to rotation about the C_2–C_{aryl} bond were measured by the dynamic ^{1}H NMR and were found to vary between 11.8 and 24.5 kcal mol^{-1}, depending on the substitution. In particular, *E*-2-(2-hydroxynapthyl)cinnamic amides, displayed a high barrier to rotation ($\Delta G_c^{\ddagger}$=24.4 kcal mol^{-1}) and could be isolated in both diastereomerically pure forms at room temperature. The X-ray structure of one *E*-2-(2-hydroxynapthyl)cinnamic amide, was resolved, enabling for the determination of the absolute configuration of the chiral axis (a*R*).

1. Introduction

Axial chirality represents one of the most interesting stereochemical features of modern synthetic chemistry. Axially chiral molecules are often used as versatile auxiliaries or as ligands in transition-metal promoted asymmetric synthesis,[1] and nature offers a large number of representatives of this class of compounds, with, in many cases, interesting pharmacological activities.[2] Axial chirality is often associated with atropisomerism and atropisomers, i.e., with the stereoisomers resulting from hindered rotation about single bonds, where the barrier to rotation is high enough to allow for the isolation of the conformers. The condition for the existence of atropisomerism has been defined as one where stereoisomers can be isolated and have a half-life of at least 1000 s.[3] The most extensively studied class of atropisomers is biaryls,[4] especially with respect to the substitution required for restricted rotation. Reported examples of other classes of atropisomeric molecules include: substituted styrenes,[5] axially chiral amides (e.g., anilides,[6] benzamides[7] and 1-naphthamides[8]), *o*-substituted arylcarbinols of the Ar–C(OH)R_2 type,[9] 5,6-disubstituted-3,4-dihydro-1*H*-pyridin-2-ones,[10] *o*-substituted *N*-aryl-4-alkyl-thiazoline-2-thiones[11] and substituted *N*-(2-hydroxynaphthalen-1yl)-*N*,*N*′-diacyl-hydrazines.[12]

As a part of the project aimed at synthesizing new chiral structures to be used as ligands in catalytic asymmetric applications, we decided to investigate the chiral 2-(2-hydroxyaryl)cinnamic amides **1** (Fig. 1), obtained from the coupling of the corresponding 2-(2-hydroxyaryl) cinnamic acids and a chiral primary amine. These molecules were chosen since they possess several potential sites of diversity (R^1, R^2, R^3 and Ar), which allow for the fine-tuning of their steric, electronic and conformational properties. In addition, we were also intrigued by the fact that they were structurally reminiscent of biaryl compounds and might display restricted rotation about the C_2–C_{aryl} bond and, depending on the energetic barrier to rotation, be resolved into two diastereomeric atropisomeric forms.

Herein we report the syntheses of several differently substituted amides of general type **1** (Fig. 1) derived from 2-(2-hydroxyphenyl)cinnamic and 2-(2-hydroxynaphthyl)-cinnamic acid. The barriers to rotation about the C_2–C_{aryl} bond were experimentally determined for both the phenyl and naphthyl derivatives by dynamic ^{1}H NMR methods

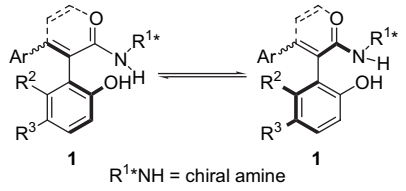

Figure 1. General structure and atropisomeric behaviour of amides **1**, and their similarity to biaryl compounds (dashed lines).

Keywords: Axial chirality; Cinnamic acid; Atropisomerism.
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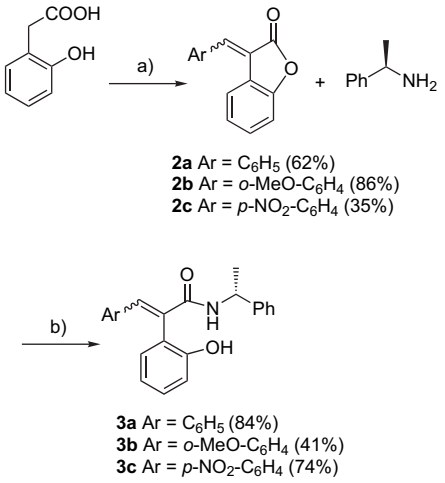
and were found to be significantly lower than those observed in biaryls bearing similar substitution pattern. In particular, *E*-2-(2-hydroxynapthyl)cinnamic amides, displayed a high barrier to rotation ($\Delta G_c^{\ddagger}$>24.4 kcal mol^{-1}) and both diastereomerically pure forms could be isolated at room temperature. The X-ray structure of one *E*-2-(2-hydroxynapthyl)cinnamic amide, was determined and the absolute configuration of the chiral axis assigned.

2. Results and discussion

The syntheses of 2-(2-hydroxyphenyl)cinnamic amides **3** were performed using 2-hydroxyphenylacetic acid, as a starting material, which was converted into lactones **2a–c** (Scheme 1 and Table 1), through a Perkin condensation with different aromatic aldehydes.[13]



Scheme 1. (a) AcONa (1 equiv), ArCHO (1 equiv), Ac_2O, reflux, 6 h and (b) (*R*)-1-phenylethylamine (2 equiv), 2-hydroxypyridine (0.2 equiv), THF, rt, 72 h.

Single-crystals of lactone *E*-**2a** (Ar=Ph) suitable for an X-ray data collection were obtained from a saturated solution of AcOEt/hexane. In the solid state, the fused rings of lactone *E*-**2a** show a very limited deviation from coplanarity, with a τ_1 torsional angle (Fig. 2) of less than 5°. A more pronounced deviation from planarity is observed at torsion τ_2 (Fig. 2), reaching a value of about 12°.

The opening of lactones **2** was then performed, using (*R*)-1-phenylethylamine. Simple aminolysis of lactone **2a** in several solvents (DCM, toluene, THF) almost led to the exclusive formation of 2-hydroxy phenylacetamide **4** [R=(*R*)-1-phenylethylamine], probably through a tandem Michael retro–Mannich sequence (Scheme 2).

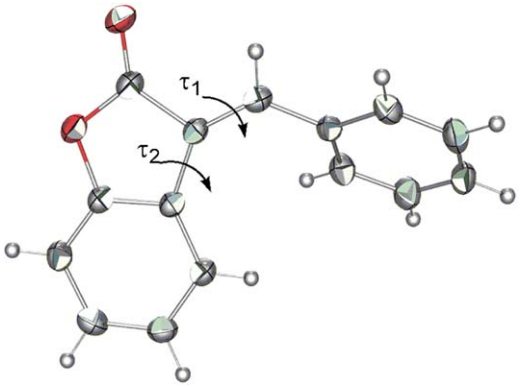
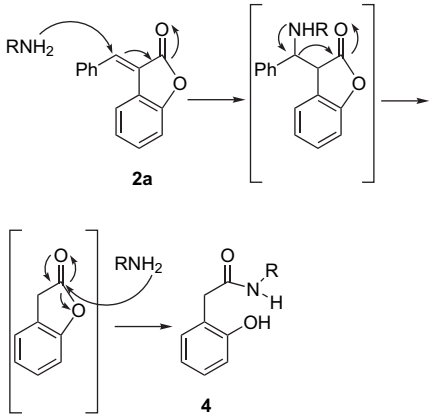


Figure 2. Ortep representation (30% probability level) of the X-ray molecular structure of lactone *E*-**2a**. Carbon, grey; hydrogen, light grey; oxygen, red.



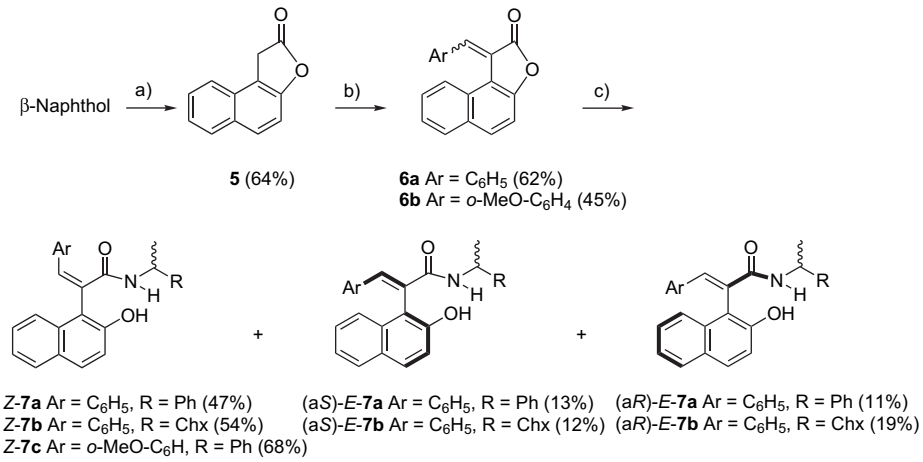
Scheme 2. Proposed mechanism for the reaction of lactone **2** with amines.

In order to favour the opening of lactone **2** with respect to the Michael addition, which is the first step of the tandem conjugate addition retro-Mannich sequence, 2-hydroxypyridine was employed as a proton transfer catalyst.[14] Under these conditions, good yields of amides **3** were obtained as separable mixtures of *E* and *Z* isomers (Table 1).

2-(2-Hydroxynaphthyl)cinnamic amides **7** were prepared starting from β-naphthol (Scheme 3), which was transformed into lactone **5**,[15] and then subjected to Perkin condensation using several aromatic aldehydes. Lactones **6** were obtained as mixtures of *E* and *Z* isomers (Table 1). X-ray quality crystals of lactone *E*-**6a** (Ar=Ph) were obtained from a saturated solution of AcOEt/hexane. The solid state molecular structure of lactone *E*-**6a** is substantially similar to that of *E*-**2a**, with the notable exception of an enhanced deviation from co-planarity, the τ_1 between the naphtholic aromatic ring and the exocyclic double bond being

Table 1. Synthesis of lactones **2** and **5**, and amides **3** and **7**

Entry	Ar	Lactone	Yield (%)	*E*/*Z*	R	*R*/*S*	Amide	Yield (%)	*E*/*Z*	a*S*/a*R*
1	C_6H_5	**2a**	62	85/15	Ph	*R*	**3a**	84	75/25	—
2	*o*-MeO–C_6H_4	**2b**	86	100/0	Ph	*R*	**3b**	41	100/0	—
3	*p*-NO_2–C_6H_4	**2c**	35	100/0	Ph	*R*	**3c**	74	76/24	—
4	C_6H_5	**6a**	62	25/75	Ph	*R*	**7a**	71	34/66	1.2/1
5	C_6H_5	**6a**	62	25/75	Chx	*S*	**7b**	88	39/61	1/1.3
6	*o*-MeO–C_6H_4	**6b**	45	0/100	Ph	*R*	**7c**	68	0/100	—



Scheme 3. (a) Glyoxal (7 equiv), KOH (1 equiv), H_2O, 30 °C, 4.5 h; (b) AcONa (1 equiv), RCHO (1 equiv), Ac_2O, reflux, 6 h and (c) *n*BuLi (3 equiv), $RCH(CH_3)NH_2$ (2.5 equiv), THF, rt, 1 h, −40 °C, **6** (1 equiv), 2 h.

about 26°. At variance, the τ_2 dihedral angle is only marginally lowered to ca. 10°. Attempts to open lactones **6** by reaction with amines in various solvents and in the presence of 2-hydroxypyridine met with limited success and the major isolated products were the 2-hydroxynaphthylacetamides derived from the conjugate addition retro-Mannich mechanism described above. To overcome this problem, we reasoned that the hardness of the amine nucleophile had to be increased, in order to favour the attack to the carbonyl of the lactone with respect to the Michael addition.

This was achieved by first deprotonating the amines, (*R*)-1-phenylethylamine or (*S*)-1-ethylcyclohexylamine, with *n*BuLi and then adding the lithium amide solution to a cold solution of the lactone (Scheme 3). In this way, no 2-hydroxynaphthylacetamide was detected, and good yields of amides **7** were obtained as separable mixtures of one *Z* isomer and two atropisomeric *E* isomers (Table 1 and Scheme 3). X-ray quality crystals of amide a*R*-*E*-**7a** (Ar=Ph and R=Ph) were obtained from a saturated solution of AcOEt/hexane. The solid state structure of amide a*R*-*E*-**7a** shows that, in the crystal, the molecule adopts a staggered conformation with a dihedral angle of ca. 89° between the naphtholic ring and the unsaturated amide plane (Fig. 3). The absolute configuration of the chiral axis, based on the fixed stereocenter of (*R*)-1-phenylethylamine, resulted to be a*R*.

Circular dichroism (CD) curves were measured for compounds a*R*-*E*-**7a** and a*S*-*E*-**7b** (Fig. 4): two nearly mirror image curves were obtained for the two compounds. In the case of a*R*-*E*-**7a**, an intense positive band at 228 nm ($\Delta\varepsilon$ +14), a negative band at 264 mn ($\Delta\varepsilon$ −8) and a weak positive band at 333 nm ($\Delta\varepsilon$ +1.7), were observed. In particular the exciton band at about 228 nm has been attributed to the long axis polarized ^1B_b transition of naphthalene,[16] while the band at 264 nm is probably due to the absorption of the cinnamic moiety.[17] These two chromophores are oriented perpendicularly to each other and can be described as two interacting orthogonal dipoles. The strong positive–negative exciton is in agreement with a positive helicity[18] and with the a*R* absolute configuration of the chiral axis, as shown also by the X-ray molecular structure. A negative band at 228 nm ($\Delta\varepsilon$ −6), a positive band at 262 mn ($\Delta\varepsilon$ +3) and a weak negative band at 335 nm ($\Delta\varepsilon$ −0.6), were observed for a*S*-*E*-**7b**. In this case a negative–positive exciton is indicative of a negative helicity and of the a*S* configuration of the chiral axis.

A study of the barrier to rotation about the C_2–C_{aryl} bond was then undertaken for all the amides synthesized. Kinetic data

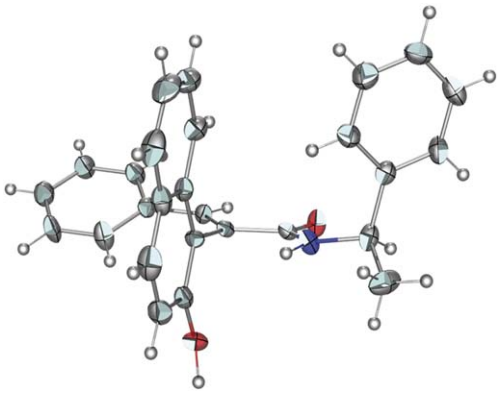


Figure 3. Ortep representation (30% probability level) of the X-ray molecular structure in amide a*R*-*E*-**7a**. Carbon, grey; hydrogen, light grey; nitrogen, blue; oxygen, red.

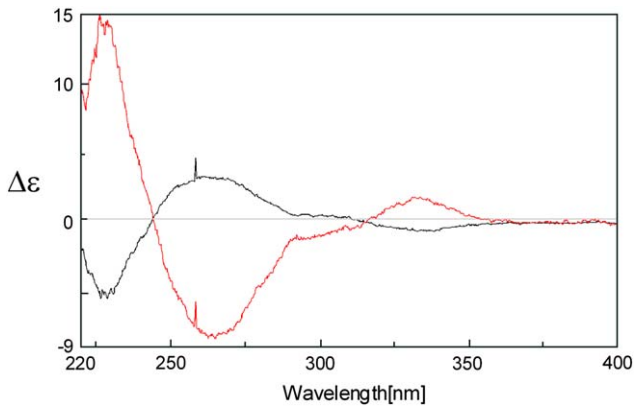


Figure 4. CD spectra of a*R*-*E*-**7a** (red curve) and a*S*-*E*-**7b** (black curve) showing nearly enantiomeric behaviour.

Table 2. Coalescence temperature and activation parameters of the configurationally unstable amides **3a–c** and *Z*-**7a–c**

Entry	Amide	T_c (K)	k_c (s^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})
1	**3a**	243	120.6	11.8
2	**3b**	245	72.5	12.2
3	**3c**	248	96.7	12.2
4	*Z*-**7a**	298	88.4	14.8
5	*Z*-**7b**	303	48.3	15.3
6	*Z*-**7c**	303	193.6	14.6

and energy barriers of interconversion of configurationally labile compounds have been conveniently investigated, among others, by means of dynamic NMR.[19] The free energy barriers to internal rotation in the phenol-substituted amides **3a–c** and *Z*-**7a–c** were estimated from their variable temperature ^{1}H NMR spectra by measuring the coalescence temperature of the N–H signal (Table 2). The rate constants k_c were calculated from the relationship $k_c=\pi\Delta\nu/\sqrt{2}$, and the free energies of activation ($\Delta G_c^{\ddagger}$) were derived by substituting k_c into the Eyring equation.[19]

For amides **3a–c**, the NMR experiments were run in CD_2Cl_2 and, as a general trend, the signals are well resolved at 298 K, broaden in the 253–233 K range and split below 233 K yielding two sets of signals (Fig. 5). The values for $\Delta G_c^{\ddagger}$ are less than 12.2 kcal mol^{-1} (Table 2, entries 1–3) and are in agreement with the free rotation of the two substituents about the chiral axis at room temperature. For amides *Z*-**7a–c**, the NMR experiments were performed in $CDCl_3$ and the coalescence is observed near room temperature, with a single set of well resolved signals above 313 K and two completely resolved sets of signals below 243 K (Fig. 4). The $\Delta G_c^{\ddagger}$ are comprised between 14.6 and 15.3 kcal mol^{-1} (Table 2, entries 4–6).

The barriers to rotation for amides *E*-**7a–b** were also investigated. In this case, in variable temperature ^{1}H NMR studies, the coalescence temperature was not reached even upon heating a DMSO-d_6 sample to 413 K. The atropisomers are stable enough to be isolated at room temperature, although it was noticed that both diastereomerically pure atropisomers slowly equilibrated to a 1/1 mixture of the a*R* and a*S* atropisomers, upon standing in solution (24 h in $CDCl_3$) at room temperature. The transformation

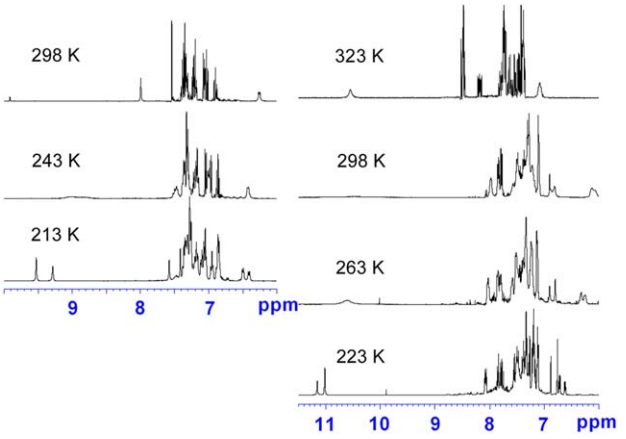


Figure 5. Variable temperature ^{1}H NMR spectra of amides **3a** (left) and *Z*-**7a**.

Table 3. Activation parameters of amides (a*R*)-*E*-**7a–b** in $CDCl_3$ at 298 K

Entry	Compound	k_c (s^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})
1	(a*R*)-*E*-**7a**	6.40×10^6	24.4
2	(a*R*)-*E*-**7b**	7.85×10^6	24.5

rates of (a*R*)-*E*-**7a** and (a*R*)-*E*-**7b** were followed at 298 K, by monitoring the time-dependent first-order variation of the relative intensities of the ^{1}H NMR spectra in $CDCl_3$. The Eyring equation was used to derive the $\Delta G_c^{\ddagger}$ values from the rate constants k_c (Table 3).

When comparing the values of the barrier to rotation for compounds **3a–c** and *Z*-**7a–c** to those observed for 2,2′,6 trisubstituted biphenyls[20] and 1,1′,10 trisubstituted-2,2′-binaphthyls[21] (actually, both amides **3a–c** and *Z*-**7a–c** are reminiscent of a trisubstituted biaryl chiral axis, see Fig. 1), it can be noted that the former are significantly lower. A similar behaviour is found in amides *E*-**7a–b** with respect to tetrasubstituted biaryl moieties. In fact, slowly interconverting atropisomeric biaryls have been observed, particularly, when associated to 2,2′,6 trisubstituted biphenyls, and 1,1′,10 trisubstituted-2,2′-binaphthyls, depending on the size of the substituents, but in general tetrasubstituted biarlys are configurationally stable compounds. In the case of our 2-(2-hydroxyaryl)cinnamic amides, the rather low barrier to rotation and the relatively fast atropisomerization process can be explained assuming that, in the lower energy transition state for rotation, the carboxamide moiety is not coplanar with the double bond, thus facilitating the rotation about the C_2–C_{aryl} bond.[22]

3. Conclusions

The syntheses of several differently substituted chiral amides formally derived from a chiral amine, either *E*-2-(2-hydroxyphenyl)cinnamic acid (**3a–c**) or both *E*- and *Z*-2-(2-hydroxynaphthyl)cinnamic acid (**7a–c**), are reported. These molecules display a restricted rotation about the C_2–C_{aryl} bond and, depending on their barrier to rotation, can be isolated in two atropisomeric forms. The barriers to rotation about the C_2–C_{aryl} were measured by dynamic ^{1}H NMR and were found to vary between 11.8 and 24.5 kcal mol^{-1}, depending on the substitution. In particular, *E*-2-(2-hydroxynapthyl)cinnamic amides **7** displayed a high barrier to rotation ($\Delta G_c^{\ddagger}>24.4$ kcal mol^{-1}) and could be isolated in both diastereomerically pure forms at room temperature. The X-ray structure of one *E*-2-(2-hydroxynapthyl)cinnamic amide, (a*R*)-*E*-**7a**, was resolved, allowing the determination of the absolute configuration of the chiral axis. The application of these new chiral structures as chiral organic catalysts and ligands for enantioselective metal catalyzed reactions is now actively being investigated in our laboratories.

4. Experimental

4.1. General

All manipulations requiring anhydrous conditions were carried out in flame-dried glassware, with magnetic stirring, and

under an atmosphere of purified nitrogen. All aldehydes were distilled before use. All other commercially available reagents were used as received. Anhydrous solvents were purchased from commercial sources and withdrawn from the container by syringe, under a slightly positive pressure of nitrogen. Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a permanganate solution. Flash column chromatography was performed using silica gel 60 A, particle size 40–64 μm, following the procedure by Still and co-workers.[23] Melting points are uncorrected. Proton NMR spectra were recorded on a 400 MHz spectrometer. Proton chemical shifts are reported in parts per million (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as an internal standard ($CDCl_3$ δ 7.26 ppm). Carbon NMR spectra were recorded on a 400 spectrometer operating at 100.56 MHz, with complete proton decoupling. Carbon chemical shifts are reported in parts per million (δ) with the solvent reference relative to (TMS) employed as an internal standard ($CDCl_3$ δ 77.0 ppm). Infrared spectra were recorded on a standard Infrared spectrophotometer; peaks are reported in cm^{-1}. Optical rotation values were measured on an automatic polarimeter with 1-dm cell at the sodium D line. CHN-analyses were performed using a Perkin Elmer 2400 Series II CHNS/O Analyzer. CD spectra were recorded at 298 K on a Jasco J-500C spectropolarimeter, in acetonitrile, in a 0.01-cm cell in the range 220–400 nm.

4.1.1. 3-[1-Phenyl-meth-(*E*)-ylidene]-3*H*-benzofuran-2-one (2a). $NaHCO_3$ (1 equiv, 32.9 mmol, 2.80 g) was dissolved in 50 mL of water. 2-Hydroxyphenylacetic acid (1 equiv, 32.9 mmol, 5 g) was added to the mixture to obtain a yellow solution. The system was stirred vigorously and warmed at 50 °C for 2 h. The solvent was evaporated under reduced pressure affording a white solid and the last traces of water were azeotropically removed by evaporation with toluene (2×30 mL) and drying under vacuum. Sodium 2-hydroxyphenylacetate (5.60 g, 32.0 mmol) was treated with benzaldehyde (3.4 mL, 33.6 mmol) and acetic anhydride (13 mL) at reflux temperature for 6 h. The hot mixture was then added to water and stirred vigorously overnight. HCl concentrated was added and the mixture was warmed at 60 °C for 5 h. The product was then extracted with toluene and successively precipitated with petroleum ether at −15 °C affording the lactone **2a** as an orange solid (2.14 g, 62% yield), mp=88 °C. IR (nujol): ν_{max}=1782, 1769, 1629, 1607, 1293, 1240, 1148, 1121, 1082, 1080, 1022, 967, 932, 877, 757, 754, 732, 703; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.90 (s, 1H, C*H*), 7.75 (d, J=7.7 Hz, 1H, Ar*H*), 7.69–7.72 (m, 2H, Ar*H*), 7.48–7.54 (m, 3H, Ar*H*), 7.37 (dddd, J_1=8.1 Hz, J_2=7.3 Hz, J_3=1.2 Hz, J_4=1.2 Hz, 1H, Ar*H*), 7.16 (d, J=8.1 Hz, 1H, Ar*H*), 7.06 (dd, J_1=7.8 Hz, J_2=7.5 Hz, 1H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ=169.2, 154.9, 141.3, 134.4, 131.4, 131.0, 129.8, 129.3, 124.1, 123.2, 122.6, 122.2, 111.6; $C_{15}H_{10}O_2$ calcd. C 81.07, H 4.54; found: C 79.96, H 4.46.

X-ray crystallographic data of ***2a***. Orthorhombic, space group *Pcab*, a=9.855(1), b=12.208(2), c=18.268(3) Å, V=2197.8(6) Å^3, Z=8, ρ=1.343 g/cm^3, μ(Mo Kα)=0.09 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares, with final R and wR values of 0.047 for 1171 reflections with $I>2\sigma I$, and 0.111 for 1928 reflections, respectively. All the crystallographic data presented in the manuscript (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 602856. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk].

4.1.2. 3-[1-(2-Methoxy-phenyl)-meth-(*E*)-ylidene]-3*H*-benzofuran-2-one (2b). 2-Hydroxyphenylacetic acid (1 equiv, 9.85 mmol, 1.50 g) was treated with sodium acetate (1 equiv, 9.85 mmol, 1.35 g), 2-methoxy-benzaldehyde (1 equiv, 9.85 mmol, 1.35 mL) and acetic anhydride (7 mL) at reflux temperature for 6 h. Water (70 mL) was then added to the hot mixture followed by vigorous stirring overnight. Concentrated HCl (10 mL) was added and the mixture was warmed at 60 °C for 5 h. The product was then extracted with toluene and the organic phase was successively washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was then purified by flash chromatography on silica gel (CH_2Cl_2/hexane=75/25) affording the desired product as a yellow solid (2.13 g, 86% yield), mp=123 °C. IR (Nujol): ν_{max}=1782, 1723, 1634, 1594, 1316, 1295, 1255, 1165, 1126, 1075, 1021, 967, 876, 773, 745; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07 (s, 1H, C*H*), 7.76 (d, J=7.6 Hz, 1H, Ar*H*), 7.65 (d, J=7.7 Hz, 1H, Ar*H*), 7.49 (dd, J_1=7.8 Hz, J_2=7.9 Hz, 1H, Ar*H*), 7.33 (dd, J_1=7.8 Hz, J_2=7.8 Hz, 1H, Ar*H*), 7.13 (d, J=8.1 Hz, 1H, Ar*H*), 7.01–7.09 (m, 3H, Ar*H*), 3.91 (s, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ=169.4, 158.7, 154.7, 137.8, 132.9, 130.9, 130.0, 123.9, 123.5, 123.1, 122.7, 122.1, 120.6, 111.5, 111.4, 56.0; $C_{16}H_{12}O_3$ calcd. C 76.19, H 4.76; found: C 76.07, H 4.57.

4.1.3. 3-[1-(4-Nitro-phenyl)-meth-(*E*)-ylidene]-3*H*-benzofuran-2-one (2c). 2-Hydroxyphenylacetic acid (1 equiv, 9.85 mmol, 1.5 g) was treated with sodium acetate (1 equiv, 9.85 mmol, 1.35 g), 4-nitro-benzaldehyde (1 equiv, 9.85 mmol, 1.50 mL) and acetic anhydride (7 mL) at reflux temperature for 6 h. The hot mixture was then poured into water (70 mL) and stirred vigorously overnight. Concentrated HCl (10 mL) was added and the mixture was warmed at 60 °C for 5 h. The product was then extracted with toluene and the organic phase was successively washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was then purified by flash chromatography on silica gel (hexane/AcOEt=70/30) affording the desired product as a yellow solid (0.92 g, 35% yield), mp=189 °C. IR (Nujol): ν_{max}=1780, 1613, 1588, 1524, 1515, 1343, 1319, 1239, 1145, 1123, 1079, 880, 774, 751, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.38 (d, J=8.5 Hz, 2H, Ar*H*), 7.86 (s, 1H, C*H*), 7.85 (d, J=8.2 Hz, 2H, Ar*H*), 7.57 (d, J=7.7 Hz, 1H, Ar*H*), 7.43 (dd, J_1=8.0 Hz, J_2=7.7 Hz, 1H, Ar*H*), 7.19 (d, J=8.0 Hz, 1H, Ar*H*), 7.08 (dd, J_1=7.7 Hz, J_2=7.7 Hz, 1H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ=168.3, 155.5, 148.8, 140.9, 137.2, 132.6, 131.8, 130.4, 124.6, 124.4, 123.3, 121.4, 112.1;

$C_{15}H_9NO_4$ calcd C 67.41, H 3.37, N 5.24; found: C 67.23, H 3.25, N 5.14.

4.2. General procedure for the synthesis of 2-(2-hydroxyphenyl)cinnamic amides

A solution of lactone (1 equiv, 1.35 mmol), (*R*)-1-phenylethylamine (2 equiv, 2.70 mmol, 350 μL) and 2-hydroxypyridine (0.2 equiv, 0.27 mmol, 28 mg) in THF (24 mL) was stirred at room temperature for 3 d. The reaction mixture was then hydrolyzed with HCl 1 M and extracted with AcOEt (12×3 mL). The combined organic layers were washed with brine and then dried over Na_2SO_4. After evaporation of the solvent in vacuo, the crude product was purified by flash chromatography on silica gel.

4.2.1. (*E*)-2-(2-Hydroxy-phenyl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (3a). Pale orange solid (0.29 g, 63% yield). IR (Nujol): ν_{max}=3397, 1644, 1612, 1595, 1514, 1293, 1247, 1234, 1015, 937, 750, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.74 (s, 1H, C*H*), 7.31–7.35 (m, 3H, Ar*H*), 7.24–7.27 (m, 3H, Ar*H*), 7.13–7.21 (m, 3H, Ar*H*), 7.03–7.10 (m, 4H, Ar*H*), 6.90–6.95 (m, 1H, Ar*H*), 6.20 (d, *J*=7.9 Hz, 1H, N*H*), 5.18 (m, 1H, C*H*), 1.44 (d, *J*=6.9 Hz, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ=168.2, 154.9, 143.2, 139.0, 134.7, 131.3, 131.1, 130.5, 129.4, 129.1, 128.7, 127.9, 127.8, 126.3, 122.3, 121.6, 117.9, 49.8, 22.3; $[\alpha]_D$ −25.6 (*c* 0.50, $CHCl_3$); $C_{23}H_{21}NO_2$ calcd C 80.19, H 7.01, N 3.90; found: C 79.80, H 6.87, N 3.96.

4.2.2. (*E*)-2-(2-Hydroxy-phenyl)-3-(2-methoxy-phenyl)-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (3b). Yellow solid (0.06 g, 41% yield), mp=125 °C. IR (Nujol): ν_{max}=3410, 3402, 3125, 1653, 1600, 1522, 1292, 1252, 1163, 1105, 1024, 759, 750, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.88 (s, 1H, C*H*), 7.23–7.37 (m, 6H, Ar*H*), 7.18 (dd, J_1=7.8 Hz, J_2=7.8 Hz, 1H, Ar*H*), 7.02 (d, *J*=8.2 Hz, 1H, Ar*H*), 6.96 (d, *J*=7.6 Hz, 1H, Ar*H*), 6.84–6.75 (m, 3H, Ar*H*), 6.62 (dd, J_1=7.5 Hz, J_2=7.5 Hz, 1H, Ar*H*), 6.28 (d, *J*=7.8 Hz, 1H, N*H*), 5.26–5.19 (m, 1H, C*H*), 1.51 (d, *J*=6.9 Hz, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ=169.3, 158.2, 155.2, 143.2, 133.7, 132.8, 131.2, 130.8, 130.5, 130.3, 129.1, 127.8, 126.5, 123.8, 122.7, 121.0, 120.7, 117.9, 110.8, 55.8, 49.8, 22.2; $[\alpha]_D$ −10.1 (*c* 0.11, $CHCl_3$); $C_{24}H_{23}NO_3$ calcd C 77.21, H 6.17, N 3.75; found: C 76.87, H 6.16, N 3.65.

4.2.3. (*E*)-2-(2-Hydroxy-phenyl)-3-(4-nitro-phenyl)-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (3c). Yellow solid (0.07 g, 56% yield), mp=70 °C. IR (Nujol): ν_{max}=3404, 3240, 1651, 1614, 1599, 1518, 1343, 1289, 1109, 1043, 1014, 852, 833, 758, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (br s, 1H, O*H*), 7.96 (d, *J*=8.4 Hz, 2H, Ar*H*), 7.65 (s, 1H, C*H*), 7.25–7.35 (m, 6H, Ar*H*), 7.14 (d, *J*=8.3 Hz, 2H, Ar*H*), 7.06 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.86–6.94 (m, 2H, Ar*H*), 6.28 (d, *J*=7.9 Hz, 1H, N*H*), 5.14–5.21 (m, 1H, C*H*), 1.46 (d, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ=167.8, 155.0, 147.6, 142.8, 141.6, 136.3, 135.6, 131.7, 130.9, 130.8, 130.0, 129.2, 127.9, 126.3, 123.8, 121.7, 121.4, 118.2, 50.0, 22.1; $[\alpha]_D$ −15.5 (*c* 0.15, $CHCl_3$); $C_{23}H_{20}N_2O_4$ calcd C 71.13, H 5.15, N 7.22; found: C 70.84, H 5.06, N 7.03.

4.3. 1*H*-Naphtho[2,1-*b*]furan-2-one (5)

The compound was prepared following a literature procedure.[14] The analytical data were in agreement with those reported.

4.4. 1-[1-Phenyl-meth-(*E*)-ylidene]-1*H*-naphtho[2,1-*b*]-furan-2-one + 1-[1-phenyl-meth-(*Z*)-ylidene]-1*H*-naphtho[2,1-*b*]furan-2-one (6a)

1*H*-Naphtho[2,1-*b*]furan-2-one (1 equiv, 10.15 mmol, 1.87 g) was treated with sodium acetate (1 equiv, 10.15 mmol, 1.38 g), benzaldehyde (1 equiv, 10.15 mmol, 1.03 mL) and acetic anhydride (7 mL) at reflux temperature for 6 h. The hot mixture was added to water (120 mL) and stirred vigorously overnight. The mixture was then acidified with concentrated HCl (15 mL) keeping the system under magnetic stirring at 60 °C for 5 h. The reaction mixture was cooled and the product was extracted in toluene, drying the organic phase over Na_2SO_4. Evaporation of toluene gave the crude product, which was purified by flash chromatography on silica gel (hexane/AcOEt=8/2) affording the desired product as a yellow solid (1.68 g, 62% yield) and as a 1/3 mixture of *E* and *Z* diastereomers.

IR (Nujol): ν_{max}=1771, 1610, 1573, 1523, 1262, 1139, 1106, 987, 889, 853, 801, 765, 740, 688; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.37 (d, *J*=8.6 Hz, 1H, Ar*H*), 8.30 (s, 1H, C*H*), 8.09 (s, 1H, C*H*), 8.04–8.07 (m, 2H, Ar*H*), 7.95 (d, *J*=8.7 Hz, 2H, Ar*H*), 7.89 (d, *J*=8.8 Hz, 1H, Ar*H*), 7.86 (d, *J*=8.3 Hz, 1H, Ar*H*), 7.69 (ddd, J_1=7.6 Hz, J_2=7.1 Hz, J_3=1.3 Hz, 1H, Ar*H*), 7.35–7.53 (m, 12H, Ar*H*), 7.16 (ddd, J_1=7.8 Hz, J_2=7.7 Hz, J_3=1.1 Hz, 1H, Ar*H*), 6.99 (d, *J*=8.5 Hz, 1H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): 170.2, 155.0, 153.1, 143.1, 140.7, 135.7, 134.0, 133.6, 132.4, 131.9, 131.6, 131.5, 131.1, 130.7, 130.6, 129.8, 129.1, 128.7, 127.5, 127.2, 125.2, 125.1, 123.7, 123.1, 122.5, 112.1, 112.0; $C_{19}H_{12}O_2$ calcd C 83.82, H 4.41; found: C 83.46, H 4.34.

X-ray crystallographic data of ***6a***. Orthorhombic, space group *Pcab*, *a*=7.932(4), *b*=13.908(10), *c*=24.500(17) Å, *V*=2703(3) Å^3, *Z*=8, ρ=1.338 g/cm^3, μ(Mo Kα)=0.09 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares, with final *R* and *wR* values of 0.068 for 971 reflections with $I>2\sigma I$, and 0.145 for 2458 reflections, respectively. CCDC No. 602857.

4.5. 1-[1-(2-Methoxy-phenyl)-meth-(*E*)-ylidene]-1*H*-naphtho[2,1-*b*]furan-2-one (6b)

1*H*-Naphtho[2,1-*b*]furan-2-one (1 equiv, 4.54 mmol, 0.83 g) was treated with sodium acetate (1 equiv, 4.54 mmol, 0.37 g), 2-methoxy-benzaldehyde (1 equiv, 4.54 mmol, 0.62 g) and acetic anhydride (6 mL) at reflux temperature for 6 h. The hot mixture was added to water (120 mL) and stirred vigorously overnight. The mixture was then acidified with HCl (15 mL) keeping the system under magnetic stirring at 60 °C for 5 h. A brown precipitate was formed. The reaction mixture was cooled and the product was extracted in toluene, drying the organic phase over Na_2SO_4. Evaporation of toluene gave the crude product, which was purified by flash chromatography on silica gel (hexane/AcOEt=75/25)

affording the desired product as an orange solid (1.47 g, 45% yield).

Mp=157 °C. IR (Nujol): ν_{max}=1775, 1599, 1524, 1292, 1254, 1112, 1001, 1020, 973, 807, 780, 744; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.58 (s, 1H, Ar*H*), 8.38 (d, *J*=8.5 Hz, 1H, Ar*H*), 8.19 (d, *J*=7.7 Hz, 1H, Ar*H*), 7.92 (d, *J*=8.2 Hz, 1H, Ar*H*), 7.86 (d, *J*=8.7 Hz, 1H, Ar*H*), 7.67 (dd, J_1=7.4 Hz, J_2=7.9 Hz, 1H, Ar*H*), 7.52–7.45 (m, 2H, Ar*H*), 7.34 (d, *J*=8.7 Hz, 1H, Ar*H*), 7.08 (dd, J_1=7.6 Hz, J_2=7.6 Hz, 1H, Ar*H*), 6.99 (d, *J*=8.3 Hz, 1H, Ar*H*), 3.96 (s, 3H, C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$): δ=166.7, 158.6, 152.8, 141.5, 138.7, 132.9, 132.4, 131.9, 131.5, 130.5, 128.9, 128.7, 125.1, 123.0, 122.8, 120.5, 117.4, 112.0, 110.8, 56.1; $C_{20}H_{14}O_3$ calcd C 79.47, H 4.63; found: C 79.44, H 4.50.

4.6. 2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (7a)

*n*BuLi (1.6 M in hexanes 4.31 mL, 6.90 mmol) was slowly added to a solution of (*R*)-1-phenylethylamine (0.742 mL, 5.75 mmol) in anhydrous tetrahydrofuran (14 mL), in a Schlenk tube, under nitrogen, at 0 °C. After stirring for 1 h the mixture was cooled to −40 °C and lactone **6a** (626 mg, 2.30 mmol) was added. The reaction mixture was stirred at −40 °C for 2 h, quenched with 1 M HCl (42 mL) and extracted with AcOEt. The organic phase was washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography giving three pale yellow solids.

4.6.1. (*E*)-2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide [(a*R*)-*E*-7a]. 0.10 g, 11% yield, mp=180 °C. IR (Nujol): ν_{max}=3403, 3397, 3115, 1650, 1600, 1582, 1342, 1276, 1247, 1211, 1158, 1079, 992, 955, 821, 775, 751, 699, 692; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.30 (s, 1H, C*H*), 7.90 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.85–7.88 (m, 1H, Ar*H*), 7.60–7.63 (m, 1H, Ar*H*), 7.39–7.41 (m, 2H, Ar*H*), 7.29 (d, *J*=8.4 Hz, 1H, Ar*H*), 7.16–7.21 (m, 4H, Ar*H*), 6.97–7.10 (m, 6H, Ar*H*), 5.82 (d, *J*=7.8 Hz, 1H, N*H*), 5.15–5.20 (m, 1H, C*H*), 1.31 (d, *J*=6.9 Hz, 3H, C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$): δ=166.5, 151.8, 143.3, 142.4, 134.4, 132.8, 131.6, 130.2, 130.0, 129.6, 129.0, 128.9, 128.8, 128.0, 127.5, 126.8, 126.1, 124.6, 124.4, 118.6, 114.0, 49.6, 22.3; $[\alpha]_D$ −200.4 (*c* 0.15, $CHCl_3$); $C_{27}H_{23}NO_2$ calcd C 82.44, H 5.85, N 3.56; found: C 80.71, H 6.17, N 3.32.

*X-ray crystallographic data of (aR)-E-**7a***. Monoclinic, space group $P2_1$, *a*=10.014(6), *b*=10.129(3), *c*=21.348(15) Å, β=99.30(6)°, *V*=2137(2) Å^3, *Z*=4, ρ=1.223 g/cm^3, μ(Mo Kα)=0.08 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares, with final *R* and *wR* values of 0.063 for 2160 reflections with $I>2\sigma I$, and 0.117 for 4114 reflections, respectively. CCDC No. 602858.

4.6.2. (*E*)-2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide [(a*S*)-*E*-7a]. 0.12 g, 13% yield, mp=181 °C. IR (Nujol): ν_{max}=3399, 3150, 1651, 1593, 1576, 1537, 1516, 1504, 1342, 1285, 1246, 1209, 1141, 1080, 923, 955, 822, 766, 754, 692; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.32 (s, 1H, C*H*), 7.90 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.88 (d, *J*=7.7 Hz, 1H, Ar*H*), 7.69 (d, *J*=8.2 Hz, 1H, Ar*H*), 7.39–7.48 (m, 2H, Ar*H*), 7.00–7.29 (m, 11H, Ar*H*), 5.84 (d, *J*=7.8 Hz, 1H, N*H*), 5.13–5.21 (m, 1H, C*H*), 1.24 (d, *J*=6.9 Hz, 3H, C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$): δ=166.3, 151.8, 143.3, 142.5, 134.4, 132.8, 131.6, 130.3, 130.0, 129.7, 129.0, 128.9, 128.0, 127.6, 126.7, 126.2, 124.6, 124.2, 118.6, 114.0, 49.6, 22.1; $[\alpha]_D$ +93.2 (*c* 0.19, $CHCl_3$); $C_{27}H_{23}NO_2$ calcd C 82.44, H 5.85, N 3.56; found: C 80.71, H 6.17, N 3.32.

4.6.3. (*Z*)-2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (*Z*-7a). 0.43 g, 47% yield, mp=81 °C. IR (Nujol): ν_{max}=3320, 3056, 1618, 1512, 1510, 1260, 1232, 1225, 975, 950, 819, 751, 698; ^{1}H NMR (400 MHz, $CDCl_3$, 313 K): δ=7.99 (d, *J*=8.5 Hz, 1H, Ar*H*), 7.84 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.78 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.25–7.51 (m, 11H, Ar*H*), 7.09–7.11 (m, 2H, Ar*H*), 6.85 (s, 1H, C*H*), 6.05 (d, *J*=7.3 Hz, 1H, N*H*), 5.13–5.20 (m, 1H, C*H*), 1.39 (d, *J*=6.9 Hz, 3H, C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$, 313 K): δ=171.2, 153.9, 141.9, 138.1, 135.2, 133.4, 130.7, 129.8, 129.2, 129.1, 129.0, 128.9, 128.7, 128.0, 127.0, 123.7, 123.3, 120.4, 118.1, 50.0, 21.1; $[\alpha]_D$ −26.1 (*c* 0.15, $CHCl_3$); $C_{27}H_{23}NO_2$ calcd C 82.44, H 5.85, N 3.56; found: C 80.99, H 5.88, N 3.34.

4.7. *N*-((*S*)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide (7b)

*n*BuLi (1.6 M in hexanes 3.80 mL, 5.94 mmol) was slowly added to a solution of (*S*)-1-cyclohexyl-ethylamine (0.74 mL, 4.95 mmol) in anhydrous tetrahydrofuran, in a Schlenk tube, under nitrogen, at 0 °C. After stirring for 1 h the mixture was cooled to −40 °C and lactone **6a** (540 mg, 1.98 mmol) was added. The reaction mixture was stirred at −40 °C for 2 h, quenched with HCl 1 M (42 mL) and extracted with AcOEt. The organic phase was washed with brine and dried over Na_2SO_4. The product obtained was purified by flash chromatography giving three different pale yellow solids.

4.7.1. (*E*)-*N*-((*S*)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide [(a*R*)-*E*-7b]. 0.09 g, 15% yield, mp=70 °C. IR (Nujol): ν_{max}=3410, 3171, 1652, 1600, 1506, 1344, 1282, 1206, 958, 820, 749, 690, 668; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.30 (s, 1H, C*H*), 7.90 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.86 (d, *J*=7.6 Hz, 1H, Ar*H*), 7.64 (d, *J*=8.3 Hz, 1H, Ar*H*), 7.37–7.43 (m, 2H, Ar*H*), 7.29 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.02–7.15 (m, 5H, Ar*H*), 5.44 (d, *J*=8.9 Hz, 1H, N*H*), 3.85–3.95 (m, 1H, C*H*), 1.47–1.65 (m, 5H, Cy*H*), 1.01–1.16 (m, 4H, Cy*H*), 0.85–0.89 (m, 4H, C*H*$_3$), 0.62–0.71 (m, 1H, C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$): δ=166.5, 151.8, 141.9, 134.6, 132.8, 131.5, 130.2, 129.8, 129.6, 128.9, 128.8, 128.0, 127.1, 124.5, 124.2, 118.5, 114.3, 50.5, 43.1, 29.5, 28.9, 26.7, 26.4, 18.0; $[\alpha]_D$ −57.9 (*c* 0.39, $CHCl_3$); $C_{27}H_{29}NO_2$ calcd C 81.40, H 7.04, N 3.52; found: C 78.43, H 7.56, N 3.15.

4.7.2. (*E*)-*N*-((*S*)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide [(a*S*)-*E*-7b]. 0.07 g, 19% yield, mp=179 °C. IR (Nujol): ν_{max}=3399, 3227, 1652, 1605, 1595, 1511, 1351, 1246, 1205, 1143,

827, 749, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.31 (s, 1H, C*H*), 7.90 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.86 (d, *J*=7.9 Hz, 1H, Ar*H*), 7.67 (d, *J*=8.2 Hz, 1H, Ar*H*), 7.37–7.46 (m, 2H, Ar*H*), 7.27 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.16–7.21 (m, 1H, Ar*H*), 7.05–7.12 (m, 4H, Ar*H*), 6.04 (br s, 1H, O*H*), 5.36 (d, *J*=9.0 Hz, 1H, N*H*), 3.88–3.97 (m, 1H, C*H*), 1.48–1.60 (m, 3H, Cy*H*), 1.23–1.38 (m, 3H, Cy*H*), 0.68–1.10 (m, 7H, Cy*H*), 0.33–0.42 (m, 1H, Cy*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ=166.3, 151.5, 141.9, 134.5, 132.8, 131.5, 130.2, 129.9, 129.6, 129.0, 128.8, 127.9, 127.1, 124.6, 118.4, 114.2, 50.2, 43.3, 29.4, 28.3, 26.6, 26.4, 26.3, 18.2; $[\alpha]_D$ +154.8 (*c* 0.12, $CHCl_3$); $C_{27}H_{29}NO_2$ calcd C 81.40, H 7.04, N 3.52; found: C 78.43, H 7.56, N 3.15.

4.7.3. (*Z*)-*N*-((*S*)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide (*Z*-7b). 0.41 g, 54% yield, mp=168 °C. IR (Nujol): ν_{max}=3333, 3150, 1602, 1555, 1305, 1258, 1218, 1204, 1169, 1146, 1107, 1000, 919, 885, 819, 818, 753, 699, 639, 635; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.62 (br s, 1H, O*H*), 7.97 (d, *J*=8.4 Hz, 1H, Ar*H*), 7.84 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.78 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.50–7.56 (m, 3H, Ar*H*), 7.35–7.45 (m, 4H, Ar*H*), 7.29 (d, *J*=8.9 Hz, 1H, Ar*H*), 6.84 (s, 1H, C*H*), 5.60 (br s, 1H, N*H*), 3.78–3.90 (m, 1H, C*H*), 1.60–0.73 (m, 11H, Cy*H*), 0.93 (d, *J*=6.5 Hz, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ=171.6, 153.9, 137.7, 133.2, 130.3, 129.7, 129.2, 129.0, 128.9, 127.1, 125.0, 123.6, 123.3, 120.5, 117.5, 50.9, 43.0, 29.3, 29.2, 26.6, 26.4, 16.8; $[\alpha]_D$ +36.5 (*c* 0.20, $CHCl_3$); $C_{27}H_{29}NO_2$ calcd C 81.40, H 7.04, N 3.52; found: C 78.43, H 7.56, N 3.15.

4.8. (*E*)-2-(2-Hydroxy-naphthalen-1-yl)-3-(2-methoxy-phenyl)-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (*Z*-7c)

*n*BuLi (1.6 M in hexanes 0.62 mL, 0.99 mmol) was slowly added to a solution of (*R*)-1-phenylethylamine (0.107 mL, 0.83 mmol) in anhydrous tetrahydrofuran, in a Schlenk tube, under nitrogen, at 0 °C. After stirring for 1 h the mixture was cooled to −40 °C and lactone **6b** (100 mg, 0.33 mmol) was added. The reaction mixture was stirred at −40 °C for 2 h, quenched with HCl 1 M (7 mL) and extracted with AcOEt. The organic phase was washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography giving a greenish-yellow solid (0.10 g, 68% yield), mp=65 °C. IR (Nujol): ν_{max}=3406, 3292, 3061, 3031, 2974, 2931, 1665, 1617, 1602, 1538, 1510, 1463, 1336, 1250, 1114, 1026, 821, 753, 700, 623; ^{1}H NMR (400 MHz, $CDCl_3$, 313 K): δ=10.50 (br s, 1H, O*H*), 8.18 (d, *J*=8.4 Hz, 1H, Ar*H*), 7.81 (d, *J*=8.0 Hz, 1H, Ar*H*), 7.77 (d, *J*=8.9 Hz, 1H, Ar*H*), 6.85–7.61 (m, 13H, Ar*H*), 6.18 (br s, 1H, N*H*), 5.00–5.07 (m, 1H, C*H*), 3.83–3.90 (m, 3H, CH_3), 1.35–1.27 (m, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$, 313 K): δ=171.1, 157.3, 153.9, 135.2, 133.6, 130.2, 130.0, 129.7, 129.0, 128.7, 127.7, 126.8, 126.5, 124.2, 123.1, 121.5, 120.4, 111.2; $[\alpha]_D$ −31.7 (*c* 0.28, $CHCl_3$); $C_{28}H_{25}NO_3$ calcd C 79.43, H 5.91, N 3.31; found: C 78.51, H 5.95, N 3.16.

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Unusual sesquiterpene glucosides from *Amaranthus retroflexus*

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Abstract—Implementing the phytochemical study of the weed *Amaranthus retroflexus*, four new sesquiterpene glucosides were isolated from the methanolic extract of the plant. The structures of these metabolites are determined on the basis of the mass spectrometry, and 1D and 2D NMR spectroscopies (DQ-COSY, TOCSY, HSQC, HSQC–TOCSY, HMBC, and NOESY). Two compounds are characterized by a new aglycone and differed from the site of glucosylation. The other two compounds are dimeric diastereoisomers.
All the glucoside sesquiterpenes were tested on the wild species *Taraxacum officinale* to evaluate the role of this weed in the habitat and on the seed of *A. retroflexus* to verify the potential autotoxic effect of the plant.

1. Introduction

One of the most useful aspects of allelopathy in manipulated ecosystems is the role in agriculture.[1] Many plants have been studied and a number of new phytotoxic secondary metabolites have been isolated and characterized.[2,3] Recent investigations are focused on the effects of weeds on crops,[4] crops on weeds,[5] and crops on crops.[6] The goal of these studies is the use of allelochemicals as growth regulators and natural pesticides to promote sustainable agriculture.[7,8]

In the search for new allelochemicals from plants of the Mediterranean area, we recently studied the weed *Amaranthus retroflexus*, known as redroot pigweed, a summer annual invasive plant, widely distributed in Italy and commonly found in cultivated lands. From the methanolic extract of the plant, we isolated and characterized new free and glucosylated nerolidol sesquiterpenes, named amarantholidols and amarantholidosides, respectively.[9] These compounds, when tested on the cultivated species *Lactuca sativa*, showed a moderate phytotoxic activity down to 10^{-9} M.

In this work we completed the study of the organic extract and described the isolation and characterization of four new nerolidol glucosides, named amarantholidosides IV–VII. Two of them, in fact, showed an unusual dimeric structure.

The amarantholidosides I–VI have been tested on the wild species *Taraxacum officinale* to verify their impact on other weeds and on the seed of *A. retroflexus* to test their potential autotoxic effects.

2. Results and discussion

The EtOAc fraction of the MeOH fresh leaf extract of *A. retroflexus* L. was chromatographed on a silica gel column (flash chromatography) using $CHCl_3$–EtOAc and $CHCl_3$–MeOH mixtures as eluents in increasing polarity. The most polar fractions yielded seven compounds: four amarantholidols A–D and three amarantholidosides I–III (**1**–**3**).[9] Continuing the phytochemical study of the fraction we isolated four new glucosides **4**–**7**, of which two of them are dimeric (Figs. 1 and 2).

Compound **4**, named amarantholidoside IV, has been identified as (3*S*,6*E*,10*R*)-10-β-D-glucopyranosyloxy-3,11-dihydroxy-3,7,11-trimethyldodeca-1,6-diene.

Its molecular formula $C_{21}H_{38}O_8$ was deduced on the basis of its ESIMS spectrum, which showed the pseudomolecular peak at *m*/*z* 441 $[M+Na]^+$, and the elemental analysis.

The mass spectrum showed fragment ion at *m*/*z* 279 and 203, both diagnostic for the presence of a hexose moiety in the molecule. The ^1H NMR spectrum (Table 1) showed, in the downfield region, an ABX system as three double doublets centered at δ 5.91, 5.19, and 5.02, a partially overlapped signal at δ 5.21, and a double doublet at δ 3.40. The doublet at δ 4.44 (J=7.5 Hz) and two double doublets at δ 3.72 and

Keywords: *Amaranthus retroflexus*; Amaranthaceae; Nerolidol glucosides; Amarantholidosides; NMR analysis; Phytotoxic effect; Autotoxic effect; *Taraxacum officinale*.
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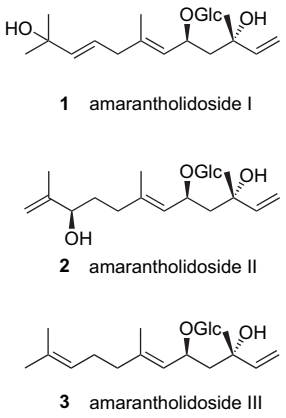

Figure 1. Structures of amarantholidosides I–III (**1**–**3**).

3.85 were in accordance with an anomer and a hydroxymethylene H-6 of a sugar moiety, respectively, while the chemical shift of six carbon signals in the ^{13}C NMR was in good agreement with a glucose unit. Accordingly, the HSQC–TOCSY experiment (Table 1) showed heterocorrelation between these glycidic carbons and the H-1′ and H-6′ protons ranging from 3.40 to 3.24 ppm. In the upfield region of the spectrum four singlet methyls at δ 1.60, 1.28, 1.17, and 1.13 and eight protons as multiplets were present.

A DQ-COSY experiment showed homocorrelations among the olefinic protons of the ABX system, the proton at δ 5.21 and a multiplet centered at δ 2.03, which correlated with a double doublet at δ 1.51. Among the protons bonded to oxygen atoms, correlations between the doublet at δ 4.44 and a signal at δ 3.27 as well as interactions among the double doublet at δ 3.40 and an overlapped signal centered at δ 1.45 were evident.

The ^{13}C NMR spectrum (Table 1) showed 21 signals confirming the presence of a glycosilated sesquiterpene. All of the carbons were identified, on the basis of a DEPT experiment, as four methyls, six methylenes, eight methines, and three tetrasubstituted carbons. Their chemical shifts indicated the presence of a terminal and an internal double bonds, a glucose moiety, and three carbinol groups (one of them secondary). All of the carbons were correlated to the respective protons using an HSQC experiment as reported in Table 1. In the same table, the results of an HMBC and HSQC–TOCSY have also been reported. These experiments were crucial for the structure elucidation. On the basis of these correlations, the carbinol carbon at δ 90.3, bonded to the proton at δ 3.40, was attributed to the C-10 carbon. Its downshift value could be explained by hypothesizing a linkage with the glucose. The heterocorrelations, in the HMBC experiment, between the carbon and the anomeric proton at δ 4.44 and, vice versa, between the anomeric carbon at δ 106.4 and the proton at δ 3.40 confirmed the hypothesis. The glucose moiety was confirmed by GC analysis and the coupling constant value of the anomeric proton in the ^{1}H NMR indicated the presence of a β-glucose.

The absolute configuration to the tertiary C-3 and secondary C-10 carbinol carbons has been assigned using two different methods. The *R* configuration at the C-10 carbon has been determined using a modified Mosher's method

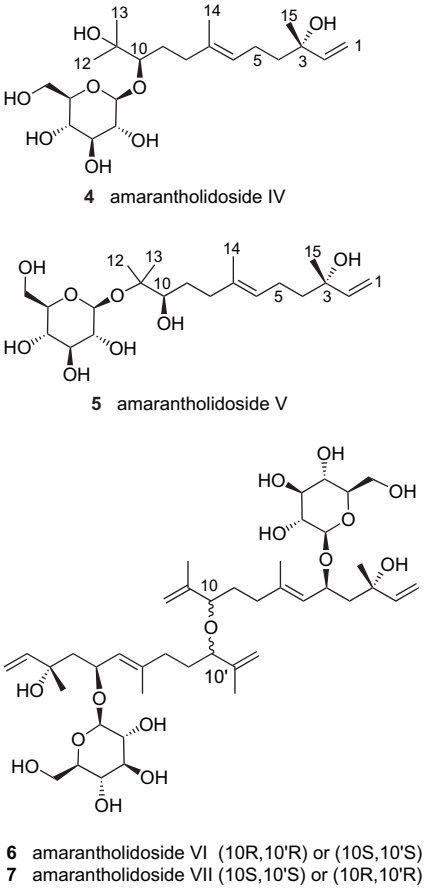

Figure 2. Structures of amarantholidosides IV–VII (**4**–**7**).

on the aglycone of amarantholidol IV obtained from treatment with β-glucosidase.[10,11] The positive and the negative $\Delta\delta_{R-S}$ values for the H-9, H-12, and H-15 protons were found, respectively, on the right and the left sides of the MTPA plane indicating a *R* configuration for C-10 carbon.

The *S* absolute configuration at the C-3 of compound **4** has been deduced using a bidentate NMR chiral solvent, as described by Kishi and co-workers.[12,13] The absolute configuration of acyclic alcohols was established from analysis of the chemical shifts' behaviors of the adjacent carbons in (*R*,*R*)- and (*S*,*S*)-bis-α-methylbenzylpropandiammine (BMBA-*p*). The positive (+0.121) and negative (−0.098) $\Delta\delta_{R-S}$ values of the amarantholidoside IV were found on the left and right of the tertiary carbinol carbon, respectively, according to an α-orientation for the hydroxyl and a β-orientation for the methyl.

Compound **5**, named amarantholidoside V, showed a molecular formula $C_{21}H_{38}O_8$ in accordance with its ESI mass spectrum, which showed the pseudomolecular peak at *m*/*z* 441 $[M+Na]^+$, and the elemental analysis. This data suggested that it was an isomer of compound **4**.

The ^{1}H NMR spectrum showed the vinyl protons at δ 5.91, 5.18, and 5.02, the H-6 olefin proton at δ 5.21, the methine H-10 at δ 3.43, two multiplets at δ 2.25 and 2.03, a double doublet at δ 1.50, three singlet methyls at δ 1.24, 1.22, and

Table 1. NMR data of amarantholidoside IV (**4**) in CD_3OD

	^1H (δ)	J (Hz)	DQ-COSY	^{13}C (δ)	DEPT	HMBC (H→C)	HSQC–TOCSY (H→C)
1t	5.19 dd	17.4, 1.5	1c, 2	112.0	CH_2	2	1, 2
1c	5.02 dd	10.8, 1.5	1t, 2			2, 3	1, 2
2	5.91 dd	17.4, 10.8	1c, 1t	146.3	CH	1, 3, 4, 15	1, 2
3	—	—	—	74.8	C	—	—
4	1.51 dd	9.3, 7.5	5	43.5	CH_2	2, 3, 5, 6, 15	4, 5, 6, 14
5	2.03 m	—	4, 6	23.7	CH_2	3, 4, 6, 7	4, 5, 6, 14
6	5.21 ov	—	5	126.1	CH	4, 5, 8, 14	4, 5, 6
7	—	—	—	136.0	C	—	—
8	2.30 m	—	9	37.0	CH_2	6, 7, 9, 10, 14	8, 9, 10
	2.25 m		9			6, 7, 9, 10, 14	8, 9, 10
9	1.45 m	—	8, 10	30.7	CH_2	7, 8	8, 9, 10
10	3.40 dd	10.5, 1.5	9	90.3	CH	glu1, 8, 9, 11, 12, 13	8, 9, 10
11	—	—	—	73.8	C	—	—
12	1.17 s	—	—	23.7	CH_3	10, 11, 13	—
13	1.13 s	—	—	26.4	CH_3	10, 11, 12	—
14	1.60 s	—	6	16.1	CH_3	6, 7, 8	—
15	1.28 s	—	—	27.6	CH_3	1, 2, 3, 4, 5	—
glu1	4.44 d	7.5	glu2	106.4	CH	10, glu2, glu3	glu1, glu2, glu3, glu4, glu6
glu2	3.27 ov	—	glu1, glu3	76.0	CH	glu1, glu3, glu4	glu1, glu2, glu3, glu4, glu6
glu3	3.27 ov	—	glu2, glu4	77.9	CH	glu1, glu2, glu4	glu1, glu2, glu3, glu4, glu6
glu4	3.37 ov	—	glu3, glu5	71.4	CH	glu5, glu6	glu2, glu3, glu4, glu6
glu5	3.37 ov	—	glu4, glu6	78.4	CH	glu6	glu2, glu3, glu4, glu6
glu6	3.72 dd	11.7, 2.1	glu5, glu6	62.6	CH_2	glu4, glu5	glu3, glu4, glu6
	3.85 dd	11.7, 5.7	glu5, glu6			glu4, glu5	glu3, glu4, glu6

d=doublet; dd=double doublet; m=multiplet; ov=overlapped; s=singlet.

1.21, and a doublet methyl at δ 1.60. In the same spectrum, the sugar signals were present as a doublet at δ 4.49 (glu1), two double doublets at δ 3.81 and 3.64 (glu6), and a double doublet at δ 3.15 (glu2) besides other signals obscured by the solvent signal.

The main differences observed in the ^{13}C NMR spectrum, when compared to amarantholidoside IV, are for C-10 and C-11 carbons (Table 2). The sugar moiety was in good accordance with the presence of a glucose and the J value of the H-glu1 proton suggested the presence of a β-anomer. The 2D NMR experiments confirmed the same aglycone of compound **4**. In the HMBC experiment, the signal at δ 81.8, assigned to the C-11 carbon, showed correlations with the anomeric proton at δ 4.49, the H-12 and H-13 methyls and with the H-10 double doublet, which itself correlates, in the HSQC experiment, to the carbon at δ 78.1. This latter carbon correlated with the H-9 protons at δ 1.35 and 2.20 and with the H-12 and H-13 methyls. This data led to the hypothesize of the presence of a linkage between the C-glu1 of

Table 2. NMR data of amarantholidoside V (**5**) in CD_3OD

	^1H (δ)	J (Hz)	DQ-COSY	^{13}C (δ)	DEPT	HMBC (H→C)	HSQC–TOCSY (H→C)
1t	5.18 dd	17.4, 1.5	1c, 2	112.0	CH_2	2, 3	1, 2
1c	5.02 dd	10.5, 1.5	1t, 2			2, 3	1, 2
2	5.91 dd	17.4, 10.5	1c, 1t	146.3	CH	1, 3, 4, 15	1, 2
3	—	—	—	73.8	C	—	—
4	1.50 dd	9.3, 7.5	5	43.5	CH_2	2, 3, 5, 6, 15	4, 5, 6, 14
5	2.03 m		4, 6	23.7	CH_2	4, 6, 7	4, 5, 6, 14
6	5.21 ov		5	126.0	CH	3, 5, 7, 8, 14	4, 5, 6
7	—	—	—	135.9	C	—	—
8	2.30 m	—	9	37.8	CH_2	6, 7, 9, 10, 14	8, 9, 10
	2.25 m		9			6, 7, 9, 10, 14	8, 9, 10
9	2.20 m	—	8, 10	30.7	CH_2	7, 8	8, 9, 10
	1.35 m						8, 9, 10
10	3.43 dd	10.5, 1.5	9	78.1	CH	8, 9, 11, 12, 13	8, 9, 10
11	—	—	—	81.8	C	glu1, 10, 12, 13	—
12	1.21 s	—		21.3	CH_3	10, 11, 13	
13	1.22 s	—		23.8	CH_3	10, 11, 12	
14	1.60 d	0.9	6	16.0	CH_3	6, 7, 8	
15	1.24 s	—		27.6	CH_3	1, 2, 3, 4, 5	
glu1	4.49 d	8.1	glu2	98.6	CH	11, glu2, glu3	glu1, glu2, glu3, glu4, glu6
glu2	3.15 dd	9.0, 7.5	glu1, glu3	75.1	CH	glu1, glu3, glu4	glu1, glu2, glu3, glu4, glu6
glu3	3.36 ov		glu2, glu4	77.7	CH	glu1, glu2, glu4	glu1, glu2, glu3, glu4, glu6
glu4	3.37 ov		glu3, glu5	71.6	CH	glu5, glu6	glu2, glu3, glu4, glu6
glu5	3.26 dt	9.0, 8.4	glu4, glu6	77.7	CH	glu6	glu2, glu3, glu4, glu6
glu6	3.64 dd	11.7, 5.1	glu5, glu6	62.6	CH_2	glu4, glu5	glu3, glu4, glu6
	3.81 dd	11.7, 2.1	glu5, glu6			glu4, glu5	glu3, glu4, glu6

d=doublet; dd=double doublet; m=multiplet; ov=overlapped; s=singlet.

the glucose and the C-11 of the aglycone. The NOEs observed, in an NOESY experiment, among the H-glu1 and H-12 protons confirmed this hypothesis. The enzymatic hydrolysis with β-glucosidase afforded the same aglycone **4a** of the previous glucoside.

Compounds **6** and **7** have been identified as two diastereomers and named amarantholidosides VI and VII, respectively.

Compounds **6** and **7** had a molecular formula $C_{42}H_{70}O_{15}$, as resulted by the elemental analysis and the ESI mass spectrum, which showed the pseudomolecular peak at *m/z* 837 $[M+Na]^+$.

In the ^1H NMR spectrum of amarantholidoside VI (Table 3), the ABX system of H-1 cis, H-1 trans, and H-2 protons and the H-6 and H-12 olefinic protons was evident. In the region of the protons geminal to oxygen, the signals of the anomeric and of the hydroxymethyl glu6 of a sugar moiety were present, and the H-10 triplet at δ 4.22 and further four protons ranging from 3.10 to 3.40 ppm were also present. In the upfield region of the spectrum three methyls at δ 1.72, 1.67, and 1.28, a methylene as triplet at δ 2.06, and a double doublet centered at δ 1.96 were identifiable. This data together with the information from the ^{13}C NMR spectrum led to the hypothesize of the presence of a $\Delta^{1,6,11}$ nerolidol sesquiterpene bonded to a glucose unit at C-5. The presence of 21 carbon signals in the ^{13}C NMR and ESI mass spectrum indicated a high degree of symmetry in the molecule. The mass spectrum also showed fragments at *m/z* 438 $[M-C_{21}H_{35}O_7+Na]^+$ and 404 $[M-C_{21}H_{35}O_8-H_2O+Na]^+$ due to the cleavage of the ether bridge, and at *m/z* 488 $[M-2\times C_6H_{11}O_5]^+$ and 472 $[M-C_6H_{11}O_5-C_6H_{11}O_6]^+$ due to the loss of both the sugar unities. In accordance with the hypothesis of a dimeric structure, the C-10 value (δ 89.8) was downshifted with respect to the known amarantholidol II.[9] This value suggested ethereal bridge among the C-10 carbons.

Amarantholidoside VII NMR data overlapped with those of the previously described compound, except slight differences for C-6–C-14 carbon values (Table 3). Unfortunately, these differences could be due to a different configuration for the C-10 and C-10′ carbons. The isolated quantities of these compounds did not allow further spectroscopic investigations and we were not able to define the configurations at C-10 and C-10′ carbons.

The amarantholidosides I–VI have been tested on the wild species *T. officinale* to define their phytotoxic role in the habitat and on the seed of *A. retroflexus* to evaluate the potential autotoxic activity; the results are reported in Figures 3 and 4, respectively.

Table 3. NMR data of amarantholidosides VI (**6**) and VII (**7**) in CD_3OD

	^1H (δ)		*J* (Hz)		DQ-COSY	^{13}C (δ)		DEPT	HMBC (H→C)	HSQC–TOCSY (H→C)
	6	**7**	**6**	**7**		**6**	**7**			
1t/1′t	5.23 dd	5.23 dd	17.1, 1.5	17.4, 1.2	1c/1′c, 2/2′,	112.0	112.0	CH_2	2/2′, 3/3′	1/1′, 2/2′
1c/1′c	5.01 dd	5.01 dd	9.0, 1.5	10.8, 1.2	1t/1′t, 2/2′				2/2′, 3/3′	1/1′, 2/2′
2/2′	5.96 dd	5.96 dd	11.1, 1.2	17.4, 10.8	1c, 1t	146.4	146.4	CH	1/1′, 3/3′	1/1′, 2/2′
3/3′	—	—	—	—	—	74.0	74.0	C	—	—
4/4′	1.96 dd	1.96 dd	14.1, 7.8	14.7, 8.1	5/5′	48.1	48.1	CH_2	2/2′, 3/3′, 5/5′, 6/6′, 15/15′	4/4′, 5/5′, 6/6′
	1.65 ov	1.65 ov							2/2′, 3/3′, 5/5′, 6/6′, 15/15′	
5/5′	4.90 ov	4.90 ov	—	—	4/4′, 6/6′	71.3	71.3	CH	glu1/1′, 3/3′, 4/4′, 6/6′	4/4′, 5/5′, 6/6′
6/6′	5.11 dd	5.13 dd	9.6, 1.2	9.0, 0.9	5/5′	126.6	126.8	CH	4/4′, 5/5′, 7/7′, 8/8′, 14/14′	4/4′, 5/5′, 6/6′
7/7′	—	—	—	—	—	141.1	141.8	C	—	—
8/8′	2.06 t	2.06 t	7.5	7.5	9/9′	36.7	36.5	CH_2	6/6′, 7/7′, 9/9′, 10/10′, 14/14′	8/8′, 9/9′, 10/10′
9/9′	1.57 dd	1.61 dd	6.6, 1.8	6.6, 1.7	8/8′, 10/10′	30.1	30.1	CH_2	7/7′, 8/8′, 10/10′, 11/11′	8/8′, 9/9′, 10/10′
	1.52 dd	1.58 dd	6.6, 1.2	6.6, 1.2	8/8′, 10/10′				7/7′, 8/8′, 10/10′, 11/11′	
10/10′	4.22 t	4.22 t	6.6	6.3	9/9′	89.8	89.6	CH	8/8′, 9/9′, 11/11′, 12/12′, 13/13′	8/8′, 9/9′, 10/10′
11/11′	—	—	—	—	—	145.5	145.9	C	—	—
12/12′	4.94 s	4.94 s	—	—	—	114.2	114.1	CH_2	10/10′, 11/11′, 13/13′	—
13/13′	1.72 s	1.73 s	—	—	—	17.1	17.1	CH_3	10/10′, 11/11′, 12/12′	—
14/14′	1.67 s	1.68 s	—	—	6/6′	16.7	16.7	CH_3	6/6′, 7/7′, 8/8′	—
15/15′	1.28 s	1.28 s	—	—	—	28.6	28.6	CH_3	2/2′, 3/3′, 4/4′	—
glu1/1′	4.23 d	4.24 d	7.8	7.5	glu2/2′	100.0	100.1	CH	5/5′, 10/10′, glu2/2′	glu1, glu2, glu3, glu4, glu6
glu2/2′	3.15 dd	3.15 dd	8.9, 7.8	8.9, 7.8	glu1/1′, glu3/3′	78.1	78.1	CH	5/5′, glu1/1′, glu3/3′, glu4/4′	glu1, glu2, glu3, glu4, glu6
glu3/3′	3.30 m	3.30 m	—	—	glu2/2′, glu4/4′	75.1	75.1	CH	glu1/1′, glu2/2′, glu4/4′	glu1, glu2, glu3, glu4, glu6
glu4/4′	3.29 ov	3.29 ov	—	—	glu3/3′, glu5/5′	71.9	71.9	CH	glu5/5′, glu6/6′	glu2, glu3, glu4, glu6
glu5/5′	3.26 m	3.26 m	—	—	glu4/4′, glu6/6′	78.1	78.1	CH	glu6/6′	glu2, glu3, glu4, glu6
glu6/6′	3.85 dd	3.86 dd	11.7, 2.1	12.3, 2.1	glu5/5′, glu6/6′	62.9	62.9	CH_2	glu4/4′, glu5/5′	glu3, glu4, glu6
	3.66 dd	3.66 dd	11.7, 5.7	12.3, 6.3	glu5/5′, glu6/6′				glu4/4′, glu5/5′	glu3, glu4, glu6

d=doublet; dd=double doublet; m=multiplet; ov=overlapped; s=singlet; t=triplet.

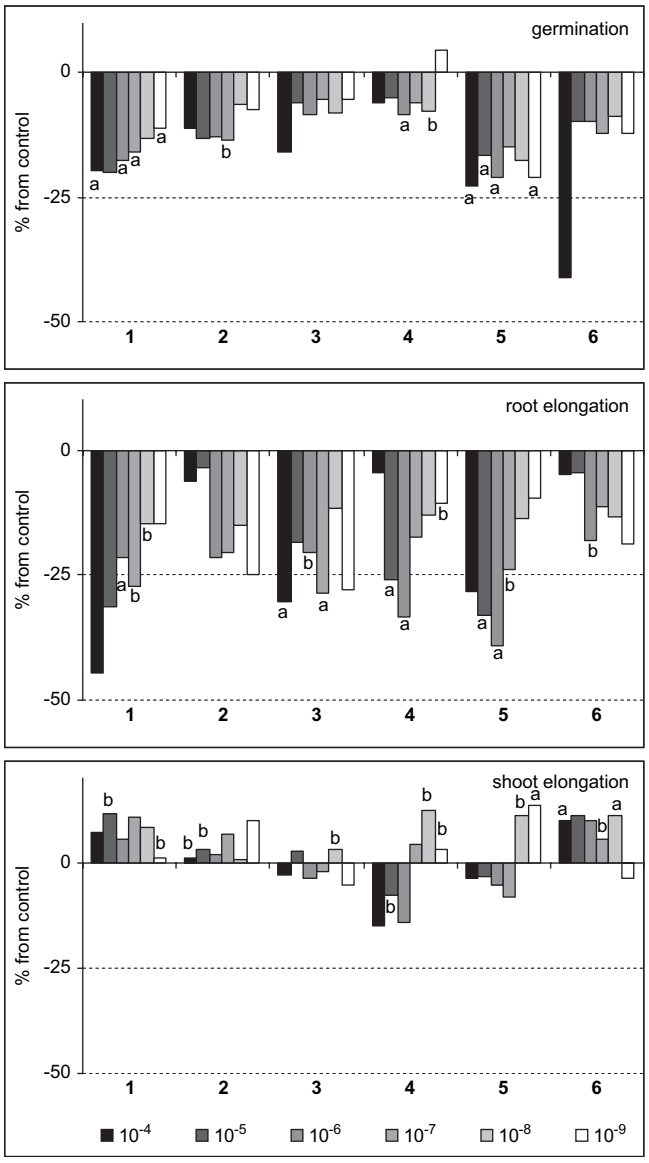

Figure 3. Bioactivity of compounds **1–6** on the germination, root elongation, and shoot elongation of *Taraxacum officinale*. Values are presented as percentage differences from control and they are significantly different with $P>0.05$ for Student's *t*-test: (a) $P<0.01$; (b) $0.01<P<0.05$. A positive percentage represents stimulation while negative values represent inhibitions.

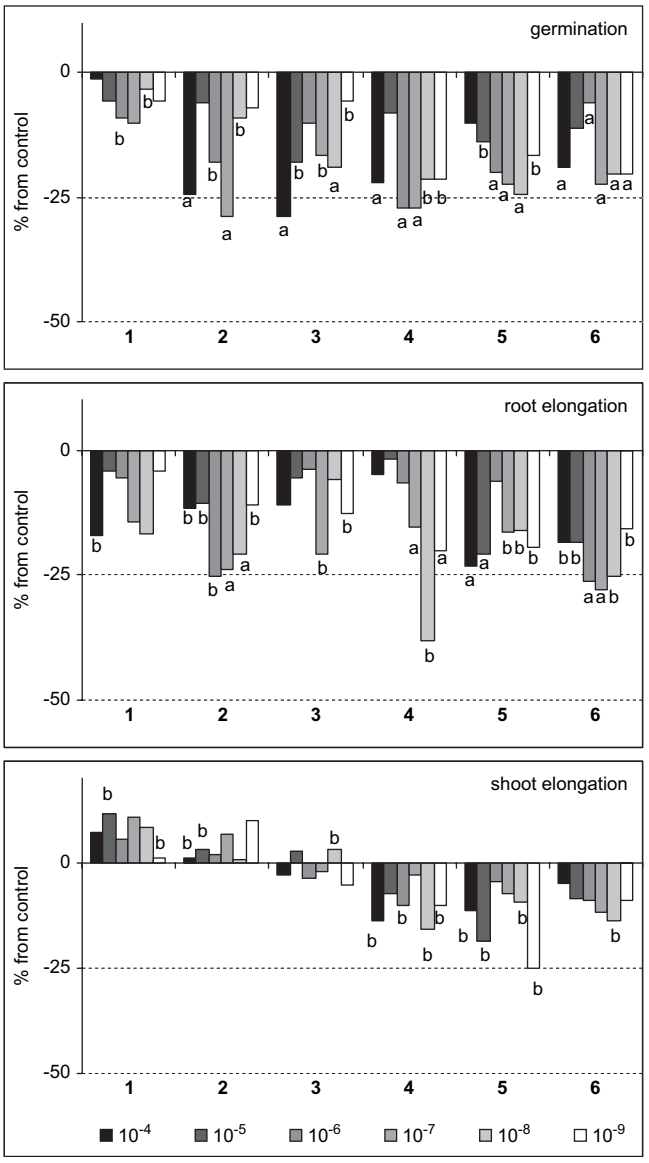

Figure 4. Bioactivity of compounds **1–6** on the germination, root elongation, and shoot elongation of *Amaranthus retroflexus*. Values are presented as percentage differences from control and they are significantly different with $P>0.05$ for Student's *t*-test: (a) $P<0.01$; (b) $0.01<P<0.05$. A positive percentage represents stimulation while negative values represent inhibitions.

On *T. officinale*, the greatest effects were registered on the root elongation. Compound **1** was more active: the chemical inhibited the root development of about 50% at the highest concentration tested. The effects on the germination were modest and with exception of compound **1** it seemed independent from the concentration. Furthermore, the autotoxicity, evident in both germination and root elongation (Fig. 4), was moderate. The results showed slow stimulating and/or inhibiting effects on shoot elongation of the test species.

To the best of our knowledge, this is the first report that describes the isolation of dimeric nerolidol derivatives from natural sources. The presence of secondary and tertiary chiral alcohols on aglicone moiety led us to use two different methods to assign the absolute configuration.

3. Experimental

3.1. General procedures

NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C on a Varian 300 spectrometer Fourier transform NMR in CD_3OD at 25 °C. Proton-detected heteronuclear correlations were measured using a gradient heteronuclear single-quantum coherence (HSQC), optimized for $^{1}J_{HC}=$ 140 Hz, a gradient heteronuclear multiple bond coherence (HMBC), optimized for $^{n}J_{HC}=8$ Hz, and a gradient heteronuclear single-quantum coherence–total correlation spectroscopy (HSQC–TOCSY), optimized for $^{n}J_{HC}=8$ Hz and for a mixing time=0.09. Optical rotations were measured on a Perkin–Elmer 141 in MeOH solution. Electrospray mass spectra were recorded using a Waters Z-Q mass spectrometer equipped with an electrospray ionization (ESI) probe

operating in positive or negative ion mode. The scan range was 80–2000 *m/z*.

The HPLC apparatus consisted of a pump (Shimadzu LC-10AD), a refractive index detector (Shimadzu RID-10A), and a Shimadzu Chromatopac C-R6A recorder. Preparative HPLC was performed using NH_2 (Luna 10 μm, 250×10 mm i.d., Phenomenex) column. Analytical HPLC was performed using RP-8 (Luna 5 μm, 250×4.6 mm i.d., Phenomenex) or Polar-RP-80A (Synergi 4 μm, 250×4.6 mm i.d., Phenomenex) columns. Analytical TLC was performed on Merck Kieselgel 60 F_{254}, RP-18 F_{254}, or RP-8 F_{254} plates with 0.2 mm layer thickness. Spots were visualized by UV light or by spraying with H_2SO_4–AcOH–H_2O (1:20:4). The plates were then heated for 5 min at 110 °C. Preparative TLC was performed on Merck Kieselgel 60 F_{254} plates, with 0.5 or 1 mm film thickness. Flash column chromatography (FCC) was performed on Merck Kieselgel 60 (230–400 mesh) at medium pressure. Column chromatography (CC) was performed on Merck Kieselgel 60 (70–240 mesh). Filtrations on solid phase extraction (SPE) cartridge were performed on Waters NH_2 or C8 Sep-Pak Cartridge.

3.2. Plant material, extraction, and isolation of the metabolites

Plants of *A. retroflexus* L. were collected in May 2003, in the vegetative state, in Recale, near Caserta (Italy), and identified by Dr. Assunta Esposito of the Second University of Naples. A voucher specimen (CE118) has been deposited at the Herbarium of the Dipartimento di Scienze della Vita of Second University of Naples.

Fresh leaves of *A. retroflexus* (42 kg) were extracted with MeOH–H_2O (1:9) for 48 h at 20 °C and then in MeOH for 5 days. The methanolic extract was dissolved in water and then extracted with EtOAc. The organic fraction was dried with Na_2SO_4 and concentrated under vacuum, yielding 18.4 g of crude residue.

The EtOAc fraction was chromatographed on silica gel, with $CHCl_3$–EtOAc and $CHCl_3$–MeOH solutions, to give four fractions A–D.

Fractions A and B, eluted with EtOAC–$CHCl_3$ (1:9), give the free nerolidols previously described. Fraction C eluted with MeOH–$CHCl_3$ (1:9) was chromatographed on Sephadex LH-20 eluting with hexane–$CHCl_3$–MeOH (2:1:1) to obtain three fractions: the first, rechromatographed on RP-18 column, eluting with MeOH–MeCN–H_2O (2:1:2), furnished pure **3** (9.0 mg); the second fraction was chromatographed by NH2 HPLC eluting with MeCN–H_2O (9:1), which was purified by RP-8 HPLC, eluting with H_2O–MeOH–MeCN (13:3:4) to give pure **1** (3.0 mg) and **2** (2.0 mg); the third fraction was chromatographed on RP-18 column eluting with H_2O–MeOH–MeCN (2:1:2) to have a fraction that was first filtered on NH_2 Sep-Pak with H_2O–MeCN (2:23) and then purified by analytical RP-8 HPLC, eluting with H_2O–MeOH–MeCN (13:3:4) to give pure glucosides **6** (6.0 mg) and **7** (2.0 mg). Fraction D eluted with MeOH–$CHCl_3$ (1:1) was chromatographed on Sephadex LH-20 eluting with hexane–$CHCl_3$–MeOH (1:1:1), collecting fractions of 25 ml volumes. The second fraction was chromatographed on RP-18 column eluting with H_2O–MeOH–MeCN (5:3:2) to have pure glucoside **4** (30.1 mg) and a mixture, which was chromatographed by FCC on SiO_2, eluting with $CHCl_3$–MeOH–0.1% TFA–H_2O (100:20:3:1). The eluate collected from 50 to 90 ml was purified on RP HPLC, using the Polar-RP-80A column and eluting with H_2O–MeOH–MeCN (15:1:4) to have pure **5** (3.0 mg).

3.3. Characterization of the metabolites 4–7

Amarantholidoside IV [(3*S*,6*E*,10*R*)-10-β-D-glucopyranosyloxy-3,11-dihydroxy-3,7,11-trimethyldodeca-1,6-diene] **4**. Colorless oil; IR ($CHCl_3$) ν_{max} cm^{-1}: 3400, 2932, 1577; ^1H NMR (300 MHz, CD_3OD): Table 1; ^{13}C NMR (75 MHz, CD_3OD): Table 1; ESIMS *m/z* 441 $[M+Na]^+$, 279 $[M-glc+Na]^+$, 203 $[glc+Na]^+$; $[\alpha]_D^{25}$ −12.2 (*c* 0.16, MeOH). Anal. Calcd for $C_{21}H_{38}O_8$: C, 60.27; H, 9.15. Found: C, 60.31; H, 9.17.

Amarantholidoside V [(3*S*,6*E*,10*R*)-11-β-D-glucopyranosyloxy-3,10-dihydroxy-3,7,11-trimethyldodeca-1,6-diene] **5**. Colorless oil; IR ($CHCl_3$) ν_{max} cm^{-1}: 3389, 2921; ^1H NMR (300 MHz, CD_3OD): Table 2; ^{13}C NMR (75 MHz, CD_3OD): Table 2; ESIMS *m/z* 441 $[M+Na]^+$, 279 $[M-glc+Na]^+$; $[\alpha]_D^{25}$ −14.6 (*c* 0.12, MeOH). Anal. Calcd for $C_{21}H_{38}O_8$: C, 60.27; H, 9.15. Found: C, 60.30; H, 9.18.

Amarantholidoside VI [(3*S*,3′*S*,5*S*,5′*S*,6*E*,6′*E*,10ξ,10′ξ)-10,10′-oxybis(5-β-D-glucopyranosyloxy-3-hydroxy-3,7,11-trimethyldodeca-1,6,11-triene] **6**. Colorless oil; IR ($CHCl_3$) ν_{max} cm^{-1}: 3397, 2932; ^1H NMR (300 MHz, CD_3OD): Table 3; ^{13}C NMR (75 MHz, CD_3OD): Table 3; ESIMS *m/z* 837 $[M+Na]^+$, 488 $[M-2\times C_6H_{11}O_5]^+$, 472 $[M-C_6H_{11}O_5-C_6H_{11}O_6]^+$, 438 $[M-C_{21}H_{35}O_7+Na]^+$, 404 $[M-C_{21}H_{35}O_8-H_2O+Na]^+$, 354 $[C_{16}H_{27}O_7+Na]^+$; $[\alpha]_D^{25}$ −26.4 (*c* 0.26, MeOH). Anal. Calcd for $C_{42}H_{70}O_{15}$: C, 60.30; H, 8.66. Found: C, 60.32; H, 8.69.

Amarantholidoside VII [(3*S*,3′*S*,5*S*,5′*S*,6*E*,6′*E*,10ξ,10′ξ)-10,10′-oxybis(5-β-D-glucopyranosyloxy-3-hydroxy-3,7,11-trimethyldodeca-1,6,11-triene] **7**. Colorless oil; IR ($CHCl_3$) ν_{max} cm^{-1}: 3394, 2931; ^1H NMR (300 MHz, CD_3OD): Table 3; ^{13}C NMR (75 MHz, CD_3OD): Table 3; ESIMS *m/z* 837 $[M+Na]^+$, 488 $[M-2\times C_6H_{11}O_5]^+$, 472 $[M-C_6H_{11}O_5-C_6H_{11}O_6]^+$, 438 $[M-C_{21}H_{35}O_7+Na]^+$, 404 $[M-C_{21}H_{35}O_8-H_2O+Na]^+$, 354 $[C_{16}H_{27}O_7+Na]^+$; $[\alpha]_D^{25}$ −43.3 (*c* 0.14, MeOH). Anal. Calcd for $C_{42}H_{70}O_{15}$: C, 60.30; H, 8.66. Found: C, 60.28; H, 8.29.

3.3.1. Enzymatic hydrolysis of amarantholidol IV. To a solution of pure amarantholidoside IV (10 mg) in acetate buffer (0.5 M, pH 5.0, 5 ml), 40 mg of β-glucosidase (Sigma) was added. After 24 h at 37 °C in stirring, the mixture was extracted with EtOAc (5 ml×2), dried over Na_2SO_4, and evaporated in vacuo. The crude extract was chromatographed on SiO_2 [hexane–$CHCl_3$–MeOH (3:6:1)] to have pure aglycone (3*S*,6*E*,10*R*)-3,10,11-trihydroxy-3,7,11-trimethyldodeca-1,6-diene (**4a**): ^1H NMR spectral data (300 MHz, CD_3OD): δ 5.91 (1H, dd, *J*=17.1, 10.5 Hz, H-2), 5.18 (1H, dd, *J*=17.1, 1.5 Hz, H-1 cis), 5.19 (1H, dd, *J*=9.3, 1.2 Hz, H-6), 5.02 (1H, dd, *J*=10.5, 1.5 Hz, H-1 trans), 3.22 (1H, dd, *J*=10.8, 1.8 Hz, H-10), 1.61 (3H, s, H-14), 1.24 (3H, s, H-15), 1.15 (3H, s, H-12), 1.12 (3H, s, H-13); ^{13}C NMR (75 MHz, CD_3OD) δ 145.0 (CH, C-2), 136.0 (C, C-7), 125.8 (CH, C-6),

112.0 (CH_2, C-1), 78.9 (CH, C-10), 73.8 (C, C-11), 74.8 (C, C-3), 43.4 (CH_2, C-4), 37.8 (CH_2, C-8), 30.7 (CH_2, C-9), 27.5 (CH_3, C-15), 26.2 (CH_3, C-13), 23.9 (CH_2, C-5), 23.7 (CH_2, C-12), 16.5 (CH_3, C-14); EIMS *m/z* 256 $[M]^+$, 238 $[M-H_2O]^+$, 223 $[M-CH_3-H_2O]^+$; $[\alpha]_D^{25}$ −14.6 (*c* 0.12, MeOH); $[\alpha]_D^{25}$ +7.8 (*c* 0.10, MeOH). Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.61; H, 10.96.

3.3.2. Preparation of (*S*)- and (*R*)-MTPA esters of 4a. (*R*)-(−)-MTPA chloride (5 μl, 26 μmol) was added to a solution of pure compound (1.5 mg) in dry pyridine (50 μl). After 6 h under magnetic stirring at room temperature, EtOAc (5 ml) and H_2O (5 ml) were added to the reaction mixture. The organic layer, separated by centrifugation at 4000 rpm for 10 min, gave a crude extract, which was purified by preparative TLC eluting with hexane–$CHCl_3$–MeOH (5:4:1).

The (*S*)-MTPA ester of **4a** had the ^{1}H NMR spectral data (300 MHz, CD_3OD): δ 5.90 (1H, dd, *J*=17.3, 10.5 Hz, H-2), 5.12 (1H, dd, *J*=17.3, 1.8 Hz, H-1 trans), 4.99 (H-10, detected by DQ-COSY spectrum), 4.92 (H-1 cis, detected by DQ-COSY spectrum), 1.59 (3H, s, H-14), 1.51 (H-9, detected by DQ-COSY spectrum), 1.24 (3H, s, H-15), 1.19 (3H, s, H-12), 1.15 (3H, s, H-13). The (*R*)-MTPA ester of **4a** had the ^{1}H NMR spectral data (300 MHz, CD_3OD): δ 5.89 (1H, dd, *J*=17.1, 10.5 Hz, H-2), 5.18 (1H, dd, *J*=17.1, 1.2 Hz, H-1 trans), 5.05 (H-1 cis, detected by DQ-COSY spectrum), 5.00 (H-10, detected by DQ-COSY spectrum), 1.76 (3H, s, H-14), 1.58 (H-9, detected by DQ-COSY spectrum), 1.24 (3H, s, H-15), 1.11 (3H, s, H-12), 1.07 (3H, s, H-13).

3.3.3. ^{13}C NMR of amarantholidol IV in the chiral solvent *R*,*R*- and *S*,*S*-BMBA-*p*. Chiral NMR solvent (*R*,*R*)-BMBA-*p* [or (*S*,*S*)-BMBA-*p*] was prepared with small modifications of method reported by Kobayashi et al.[13] 1,3-Diiodopropane (10.3 mmol, 1 equiv) was added dropwise over 7 min to (*R*)-α-phenetylamine [or (*S*)-α-phenetylamine] (41.3 mmol, 4 equiv) at 130 °C. After stirring for 30 min, the mixture was cooled to 80 °C and then poured into aqueous 50% NaOH solution (300 ml). The resulting free amines were extracted with EtOAc (300 ml) and the organic layer was washed with brine, dried over anhydrous K_2CO_3, filtered, and evaporated to give the crude oil. The pure BMBA-*p* was obtained by distillation as reported by Hulst et al.[14] (*R*,*R*)-BMBA-*p* (colorless oil) had ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 7.40–7.20 (5H, overlapped), 3.71 (2H, q, *J*=6.6 Hz), 2.54 (2H, dt, *J*=6.6, 5.1 Hz), 2.47 (2H, dt, *J*=6.6, 5.1 Hz), 1.62 (2H, m), 1.34 (6H d, *J*=6.6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3 (C), 128.3 (CH), 126.6 (CH), 126.4 (CH), 58.3 (CH), 46.3 (CH_2), 29.9 (CH_2), 24.1 (CH_3); $[\alpha]_D^{20}$ +66.2 (*c* 0.25, $CHCl_3$). (*S*,*S*)-BMBA-*p* (colorless oil) had ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 7.40–7.20 (5H, overlapped), 3.71 (2H, q, *J*=6.6 Hz), 2.54 (2H, dt, *J*=6.6, 5.1 Hz), 2.47 (2H, dt, *J*=6.6, 5.1 Hz), 1.62 (2H, m), 1.34 (6H, d, *J*=6.6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3 (C), 128.3 (CH), 126.6 (CH), 126.4 (CH), 58.3 (CH), 46.3 (CH_2), 29.9 (CH_2), 24.1 (CH_3); $[\alpha]_D^{20}$ −66.2 (*c* 0.25, $CHCl_3$).

A Varian Mercury 300 spectrometer (75 MHz) was used to collect the ^{13}C NMR data of amarantholidoside IV (**4**, 10 mg) in the chiral solvent BMBA-*p* (350 μl)–CD_3OD (300 μl), with readout of NMR spectra being adjusted to 0.001 ppm/point (sw=23980.8, fn=524288).

3.4. Phytotoxicity test

Seeds of *T. officinale* and *A. retroflexus*, collected during 2005, were obtained from Herbiseed (Twyford, UK).

All undersized or damaged seeds were discarded and the assay seeds were selected for uniformity.

The test solution (10^{-4} M) was prepared using 2-[*N*-morpholino]ethanesulfonic acid (MES; 10 mM, pH 6) and the rest (10^{-5}–10^{-9} M) was obtained by dilution. Parallel controls were performed. After adding 10 seeds and 1.0 ml of test solutions, Petri dishes were sealed with Parafilm® to ensure closed-system models. Seeds were placed in a growth chamber KBW Binder 240 at 27 °C in the dark. Germination percentage was determined daily for 7 days (no more germination occurred after this time).

After growth, the plants were frozen at −20 °C to avoid subsequent growth until the measurement process. Data are reported as percentage differences from control. Thus, zero represents the control, positive values represent the stimulation of the parameter studied, and negative values represent inhibition.

Statistical treatment. The statistical significance of differences between groups was determined by a Student's *t*-test, calculating mean values for every parameter (germination average, shoot, and root elongation) and their population variance within a Petri dish. The level of significance was set at $P<0.05$.

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Stereoselective syntheses of (−)-chloramphenicol and (+)-thiamphenicol

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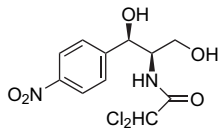
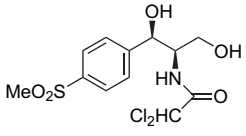
Abstract—Chloramphenicol and thiamphenicol have been enantioselectively synthesized using an asymmetric halohydrin reaction as a key step. In particular, halomethoxylation reaction was used, where *O*-methyl functions as a hydroxyl protecting group and eliminates an additional protection step.

1. Introduction

Chloramphenicol **1** is one of the oldest antibacterial agents, which was first isolated from *Streptomyces venezuelae* in 1947.[1] It is biologically active only as its 2*R*,3*R* enantiomer and might be the first antibiotic obtained commercially in optically active form by chemical synthesis. It is widely used as a broad spectrum antibiotic and has especially been effective in the treatment of typhi, dysentery, salmonella, rickettsia, and ocular bacterial infections.



1: (-)-chloramphenicol



2: (+)-thiamphenicol

Thiamphenicol **2** is an analogue of chloramphenicol and is active against both gram-positive and gram-negative microorganisms.[2] Due to the potent biological activity of compounds **1** and **2**, a number of chemical syntheses of racemic compounds and a few asymmetric syntheses have been described.[3–6] Herein, we report in detail the stereoselective syntheses of (−)-chloramphenicol **1** and (+)-thiamphenicol **2** using an asymmetric halohydrin (halohydroxylation as well as halomethoxylation) reaction as a key step.

Recently, a silver(I)-promoted asymmetric halohydrin (hydroxylation as well as halomethoxylation) reaction of chiral α,β-unsaturated carboxylic acids has been developed in our laboratory.[7] Accordingly, we anticipated that the Ag_2O-promoted asymmetric bromohydroxylation reaction of cinnamoyl substrate **3** containing oxazolidinone chiral auxiliary[8] at a lower temperature (e.g., −10 °C) might provide the carboxybromohydrin **4** as the major diastereomer with the desired stereochemistry for the synthesis of (−)-chloramphenicol. When the Ag_2O-promoted bromohydroxylation reaction of **3a** was performed at −10 °C instead of 0 °C (Table 1; entry 1), it gave, as anticipated, **4a** as the major diastereoisomer (entry 2). Unlike reaction at 0 °C (entry 4), $AgNO_3$-promoted reaction of **3a** also provided **4a** as a major isomer (entry 5). However, Ag_2O and $AgNO_3$-promoted bromohydroxylation of *p*-nitrocinnamoyl substrate **3b** showed poor diastereoselectivity (entries 6–9). The diastereoselectivity could not be improved by performing the reaction under a variety of reaction conditions.

Initially, the synthesis of chloramphenicol began with the α-bromo-β-hydroxy carbonyl compound **4a** (Scheme 1). Reaction of **4a** with NaN_3 in DMF at 25 °C gave the α-azido-β-hydroxy carbonyl compound **6a** (89%). Two-step reduction of azido carbonyl **6a** with $LiBH_4$ in THF–MeOH yielded azidodiol **7a** (90%) followed by reduction with hydrogen and Pd/C (10%) in MeOH under atmospheric pressure provided the amino alcohol **8a** in 99% yield. Compound **8a** would provide the (−)-chloramphenicol upon simple chemical modification by following the literature procedure,[4e] that requires an additional aryl nitration. Optical purity of **8a** was compared with previously reported values ($[\alpha]_D^{26}$ −26.0, *c* 1, MeOH; lit.[9] $[\alpha]_D^{22}$ −26.5, *c* 1, MeOH).

To avoid the nitration step, we initiated the synthesis of (−)-chloramphenicol from 4-nitrocinnamoyl compound **9a** containing Oppolzer's (2*R*)-bornanesultam[10] as a chiral

Keywords: Enantioselective synthesis; (−)-Chloramphenicol; (+)-Thiamphenicol; Asymmetric; Halohydrin reaction.
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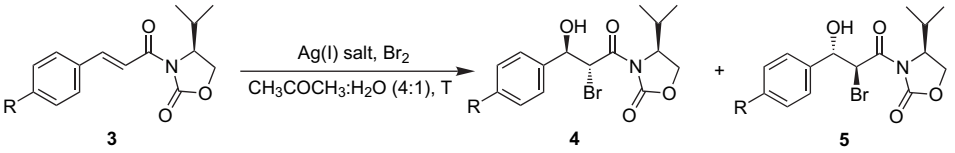
Table 1. Asymmetric bromohydroxylation of **3** under different reaction conditions[a]



Entry	Substrate	R	Ag(I) salt	T (°C)	Ratio[b] (**4**:**5**)	Yield[c] (%)
1	**3a**	H	Ag_2O	0	50:50	97
2	**3a**	H	Ag_2O	−10	72:28 (74:26)	93
3	**3a**	H	Ag_2O	−20	—	NR[d]
4	**3a**	H	$AgNO_3$	0	35:65 (34:66)	92
5	**3a**	H	$AgNO_3$	−10	64:36 (67:33)	93
6	**3b**	NO_2	Ag_2O	0	48:52	90
7	**3b**	NO_2	Ag_2O	−10	50:50	91
8	**3b**	NO_2	$AgNO_3$	0	47:53	92
9	**3b**	NO_2	$AgNO_3$	−10	50:50	90

[a] For **3a**: Ag_2O-promoted bromohydroxylation reactions were performed using 0.7 equiv of Ag_2O and 1.2 equiv of Br_2 in 20% aqueous acetone and $AgNO_3$-promoted bromohydroxylation were performed using 2.0 equiv of $AgNO_3$ and 1.2 equiv of Br_2, for **3b**: Ag_2O-promoted bromohydroxylation reactions were performed using 1.0 equiv of Ag_2O and 1.2 equiv of Br_2 in 20% aqueous acetone and $AgNO_3$-promoted bromohydroxylation were performed using 2.0 equiv of $AgNO_3$ and 2.0 equiv of Br_2.

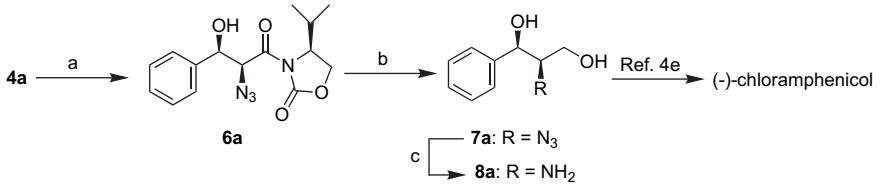
[b] Determined from the ^{1}H NMR spectrum of the crude reaction mixture. Ratios in the parentheses refer to the ratio of isolated **4** and **5** after column chromatography.

[c] Combined isolated yields of **4** and **5** after column chromatography.

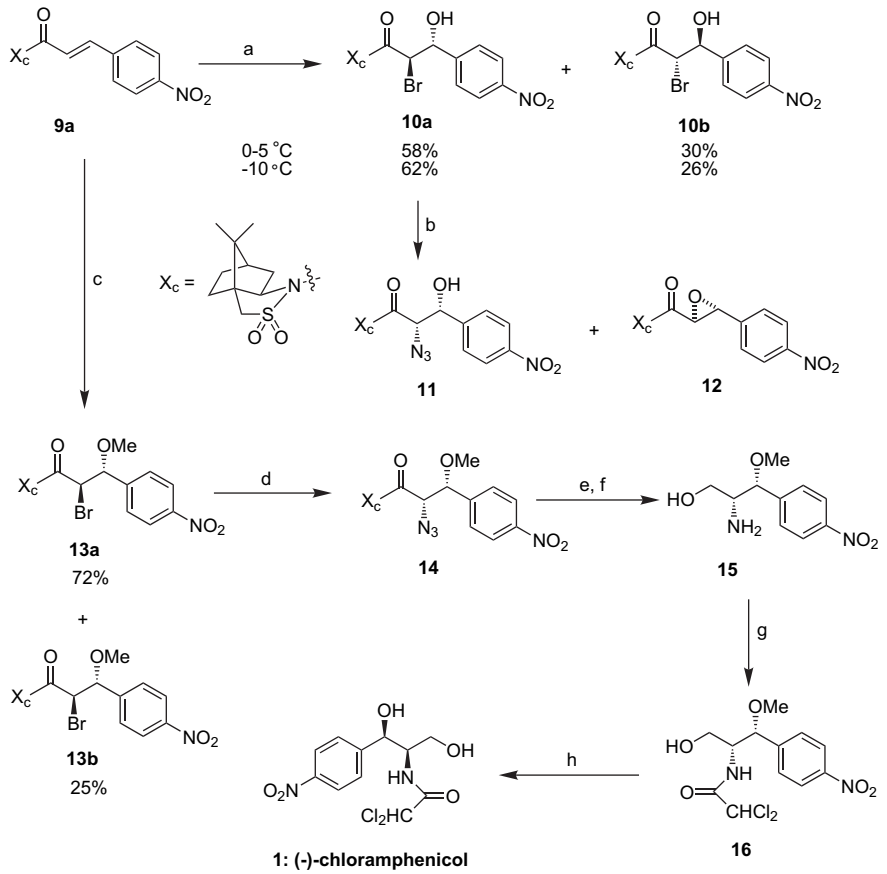
[d] >90% of **3a** was recovered.

auxiliary (Scheme 2). $AgNO_3$-promoted bromohydroxylation of **9a** with Br_2 in aqueous acetone provided the compound **10a** in 58% and 62% yields at 0 °C and at −10 °C, and the minor diastereomer **10b** in 30% and 26% yields, respectively. Unlike **4a**, reaction of **10a** with NaN_3 in DMF at 25 °C yielded a non-separable mixture (40:60) of azido carbonyl **11** and epoxy carbonyl compound **12**. The protection of β-hydroxyl functionality of **10a** was found to be essential for the replacement of bromide with azide.[4f] For this purpose and to eliminate an additional protection step we utilized our halomethoxylation reaction, where *O*-methyl functions as a hydroxyl protecting group. $AgNO_3$-promoted bromomethoxylation of **9a** with Br_2 in MeOH/CH_2Cl_2 at 0 °C gave the desired α-bromo-β-methoxy carbonyl compound **13a** in 72% yield along with minor diastereomer **13b** in 25% yield. There was no appreciable change in diastereoselectivity when the bromomethoxylation was performed at even lower temperature viz. −15 °C and −30 °C. It should be noted that the bromomethoxylation of the 4-nitrocinnamoyl substrate containing an oxazolidine chiral auxiliary (**3b**) showed, similar to the bromohydroxylation, poor diastereoselectivity (dr 52:48). Reaction of **13a** with NaN_3 in DMF at 60 °C gave the α-azido-β-methoxy carbonyl compound **14** in 92% yield. Two-step reduction of azido carbonyl **14** with $LiBH_4$ in THF followed by Ph_3P in H_2O–THF provided the amino alcohol **15** in 82% yield. N-acylation of **16** with Cl_2CHCO_2Me at 90 °C for 1 h yielded the compound **16**. Finally, demethylation of **16** with BBr_3 in CH_2Cl_2 at low temperature completed the intended synthesis of (−)-chloramphenicol. The specific optical rotation of the synthetic (−)-chloramphenicol **1** ($[\alpha]_D^{26}$ −25.4, *c* 1, EtOAc) was compared with previously reported[11] values ($[\alpha]_D^{23}$ −25.5, *c* 1, EtOAc).

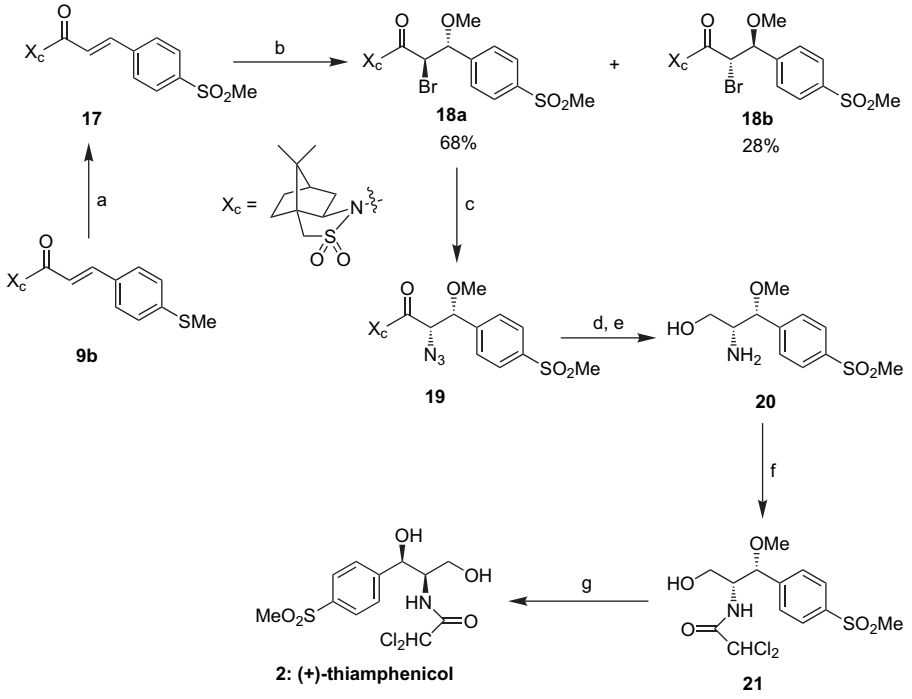
Similarly, the synthesis of (+)-thiamphenicol commenced (Scheme 3) with a Ag(I)-promoted asymmetric bromomethoxylation reaction of the substrate **17**, which afforded the α-bromo-β-methoxy carbonyl compound **18a** in 68% yield and a minor isomer **18b** (28%). Substrate **17** was obtained in 92% yield by MMPP oxidation of **9b**. Replacement of the bromide of **18a** by azide in DMF at 60 °C yielded the α-azido-β-methoxy carbonyl compound **19** in 92% yield. Reduction of the azido carbonyl **19** was performed in two steps with $LiBH_4$ in THF followed by Ph_3P in THF–H_2O to afford the amino alcohol **20**. Transformation of 3-hydroxy-protected 2-amino-1,3-propanediol **20** into (+)-thiamphenicol was readily accomplished by first forming the *N*-dichloroacetamide followed by demethylation. Treatment of **20** with the excess of Cl_2CHCO_2Me at 90 °C afforded **21** in 85% yield and (+)-thiamphenicol **2** was obtained in 84% isolated yield by demethylation of **21** with 2.2 equiv of BBr_3 in CH_2Cl_2. The identity and optical purity of the synthetic (+)-thiamphenicol **2** was confirmed by comparing with its spectral and physical properties with that of those reported in the literature ($[\alpha]_D^{26}$ +12.8, *c* 1, EtOH; lit.[2] $[\alpha]_D^{25}$ +12.9, *c* 1, EtOH).



Scheme 1. Reagents and conditions: (a) NaN_3, DMF, 25 °C, 4 h, 89%; (b) $LiBH_4$, THF–MeOH, 0 °C, 1 h, 90% and (c) Pd/C (10%), MeOH, H_2, rt, 12 h, 99%.



Scheme 2. Reagents and conditions: (a) $AgNO_3$, Br_2, acetone: H_2O (4:1), 30 min; (b) NaN_3, DMF, 25 °C, 4 h; (c) $AgNO_3$, Br_2, MeOH, 0 °C, 30 min, 72% (**13a**), 25% (**13b**); (d) NaN_3, DMF, 60 °C, 4 h, 92%; (e) $LiBH_4$, THF–MeOH; (f) Ph_3P, THF–H_2O, 25 °C, 5 h, 82% (for two steps); (g) Cl_2CHCO_2Me (excess), 90 °C, 1 h, 87% and (h) BBr_3, CH_2Cl_2, −78 °C to −20 °C, 10 h, 80%.



Scheme 3. Reagents and conditions: (a) MMPP, MeOH, rt, 2 h, 92%; (b) $AgNO_3$, Br_2, MeOH, 0 °C, 30 min, 68% (**18a**), 28% (**18b**); (c) NaN_3, DMF, 60 °C, 4 h, 92%; (d) $LiBH_4$, THF–MeOH; (e) Ph_3P, THF–H_2O, 25 °C, 5 h, 82% (for two steps); (f) Cl_2CHCO_2Me (excess), 90 °C, 1 h, 85% and (g) BBr_3, CH_2Cl_2, −78 °C to −20 °C, 10 h, 84%.

In conclusion, asymmetric halohydrin reaction—halohydroxylation and halomethoxylation—provides an efficient strategy for the synthesis of enantiomerically pure (−)-chloramphenicol and (+)-thiamphenicol. This strategy can also be extended toward synthesizing other structurally related compounds and analogues.

2. Experimental

2.1. General

All reactions were conducted using an oven-dried glassware under an atmosphere of Argon (Ar). Commercial grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Flash chromatography was carried out using Spectrochem Silica gel (230–400 mesh) purchased from Spectrochem, India. TLC was performed on aluminum-backed plates coated with Silica gel 60 with F_{254} indicator (Merck). Substrates **3** and **9** were synthesized by following the literature procedures.[8,10,12]

The ^{1}H NMR spectra were measured with Bruker-200 (200 MHz) and ^{13}C NMR spectra were measured with Bruker-200 (50 MHz) using $CDCl_3$, C_2D_6SO, CD_3OD, and CD_3CN. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield to $CDCl_3$ (δ=7.26), C_2D_6SO (δ=2.49), CD_3OD (δ=3.30), and CD_3CN (δ=1.93); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the central $CDCl_3$ resonance (δ=77.0), C_2D_6SO (δ=39.7), CD_3OD (δ=49.0), and CD_3CN (δ=118.2 and 1.3). Coupling constants in ^{1}H NMR are expressed in Hertz. Elemental analyses were carried out on a Perkin–Elmer 2400-II. Melting points were measured in Toshniwal (India) melting point apparatus.

2.1.1. Halohydroxylation of substrates 3. To a solution of the substrate **3** (1 mmol) in 20% aqueous acetone (20 mL) Ag(I) [for **3a** Ag_2O (0.7 mmol) or $AgNO_3$ (1.2 mmol) and Br_2 (1.2 mmol); for **3b** Ag_2O (1.0 mmol) or $AgNO_3$ (2 mmol)] and Br_2 (2.0 mmol) were added, respectively, at 0–5 °C and allowed to stir for 20–30 min. The reaction mixture was extracted with Et_2O at least three times, washed with water, and dried over Na_2SO_4. The organic solution was filtered through a small Celite pad (otherwise locking problem or poor base line was found in the ^{1}H NMR of the crude mixture) and the filtrate was concentrated under vacuum. Flash column chromatography of the crude mixture using petroleum ether–EtOAc as eluent gave the desired carboxyhalohydrins in pure form. Compounds **4a** and **5a** were characterized by spectral analysis.[7b]

2.1.1.1. *anti*-(4*S*,2′*S*,3′*S*)-3-[2′-Bromo-3′-hydroxy-3′-(4-nitrophenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (4b). Colorless gummy liquid. $[\alpha]_D^{25}$ +52.91 (*c* 0.9, $CHCl_3$); FTIR (KBr): 3445 (br), 1778, 1682, 1626, 1519, 1385, 1344, 1299, 1230, 1204, 1143, 1100, 1057, 1030, 988, 975, 848, 750, 714, 669, 634, 532, 488 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.24 (d, *J*=8.7 Hz, 2H), 7.63 (d, *J*=8.7 Hz, 2H), 5.82 (d, *J*=8.1 Hz, 1H), 5.33 (d, *J*=8.1 Hz, 1H), 4.60–4.40 (m, 1H), 4.40–4.15 (m, 2H), 2.50–2.0 (m, 1H), 0.96 (d, *J*=2.0 Hz, 3H), 0.90 (d, *J*=2.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.7, 154.8, 148.6, 147.7, 127.3 (2C), 123.8 (2C), 74.7, 63.7, 59.1, 44.4, 28.8, 17.7, 14.5; Anal. Calcd for $C_{15}H_{17}BrN_2O_6$: C, 44.90; H, 4.27; N, 6.98. Found: C, 45.11; H, 4.58; N, 6.79%.

2.1.1.2. *anti*-(4*S*,2′*R*,3′*R*)-3-[2′-Bromo-3′-hydroxy-3′-(4-nitrophenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (5b). Colorless gummy liquid. $[\alpha]_D^{25}$ +5.15 (*c* 1, $CHCl_3$); FTIR (KBr): 3464 (br), 1780, 1705, 1523, 1388, 1348, 1205, 1107, 1051, 857, 754, 744, 699, 667, 614, 530 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.24 (d, *J*=11.2 Hz, 2H), 7.65 (d, *J*=11.2 Hz, 2H), 5.94 (d, *J*=7.7 Hz, 1H), 5.27 (d, *J*=7.7 Hz, 1H), 4.50–4.15 (m, 3H), 2.45–2.15 (m, 1H), 0.89 (d, *J*=7.0 Hz, 3H), 0.75 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.8, 154.9, 148.3, 147.9, 126.9 (2C), 123.6 (2C), 74.6, 63.8, 58.8, 44.4, 28.5, 17.8, 14.6; Anal. Calcd for ($C_{15}H_{17}BrN_2O_6$+1.5·H_2O): C, 42.07; H, 4.71; N, 6.54. Found: C, 42.17; H, 4.93; N, 6.60%.

2.1.1.3. *syn*-(4*S*,2′*S*,3′*R*)-3-(2′-Azido-3′-hydroxy-3′-phenyl-propionyl)-4-(1-methylethyl)-2-oxazolidinone (6a). To a stirred solution of **5a** (0.40 g, 1.12 mmol) in 5 mL DMF at room temperature was added NaN_3 (0.108 g, 1.66 mmol) and stirred for 6 h. The reaction mixture was quenched with water and extracted with EtOAc (3× 50 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was then purified by flash column chromatography to obtain pure **6a** (0.318 g, 89%) as a colorless gummy liquid. $[\alpha]_D^{26}$ +39.58 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3483 (br), 2115, 1778, 1705, 1485, 1453, 1388, 1300, 1205, 1142, 1104, 1057, 1022, 974, 864, 757, 731, 704, 668, 614, 553, 531 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.52–7.20 (m, 5H), 5.39 (d, *J*=5.1 Hz, 1H), 5.17 (d, *J*=5.1 Hz, 1H), 4.35–3.95 (m, 3H), 2.50–2.25 (m, 1H), 0.89 (t, *J*=6.9 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.5, 153.4, 138.9, 128.5 (3C), 126.3 (2C), 74.4, 65.5, 63.8, 58.9, 28.2, 17.8, 14.5; Anal. Calcd for ($C_{15}H_{18}N_4O_4$+1·H_2O): C, 53.56; H, 5.99; N, 16.66. Found: C, 53.12; H, 5.65; N, 16.88%.

2.1.1.4. *syn*-(2*R*,3*R*)-[2-Azido-3-hydroxy-3-phenyl-1-propanol] (7a). To a stirred solution of **6a** (0.40 g, 1.24 mmol) in 5 mL THF were added 1 mL MeOH followed by $LiBH_4$ (0.028 g, 1.24 mmol) at 0 °C under an argon atmosphere and stirred for 1 h. The reaction mixture was quenched with slow addition of H_2O at 0 °C and extracted with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was then purified by flash column chromatography to obtain pure **7a** (0.215 g, 90%) as colorless gummy liquid. $[\alpha]_D^{26}$ +76.26 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3393 (br), 2140, 2112, 1723, 1619, 1531, 1313, 1228, 1121, 1115, 994, 961, 835, 753, 610, 543 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50–7.25 (m, 5H), 4.81 (d, *J*=6.0 Hz, 1H), 3.75–3.45 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.2, 128.6 (2C), 128.4, 126.3 (2C), 74.3, 68.7, 62.4; Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.17; H, 6.01; N, 21.34%.

2.1.1.5. *syn*-(2*R*,3*R*)-[2-Amino-3-hydroxy-3-phenyl-1-propanol] (8a). To a stirred solution of **7a** (0.20 g,

1.02 mmol) in 5 mL dry MeOH under hydrogen atmosphere (1 atm) was added Pd/C (10%) (0.015 g) at 0 °C under hydrogen atmosphere and stirred for 12 h at room temperature. The reaction mixture was filtered through a half-inch bed of Celite and the filtrate was evaporated under reduced pressure (at<40 °C) to obtain pure **8a** (0.168 g, 99%) as a colorless gummy liquid. $[\alpha]_D^{26}$ −26.0 (*c* 1, MeOH) [lit.[9] $[\alpha]_D^{22}$ −26.5 (*c* 1, MeOH)]; FTIR (KBr): 3372 (br), 1592, 1519, 1355, 1204, 1164, 1018, 883, 851, 766, 741, 612, 528, 519 cm^{-1}; ^1H NMR [200 MHz, $CDCl_3$:CD_3OD (3:1)]: δ 7.70–7.20 (m, 5H), 4.50 (d, *J*=8.6 Hz, 1H), 3.55–3.10 (m, 2H), 3.00–2.55 (m, 1H); ^{13}C NMR [50 MHz, $CDCl_3$:CD_3OD (1:1)]: δ 139.1, 128.5 (2C), 127.3 (3C), 70.1, 65.5, 62.3; Anal. Calcd for ($C_9H_{13}NO_2$+1·H_2O): C, 58.36; H, 8.16; N, 7.56. Found: C, 58.77; H, 8.10; N, 7.76%.

2.1.1.6. *anti*-(2*R*,2′*R*,3′*R*)-*N*-[2′-Bromo-3′-hydroxy-3′-(4-nitrophenyl)-propionyl]-bornanesultam (10a). Colorless gummy liquid. $[\alpha]_D^{25}$ −99.41 (*c* 0.8, $CHCl_3$); FTIR (KBr): 3495 (br), 1779, 1737, 1697, 1607, 1524, 1439, 1389, 1349, 1302, 1206, 1106, 1056, 983, 945, 857, 839, 754, 700, 670, 521 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.26 (d, *J*=8.7 Hz, 2H), 7.59 (d, *J*=8.7 Hz, 2H), 5.47 (d, *J*=6.4 Hz, 1H), 4.76 (d, *J*=6.4 Hz, 1H), 4.16–3.94 (m, 2H), 3.52 (d, *J*=1.8 Hz, 2H), 2.29–2.02 (m, 2H), 2.00–1.77 (m, 3H), 1.64–1.26 (m, 2H), 1.14 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$): 166.7, 147.8, 145.8, 127.9 (2C), 123.7 (2C), 75.3, 65.1, 52.6, 48.6, 47.7, 45.3, 44.3, 37.6, 32.9, 26.3, 19.9, 19.5; Anal. Calcd for $C_{19}H_{23}BrN_2O_6S$: C, 46.82; H, 4.76; N, 5.75. Found: C, 46.61; H, 4.98; N, 5.43%.

2.1.1.7. *anti*-(2*R*,2′*S*,3′*S*)-*N*-[2′-Bromo-3′-hydroxy-3′-(4-nitrophenyl)-propionyl]-bornanesultam (10b). Colorless gummy liquid. $[\alpha]_D^{25}$ −1.19 (*c* 0.75, $CHCl_3$); FTIR (KBr): 3448 (br), 1692, 1600, 1522, 1386, 1347, 1216, 1166, 1136, 1117, 1067, 856, 760, 699, 537, 499 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.25 (d, *J*=8.8 Hz, 2H), 7.60 (d, *J*=8.8 Hz, 2H), 5.31 (d, *J*=6.7 Hz, 1H), 4.83 (d, *J*=6.7 Hz, 1H), 4.17–3.92 (m, 2H), 3.56 (d, *J*=2.0 Hz, 2H), 2.30–2.00 (m, 2H), 2.00–1.76 (m, 3H), 1.68–1.25 (m, 2H), 1.15 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.8, 147.9, 145.9, 127.8 (2C), 123.6 (2C), 75.4, 65.4, 52.7, 48.6, 47.6, 45.2, 44.4, 37.8, 32.7, 26.1, 20.0, 19.6; Anal. Calcd for $C_{19}H_{23}BrN_2O_6S$: C, 46.82; H, 4.76; N, 5.75. Found: C, 47.19; H, 5.01; N, 5.76%.

2.1.1.8. *anti*-(2*R*,2′*R*,3′*R*)-*N*-[2′-Bromo-3′-methoxy-3′-(4-nitrophenyl)-propionyl]-bornanesultam (13a). To a stirred solution of **9a** (0.50 g, 1.28 mmol) in 5 mL MeOH and 1.5 mL CH_2Cl_2 (0–5 °C) were added $AgNO_3$ (0.435 g, 2.56 mmol) and Br_2 (0.409 g, 2.56 mmol) and allowed to stir at that temperature for 20–30 min. The reaction mixture was quenched with water and extracted with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was then purified by flash column chromatography to obtain pure **13a** (0.42 g, 72%) as white solid. Mp 153–155 °C; $[\alpha]_D^{26}$ −89.74 (*c* 1.0, $CHCl_3$); FTIR (KBr): 1696, 1608, 1524, 1456, 1384, 1347, 1218, 1167, 1136, 1101, 967, 857, 834, 758, 698, 558, 535, 500 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.24 (d, *J*=8.7 Hz, 2H), 7.60 (d, *J*=8.7 Hz, 2H), 4.79 (s, 2H), 4.15–3.95 (m, 2H), 3.52 (d, *J*=1.1 Hz, 2H), 3.22 (s, 3H), 2.30–2.05 (m, 2H), 2.00–1.80 (m, 3H), 1.55–1.30 (m, 2H), 1.15 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.1, 148.1, 144.4, 129.2 (2C), 123.3 (2C), 82.1, 64.8, 58.0, 52.7, 48.7, 47.7, 45.1, 44.3, 37.7, 32.5, 26.2, 20.4, 19.6; Anal. Calcd for $C_{20}H_{25}BrN_2O_6S$: C, 47.91; H, 5.03; N, 5.59. Found: C, 47.88; H, 5.02; N, 5.86%.

2.1.1.9. *anti*-(2*R*,2′*S*,3′*S*)-*N*-[2′-Bromo-3′-methoxy-3′-(4-nitrophenyl)-propionyl]-bornanesultam (13b). Colorless gummy liquid. $[\alpha]_D^{24}$ +5.31 (*c* 0.9, $CHCl_3$); FTIR (KBr): 3422 (br), 1686, 1522, 1384, 1347, 1302, 1216, 1166, 1136, 1116, 1066, 1041, 993, 856, 760, 699, 614, 533, 498 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.24 (d, *J*=8.7 Hz, 2H), 7.62 (d, *J*=8.7 Hz, 2H), 4.95 (d, *J*=6.5 Hz, 1H), 4.81 (d, *J*=6.5 Hz, 1H), 4.17–3.92 (m, 2H), 3.53–3.51 (m, 2H), 3.21 (s, 3H), 2.32–2.03 (m, 2H), 2.00–1.81 (m, 3H), 1.56–1.27 (m, 2H), 1.15 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.2, 148.0, 144.2, 128.9 (2C), 123.3 (2C), 82.9, 65.3, 57.7, 52.7, 48.6, 47.9, 45.7, 44.5, 37.7, 32.5, 26.7, 20.2, 19.6; Anal. Calcd for ($C_{20}H_{25}BrN_2O_6S$+1·H_2O): C, 46.25; H, 5.24; N, 5.39. Found: C, 46.19; H, 5.19; N, 5.48%.

2.1.1.10. *syn*-(2*R*,2′*S*,3′*R*)-*N*-[2′-Azido-3′-methoxy-3′-(4-nitrophenyl)-propionyl]-bornanesultam (14). To a stirred solution of **13a** (0.50 g, 1.05 mmol) in 10 mL DMF at 60 °C was added NaN_3 (0.11 g, 1.50 mmol) and stirred for 8 h at 60 °C. The reaction mixture was quenched with water and extracted with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was then purified by flash column chromatography to obtain pure **14** (0.48 g, 92%) as white solid. Mp 152–154 °C; $[\alpha]_D^{26}$ −76.57 (*c* 1.0, $CHCl_3$); FTIR (KBr): 2140, 2111, 1711, 1607, 1519, 1333, 1216, 1166, 1135, 1106, 1067, 831, 761, 541 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.21 (d, *J*=6.8 Hz, 2H), 7.59 (d, *J*=6.8 Hz, 2H), 4.90 (d, *J*=5.7 Hz, 1H), 4.50 (d, *J*=5.7 Hz, 1H), 4.00–3.80 (m, 2H), 3.45 (s, 2H), 3.30 (s, 3H), 2.25–1.60 (m, 5H), 1.50–1.10 (m, 2H), 0.90 (s, 3H), 0.68 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.6, 148.3, 143.9, 128.8 (2C), 123.7 (2C), 83.4, 65.9, 65.2, 57.8, 53.0, 48.4, 47.5, 44.7, 37.9, 32.7, 26.4, 20.0, 19.7; Anal. Calcd for $C_{20}H_{25}N_5O_6S$: C, 51.83; H, 5.44; N, 15.11. Found: C, 51.89; H, 5.34; N, 14.89%.

2.1.1.11. *syn*-(2*R*,3*R*)-[2-Amino-3-methoxy-3-(4-nitrophenyl)-1-propanol] (15). To a stirred solution of **14** (0.30 g, 0.72 mmol) in 5 mL THF were added 1 mL MeOH followed by $LiBH_4$ (0.017 g, 0.72 mmol) at 0 °C under an argon atmosphere and stirred for 1 h. The reaction mixture was quenched with slow addition of H_2O at 0 °C and extracted with EtOAc (3×40 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was taken in 5 mL THF and 1 mL H_2O mixture, to that Ph_3P (0.226 g, 0.86 mmol) was added and stirred for 12 h in dark. The reaction mixture was diluted with EtOAc (50 mL) and evaporated under reduced pressure. The crude compound was purified by column chromatography to afford pure **15** (0.106 g, 82%) as a colorless gummy liquid. $[\alpha]_D^{26}$ −65.59 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3367 (br), 1605, 1522, 1348, 1108, 854, 829, 753, 701, 617, 542 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.22 (d, *J*=8.7 Hz, 2H), 7.49 (d, *J*=8.7 Hz, 2H), 4.25 (d, *J*=6.5 Hz, 1H), 3.60–3.40 (m,

1H), 3.40–3.10 (m, 2H), 3.24 (s, 3H), 2.94 (br s, NH), 2.40 (br s, OH); ^{13}C NMR ($CDCl_3$): δ 147.7, 146.9, 128.0 (2C), 123.7 (2C), 84.1, 62.8, 58.2, 57.4; Anal. Calcd for ($C_{10}H_{14}N_2O_4$+1.5·H_2O): C, 47.43; H, 6.77; N, 11.06. Found: C, 47.43; H, 6.28; N, 11.39%.

2.1.1.12. 2,2-Dichloro-*N*-[1-hydroxymethyl-2-methoxy-2-(4-nitrophenyl)-ethyl]-acetamide (16). Compound **15** (0.15 g, 0.66 mmol) was taken in 25 mL of $Cl_2CHCOOMe$ and stirred at 90 °C for 45 min and after the completion of reaction, unreacted $Cl_2CHCOOMe$ was evaporated under reduced pressure, the crude material was then purified by column chromatography to obtain pure **16** (0.193 g, 87%) as a colorless gummy liquid. $[\alpha]_D^{26}$ −60.97 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3403, 1685, 1607, 1522, 1464, 1348, 1217, 1087, 1015, 859, 811, 754, 725, 702, 666, 542 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.23 (d, *J*=8.7 Hz, 2H), 7.50 (d, *J*=8.7 Hz, 2H), 7.05 (d, *J*=8.5 Hz, NH), 5.80 (s, 1H), 4.73 (d, *J*=3.1 Hz, 1H), 4.20–4.00 (m, 1H), 3.82 (d, *J*=5.3 Hz, 2H), 3.37 (s, 3H), 1.95 (br s, OH); ^{13}C NMR ($CDCl_3$): δ 164.2, 147.7, 145.4, 127.5 (2C), 123.7 (2C), 80.9, 66.1, 61.9, 57.8, 56.3; Anal. Calcd for $C_{12}H_{14}Cl_2N_2O_5$: C, 42.75; H, 4.19; N, 8.31. Found: C, 42.07; H, 4.45; N, 8.79%.

2.1.1.13. (−)-Chloramphenicol (1). To a stirred solution of **16** (0.15 g, 0.42 mmol) in 5 mL DCM at –78 °C was added 1 M solution of BBr_3 in DCM (1.11 mL, 1.11 mmol) and the temperature was raised to –20 °C under an argon atmosphere and stirred for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3×40 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography to afford pure (−)-chloramphenicol **1** (0.115 g, 0.34 mmol) as white solid. Mp 150–152 °C [lit.[11] 149.7–150.7 °C]; $[\alpha]_D^{26}$ −25.16 (*c* 1.0, EtOAc) [lit[11] $[\alpha]_D^{23}$ −25.5 (*c* 1, EtOAc)]. Spectroscopic data consistent with that reported in the literature.[4i]

2.1.1.14. (2*R*)-*N*-[(2-Methanesulfonyl-phenyl)-propenoyl]-bornanesultam (17). To a stirred solution of **9b** (2.0 g, 5.13 mmol) in 25 mL of dry MeOH at room temperature were added magnesium mono peroxy phthalate (6.0 g, 12.82 mmol) and stirred for 2 h. The reaction mixture was filtered through one-inch bed of Celite, the filtrate was taken and the MeOH was evaporated under reduced pressure. The gummy material was dissolved in EtOAc and washed with saturated $NaHCO_3$ solution; the organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude compound was purified by column chromatography to afford pure **17** (2 g, 92%) as white solid. Mp 170–172 °C; $[\alpha]_D^{25}$ −97.48 (*c* 0.5, $CHCl_3$); FTIR (KBr): 1676, 1629, 1408, 1334, 1309, 1236, 1219, 1150, 1136, 1116, 1089, 1066, 987, 959, 830, 781, 768, 663, 541, 499 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.94 (d, *J*=8.3 Hz, 2H), 7.77 (d, *J*=15.6 Hz, 1H), 7.73 (d, *J*=8.3 Hz, 1H), 7.26 (d, *J*=15.6 Hz, 1H), 4.10–3.90 (m, 1H), 3.52 (d, *J*=5.3 Hz, H), 3.05 (s, 3H), 2.15 (d, *J*=6.8 Hz, 2H), 2.10–1.75 (m, 3H), 1.55–1.25 (m, 2H), 1.19 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 163.3, 142.6, 141.6, 139.4, 129.1 (2C), 127.9 (2C), 121.1, 65.2, 53.1, 48.6, 47.8, 44.6, 44.3, 38.3, 32.8, 26.4, 20.7, 19.8; Anal. Calcd for $C_{20}H_{25}NO_5S_2$: C, 56.71; H, 5.95; N, 3.31. Found: C, 56.99; H, 6.01; N, 3.56%.

2.1.1.15. *anti*-(2*R*,2′*R*,3′*R*)-*N*-[2′-Bromo-3′-methoxy-3′-(2-methanesulfonyl-phenyl)-propionyl]-bornanesultam (18a). White solid. Mp 185–187 °C; $[\alpha]_D^{26}$ −81.49 (*c* 1.0, $CHCl_3$); FTIR (KBr): 1696, 1409, 1385, 1336, 1309, 1219, 1151, 1117, 1099, 1058, 958, 754, 571, 534 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.96 (d, *J*=8.2 Hz, 2H), 7.64 (d, *J*=8.2 Hz, 2H), 4.78 (s, 2H), 4.10–3.90 (m, 1H), 3.52 (s, 2H), 3.22 (s, 3H), 3.08 (s, 3H), 2.20–2.05 (m, 2H), 2.00–1.80 (m, 3H), 1.60–1.30 (m, 2H), 1.15 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.2, 143.5, 140.8, 129.3 (2C), 127.3 (2C), 82.4, 64.9, 58.1, 52.8, 48.8, 47.8, 45.3, 44.4 (2C), 37.4, 32.6, 26.3, 20.6, 19.8; Anal. Calcd for $C_{21}H_{28}BrNO_6S_2$: C, 47.19; H, 5.28; N, 2.62. Found: C, 46.97; H, 5.42; N, 2.99%.

2.1.1.16. *anti*-(2*R*,2′*S*,3′*S*)-*N*-[2′-Bromo-3′-methoxy-3′-(2-methanesulfonyl-phenyl)-propionyl]-bornanesultam (18b). Colorless gummy liquid. $[\alpha]_D^{25}$ −69.47 (*c* 0.96, $CHCl_3$); FTIR (KBr): 1697, 1412, 1388, 1361, 1333, 1309, 1221, 1144, 1121, 1106, 1062, 1021, 968, 845, 734, 563, 519 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.95 (d, *J*=8.3 Hz, 2H), 7.66 (d, *J*=8.3 Hz, 2H), 4.94 (d, *J*=6.2 Hz, 1H), 4.82 (d, *J*=6.2 Hz, 1H), 4.11–3.89 (m, 1H), 3.54–3.51 (m, 2H), 3.23 (s, 3H), 3.07 (s, 3H), 2.22–2.05 (m, 2H), 2.03–1.81 (m, 3H), 1.60–1.28 (m, 2H), 1.14 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.3, 143.4, 140.8, 129.9 (2C), 127.1 (2C), 82.3, 65.0, 58.0, 52.9, 48.7, 47.6, 45.1, 44.2, 37.5, 32.5, 26.2, 20.4, 19.6; Anal. Calcd for ($C_{21}H_{28}BrNO_6S_2$+0.5·H_2O): C, 46.41; H, 5.38; N, 2.58. Found: C, 46.70; H, 5.51; N, 2.63%.

2.1.1.17. *syn*-(2*R*,2′*S*,3′*R*)-*N*-[2′-Azido-3′-methoxy-3′-(2-methanesulfonyl-phenyl)-propionyl]-bornanesultam (19). Colorless gummy liquid. $[\alpha]_D^{26}$ −67.35 (*c* 1.0, $CHCl_3$); FTIR (KBr): 2925, 2112, 1725, 1691, 1409, 1311, 1218, 1151, 1104, 959, 767, 536 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.92 (d, *J*=8.1 Hz, 2H), 7.62 (d, *J*=8.1 Hz, 2H), 4.90 (d, *J*=5.5 Hz, 1H), 4.49 (d, *J*=5.5 Hz, 1H), 4.10–3.85 (m, 1H), 3.45 (s, 2H), 3.36 (s, 3H), 3.07 (s, 3H), 2.20–1.80 (m, 5H) 1.50–1.10 (m, 2H), 1.98 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.6, 142.9, 140.9, 128.7 (2C), 128.0 (2C), 83.5, 65.1, 57.6, 52.9, 48.8, 47.8, 45.4, 44.5 (2C), 38.2, 32.7, 26.3, 20.2, 19.8; Anal. Calcd for $C_{21}H_{28}N_4O_6S_2$: C, 50.79; H, 5.68; N, 11.28. Found: C, 51.11; H, 5.97; N, 11.67%.

2.1.1.18. *syn*-(2*R*,3*R*)-[2-Amino-3-methoxy-3-(4-methanesulfonyl-phenyl)-1-propanol] (20). Colorless gummy liquid. $[\alpha]_D^{26}$ −61.97 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3370 (br), 2931, 1598, 1465, 1408, 1303, 1149, 1088, 960, 833, 772, 547, 505 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.94 (d, *J*=8.3 Hz, 2H), 7.52 (d, *J*=8.3 Hz, 2H), 4.89 (br s, 1H), 4.22 (d, *J*=6.3 Hz, 1H), 3.60–3.20 (m, 2H), 3.24 (s, 3H), 3.07 (s, 3H), 3.05–2.80 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 146.0, 140.0, 128.1 (2C), 127.5 (2C), 84.3, 62.9, 58.2, 57.3, 44.4; Anal. Calcd for ($C_{11}H_{17}NO_4S$+1·H_2O): C, 47.64; H, 6.91; N, 5.05. Found: C, 47.33; H, 7.03; N, 4.89%.

2.1.1.19. 2,2-Dichloro-*N*-[1-hydroxymethyl-2-methoxy-2-(4-methanesulfonyl-phenyl)-ethyl]-acetamide (21). White solid. Mp 112–114 °C; $[\alpha]_D^{26}$ −55.68 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3495, 3278, 3003, 1692, 1547, 1409,

1301, 1289, 1149, 1086, 1073, 808, 772, 686, 557, 544 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.93 (d, J=8.3 Hz, 2H), 7.52 (d, J=8.3 Hz, 2H), 7.05 (d, J=8.8 Hz, 1H), 5.82 (s, 1H), 4.70 (d, J=3.2 Hz, 1H), 4.20–3.90 (m, 1H), 3.78 (d, J=5.5 Hz, 2H), 3.35 (s, 3H), 3.05 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 164.2, 144.6, 140.1, 127.6 (2C), 127.5 (2C), 80.7, 66.2, 61.7, 57.8, 56.5, 44.3; Anal. Calcd for $C_{13}H_{17}Cl_2NO_5S$: C, 42.17; H, 4.63; N, 3.78. Found: C, 41.87; H, 4.72; N, 3.90%.

2.1.1.20. (+)-Thiamphenicol (2). White solid. Mp 163–165 °C [lit.[2] 164.3–166.3 °C]; $[\alpha]_D^{26}$ +12.61 (*c* 1.0, EtOH) [lit.[2] $[\alpha]_D^{25}$ +12.9 (*c* 1, EtOH)]. Spectroscopic data consistent with that reported in the literature.[4i]

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A novel conversion of acetylenic 1,2,4-triazoles into 3-alkyl-5-arylpyridazines

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Abstract—Bromination of 2-aryl-1-[1,2,4]triazol-1-ylalk-3-yn-2-ols gives 6-bromo-7-hydroxy-5-alkyl-7-aryl-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ylium salts, which are converted by treatment with strong alkali into novel 3-alkyl-5-arylpyridazines.

1. Introduction

Pyridazines are an important class of heterocycle, which have been the subject of extensive research, particularly in the pharmaceutical and agrochemical areas, and their synthesis and applications have been comprehensively reviewed.[1–4] While there are numerous general methods for the synthesis of pyridazines, there are only few methods for making 3-substituted-5-arylpyridazines. These have usually been based on cycloaddition chemistry, for example, alkyl or alkylstannyl acetylenes undergo [4+2] cycloaddition with 3-aryl-1,2,4,5-tetrazines to give mixtures of regioisomers, which can be manipulated to give a variety of 3,5-diarylpyridazines,[5] and monohaloazodienes react with enamines to give 3-alkyl-5-arylpyridazines in variable yields.[6] In another approach, addition of diazomethane to diarylcyclopropene carboxylates gives diazabicyclohexenes, which lose nitrogen in situ to give diarylpyridazine esters, which are in turn hydrolysed and decarboxylated to give 3,5-diarylpyridazines.[7] In this paper, we wish to report a novel route to 3-alkyl-5-arylpyridazines from 1,2,4-triazolyl alkynols. Our route involves the intramolecular attack of the triazole ring nitrogen on a bromonium ion or bromovinyl cation generated by bromination of an acetylene to give a fused triazolium salt, which then breaks down on treatment with aqueous alkali to give the 3-alkyl-5-arylpyridazines.

Substituted 1,2,4-triazoles have received a great deal of attention owing to their biological activity against both agricultural[8] and human fungi.[9] In particular, tertiary triazolyl alcohols of general type **1** have been of great interest because of their outstanding potency on a wide range of fungal pathogens. In the agrochemical field extensive work by many groups[10] has shown that R and R^1 in **1** can be aryl rings or alkyl chains, which in turn can be substituted by many different groups such as ethers, ketones, esters or even another triazole ring. Important examples of antifungal triazoles are the agricultural fungicide epoxiconazole[11] **2** and the pharmaceutical fungicide fluconazole **3**[9] (Fig. 1).

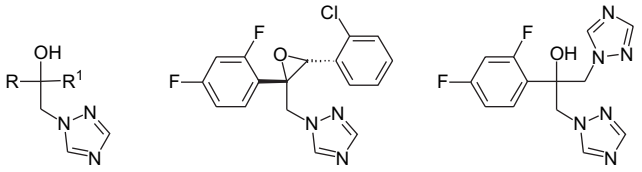

Figure 1. Structures of fungicidal 1,2,4-triazoles **1**–**3**.

2. Results

During our research into fungicides for agricultural use we found that triazoles **1** where R was a substituted phenyl group and R^1 was an alkenyl or alkynyl group, showed high fungicidal activity. We developed a simple synthesis of acetylenic triazoles **6a**–**f**[12] (Scheme 1). Lithium acetylides, generated from the acetylenes by treatment with *n*-butyl lithium, were added smoothly to chloroacetophenones **4a**–**f** to give moderate to excellent yields of the chlorohydrins **5a**–**f**. The crude chlorohydrins were reacted directly with the anion of 1,2,4-triazole, generated with sodium hydride in DMF, to give the 1,2,4-triazolyl alkynols **6a**–**f** in moderate to good yields. For the synthesis of the ethynyl compound **6a**, the trimethylsilyl acetylene chlorohydrin **5a** was used and the trimethylsilyl group was removed by acidic work-up after reaction with 1,2,4-triazole.

Keywords: Pyridazines; Triazoles; Acetylenes; Triazolium; Cyclisation.
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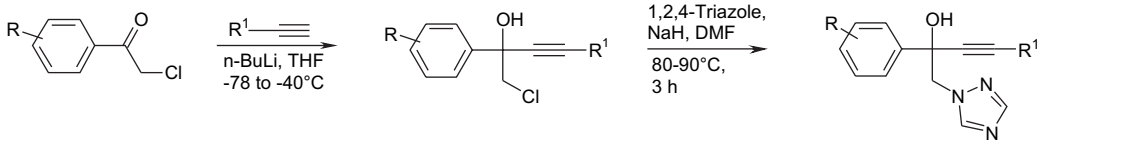


4a R = 2,4-di-Cl
4b R = 4-Cl
4c R = 2,4-di-F

	crude yield
5a R = 2,4-di-Cl, R^1 = $Si(CH_3)_3$,	88%
5b R = 2,4-di-Cl, R^1 = CH_3,	92%
5c R = 2,4-di-Cl, R^1 = C_2H_5,	37%
5d R = 2,4-di-Cl, R^1 = n-C_5H_{11},	100%
5e R = 4-Cl, R^1 = C_2H_5,	100%
5f R = 2,4-di-F, R^1 = C_2H_5	85%

	yield from **4a-e**
6a R = 2,4-di-Cl, R^1 = H,	41%
6b R = 2,4-di-Cl, R^1 = CH_3,	20%
6c R = 2,4-di-Cl, R^1 = C_2H_5,	58%
6d R = 2,4-di-Cl, R^1 = n-C_5H_{11},	59%
6e R = 4-Cl, R^1 = C_2H_5,	41%
6f R = 2,4-di-F, R^1 = C_2H_5,	55%

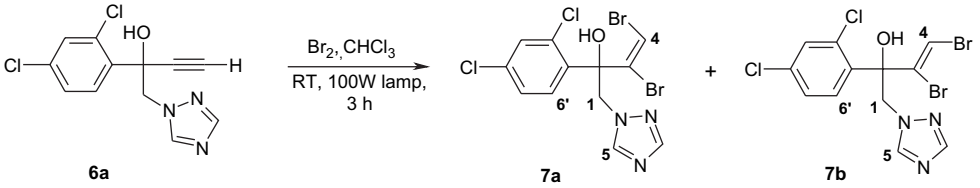
Scheme 1. Synthesis of triazolyl alkynols **6a–f**.

We wished to make some triazoles of type **1** where R was a substituted phenyl group and R^1 was a halogenated alkyl group, and it seemed likely that with the alkynyl analogues **6a–f** in hand, simple addition of halogens would quickly give examples for biological testing. Accordingly bromine was added to the ethynyl compound **6a** in chloroform at room temperature, but gave no reaction. However, in the presence of light (100 W tungsten lamp) smooth bromination took place and after 3 h a nearly quantitative yield of *E*- and *Z*-isomers **7a** and **7b** in an approximately 2:5 ratio was obtained (Scheme 2). The stereochemistry of **7a** and **7b** was assigned by ^{1}H NMR. In the *Z*-isomer **7b** the protons H-1, H-5 and H-6′ showed an NOE when olefinic proton H-4 was irradiated, whereas in the *E*-isomer **7a**, when proton H-4 was irradiated no NOEs were detected.

In the expectation that the alkyl acetylenes **6b–f** would undergo similar radical bromination, we were surprised to find that when bromine was added to the compounds in chloroform at room temperature preparatory to carrying out the light reaction, an exothermic reaction occurred, leading to a rapid decolourisation followed by gradual precipitation of white crystalline solids. After treatment with aqueous alkali to neutralise the reaction these solids yielded new compounds, identified as the novel pyridazines **8b–f** (Scheme 3).

The mass spectra for each of **8b–f** showed a major ion for the loss of two carbon atoms, one nitrogen atom and water from the starting materials **6b–f**, with no incorporation of bromine. There was no alcohol present in their IR spectra. In the ^{1}H NMR spectrum, the triazole protons, typically as singlets at around 7.80 and 8.20 ppm, were replaced by new singlets at around 7.30 and 9.30 ppm. An ^{1}H–^{13}C HMBC study of compound **8e** confirmed all the key connectivities. Pyridazine proton H-4 correlated with carbons C-6 and C-1′, pyridazine proton H-6 correlated with C-4 and C-5 and the ethyl CH_2 protons correlated with C-3 and C-4. Additionally, when pyridazine proton H-6 was irradiated an NOE was shown by the benzene proton H-2′ and when the ethyl CH_2 protons were irradiated an NOE was shown by H-4. The microanalyses were in agreement with the proposed structures.

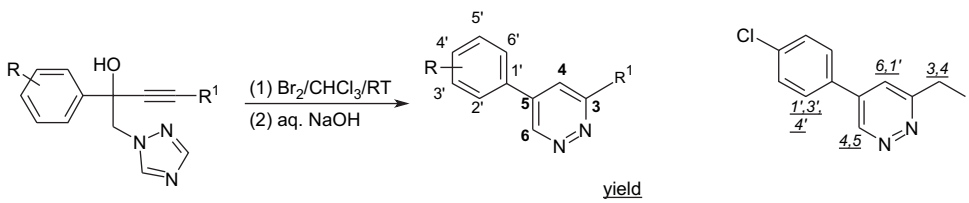
Having identified the final products we then turned our attention to the precipitates formed in the bromination



6a **7a** **7b**

7a:**7b**, 2:5

Scheme 2. Reaction of triazolyl alkynol **6a** with bromine.



6b R = 2,4-di-Cl, R^1 = CH_3
6c R = 2,4-di-Cl, R^1 = C_2H_5
6d R = 2,4-di-Cl, R^1 = n-C_5H_{11}
6e R = 4-Cl, R^1 = C_2H_5
6f R = 2,4-di-F, R^1 = C_2H_5

	yield
8b R = 2,4-di-Cl, R^1 = CH_3	89%
8c R = 2,4-di-Cl, R^1 = C_2H_5	26%
8d R = 2,4-di-Cl, R^1 = n-C_5H_{11}	40%
8e R = 4-Cl, R^1 = C_2H_5	57%
8f R = 2,4-di-F, R^1 = C_2H_5	80%

8e
^{1}H-^{13}C correlations

Scheme 3. Bromination of triazolyl alkynols **6b–f** to give pyridazines **8b–f**.

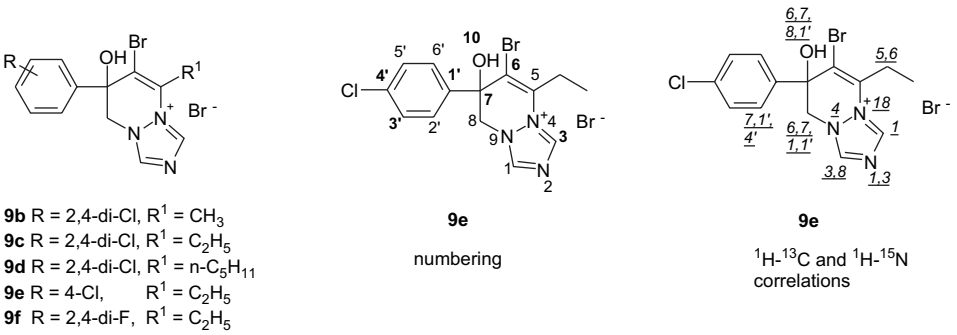


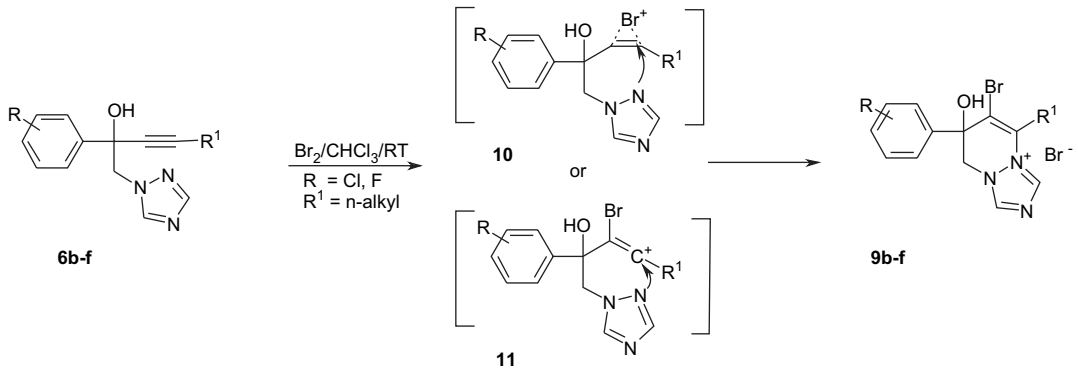
Figure 2. Structures and NMR correlations for triazolium salts **9b–f**.

reaction before work-up, which were found to be extremely soluble in water and to have very high melting points. The electrospray mass spectra showed strong ions corresponding to the addition of one bromine atom and the microanalyses were consistent with the addition of two bromine atoms to the starting materials **6b–f**. Bearing in mind the structures of the pyridazine final products and the putative mechanisms for their formation, it seemed possible that the precipitates could be the novel triazolium salts of structures **9b–f**. In the ^{1}H NMR the signals for the triazole protons, typically singlets at around 7.80 and 8.20 ppm in the starting materials **6b–f**, were replaced by two very low field singlets at around 9.5 and 10.00 ppm, which was consistent with the structures being highly electron deficient triazolium salts (Fig. 2).

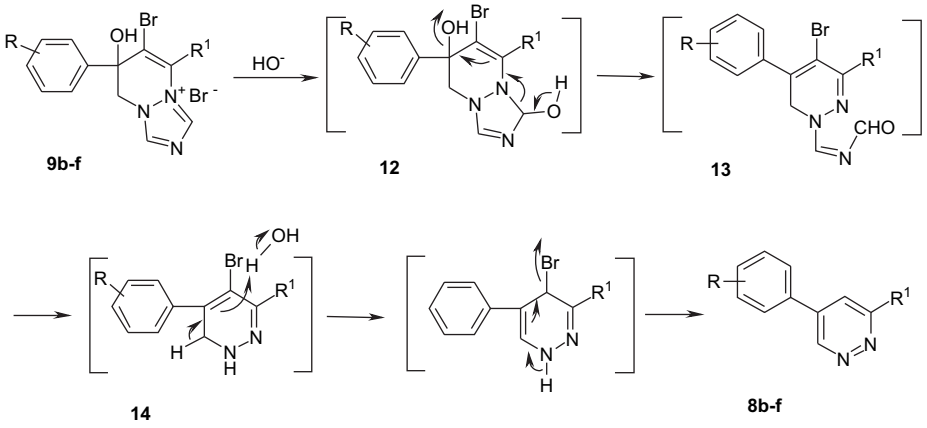
The structures were confirmed as **9b–f** by an ^{1}H–^{13}C HMBC experiment on compound **9e**, which showed that triazole H-1 correlated to triazole C-3 and methylene C-8, triazole proton H-3 correlated to triazole C-1, quaternary benzylic carbon C-7 correlated to benzene ring protons H-2′/H-6′ and methylene protons H-8 and the hydroxyl proton correlated to methylene carbon C-8 and vinyl carbon C-6. In addition an ^{1}H–^{15}N HMBC study was carried out. This showed that ethyl CH_2 and ring methylenes H-8 correlated to triazolium N-4, ring methylenes H-8 correlated with triazolium N-9 and triazoliums H-1 and H-3 correlated to triazolium N-2. The chemical shifts of N-4 and N-9 were very similar, as expected for a triazolium salt, while N-2 was at slightly lower field. The yields of the triazolium salts **9b–f** from triazoles **6b–f** were 84–92%.

3. Discussion

The mechanism of formation of triazolium salts **9b–f** was rationalised as addition of bromine to the triple bond to give an ionic intermediate, which is then intercepted by a triazole nitrogen (Scheme 4). The addition of bromine to triple bonds in a range of solvents is known to proceed to give either a cyclic bromonium ion or vinyl cation,[13] which then reacts with an available nucleophile such as a bromide ion or a solvent molecule to give mainly *E*-products. In the case of electron deficient acetylenes, nucleophilic attack by bromine or bromide ion has also been proposed[14] as the first step, but it would seem unlikely in this instance, as the acetylene is not activated. In the present case we therefore, propose that a cyclic bromonium ion **10** or vinyl cation **11** is formed, which reacts in a 6-*endo-trig* attack by the 2-nitrogen of the triazole to form the triazolium salt **9b–f**. 6-*endo-trig* cyclisation is favoured by Baldwin's rules,[15] but seems to have been rather rarely reported for attack of nitrogen nucleophiles onto acetylenes, having been more commonly observed when a nitrogen anion undergoes nucleophilic addition to an electron deficient acetylene[16] or in metal catalysed reactions.[17] However, a useful synthesis of iodo isoquinolines[18] has been developed based on a 6-*endo-trig* cyclisation of *t*-butylimines onto arylacetylenes in the presence of iodine or iodine monochloride and Larock has proposed a similar mechanism to ours, with attack of the imine nitrogen onto an iodonium ion. In the latter case the cyclisation onto alkyl acetylenes proceeded poorly with iodine, but the yields were much higher when silver nitrate or cuprous iodide was used to



Scheme 4. Proposed mechanism of conversion of triazolyl alkynols **6b–f** to triazolium salts **9b–f**.



Scheme 5. Possible mechanism of conversion of triazolium salts **9b–f** to pyridazines **8b–f**.

activate the triple bond. The reaction with the ethynyl compounds was not reported.

The difference between ethynyl compound **6a** and alkyl acetylenes **6b–f** in their mode of reaction with bromine is striking. There is some evidence that terminal acetylenes are less reactive to bromine than disubstituted acetylenes,[19] which is consistent with the lack of reaction of bromine with ethynyl compound **6a**. Additionally, in a recently reported case of competition between disubstituted and monosubstituted acetylenes in reaction with an iminium ion, the only product obtained was from the disubstituted acetylene, with none from the terminal acetylene being found.[20] In our case we presume that the alkyl groups in **6b–f** both impart greater nucleophilicity to the triple bond and provide extra stabilisation of the vinyl cation or bromonium ion by hyperconjugation.

A possible mechanism for conversion of the triazolium salts **9b–f** to the pyridazines **8b–f** is shown in Scheme 5, although the exact order of steps and identity of the intermediates can only be a matter of conjecture, as no intermediates could be isolated. It is likely to start with the known addition of hydroxide ion to triazolium rings[21] to give a pseudo-bases of type **12**, or their regioisomers, followed by ring-opening and elimination of water to give **13**. Cleavage of the formamido methylene group to **14**, followed by a prototropic shift and elimination of HBr could then lead to the pyridazines **8b–f**.

The reaction to form the triazolium salts **9b–f** followed by the transformation to the pyridazines was general for a small selection of acetylenic triazoles tried. The bromination reaction to form the triazolium salts went in high yield, but it was found that conversion to the pyridazines could be considerably improved by dissolving the salts in a small amount of water and adding the subsequent solution to hot 5 N sodium hydroxide, followed by extraction into ethyl acetate after a few minutes (Table 1).

For comparison we attempted chlorination of the acetylenes. With the ethynyl compound **6a** chlorination proceeded to give a mixture of *E*- and *Z*-isomers, but only in the presence of light. No reaction took place at room temperature. With the ethyl acetylene **6c** the reaction with chlorine with or without light gave very messy reactions from which no addition products or triazolium salts could be isolated.

4. Conclusion

In conclusion we have discovered a novel synthesis of 3-alkyl-5-arylpyridazines, which to our knowledge is the first example of formation of a pyridazine from a 1,2,4-triazole, and which constitutes a useful additional approach to specifically substituted examples of these ring systems.

5. Experimental

5.1. General

Melting points were taken using a Büchi B-545 apparatus, and were uncorrected. Infrared Spectra were run on a Perkin–Elmer Spectrum One spectrometer as solid or liquid thin films on a KBr window. ^{1}H and ^{13}C NMR spectra were measured on a Varian Inova-400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), HMBC and HSQC spectra were measured on a Varian Inova-500 NMR spectrometer (^{1}H, 500 MHz). Chemical shifts are in parts per million relative to TMS

Table 1. Reaction of triazoles **6b–f** to form triazolium salts **9b–f** and pyridazines **8b–f**

Starting triazole	R	R^1	Triazolium salt	Isolated yield from **6b–f** (%)	Pyridazine	Isolated yield from **9b–f** (%)
6b	2,4-Di-Cl	CH_3	**9b**	89	**8b**	100
6c	2,4-Di-Cl	C_2H_5	**9c**	92	**8c**	28
6d	2,4-Di-Cl	*n*-C_5H_{11}	**9d**	88	**8d**	45
6e	4-Cl	C_2H_5	**9e**	84	**8e**	68
6f	2,4-Di-F	C_2H_5	**9f**	88	**8f**	91

(^{1}H, ^{13}C 0.0 ppm) and coupling constants (J) are measured in hertz (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, qd = quartet of doublets, qq = quartet of quartets). Mass spectra were recorded on Micromass PlatformLC. Microanalyses were performed by MEDAC Ltd, Englefield Green, Surrey, UK. All commercially available compounds were used without further purification. Flash chromatography was performed on Merck Kieselgel 60 silica gel, and thin-layer chromatography was performed using Analtech Silica Gel GF 2000 micron plates.

5.2. General procedure for the synthesis of 1-chloro-2-arylalkyn-2-ols (5a–f)

n-Butyl lithium (30 mmol of a 1.6 M solution in hexane) was added dropwise to the alkyne (30 mmol) in 25 mL dry THF at −78 °C, and after completion of the addition the reaction mixture was stirred for 1 h. The haloacetophenone (20 mmol) in 50 mL dry THF was added dropwise keeping the temperature below −70 °C. After completion of the addition the reaction mixture was stirred for 1 h and then warmed to −40 °C, and then poured carefully into water and extracted four times with 50 mL diethyl ether. The ethereal extracts were combined, washed with dilute hydrochloric acid followed by water, and then dried over magnesium sulfate. After evaporation the products **5a–f** were obtained as oils, which were characterised by ^{1}H NMR, IR and MS, and were used for the next step without further purification.

5.2.1. 1-Chloro-2-(2,4-dichlorophenyl)-4-trimethylsilanylbut-3-yn-2-ol (5a). Pale yellow oil, crude yield 88%: IR (cm^{-1}) 3480, 2170, 1580, 1490, 1373, 840. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J=8.7 Hz), 7.47 (d, 1H, J=2.15 Hz), 7.36 (dd, 1H, J=8.7, 2.15 Hz), 4.25 (d, 2H, J=11.0 Hz), 4.02 (d, 2H, J=11.0 Hz), 3.36 (s, OH), 0.20 (s, 9H).

5.2.2. 1-Chloro-2-(2,4-dichlorophenyl)-pent-3-yn-2-ol (5b). Pale yellow oil, crude yield 92%: IR (cm^{-1}) 3460, 2244, 1585, 1467, 1376, 1048, 823, 795. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 1H, J=8.6 Hz), 7.43 (d, 1H, J=2.15 Hz), 7.31 (dd, 1H, J=8.6, 2.15 Hz), 4.19 (d, 1H, J=11.15 Hz), 3.96 (d, 1H, J=11.15 Hz), 1.91 (s, 3H).

5.2.3. 1-Chloro-2-(2,4-dichlorophenyl)-hex-3-yn-2-ol (5c). Pale yellow oil, crude yield 37%: IR (cm^{-1}) 3460, 2239, 1586, 1467, 1377, 1048, 823, 793. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 1H, J=8.7 Hz), 7.31 (dd, 1H, J=8.7, 2.15 Hz), 4.17 (d, 1H, J=11.1 Hz), 3.97 (d, 1H, J=11.1 Hz), 3.11 (s, OH), 2.28 (q, 2H, J=7.5 Hz), 1.16 (t, 3H, J=7.5 Hz).

5.2.4. 1-Chloro-2-(2,4-dichlorophenyl)-non-3-yn-2-ol (5d). Pale yellow oil, crude yield 100%: IR (cm^{-1}) 3460, 2230, 1586, 1467, 1377, 1049, 780. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 1H, J=8.6 Hz), 7.31 (dd, 1H, J=8.6, 2.15 Hz), 4.19 (d, 1H, J=11.1 Hz), 3.96 (d, 1H, J=11.1 Hz), 2.26 (t, 2H, J=7.1 Hz), 3.10 (s, OH), 1.49–1.59 (m, 4H), 1.25–1.41 (m, 2H), 0.89 (t, 3H, J=7.0 Hz).

5.2.5. 1-Chloro-2-(4-chlorophenyl)-hex-3-yn-2-ol (5e). Pale yellow oil, crude yield 100%: IR (cm^{-1}) 3420, 2232, 1489, 1091, 1014, 828. ^{1}H NMR ($CDCl_3$): δ 7.60 (d, 2H, J=8.7 Hz), 7.37 (d, 2H, J=8.7 Hz), 3.74 (d, 1H, J=11.0 Hz), 3.68 (d, 1H, J=11.0 Hz), 2.98 (s, OH), 2.32 (q, 2H, J=7.5 Hz), 1.20 (t, 3H, J=7.5 Hz).

5.2.6. 1-Chloro-2-(2,4-difluorophenyl)-hex-3-yn-2-ol (5f). Pale yellow oil, crude yield 85%: IR (cm^{-1}) 3454, 2238, 1614, 1499, 1272, 1139, 1097, 971, 849. ^{1}H NMR ($CDCl_3$): δ 7.75 (td, J=8.8, 6.5 Hz), 6.92 (qq, 1H, J=8.8, 2.5, 1.0 Hz), 6.84 (qd, 1H, J=8.6, 2.6 Hz), 4.00 (d, 1H, J=11.0 Hz), 3.91 (d, 1H, J=11.0 Hz), 3.02 (s, OH), 2.28 (q, 2H, J=7.5 Hz), 1.17 (t, 3H, J=7.5 Hz).

5.3. General procedure for the synthesis of 2-aryl-1-[1,2,4]triazol-1-ylalkyn-2-ols (6a–f)

1,2,4-Triazole (28 mmol) was added portionwise to a suspension of sodium hydride (29 mmol of a 50% dispersion in oil) in dry DMF. After stirring at room temperature for 30 min, the crude 1-chloro-2-arylalkyn-2-ol (14 mmol) in 10 mL dry DMF was added dropwise. After completion of the addition the reaction mixture was heated to 80–90 °C for 3 h. The reaction mixture was cooled and poured into 300 mL water and extracted with 100 mL diethyl ether three times. The combined extracts were washed with water, dried over magnesium sulfate and evaporated to give residues, which were either recrystallised or purified by flash column chromatography on silica gel to give the products **6a–f**.

5.3.1. 2-(2,4-Dichlorophenyl)-1-[1,2,4]triazol-1-yl-but-3-yn-2-ol (6a). White solid, yield 41%: mp 129–131 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3263, 3034, 1513, 1137, 1079, 1049, 803. ^{1}H NMR ($CDCl_3$): δ 8.13 (s, 1H), 7.77 (d, 1H, J=8.6 Hz), 7.94 (s, 1H), 7.44 (d, 1H, J=2.15 Hz), 7.26 (dd, 1H, J=8.6, 2.15 Hz), 4.93 (d, 1H, J=14.1 Hz), 4.84 (s, 1H), 4.63 (d, 1H, J=14.1 Hz), 2.56 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 151.84, 144.54, 135.39, 134.89, 131.94, 130.97, 129.13, 127.49, 80.88, 75.94, 70.47, 56.51. MS m/z=282 (2^{35}Cl) $[M]^+$, 284 (^{35}Cl, ^{37}Cl) $[M+2]^+$, 286 (2^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{12}H_9Cl_2N_3O$: C 51.09; H 3.22; N 14.89. Found: C 51.25; H 3.33; N 14.66.

5.3.2. 2-(2,4-Dichlorophenyl)-1-[1,2,4]triazol-1-ylpent-3-yn-2-ol (6b). White crystalline solid, yield 20% from 2,4-dichloroacetophenone: mp 145–147 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3064, 1510, 1203, 1131, 1074, 1048, 800. ^{1}H NMR ($CDCl_3$): δ 8.02 (s, 1H), 7.84 (s, 1H), 7.65 (d, 1H, J=8.6 Hz), 7.34 (d, 1H, J=2.15 Hz), 7.15 (dd, 1H, J=8.6, 2.15 Hz), 4.75 (d, 1H, J=14.0 Hz), 4.61 (d, 1H, J=14.0 Hz), 4.35 (s, 1H), 1.70 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 151.72, 144.43, 135.93, 134.97, 131.99, 130.89, 129.05, 127.31, 84.47, 76.70, 70.74, 56.82, 3.52. MS m/z=296 (2^{35}Cl) $[M]^+$, 298 (^{35}Cl, ^{37}Cl) $[M+2]^+$, 300 (2^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{13}H_{11}Cl_2N_3O$: C 52.72; H 3.74; N 14.19. Found: C 52.95; H 3.65; N 13.90.

5.3.3. 2-(2,4-Dichlorophenyl)-1-[1,2,4]triazol-1-ylhex-3-yn-2-ol (6c). White solid, yield 58% from 2,4-dichloroacetophenone: mp 133–134 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3150, 1506, 1463, 1378, 1130, 1048, 798. ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1H), 7.91 (s, 1H), 7.73 (d, 1H, J=8.6 Hz), 7.41 (d, 1H, J=2.15 Hz), 7.23 (dd, 1H, J=8.6, 2.15 Hz), 4.83 (d, 1H, J=14.0 Hz), 4.65 (d, 1H, J=14.0 Hz), 4.38 (s, 1H), 2.13 (q, 2H, J=7.6 Hz), 1.03 (t, 3H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 151.78, 144.47,

135.91, 134.72, 132.02, 130.91, 129.07, 127.32, 90.09, 76.80, 70.78, 56.90, 13.21, 12.29. MS *m/z*=310 (2^{35}Cl) $[M]^+$, 312 (^{35}Cl, ^{37}Cl) $[M+2]^+$, 314 (2^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{14}H_{13}Cl_2N_3O$: C 54.21; H 4.22; N 13.55. Found: C 54.01; H 4.48; N 13.38.

5.3.4. 2-(2,4-Dichlorophenyl)-1-[1,2,4]triazol-1-ylnon-3-yn-2-ol (6d). White crystalline solid, yield 59% from 2,4-dichloroacetophenone: mp 83–84 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3078, 1509, 1463, 1135, 800. ^{1}H NMR ($CDCl_3$): δ 8.01 (s, 1H), 7.83 (s, 1H), 7.65 (d, 1H, *J*=8.7 Hz), 7.33 (d, 1H, *J*=2.15 Hz), 7.14 (dd, 1H, *J*=8.7, 2.15 Hz), 4.75 (d, 1H, *J*=14.0 Hz), 4.55 (d, 1H, *J*=14.0 Hz), 4.28 (2, 1H), 2.02 (t, 2H, *J*=7.0 Hz), 1.32 (t, 2H, *J*=7.0 Hz), 1.13–1.18 (m, 2H), 0.76 (t, 3H, *J*=7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 151.84, 144.45, 135.91, 134.96, 131.99, 130.90, 129.07, 127.33, 89.02, 77.39, 70.85, 56.88, 30.94, 27.77, 22.05, 18.54, 13.90. MS *m/z*=352 (2^{35}Cl) $[M]^+$, 354 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{17}H_{19}Cl_2N_3O$: C 57.96; H 5.44; N 11.93. Found: C 57.70; H 5.71; N 12.19.

5.3.5. 2-(4-Chlorophenyl)-1-[1,2,4]triazol-1-ylhex-3-yn-2-ol (6e). Pale yellow gum, yield 41% from 4-chloroacetophenone: IR (cm^{-1}) 3079, 1508, 1488, 1130, 1084, 831. ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1H), 7.59 (s, 1H), 7.55 (dt, 2H, *J*=7.8, 2.0 Hz), 7.84 (dt, 2H, *J*=7.8, 2.0 Hz), 4.84 (s, 2H), 4.14 (s, 1H), 2.16 (q, 2H, *J*=7.5 Hz), 1.05 (t, 3H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 151.75, 144.36, 139.43, 134.49, 128.62, 127.21, 90.39, 78.22, 72.19, 60.96, 13.47, 12.24. MS *m/z*=276 (^{35}Cl) $[M]^+$, 278 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{14}H_{14}ClN_3O$: C 60.98; H 5.12; N 15.24. Found: C 61.26; H 4.83; N 15.01.

5.3.6. 2-(2,4-Difluorophenyl)-1-[1,2,4]triazol-1-ylhex-3-yn-2-ol (6f). White crystalline solid, yield 55% from 2,4-difluoroacetophenone: mp 76–78 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3108, 1615, 1600, 1509, 1492, 1269, 964. ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1H), 7.85 (s, 1H), 7.56 (td, 1H, *J*=9.0, 6.4 Hz), 6.73–6.80 (m, 2H), 4.53 (q, 2H, *J*=11.3 Hz), 4.27 (s, 1H), 2.06 (q, 2H, *J*=7.5 Hz), 0.96 (t, 3H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 163.01 (d, *J*=250 Hz), 159.60 (d, *J*=250 Hz), 151.80, 144.90, 129.06 (dd, *J*=9.6, 4.6 Hz), 123.78 (dd, *J*=11.10, 3.8 Hz), 111.19 (dd, *J*=21.1, 3.4 Hz), 104.58 (t, *J*=25.7 Hz), 89.34, 77.34, 69.51, 58.17, 13.36, 12.22. MS *m/z*=287 $[MH]^+$. Anal. Calcd for $C_{14}H_{13}F_2N_3O$: C 60.65; H 4.73; N 15.15. Found: C 60.35; H 4.89; N 15.42.

5.4. Preparation of (*E*)- and (*Z*)-3,4-dibromo-2-(2,4-dichlorophenyl)-1-[1,2,4]triazol-1-ylbut-3-en-2-ols (7a) and (7b)

2-(2,4-Dichlorophenyl)-1-[1,2,4]triazol-1-yl-but-3-yn-2-ol (0.99 g, 3.5 mmol) was stirred as a slurry in 5 mL chloroform and a few drops of a solution of bromine (0.56 g, 3.5 mmol) in 5 mL chloroform were added. The reaction mixture was irradiated with a 100 W tungsten lamp and after 10 min some decolourisation occurred. The remainder of the bromine in chloroform solution was added and irradiation was continued with stirring until all the colour had disappeared. The reaction mixture was poured into 25 mL water containing a few millilitres of 2 N sodium hydroxide and was extracted twice with 25 mL ethyl acetate. The organic extract was washed with 10 mL water, dried over magnesium sulfate and evaporated to give 1.66 g (100%) of a white foam, shown by ^{1}H NMR to consist of a 2:5 mixture of *E*:*Z* isomers **7a** and **7b**. The isomers were separated by HPLC on elution with 99:1 *t*-butyl ether/methanol, to give 0.41 g of the *E*-isomer **7a** as a white crystalline solid, and 0.90 g of the *Z*-isomer **7b** as a white powdery solid.

5.4.1. (*E*)-3,4-Dibromo-2-(2,4-dichlorophenyl)-1-[1,2,4]triazol-1-ylbut-3-en-2-ol (7a). White crystalline solid, yield 26%: mp 138–141 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3075, 1511, 1466, 1200, 1132, 1080, 1015. ^{1}H NMR ($CDCl_3$): δ 7.84 (s, 1H), 7.81 (s, 1H), 7.38 (d, 1H, *J*=2.15 Hz), 7.82 (d, 1H, *J*=8.7 Hz), 7.09 (dd, *J*=8.7, 2.15 Hz), 6.78 (s, 1H), 5.19 (d, 1H, *J*=13.8 Hz), 4.91 (d, 1H, *J*=13.8 Hz), 4.85 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 151.69, 144.48, 136.59, 135.27, 131.43, 130.49, 129.88, 127.02, 124.81, 105.45, 78.17, 56.45. MS *m/z*=442 $[2^{79}Br]^+$, 444 $[^{79}Br, ^{81}Br]^+$, 446 $[2^{81}Br]^+$. Anal. Calcd for $C_{12}H_9Br_2Cl_2N_3O$: C 32.61; H 2.05; N 9.51. Found: C 32.78; H 2.46; N 9.22.

5.4.2. (*Z*)-3,4-Dibromo-2-(2,4-dichlorophenyl)-1-[1,2,4]triazol-1-ylbut-3-en-2-ol (7b). White powdery solid, yield 58%: mp 162–164 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3031, 1516, 1135, 1020. ^{1}H NMR ($CDCl_3$): δ 7.84 (s, 1H), 7.72 (s, 1H), 7.40 (d, 1H, *J*=8.6 Hz), 7.26 (d, 1H, *J*=2.15 Hz), 7.08 (dd, 1H, *J*=8.6, 2.15 Hz), 6.79 (s, 1H), 5.21 (d, 1H, *J*=14.1 Hz), 4.87 (d, 1H, *J*=14.1 Hz). ^{13}C NMR ($CDCl_3$): δ 151.79, 144.41, 135.72, 135.25, 131.97, 131.19, 130.14, 127.56, 114.21, 80.15, 55.00. MS *m/z*=442 $[2^{79}Br]^+$, 444 $[^{79}Br, ^{81}Br]^+$, 446 $[2^{81}Br]^+$. Anal. Calcd for $C_{12}H_9Br_2Cl_2N_3O$: C 32.61; H 2.05; N 9.51. Found: C 32.40; H 2.31; N 9.28.

5.5. General procedure for the synthesis of 6-bromo-7-aryl-7-hydroxy-5-alkyl-7,8-dihydro-[1,2,4]triazolo-[1,2-*a*]pyridazine-4-ylium bromides (9b–f)

Bromine (18 mmol) in chloroform (10 mL) was added dropwise to a stirred solution of the triazolyl acetylene (18 mmol) in chloroform (50 mL) at a rate sufficient to allow decolourisation and to maintain the temperature at 30 °C or less. After all the bromine had been added the resultant yellow mixtures were stirred for 1 h and the white precipitates were filtered, washed well with chloroform and air dried to give the products **9b–f** as white solids, which were analysed without further purification.

5.5.1. 6-Bromo-7-(2,4-dichlorophenyl)-7-hydroxy-5-methyl-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazine-4-ylium bromide (9b). White solid, yield 89%: mp 324–325 °C (dec). IR (cm^{-1}) 3148, 2179, 1351, 1089. ^{1}H NMR (DMSO-d_6): δ 9.85 (s, 1H), 9.51 (s, 1H), 7.93 (d, 1H, *J*=8.6 Hz), 7.77 (d, 1H, *J*=2.15 Hz), 7.64 (dd, 1H, *J*=8.6, 2.15 Hz), 5.19 (d, 1H, *J*=14.2 Hz), 5.11 (d, 1H, *J*=14.2 Hz), 2.61 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 149.69, 145.39, 135.88, 131.84, 130.63, 130.25, 128.85, 127.81, 120.16, 71.72, 53.78, 17.15. MS *m/z*=374 (^{79}Br, 2^{35}Cl) $[M]^+$, 376 (^{81}Br, 2^{35}Cl) $[M+2]^+$, 378 (^{81}Br, ^{35}Cl, ^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{13}H_{12}Br_2ClN_3O$: C 34.24; H 2.43; N 9.22. Found: C 33.98; H 2.57; N 8.89.

5.5.2. 6-Bromo-7-(2,4-dichlorophenyl)-5-ethyl-7-hydroxy-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ylium bromide (9c). White solid, yield 92%: mp 323–324 °C (dec). IR (cm^{-1}) 3158, 2256, 1349. ^1H NMR (DMSO-d_6): δ 9.95 (s, 1H), 9.52 (s, 1H), 7.95 (d, 1H, J=8.6 Hz), 7.77 (d, 1H, J=2.15 Hz), 7.64 (dd, 1H, J=8.6, 2.15 Hz), 7.54 (s, OH), 5.19 (d, 1H, J=14.4 Hz), 5.09 (d, 1H, J=14.4 Hz), 3.04 (q, 2H, J=7.5 Hz), 1.50–1.70 (m, 2H), 1.44–1.21 (m, 4H), 1.23 (q, 1H, J=11.0 Hz). ^{13}C NMR (DMSO-d_6): δ 149.86, 145.11, 135.95, 134.69, 133.14, 131.85, 130.59, 130.28, 127.83, 119.87, 71.67, 53.80, 23.83, 10.36. MS m/z=388 (^{79}Br, $2^{35}Cl$) $[M]^+$, 390 (^{81}Br, $2^{35}Cl$) $[M+2]^+$, 392 (^{81}Br, ^{35}Cl, ^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{14}H_{13}Br_2Cl_2N_3O$: C 35.78; H 2.79; N 8.94. Found: C 35.56; H 2.52; N 8.67.

5.5.3. 6-Bromo-7-(2,4-dichlorophenyl)-7-hydroxy-5-pentyl-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ylium bromide (9d). White solid, yield 88%: mp 272–273 °C (dec). IR (cm^{-1}) 3118, 3048, 2163, 1352, 1084. ^1H NMR (DMSO-d_6): δ 9.96 (s, 1H), 9.53 (s, 1H), 7.95 (d, 1H, J=8.6 Hz), 7.77 (d, 1H, J=2.15 Hz), 7.64 (dd, 1H, J=8.6, 2.15 Hz), 7.52 (s, OH), 5.19 (d, 1H, J=14.2 Hz), 5.11 (d, 1H, J=14.2 Hz), 3.03 (t, 2H, J=7.5 Hz), 1.65 (octet, 2H, J=7.5, 7.0 Hz), 1.50–1.30 (m, 4H), 0.89 (t, 3H, J=7.25 Hz). ^{13}C NMR (DMSO-d_6): δ 149.84, 145.15, 135.99, 134.69, 132.25, 131.73, 130.57, 130.24, 127.83, 120.49, 71.74, 53.70, 30.31, 29.73, 25.47, 21.81. MS m/z=430 (^{79}Br, $2^{35}Cl$) $[M]^+$, 432 (^{81}Br, $2^{35}Cl$) $[M+2]^+$, 434 (^{81}Br, ^{35}Cl, ^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{17}H_{19}Br_2Cl_2N_3O$: C 39.87; H 3.74; N 8.21. Found: C 39.66; H 3.59; N 8.05.

5.5.4. 6-Bromo-7-(4-chlorophenyl)-5-ethyl-7-hydroxy-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ylium bromide (9e). Pale yellow solid, yield 84%: mp 285–286 °C (dec). IR (cm^{-1}) 3195, 2162, 1491, 1347, 1090. ^1H NMR (DMSO-d_6): δ 9.94 (s, 1H), 9.47 (s, 1H), 7.54 (d, 1H, J=8.6 Hz), 7.48 (d, 1H, J=8.6 Hz), 7.27 (s, OH), 5.11 (d, 1H, J=14.0 Hz), 5.01 (d, 1H, J=14.0 Hz), 3.03 (q, 2H, J=7.5 Hz), 1.25 (q, 3H, J=7.5 Hz). ^{13}C NMR (DMSO-d_6): δ 149.15, 145.05, 139.13, 133.75, 133.37, 128.45, 128.17, 121.52, 71.81, 56.49, 24.07, 10.80. MS m/z=354 (^{79}Br, $2^{35}Cl$) $[M]^+$, 356 (^{81}Br, $2^{35}Cl$) $[M+2]^+$, 358 (^{81}Br, ^{35}Cl, ^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{14}H_{14}Br_2ClN_3O$: C 38.60; H 3.24; N 9.65. Found C 38.30; H 3.06; N 9.30.

5.5.5. 6-Bromo-7-(2,4-difluorophenyl)-5-ethyl-7-hydroxy-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ylium bromide (9f). White solid, yield 88%: mp 294–295 °C (dec). IR (cm^{-1}) 3185, 2162, 1501, 1114. ^1H NMR (DMSO-d_6): δ 9.95 (s, 1H), 9.53 (s, 1H), 7.79 (td, 1H, J=8.8, 6.5 Hz), 7.45 (s, OH), 7.42 (qd, 1H, J=9.0, 2.6 Hz), 7.26 (td, 1H, J=8.6, 2.5 Hz), 5.21 (d, 1H, J=14.2 Hz), 4.82 (d, 1H, J=14.2 Hz), 3.03 (qd, 2H, J=7.5, 1.2 Hz), 1.23 (t, 3H, J=7.5 Hz); ^{13}C NMR (DMSO-d_6): δ 163.0 (d, J=248 Hz), 158.5 (d, J=248 Hz), 149.69, 144.94, 132.96, 129.72, 123.52 (d, J=14.20 Hz), 120.42, 111.72 (d, J=28.4 Hz), 104.77 (t, J=26.50 Hz), 70.40, 54.43, 23.97, 10.69; MS m/z=354 (^{79}Br, $2^{35}Cl$) $[M]^+$, 356 (^{81}Br, $2^{35}Cl$) $[M+2]^+$, 358 (^{81}Br, ^{35}Cl, ^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{14}H_{13}BrF_2N_3O$; C 38.44; H 2.97; N 9.61. Found C 38.60; H 2.94; N 9.69.

5.6. General procedure for the synthesis of 5-aryl-3-alkylpyridazines (8b–f)

The triazolium salt (1.1 mmol) was stirred in water (20 mL) and warm 5 N sodium hydroxide (20 mL) was added quickly. The mixture was shaken for a few minutes and then extracted with ethyl acetate, and the ethyl acetate extracts were washed with water, dried over magnesium sulfate and evaporated. The residues were purified by flash column chromatography (hexane/ethyl acetate, 3:7) to give the pyridazines **8b–f** as solids.

5.6.1. 5-(2,4-Dichlorophenyl)-3-methylpyridazine (8b). White solid, yield 100%: mp 153–155 °C (hexanes/ethyl acetate). IR (cm^{-1}) 1596, 1475, 1359, 1105, 861, 822. ^1H NMR ($CDCl_3$): δ 9.13 (s, 1H), 7.57 (d, 1H, J=1.9 Hz), 7.42 (s, 1H), 7.41 (dd, 1H, J=8.3, 1.9 Hz), 7.29 (d, 1H, J=8.3 Hz), 2.81 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 159.78, 149.17, 136.67, 136.18, 133.26, 132.79, 131.57, 130.38, 127.92, 126.60, 22.37. MS m/z=238 ($2^{35}Cl$) $[M]^+$, 240 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{11}H_8Cl_2N_2$: C 55.25; H 3.37; N 11.72. Found C 54.88; H 3.50; N 11.45.

5.6.2. 5-(2,4-Dichlorophenyl)-3-ethylpyridazine (8c). Beige solid, yield 28%: mp 98–100 °C (hexanes/ethyl acetate). IR (cm^{-1}) 1597, 1477, 1106, 861, 818. ^1H NMR ($CDCl_3$): δ 9.14 (s, 1H), 7.57 (d, 1H, J=1.9 Hz), 7.42 (s, 1H), 7.41 (dd, 1H, J=8.3, 1.9 Hz), 7.30 (d, 1H, J=8.3 Hz), 3.10 (q, 2H, J=7.6 Hz), 1.43 (t, 3H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 164.45, 149.31, 136.70, 136.09, 133.28, 132.97, 131.58, 130.37, 127.90, 125.51, 29.51, 13.62. MS m/z=252 ($2^{35}Cl$) $[M]^+$, 256 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{12}H_{10}C_{l2}N_2$: C 56.91; H 3.95; N 11.07. Found C 56.80; H 3.79; N 11.05.

5.6.3. 5-(2,4-Dichlorophenyl)-3-pentylpyridazine (8d). White solid, yield 45%: mp 60–64 °C (hexanes/ethyl acetate). IR (cm^{-1}) 1598, 1476, 1104, 864, 820. ^1H NMR ($CDCl_3$): δ 9.13 (s, 1H), 7.57 (d, 1H, J=2.15 Hz), 7.41 (dd, 1H, J=8.3, 2.15 Hz), 7.40 (s, 1H), 7.30 (d, 1H, J=8.3 Hz), 3.05 (d, 1H, J=7.8 Hz), 1.83 (quintet, 2H, J=7.5 Hz), 1.40 (m, 4H), 0.91 (t, 3H, J=7.25 Hz). ^{13}C NMR ($CDCl_3$): δ 163.58, 149.23, 136.56, 136.09, 133.30, 132.96, 131.57, 130.37, 127.89, 125.97, 36.28, 31.40, 29.66, 29.31, 22.40, 13.93. MS m/z=294 ($2^{35}Cl$) $[M]^+$, 296 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{15}H_{16}Cl_2N_2$: C 61.02; H 5.46; N 9.49. Found C 61.27; H 5.60; N 8.99.

5.6.4. 5-(4-Chlorophenyl)-3-ethylpyridazine (8e). Pale yellow solid, yield 68%: mp 108–109 °C (hexanes/ethyl acetate). IR (cm^{-1}) 1596, 1493, 1090, 822. ^1H NMR ($CDCl_3$): δ 9.28 (d, 1H, J=2.15 Hz), 7.61 (d, 1H, J=8.7 Hz), 7.52 (d, 1H, J=8.7 Hz), 7.47 (d, 1H, J=2.15 Hz), 3.09 (q, 2H, J=7.6 Hz), 1.43 (t, 3H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 164.84, 147.58, 137.65, 136.36, 133.26, 129.72, 128.35, 122.57, 29.48, 13.74. MS m/z=218 ($2^{35}Cl$) $[M]^+$, 220 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{12}H_{11}ClN_2$: C 65.90; H 5.07; N 12.81. Found C 65.72; H 5.33; N 12.52.

5.6.5. 5-(2,4-Difluorophenyl)-3-ethylpyridazine (8f). Pale yellow solid, yield 91%: mp 53–54 °C (hexanes/ethyl acetate). IR (cm^{-1}) 1595, 1504, 1139, 843. ^1H NMR ($CDCl_3$): δ

9.22 (s, 1H), 7.51 (td, 1H, J=7.5, 6.4 Hz), 7.49 (s, 1H), 7.06 (qq, 1H, J=7.0, 2.4, 1.0 Hz), 7.01 (qd, 1H, J=8.6, 2.4 Hz), 3.09 (q, 2H, J=7.5 Hz), 1.43 (t, 3H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 164.66, 163.79 (dd, J=253, 11.9 Hz), 160.44 (dd, J=253, 11.9 Hz), 148.72 (d, J= 4.0 Hz), 133.43, 131.08 (dd, J=9.6, 4.6 Hz), 124.57 (d, J=4 Hz), 119.30 (d, J=13 Hz), 112.65 (q, J=21, 4 Hz), 105.15 (t, J=25 Hz), 29.52, 13.67. MS m/z=220 $[M]^+$. Anal Calcd for $C_{12}H_{10}F_2N_2$: C 65.44; H 4.58; N 12.72; Found C 65.09; H 4.68; N 12.51.

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Synthesis of conformationally diverse tetrathiacalix[4]arene(amido)crowns and tetrathiacalix[4]arene amides with pendant amine functions

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Abstract—A series of conformationally diverse novel tetrathiacalix[4]arene(amido)crowns and amides from tetrakis((ethoxycarbonyl)-methoxy)*p-tert*-butyl tetrathiacalix[4]arene and its debutylated analog have been prepared by their reaction with diamines [$H_2N(CH_2)_nNH_2$; n=2,3,4, and 6] and polyamines. It has been determined that the length of the alkyl spacer in diamines is pivotal for the formation of either the tetrathiacalix[4]arene bis(amido)crowns or tetrathiacalix[4]arene amides with pendant amine functions. The synthesized compounds represent potential building blocks for achieving sophisticated molecular assemblies for molecular organization and recognition. Single crystal X-ray analysis of tetrathiacalix[4]arene bis(amido)crown **6a** revealed that it has a 1,3-alternate conformation, which forms supramolecular complexes with chloroform.

1. Introduction

Calixamidocrowns represent a new class of synthetic molecular receptors, which combine the structure and properties of calixarenes[1] and amidocrown[2] compounds. The first 1,3-calix[4]arene(amido)crown[3] was synthesized and evaluated by Reinhoudt et al. in 1991 while Bitter et al.[4] reported the synthesis of doubly bridged proximal calix[4]arene(amido)-crown compounds through intramolecular ring closure of chloroalkylamide precursors in 1998. Recently Samanta et al.[5] have reported *N*-(4-aminophthalimidoethyl)calix[4]-amidocrown as a fluorescent sensor for iron(III) and copper(II).

It was envisaged that similar analogs of tetrathiacalix[4]-arenes,[6] which contain sulfur atoms in lieu of methylene bridges in calixarenes could provide conformationally diverse receptors with enhanced potential for interaction with a variety of guests. The new molecular receptors, in principle, would offer immense possibilities for further exploration. While our work in this area was in progress, a report[7] describing the low yield synthesis of proximally bridged tetrathiacalix[4]arene(amido)crown appeared, which has prompted us to report our initial work on tetrathiacalix[4]arene(amido)-crown derivatives with variable ring size and conformations for possible applications in nuclear-waste remediation, sensing, and radiopharmacy.

2. Results and discussion

2.1. Synthesis

Tetrathiacalix[4]arenes **1a**[8] and **1b**[9,10] were obtained by the base catalyzed condensation of *p-tert*-butylphenol and sulfur as reported previously by us and others.[8–11] They were esterified[12] by reaction with bromoethylacetate in the presence of sodium carbonate and cesium carbonate in separate reactions to give tetrathiacalix[4]arene esters **2**, **3**, and **4**. Compounds **2**, **3**, and **4** were further reacted with alkyl diamines of varying chain lengths [$NH_2(CH_2)_nNH_2$; n=2, 3,4, and 6] and a polyamine by refluxing in toluene/methanol (1:1) in the case of **2** and **4**; and THF/methanol (1:1) in the case of **3** (Schemes 1–3) to yield tetrathiacalix[4]arene-(amido)crowns and tetrathiacalix[4]arene amides with pendant amine function as described in this paper.

2.2. Characterization of products

It was observed that the reaction of **2** with 1,2-diamino-ethane and 1,3-diaminopropane resulted in the formation of products designated as **5a** and **5b**. Molecular mass determination and absence of free amino group in their spectra (IR and NMR) revealed that both **5a** and **5b** were cyclic (amido)crown compounds. The molecular ion peaks at

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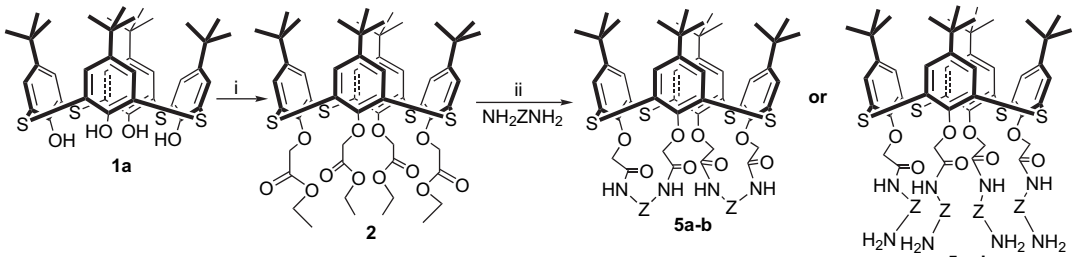
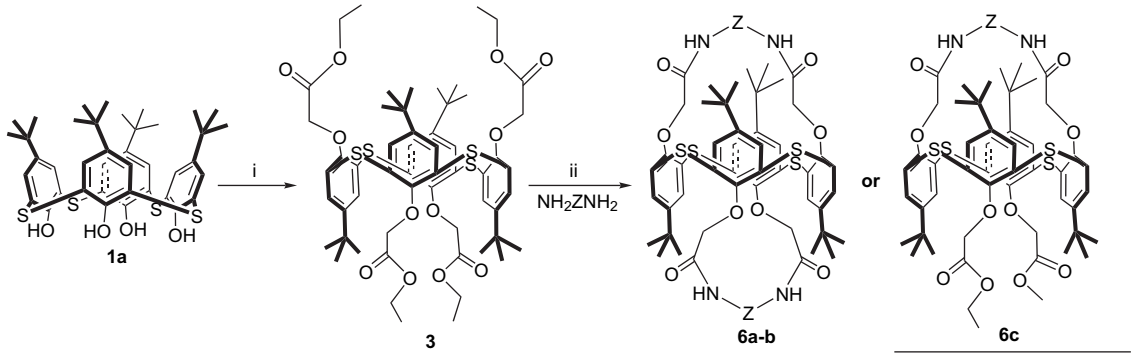


	Z
5a	CH_2CH_2
5b	$CH_2CH_2CH_2$

	Z
5c	$CH_2CH_2CH_2CH_2$
5d	$CH_2CH_2CH_2CH_2CH_2CH_2$

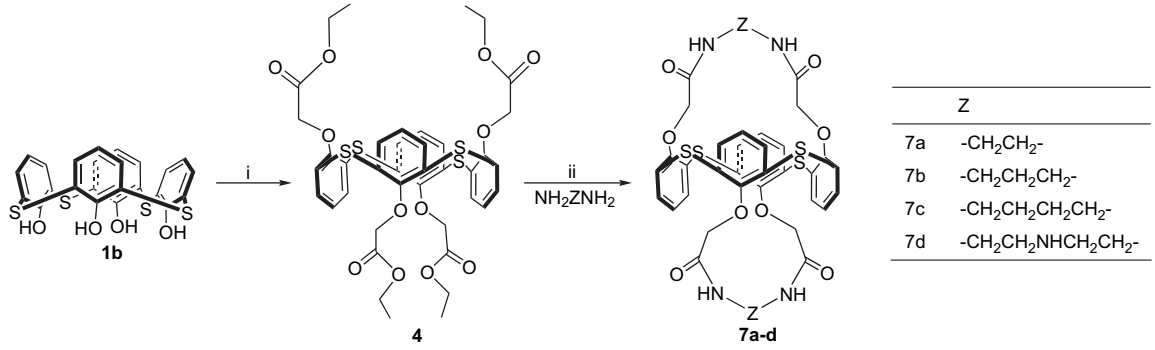
Scheme 1. (i) $Na_2CO_3/BrCH_2COOC_2H_5$, acetone; (ii) toluene/methanol (1:1).



	Z
6a	$-CH_2CH_2-$
6b	$-CH_2CH_2CH_2-$

	Z
6c	$-CH_2CH_2CH_2CH_2-$

Scheme 2. (i) $Cs_2CO_3/BrCH_2COOC_2H_5$, acetone; (ii) THF/methanol (1:1).



	Z
7a	$-CH_2CH_2-$
7b	$-CH_2CH_2CH_2-$
7c	$-CH_2CH_2CH_2CH_2-$
7d	$-CH_2CH_2NHCH_2CH_2-$

Scheme 3. (i) $Cs_2CO_3/BrCH_2COOC_2H_5$, acetone; (ii) toluene/methanol (1:1).

1001 [M^+] and 1029 [M^+] for **5a** and **5b**, respectively, in the FABMS spectrum confirmed the formation of tetrathiacalix[4]arene bis(amido)crowns. Since the formation of tetrathiacalix[4]arene(amido)crowns could in principle encompass the ester functionalities at either the proximal positions (a,b and c,d) or the distal positions (a,c and b,d) (Fig. 1), the issue was resolved by NMR experiments. For instance, the ^1H NMR spectrum of **5a** exhibited a pair of doublets for the ArOCH_2 protons at δ 3.97 and 5.09 to reveal the non-equivalence of the geminal protons attached to the phenolic function of tetrathiacalix[4]arene. A similar pattern

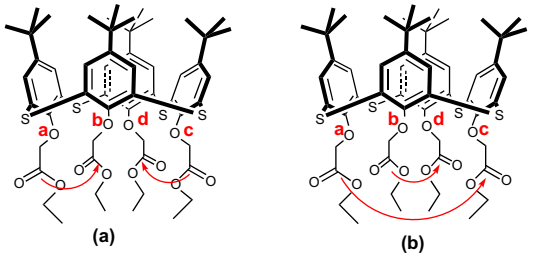


Figure 1. Possibility of (amido)crown formation by utilizing ester groups at (a) a, b and c, d and (b) a, b and c, d.

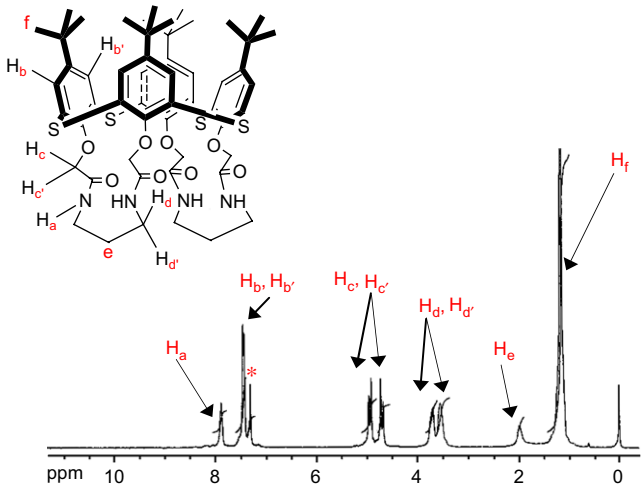


Figure 2. ^{1}H NMR spectrum of **5b**.

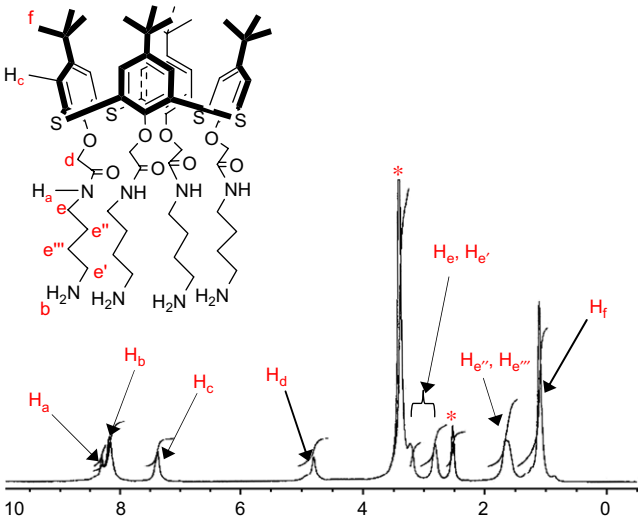


Figure 3. ^{1}H NMR spectrum of **5c**.

for ArOCH_2 protons was observed for **5b** with a pair of doublets at δ 4.69 and 4.93 (Fig. 2). It was evident that the ArOCH_2 protons would be non-equivalent only if the tetrathiacalix[4]arene(amido)crown formation takes place by condensation with the ester groups present at proximal positions. In the event that the tetrathiacalix[4]arene(amido)crown formation had involved the distal groups, the ArOCH_2 protons would appear as a singlet due to magnetic equivalence.

The appearance of one signal for the *tert*-butyl groups and two singlets in the aromatic region at 7.29 and 7.32 ppm in the case of **5a** and at 7.38 and 7.40 ppm for **5b** suggested that the synthesized compounds might possibly exist as proximally substituted cyclic amides with a cone or 1,2-alternate conformation of the tetrathiacalixarene core. The possibility of a 1,2-alternate conformation of tetrathiacalix[4]arene was excluded with the help of a NOESY spectrum. No correlation was found between the *tert*-butyl groups and the amide function. When **2** was reacted with higher diamines (1,4-diaminobutane and 1,6-diaminohexane), it gave new compounds **5c** and **5d**. The ^{1}H NMR spectrum of **5c** (Fig. 3) revealed the appearance of a broad singlet for the ArOCH_2 protons at 4.79 ppm along with singlets at δ 7.36, 8.16, and 8.29 as depicted in Figure 3. The broad singlets at δ 8.16 and 8.29 exchanged with deuterium when shaken with D_2O. This indicated the presence of two types of NH protons, which could be attributed to the –$CH_2CH_2CH_2CH_2NH_2$ and ArOCH_2-CON*H*CH_2 protons, respectively. Thus, **5c** could be identified as tetrathiacalix[4]arene amide with pendant amine functions. This was further supported by the [M^+] peak at 1233 observed in its FABMS spectrum. Compound **5d** also revealed similar ^{1}H NMR and mass spectral patterns.

When tetraester **3** was subjected to aminolysis with diamines containing varying spacer lengths, it yielded a series of compounds **6a–c**. The products **6a** and **6b** exhibited rather simple ^{1}H NMR spectra with one singlet each for the ArOCH_2, the aromatic, and the *tert*-butyl protons (Fig. 4). This could be attributed to the highly symmetric nature of the tetrathiacalix[4]arene bis(amido)crown compounds. The 1,3-alternate conformation of **6a** was unequivocally proved by its single crystal X-ray diffraction analysis (see Section 2.3).

The ^{1}H NMR spectrum of **6c** exhibited a deuterium exchangeable broad triplet for the ArOCH_2CON*H*CH_2 protons at δ 5.83, which integrated for two protons suggesting the formation of two amide linkages. Absence of signals for

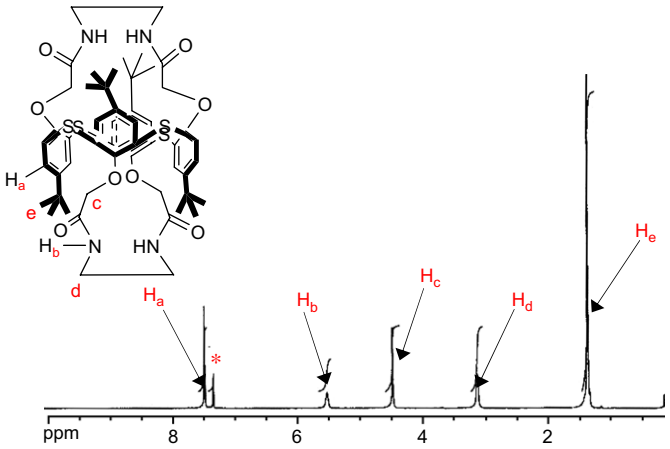


Figure 4. ^{1}H NMR spectrum of **6a**.

the –NH_2 protons suggested the possibility of formation of tetrathiacalix[4]arene mono(amido)crown derivative. Two broad signals at δ 3.19 and 1.09 for the CONHCH_2CH$_2$ and the CONHCH$_2$CH_2 protons, respectively, indicated the formation of tetrathiacalix[4]arene mono(amido)crown with the possibility of two uncondensed ester groups in **6c**. A quartet at δ 4.11 for the OCH_2CH$_3$ protons integrating for two protons and a triplet for three protons at δ 1.19 for the OCH$_2$CH_3 protons suggested the presence of only one ethyl ester group. However, a singlet at δ 3.65 integrating for three protons in its ^{1}H NMR spectrum and a signal at δ 51 for OCH_3 carbon in DEPT-135 spectrum suggested that one methyl ester function was present in **6c**. This was confirmed by the appearance of three signals for the ArOCH_2 protons at δ 4.45, 4.43, and 4.39 in the ratio of 2:1:1 in the ^{1}H NMR spectrum of **6c** (Fig. 5).

Though the products obtained in the reaction of **3** with 1,6-diaminohexane and diethylene triamine could not be fully characterized due to their insolubility in common solvents, it could be inferred on the basis of solubility characteristics and R_f values that bis(amido)crowns were not present in the reaction mixture.

When the debutylated tetraester **4** was subjected to aminolysis with diamines with varying spacer lengths, it yielded a series of compounds **7a**–**d**. All these compounds exhibited a rather simple pattern of ^{1}H NMR spectra with one doublet and one triplet for the aromatic protons and one singlet for the ArOCH_2 protons (Fig. 6), suggesting a highly symmetric nature for **7a**–**d**. A deuterium exchangeable broad triplet integrating for four NH protons suggested the presence of four amide linkages in the tetrathiacalix[4]arene core. Absence of signals for the NH_2 protons, the proton integration for the methylene groups present in the corresponding spacer chain as well as FAB mass spectrometric analysis confirmed that the compounds in hand were tetrathiacalix[4]arene bis(amido)crowns.

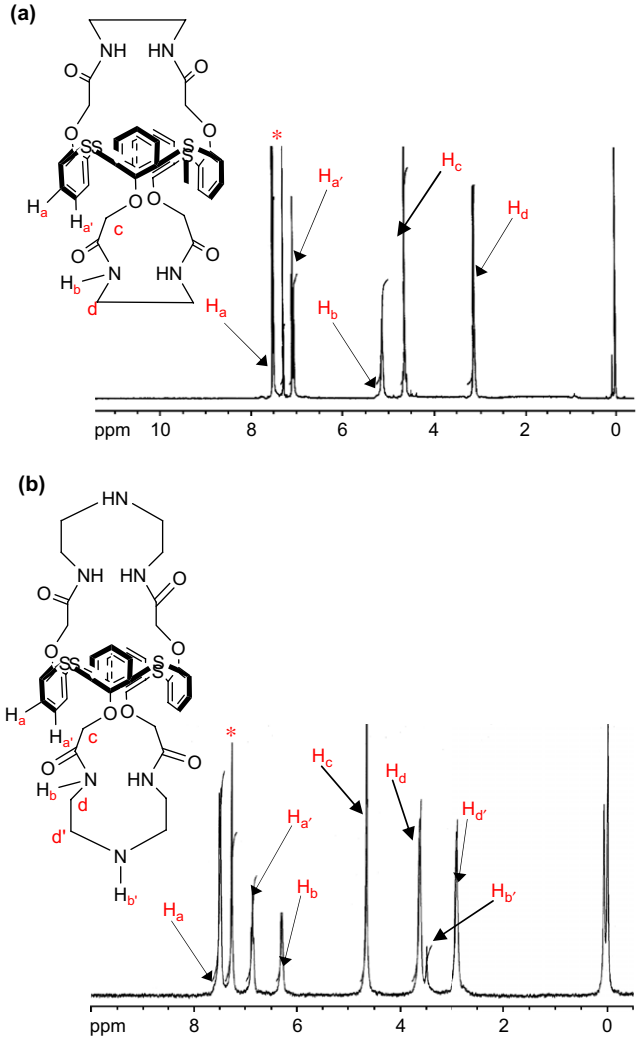


Figure 6. ^{1}H NMR spectra of (a) **7a** and (b) **7e**. * Indicates residual solvent peak or water peak.

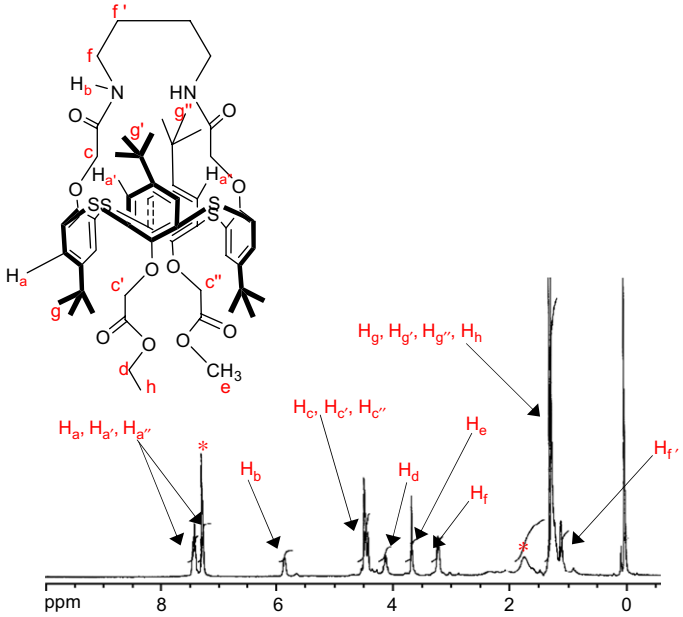


Figure 5. ^{1}H NMR spectrum of **6c**.

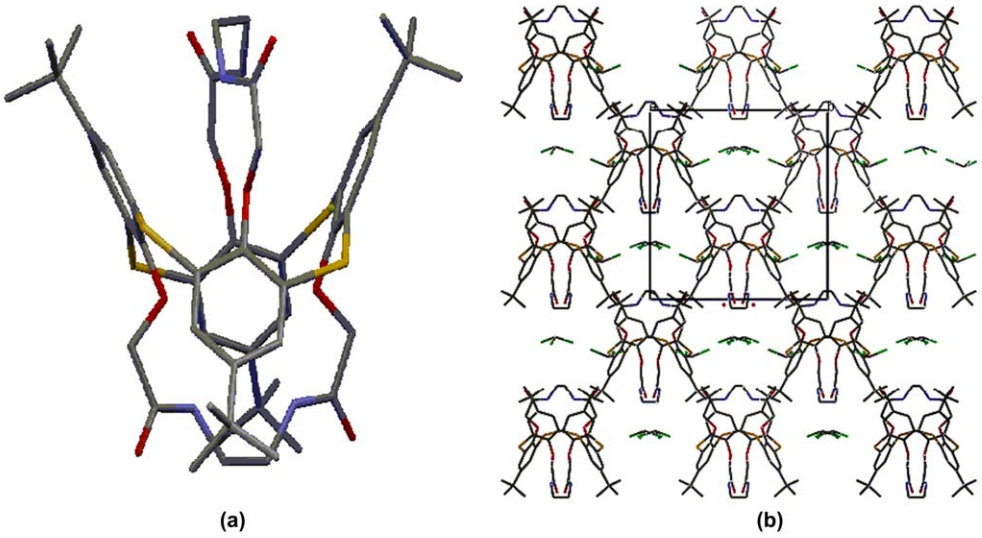


Figure 7. (a) X-ray structure of **6a** and (b) crystal packing of **6a** along *a* axis showing unit cell having four tetrathiacalix[4]arene molecules (hydrogen atoms have been omitted for clarity).

2.3. X-ray crystallographic analysis of 6a

A definitive proof for the geometry of **6a** was obtained by single crystal X-ray analysis (Fig. 7a). Colorless crystals of **6a** with space group I-4 were obtained by slow evaporation of a chloroform solution. The torsion angles at the sulfur bridges revealed a sequence of ++, −−, ++, −− that is consistent with the 1,3-alternate conformation found in calix[4]arene[13] and tetrathiacalix[4]arene derivatives.[14] The average distances between two adjacent and two opposite sulfur atoms are 5.58 and 7.76 Å, respectively, while the typical distances between the corresponding CH_2 groups in 1,3-alternate calix[4]arene are 5.0 and 7.1 Å. This indicated that the cavity of tetra-*tert*-butyl tetrathiacalix[4]arenes is bigger than the classical tetra-*tert*-butylcalix[4]arenes. The unit cell of **6a** consists of four thiacalix[4]arene molecules, eight chloroform, and eight water molecules (Fig. 7b). The distance of the two distal rings ranges from 5.28 Å (lower rim) to 7.94 Å (upper rim) with an inclination angle of around 54°. All the four amido chains have their carbonyl groups *exo* with respect to the thiacalix[4]arene cavity. The hydrogen of the amide group is *endo* to the thiacalix[4]arene cavity and is not involved in intra or intermolecular hydrogen bonding. Each chloroform molecule is intermolecularly hydrogen bonded to the bridging sulfur atom of one thiacalix[4]arene molecule and the carbonyl oxygen of the other thiacalix[4]-arene molecule. These intermolecular interactions between tetrathiacalix[4]arene and chloroform molecules lead to the formation of supramolecular aggregates with large cavities as depicted in Figure 7b.

2.4. Discussion

It has been observed that the reaction of **2** with ethylene and propylene diamines proceeds smoothly to result in the formation of proximally bridged tetrathiacalix[4]arene(amido)-crowns, **5a** and **5b**. When the reaction is carried out with 1,4-diaminobutane, it does not provide proximally bridged (amido)crown compounds as expected but instead provides a tetrathiacalix[4]arene amide with pendant primary amine functionality. This implies that the length of the alkyl chain of the condensing diamines plays an important role in their reaction with tetrathiacalix[4]arene esters. Accordingly, the reaction when carried out with a diamine with a larger spacer unit (e.g., 1,6-diaminohexane) gives the 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[((*N*-6-aminohexyl)aminocarbonyl)-methoxy]tetrathiacalix[4]arene in appreciable yields.

It is known that tetrathiacalix[4]arene tetraesters in their 1,3-alternate conformation[1] possess larger annuli (i.e., a greater distance between the distal ester moieties) than their cone counterparts. They are therefore expected to require larger diamino components to curtail mobility as compared to the cone conformers and should therefore yield different results on their condensation with diamines of varying spacer lengths. Thus, the 1,3-alternate conformation of *p-tert*-butyl thiacalix[4]arene tetraethylester **3** when reacted with 1,2-diaminoethane and 1,3-diaminopropane, yields bis(amido)-crowns in good yields. However, the reaction with 1,4-diaminobutane, even when refluxing is continued for seven days, provides a mixture, which on purification by column chromatography gives *p-tert*-butyl tetrathiacalix[4]arene mono(amido)crown (**6c**) with two unreacted ester moieties.

The formation of **6c** is interesting in this reaction as it indicates that there is a competition between the solvent and the diamines used. The basic diamine promotes the methanolysis of one of the ester functions in tetra-*tert*-butyl tetrathiacalix[4]arene to yield **6c**. This point is currently being investigated in our laboratories. This presumably leads to a change in the 1,3-alternate conformation in such a way that further reaction is hindered.

The aminolysis reaction of the debutylated analog of tetrathiacalix[4]arene, **4**, with 1,2-diaminoethane and 1,3-diaminopropane yielded the tetrathiacalix[4]arene bis-(amido)crowns in good yields (81–85%) while its reaction with 1,4-diaminobutane and diethylene triamine gave tetrathiacalix[4]arene bis(amido)crowns in low yields (8–15%). The better yields of the cyclized tetrathiacalix[4]arene 1,3-bis(amido)crowns (**7a**, **7b**) in comparison to their *p-tert*-butyl tetrathiacalix[4]arene analogs could be attributed to

steric crowding due to the neighboring *tert*-butyl groups and the aromatic rings in the latter series of compounds. It has been observed that the absence of *p*-*tert*-butyl groups in the tetrathiacalix[4]arenes allows them to enjoy greater conformational mobility to react with larger diamines to provide tetrathiacalix[4]arene bis(amido) crowns even with 1,4-diaminobutane and diethylene triamine (**7c**, **7e**) but the same has not been observed in the case of *p*-*tert*-butyl tetrathiacalix[4]arene esters.

It is worth mentioning that Lhotak et al.[7] have recently synthesized bis(amido)crowns with ethylene, propylene, and butylene spacer groups under different reaction conditions (refluxing in ethanol, 16 h) in 36, 19, and 9% yields, respectively, as against our conditions, which involve refluxing of reactants in a mixture of toluene and methanol for 24 h, which gave significantly different results. In our experiments, toluene was used to solubilize **2** and **4** while methanol under basic conditions leads to trans esterification of ethyl ester group to provide a more reactive methyl ester, which apparently facilitates the aminolysis reaction to allow isolation of tetrathiacalix[4]arene bis(amido)crown compounds **5a** and **5b** in 71 and 69% yields, respectively. Tetrathiacalix[4]arene bis(amido)crowns with a butylene spacer group could not be obtained under these conditions, which allowed the isolation of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[((*N*-4-aminobutyl)aminocarbonyl)-methoxy]tetrathiacalix[4]arene (**5c**) in 83% yield. Since **3** was not completely soluble in toluene/methanol, an alternative solvent system (THF/methanol) was used in this case.

It has been observed that the alkyl spacer group of the diamine plays a greater role in the aminolysis reaction of tetrathiacalix[4]arene tetraesters as compared to that of their calix[4]arene analogs, which provide the proximally bridged calix[4]arene amidocrown compounds even with larger spacer units (1,4-diaminobutane, diethylene triamine, and triethylene tetramine). The aminolysis reaction of the cone conformers of tetrathiacalix[4]arene esters with higher diamines (1,4-diaminobutane and 1,6-diaminohexane) gave tetrakis[(alkyl)aminocarbonyl-methoxy]tetrathiacalix[4]-arene amides with pendant amine functionality. The 1,3-alternate conformer of tetrathiacalix[4]arene tetraethylacetate, however, gave tetrathiacalix[4]arene bis(amido)crown derivatives in their 1,3-alternate conformation to pave the way for obtaining molecular capsules.

In conclusion, a new strategy has enabled the synthesis of conformationally diverse tetrathiacalix[4]arene(amido)-crown compounds of different sizes. These could serve as building blocks for the synthesis of larger and more sophisticated molecular assemblies and molecular capsules of tetrathiacalix[4]arene(amido)crowns in the 1,3-alternate conformation thereby opening up a new dimension to tetrathiacalix[4]arene(amido)crown chemistry.

3. Experimental

3.1. General

All the reagents used in the study were purchased from Sigma–Aldrich or Merck and were considered chemically pure to be used without further purification. The solvents used were distilled. Melting points were recorded on an electric melting point apparatus (Toshniwal, India) and are uncorrected. IR spectra were recorded on a Nicolet Protégé 460 spectrometer in KBr discs while CHN analyses were obtained by using a Perkin–Elmer 240C elemental analyzer. ^{1}H NMR spectra were recorded on a 300 MHz Bruker DPX 300 instrument at room temperature using tetramethylsilane (TMS) as an internal standard. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 Mass spectrometer/Data System using Argon/Xenon (6 kV, 10 mA) as the FAB gas.

3.2. Preparation of the starting materials

p-*tert*-Butyl tetrathiacalix[4]arene[8] (**1a**) and tetrathiacalix[4]arene[9] (**1b**) were synthesized by methods reported earlier. The tetra acetates **2**, **3**, and **4** were synthesized by the method[10] reported in the literature, which involved the use of ethylbromoacetate and acetone/M_2CO_3 system (M=Na and Cs) for effecting the condensation reactions.

3.3. General procedure for the synthesis of tetrathiacalix[4]arene amides

A mixture of tetrathiacalix[4]arene tetraethylacetate (0.5 g, 0.493 mmol) and diamine (9.86 mmol) was refluxed in toluene/methanol (1:1) (30 mL) or THF/methanol (1:1) (30 mL). After removing the solvents, the crude mixture was precipitated with methanol to provide compounds, which were purified either by crystallization from appropriate solvents or by column chromatography.

3.3.1. (a,b;c,d)-5,11,17,23-Tetra-*tert*-butyl tetrathiacalix[4]arene(ethyleneamido)biscrown, 5a. White solid recrystallized from $CHCl_3$/MeOH (0.35 g, 71%), mp 240 °C (dec). IR (KBr, ν/cm^{-1}): 3335, 1677. Anal. Calcd for $C_{52}H_{64}N_4O_8S_4$: C, 62.37; H, 6.44; N, 5.60. Found: C, 62.48; H, 6.40; N, 5.58. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.34 (br s, 4H, CON*H*), 7.32 (s, 4H, Ar*H*), 7.29 (s, 4H, Ar*H*), 5.09 (d, J=13.8 Hz, 4H, ArOCH_2), 3.97 (d, J=13.8 Hz, 4H, ArOCH_2), 3.63 (br s, 4H, CONHCH_2), 3.51 (br s, 4H, CONHCH_2), 1.05 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{52}H_{64}N_4O_8S_4$: m/z=1001.35 [M$^+$]; found: m/z=1001 [M$^+$, 100%].

3.3.2. (a,b;c,d)-5,11,17,23-Tetra-*tert*-butyl tetrathiacalix[4]arene(propyleneamido)biscrown, 5b. White solid recrystallized from $CHCl_3$/MeOH (0.35 g, 69%), mp 266 °C (dec). IR (KBr, ν/cm^{-1}): 3334, 1676. Anal. Calcd for $C_{54}H_{68}N_4O_8S_4$: C, 63.01; H, 6.66; N, 5.44. Found: C, 62.91; H, 6.72; N, 5.48. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.84 (br s, 4H, CON*H*), 7.40 (s, 4H, Ar*H*), 7.38 (s, 4H, Ar*H*), 4.93 (d, J=14.6 Hz, 4H, ArOCH_2), 4.69 (d, J=14.6 Hz, 4H, ArOCH_2), 3.67 (br s, 4H, CONHCH_2), 3.52 (br s, 4H, CONHCH_2), 1.96 (m, 4H, CONHCH$_2$CH_2), 1.12 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{54}H_{68}N_4O_8S_4$: m/z=1029.40 [M$^+$]; found: m/z=1029 [M$^+$, 100%].

3.3.3. 5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[((*N*-4-aminobutyl)aminocarbonyl)-methoxy]tetrathiacalix[4]arene, 5c. White solid recrystallized from MeOH/H_2O (0.51 g, 83%), mp 268 °C. IR (KBr, ν/cm^{-1}): 3414,

1676. Anal. Calcd for $C_{64}H_{96}N_8O_8S_4$: C, 62.30; H, 7.84; N, 9.08. Found: C, 62.42; H, 7.76; N, 9.10. ^{1}H NMR (300 MHz, DMSO-d_6[†]) δ_H 8.29 (br s, 4H, CON*H*), 8.16 (br s, 8H, CH_2NH_2), 7.36 (s, 8H, Ar*H*), 4.79 (s, 8H, ArOCH_2), 3.21 (m, 8H, CONHCH_2), 2.80 (m, 8H, CH_2NH_2), 1.64 (m, 16H, NHCH_2CH_2CH_2), 1.08 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{64}H_{96}N_8O_8S_4$: *m*/*z*=1233.76 [M$^+$]; found: *m*/*z*=1233 [M$^+$, 100%].

3.3.4. 5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis [((*N*-6-aminohexyl)aminocarbonyl)-methoxy]tetrathiacalix[4]arene, 5d. White solid recrystallized from MeOH/H_2O (0.53 g, 81%), mp 130 °C. IR (KBr, ν/cm^{-1}): 3339, 1642. Anal. Calcd for $C_{72}H_{112}N_8O_8S_4$: C, 64.25; H, 8.39; N, 8.33. Found: C, 64.36; H, 8.36; N, 8.38. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.34 (s, 8H, Ar*H*), 5.83 (br s, 4H, CON*H*), 5.30 (br s, 8H, CH_2NH_2), 4.82 (s, 8H, ArOCH_2), 3.36 (br s, 8H, CONHCH_2), 2.69 (br s, 8H, CH_2NH_2), 1.60–1.33 (m, 32H, NHCH_2(CH_2)$_4$), 1.11 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{72}H_{112}N_8O_8S_4$: *m*/*z*=1345.97 [M$^+$]; found: *m*/*z*=1346 [M$^+$, 100%].

3.3.5. (a,c;b,d)-5,11,17,23-Tetra-*tert*-butyl tetrathiacalix[4]arene(ethyleneamido)biscrown, 6a. White solid recrystallized from $CHCl_3$/MeOH (0.32 g, 65%), mp 297 °C (dec). IR (KBr, ν/cm^{-1}): 3410, 1688. Anal. Calcd for $C_{52}H_{64}N_4O_8S_4$: C, 62.37; H, 6.44; N, 5.61. Found: C, 62.26; H, 6.52; N, 5.58. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.40 (s, 8H, Ar*H*), 5.44 (br s, 4H, CON*H*), 4.40 (s, 8H, ArOCH_2), 3.05 (br s, 8H, CONHCH_2), 1.28 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{52}H_{64}N_4O_8S_4$: *m*/*z*=1001.35 [M$^+$]; found: *m*/*z*=1001 [M$^+$, 100%].

3.3.6. (a,c;b,d)-5,11,17,23-Tetra-*tert*-butyl tetrathiacalix[4]arene (propyleneamido)biscrown, 6b. White solid recrystallized from $CHCl_3$/MeOH (0.30 g, 61%), mp 307 °C (dec). IR (KBr, ν/cm^{-1}): 3415, 1685. Anal. Calcd for $C_{54}H_{68}N_4O_8S_4$: C, 63.01; H, 6.66; N, 5.44. Found: C, 63.09; H, 6.69; N, 5.51. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.39 (s, 8H, Ar*H*), 5.46 (s, 4H, CON*H*), 4.33 (s, 8H, ArOCH_2), 3.11 (br s, 8H, CONHCH_2), 1.66 (br s, 4H, CONHCH$_2$CH_2), 1.28 (s, 36H, C(CH_3)$_3$), FABMS: calcd for $C_{54}H_{68}N_4O_8S_4$: *m*/*z*=1029.40 [M$^+$]; found: *m*/*z*=1029 [M$^+$, 100%].

3.3.7. (a,c)-5,11,17,23-Tetra-*tert*-butyl tetrathiacalix[4]-arene(butyleneamido)monocrown, 6c. White solid purified by column chromatography (9.6:0.4 chloroform/ethyl actetate, R_f=0.46) (0.17 g, 33%), mp 210 °C (dec). IR (KBr, ν/cm^{-1}): 3403, 1769, 1737, 1682. Anal. Calcd for $C_{55}H_{70}N_2O_{10}S_4$: C, 63.07; H, 6.74; N, 2.67. Found: C, 63.19; H, 6.78; N, 2.61. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.41 (d, *J*=5.2 Hz, 2H, Ar*H*), 7.39 (d, *J*=5.8 Hz, 2H, Ar*H*), 7.25 (s, 4H, Ar*H*), 5.83 (s, 2H, CON*H*), 4.45 (s, 4H, ArOCH_2), 4.44 (s, 2H, ArOCH_2), 4.39 (s, 2H, ArOCH_2), 4.11 (q, *J*=21.2 Hz, 2H, OCH_2CH$_3$), 3.65 (s, 3H, OCH_3), 3.19 (br s, 4H, NHCH_2CH$_2$), 1.24 (s, 36H, C(CH_3)$_3$), 1.19 (t, *J*=13.9 Hz, 3H, OCH$_2$CH_3), 1.09 (br s, 4H, CONHCH$_2$CH_2). DEPT-135 (75 MHz, $CDCl_3$) δ 131.2, 130.9, 125.5 (aromatic *C*H), 69.2, 64.8, 64.4, 64.2 (Ar-OCH_2 & –CO(O)CH_2CH$_3$), 51.2 (–OCH_3), 37.1 (–CONHCH_2), 31.1, 30.8 (Ar-C-CH_3), 25.8 (–CONHCH$_2$CH_2), 14.1 (–CO(O)CH$_2$CH_3), FABMS: calcd for $C_{55}H_{70}N_2O_{10}S_4$: *m*/*z*=1047.41 [M$^+$]; found: *m*/*z*=1047 [M$^+$, 100%].

3.3.8. (a,c;b,d)-Tetrathiacalix[4]arene(ethyleneamido)-biscrown, 7a. White solid recrystallized from $CHCl_3$/MeOH (0.393 g, 85%), mp 307 °C (dec). IR (KBr, ν/cm^{-1}): 3414, 1686. Anal. Calcd for $C_{36}H_{32}N_4O_8S_4$: C, 55.65; H, 4.15; N, 7.21. Found: C, 55.59; H, 4.09; N, 7.26. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.49 (d, *J*=7.7 Hz, 8H, Ar*H*), 7.07 (t, *J*=15.5 Hz, 4H, Ar*H*), 5.11 (s, 4H, CON*H*), 4.65 (s, 8H, ArOCH_2), 3.12 (s, 8H, CONHCH_2), FABMS: calcd for $C_{36}H_{32}N_4O_8S_4$: *m*/*z*=776.92 [M$^+$]; found: *m*/*z*=777 [M$^+$, 100%].

3.3.9. (a,c;b,d)-Tetrathiacalix[4]arene(propyleneamido)-biscrown, 7b. White solid recrystallized from $CHCl_3$/MeOH (0.388 g, 81%), mp 308 °C (dec). IR (KBr, ν/cm^{-1}): 3415, 1688. Anal. Calcd for $C_{38}H_{36}N_4O_8S_4$: C, 56.70; H, 4.61; N, 6.96. Found: C, 56.58; H, 4.68; N, 6.91. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.47 (d, *J*=7.7 Hz, 8H, Ar*H*), 7.05 (t, *J*=15.4 Hz, 4H, Ar*H*), 5.09 (br s, 4H, CON*H*), 4.62 (s, 8H, ArOCH_2), 3.24 (m, 8H, CONHCH_2), 1.71 (br s, 4H, NHCH$_2$CH_2), FABMS: calcd for $C_{38}H_{36}N_4O_8S_4$: *m*/*z*=804.97 [M$^+$]; found: *m*/*z*=805 [M$^+$, 95%].

3.3.10. (a,c;b,d)-Tetrathiacalix[4]arene(butyleneamido)-biscrown, 7c. White solid recrystallized from $CHCl_3$/MeOH (0.039 g, 8%), mp 310 °C (dec). IR (KBr, ν/cm^{-1}): 3418, 1686. Anal. Calcd for $C_{41}H_{42}N_4O_7S_4$: C, 59.25; H, 5.09; N, 6.74. Found: C, 59.38; H, 5.11; N, 6.79. ^{1}H NMR (300 MHz, DMSO-d_6[†]) δ_H 7.48 (d, *J*=7.7 Hz, 8H, Ar*H*), 7.04 (t, *J*=15.4 Hz, 4H, Ar*H*), 5.04 (s, 4H, CON*H*), 4.60 (s, 8H, ArOCH_2), 3.24 (m, 8H, CONHCH_2), 1.71 (br s, 4H, NHCH$_2$CH_2), FABMS: calcd for $C_{41}H_{42}N_4O_7S_4$: *m*/*z*=831.05 [M$^+$]; found: *m*/*z*=831 [M$^+$, 95%].

3.3.11. (a,c;b,d)-Tetrathiacalix[4]arene(diethylenetriaminoamido)biscrown, 7d. White solid recrystallized from $CHCl_3$/MeOH (0.077 g, 15%), mp 315 °C (dec). IR (KBr, ν/cm^{-1}): 3409, 3272, 1657. Anal. Calcd for $C_{40}H_{42}N_6O_8S_4$: C, 53.58; H, 4.25; N, 10.41. Found: C, 53.42; H, 4.36; N, 10.28. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.50 (d, *J*=7.3 Hz, 8H, Ar*H*), 6.88 (t, *J*=14.7 Hz, 4H, Ar*H*), 6.29 (s, 4H, CON*H*), 4.64 (s, 8H, ArOCH_2), 3.62 (br s, 8H, CONHCH_2CH$_2$), 3.49 (br s, 2H, CH$_2$N*H*CH$_2$), 2.89 (br s, 8H, CONHCH$_2$CH_2), FABMS: calcd for $C_{40}H_{42}N_6O_8S_4$: *m*/*z*=863.06 [M$^+$]; found: *m*/*z*=863 [M$^+$, 100%].

3.4. X-ray crystallography

Crystals suitable for single crystal X-ray diffraction were obtained by slow cooling of a warm solution of **6a**, in chloroform, having molecular formula $C_{56}H_{64}Cl_{12}N_4O_{12}S_4$, M=1538.75, tetragonal, space group I-4 with *a*=15.251(3), *b*=15.251(3), *c*=16.342(4), α=90.0, β=90.0, γ=90.0°, and D_c=1.344 g/cm^3 for *Z*=2. Intensity diffraction data were calculated up to θ=20.50° by using 2ω step scanning mode with Mo K$_\alpha$ radiation (λ=0.71073 Å) at 298 K. A total of 3343 reflections were calculated and used in structure analysis and refinement. All the non-hydrogen atoms were

[†] **5c** and **7c** were not completely soluble even in DMSO-d_6, hence they were solubilized by heating with NaCl.

refined anisotropically using restraints on the bond lengths and thermal parameters. All hydrogen atoms were placed in their geometrical positions and were not refined. Using observed data and refinement of 203 parameters with no restraints, the final R index was R_{all}=0.0924, R_{gt}=0.0824, wR_{ref}=0.2384, and wR_{gt}=0.2254. All calculations and structure solution was accomplished by using SHELXTL-PC VERSION of software. Crystallographic data for the structure have been deposited with Cambridge Crystallographic Database as supplementary publication number CCDC (295846).

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$RuCl_2(DMSO)_4$ catalyzes the β-alkylation of secondary alcohols with primary alcohols through a hydrogen autotransfer process

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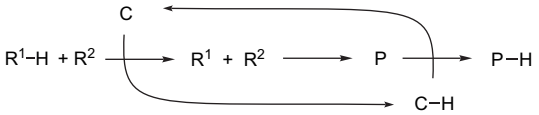
Abstract—The electrophilic β-alkylation of secondary alcohols with primary alcohols is accomplished by a hydrogen autotransfer process catalyzed by $RuCl_2(DMSO)_4$. The reaction can produce either simple alkylated secondary alcohols or α,β-unsaturated ketones with good to excellent results just by choosing the appropriate starting secondary alcohol (methyl or longer chain secondary alcohol, respectively), as well as quinolines (by using 2-aminobenzyl alcohol).

1. Introduction

Alcohols are one of the most important classes of organic compounds owing to their wide variety of uses in industrial and laboratory chemistry. Although a plethora of methods for the synthesis of alcohols are known,[1] their simple creation by carbon–carbon bond manipulation is very unusual. In this approach, the usual protocol involves the oxidation of alcohol to ketone, followed by alkylation, and final reduction of the carbonyl moiety to the alcohol. Therefore, any new strategy for simple alkylation of alcohols would be welcome, more if it is environmentally benign and supports the sustainable chemical industry.[2]

The hydrogen autotransfer process, which can be considered as a new type of domino reaction,[3] involves an initial removal of hydrogen from at least one of the initial reagents (R^1-H) by a catalyst (C), followed by reaction of the new reagents (R^1 and R^2) to form a new compound (P), which is in turn the hydrogen acceptor of the previously formed hydrogenated catalyst (C-H), renewing the catalyst (Scheme 1). This strategy has been used in the alkylation of different carbonyl derivatives using primary alcohols as electrophiles.[4] The reaction starts with the oxidation of the primary alcohol to give the corresponding aldehyde and the hydride metal derivative, followed by condensation with the carbonyl derivative to render the corresponding α,β-unsaturated carbonyl derivative, which is finally reduced with the hydride metal derivative to give the corresponding carbonyl compound.[5] In the case of using methyl ketones as starting materials, the presence and extra equivalent of primary alcohol forced the process to yield the related secondary alkylated alcohol[6] after a final Meerwein–Ponndorf–Verley reduction.[7]



$$\text{Atom Efficiency (\%)} = \text{Yield (\%)} \times \frac{\text{Mw of Final Product}}{\sum_i (\text{Equiv.} \times \text{Mw of all reagents})_i}$$

Scheme 1. General scheme for a hydrogen autotransfer process.

Despite the high atom efficiency obtained in the α-alkylation of methyl ketone derivatives with alcohols through a hydrogen autotransfer process, the related process using 2-alkanol derivatives, as masked ketones, has been scarcely reported. In fact, there are only two examples of this process.[8] The first one uses the air sensitive $RuCl_2(PPh_3)_3$ as catalyst, a double amount of primary alcohol, and a large excess of 1-dodecene as sacrificial additive.[9] The second one uses the very expensive catalyst $[Cp^*IrCl_2]_2$, sodium *tert*-butoxide, and a slight excess of the primary alcohol.[10] The yields in both cases are comparable, in the range of 70–80%.

Here we report an alternative protocol for the β-alkylation of secondary alcohols with primary alcohols catalyzed by $RuCl_2(DMSO)_4$.[11]

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2. Results and discussion

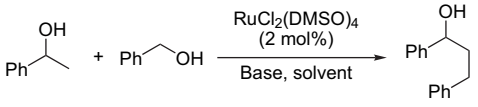
2.1. β-Alkylation of 2-alkanol derivatives using primary alcohols as electrophiles

The alkylation of equimolecular amounts of 1-phenylethanol (**1a**) with benzylic alcohol to give the corresponding alcohol **3a** was chosen as the reaction model in order to optimize all different parameters, with the solvent being the first one (Table 1). The reaction in toluene gave the expected product with modest yield after seven days, while the reaction failed using other more polar solvents, such as water, MeCN or DMSO (entries 1–4).

Despite these disappointing results, we found that the reaction using 1,4-dioxane gave the expected compound **3a** with an excellent yield (Table 1, entry 5). The reaction can also be performed in solvent-free conditions[12] giving slightly lower results but in only three days (entry 6). After finding dioxane as the best solvent, we studied the influence of the amount of base (KOH), the decrease or increase from 2 equiv being detrimental (Table 1, entries 5 and 7–9). The increase of the temperature also renders lower results (entries 10 and 11). Finally the nature of base was also tested at different temperatures, giving in all cases worse results (entries 12–14).

On the basis of the above results, we next examined the reactions of various 2-alkanols with primary alcohols under optimized conditions (Table 2). The standard reaction to give compound **3a** permitted us to compare our results with those of literature. Thus, the reaction using the catalyst $RuCl_2(PPh_3)_3$ gave 82% yield,[9] while using $[Cp^*IrCl_2]_2$ gave 75% yield,[10] both yields being lower than those in our case (Table 2, entry 1). Our protocol gave not only better chemical yield for compound **3a** but also better atom efficiency (see Scheme 1: in our case 57% and in the literature 12[9] and 43%[10]) than the reported procedures.

Table 1. Optimization of β-alkylation of alcohols[a]

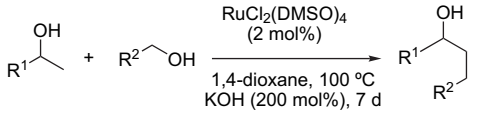


1a **2a** **3a**

Entry	Solvent	Base (%)	T (°C)	t (day)	Yield (%)[b]
1	PhMe	KOH (200)	100	7	56[c]
2	H_2O	KOH (200)	100	3	0[d]
3	MeCN	KOH (200)	100	3	0[d]
4	DMSO	KOH (200)	100	3	0[d]
5	Dioxane	KOH (200)	100	7	98
6	—[e]	KOH (200)	100	3	91
7	Dioxane	KOH (100)	100	7	38
8	Dioxane	KOH (300)	100	7	87
9	Dioxane	KOH (600)	100	7	56
10	Dioxane[f]	KOH (200)	120	3	92
11	THF[f]	KOH (200)	120	3	73
12	Dioxane	KOBu^t (200)	100	3	85
13	Dioxane[f]	KOBu^t (200)	120	2	73
14	Dioxane	$NaNH_2$ (200)	100	3	76

[a] All reactions were performed using 5 mmol (100 mol %) of each alcohol.
[b] Yields determined by ^{1}H NMR using *N*,*N*-diphenyl formamide as internal standard.
[c] Forty-three percent of corresponding ketone was detected.
[d] Initial reagents were recovered unchanged.
[e] The reaction was performed under solvent-free conditions.
[f] The reaction was performed in a pressure tube.

Table 2. β-Alkylation of 2-alkanol derivatives **1** with primary alcohols **2**[a]



1 **2** **3**

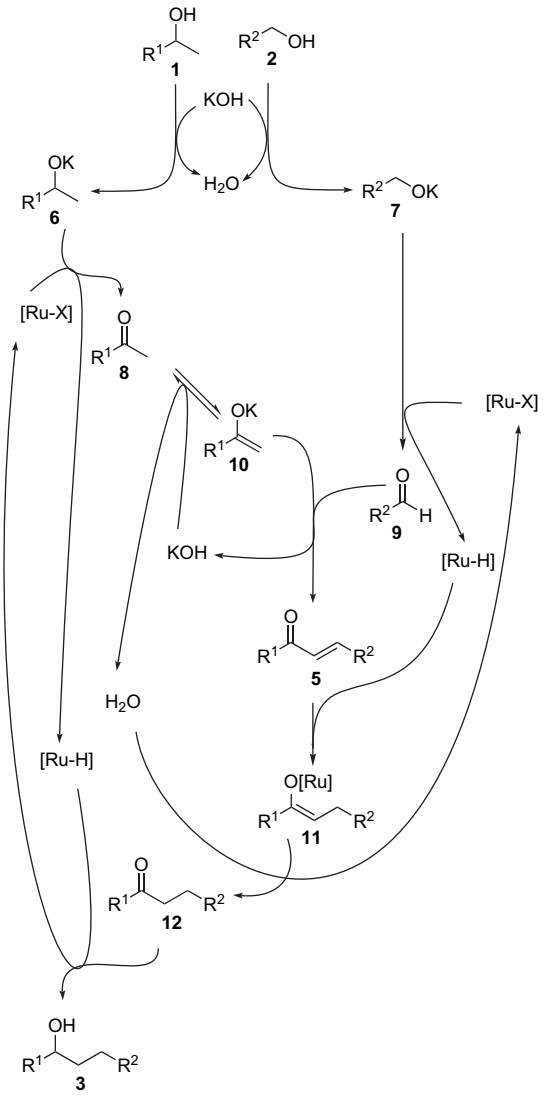
Entry	R^1	R^2	Compd no.	Yield (%)[b]
1	Ph	Ph	**3a**	95
2	Ph	4-ClC_6H_4	**3b**	69
3	Ph	3-ClC_6H_4	**3c**	98[c]
4	Ph	4-$MeOC_6H_4$	**3d**	98[c]
5	Ph	1-Naphthyl	**3e**	85
6	Ph	2-Furyl	**3f**	98[c]
7	Ph	Pr^i	**3g**	42 (47)
8	4-$F_3CC_6H_4$	Ph	**3h**	80
9	4-MeC_6H_4	Ph	**3i**	98[c]
10	4-MeC_6H_4	4-ClC_6H_4	**3j**	76
11	4-MeC_6H_4	3,4-$(MeO)_2C_6H_3$	**3k**	71
12	Bu^t	Ph	**3l**	48 (58)
13	n-C_5H_{11}	Ph	**3m**	<5

[a] All reactions were performed using 5 mmol (100 mol %) of each alcohol.
[b] Isolated yield after column chromatography (silica gel: hexane/ethyl acetate); in parenthesis: yields obtained under solvent-free conditions after three days.
[c] Compound obtained pure after work-up.

The reaction gave homogeneous results for primary aromatic alcohols, independent of the nature of the substituent on the aromatic ring, even using heteroaromatic derivatives (Table 2, entries 1–6). However, the reaction with aliphatic primary alcohols gave lower chemical yield, also under solvent-free conditions (entry 7). The reaction gave good results when different aromatic secondary ethanol derivatives **1** were tested (entries 8–11), with the yield being lower for substituted aliphatic alcohols or null for non-substituted reagents (entries 12 and 13, respectively).

Concerning a possible mechanism, and considering the previously proposed catalytic cycle for the related α-alkylation of ketones[4n] (deduced by detecting different by-products such as aldehydes and α,β-unsaturated ketones, as well as by isotopic labelling experiments), we propose the catalytic cycle shown in Scheme 2 which contains an extra oxidation–reduction step.

Probably, in the reaction medium the initial ruthenium complex evolves to form the real catalyst, which could be a polymetallic species, even bearing hydroxy groups,[13] although the permanence of chlorine ligands cannot be ruled out. In turn, this intermediate reacts with alkoxide derivatives to form the corresponding mono- or dihydride ruthenium catalytic active species.[14] The necessary use of stoichiometric amounts of base can indicate that its role is not only in the deprotonation of the in situ formed ketone **8** but also in the deprotonation of the alcohols **1** and **2**. The corresponding oxidized carbonyl compounds **8** and **9** suffer a classical basic aldol condensation to render the α,β-unsaturated ketone **5**. The last steps are the reduction of carbon–carbon double bond through a Michael-type addition to form the α-alkylated ketone **12** and final reduction of the carbonyl group to the alcohol **3**,[15] renewing the catalyst.



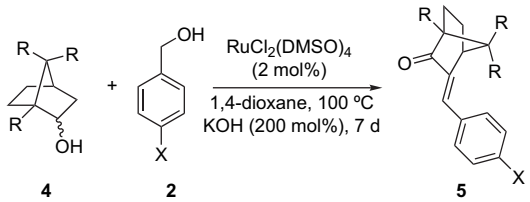
Scheme 2. Proposed catalytic cycle for the β-alkylation of 2-alkanols with primary alcohols.

2.2. Reaction of secondary bicyclic alcohols with primary alcohols

When the same above protocol was followed using bicyclic alcohols **4** as secondary alcohol partners, ketone derivatives **5** were isolated instead of the expected alcohol of type **3** (Table 3). The reason for this fact is not yet very clear but it would be related with the higher stability of trisubstituted carbon–carbon double bond, as well as the higher instability of ruthenium bicyclic enolate of type **11**, which would make more difficult the corresponding Michael-type addition of the ruthenium hydride intermediate, the reoxidation of this hydride complex being accomplished either by the molecular oxygen[16] or by direct generation of hydrogen.[17]

The reaction worked nicely for different substituted benzylic alcohols **2**, giving similar results for the protocol using dioxane as solvent as well as for solvent-free conditions (entry 4). The use of borneol or isoborneol did not have any important difference, obtaining similar results (Table 3, entries 5 and 6). The *Z*-configuration of the double bond

Table 3. Reaction of secondary bicyclic alcohols **4** with benzylic alcohols **2**[a]



Entry	R	Alcohol **4**	X	Compd no.	Yield (%)[b]
1	H	Mixture[c]	H	**5a**	85
2	H	Mixture[c]	MeO	**5b**	96
3	Me	*endo*	H	**5c**	71
4	Me	*endo*	Me	**5d**	47 (34)
5	Me	*endo*	MeO	**5e**	62
6	Me	*exo*	MeO	**5e**	73

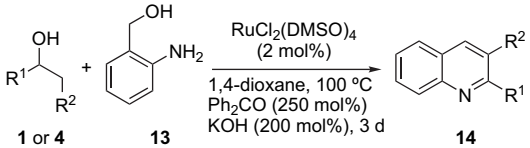
[a] All reactions were performed using 5 mmol (100 mol %) of each alcohol.
[b] Isolated yield after column chromatography (silica gel: hexane/ethyl acetate); in parenthesis: yields obtained under solvent-free conditions after three days.
[c] Mixture of isomer *endo*:*exo*=83:17.

was unambiguously determined by the X-ray of compound **5e** and by NOESY experiments of compounds **5a** and **e**.[4n]

2.3. Synthesis of quinolines

Finally, it should be pointed out that the above reaction with 2-aminobenzyl alcohol **13** gave the corresponding quinolines **14** (Table 4).[18] The tentative mechanism pathway would involve the oxidation of both alcohols to the corresponding carbonyl compounds of type **8** and **9**, followed by either the ketone-imine formation and final aldol condensation process, or by an aldol reaction to give the corresponding α,β-unsaturated ketone of type **5** and final ring closing imine formation. Benzophenone was used as hydride scavenger, in order to reoxidize the ruthenium hydride intermediate and renewing the starting ruthenium catalyst. The reaction worked nicely for aromatic and heteroaromatic substituted ethanol derivatives, giving pure quinoline derivative **14** in practically quantitative yield after acidic/basic

Table 4. Synthesis of quinolines[a]



Entry	Compd no.	R^1	R^2	Yield (%)[b]
1	**14a**	Ph	H	98[c] (98)[c]
2	**14b**	4-MeC_6H_4	H	98[c]
3	**14c**	2-Furyl	H	98[c]
4	**14d**	Et	Me	98[c,d]
5	**14e**	$-(CH_2)_4-$		71[d] (89)
6	**14f**			41[d,e]

[a] All reactions were performed using 5 mmol (100 mol %) of each alcohol.
[b] Isolated yield after acidic/basic aqueous extraction; in parenthesis: yields obtained under solvent-free conditions after three days.
[c] Compound obtained pure after work-up.
[d] Yield after seven days' reaction time.
[e] Purified by column chromatography (silica gel: hexane/ethyl acetate).

aqueous extraction (entries 1–3). Surprisingly, the reaction gave excellent results also for non-substituted secondary alcohols, which could indicate that prior to the aldol reaction, the formation of imine derivative takes place. Finally, it should be pointed out that the reaction performed under solvent-free conditions gave in some cases better chemical yields in shorter reaction times.

3. Conclusion

In summary, we have described here the use of $RuCl_2(DMSO)_4$ for a simple and direct β-alkylation of secondary alcohols with not only high yields but also atom efficiency, using secondary alcohols as the source of nucleophiles and primary alcohols as the electrophilic partners. The final product depends strongly on the alcohol nature, obtaining either the simple alkylation for 2-alkanol derivatives or α,β-unsaturated ketones when methylenic bicyclic alcohols were used as starting materials. In this way, wide variety of quinolines could be prepared with excellent yields just by using 2-aminobenzyl alcohol derivative as alkylating agent. It is worthy to note that this procedure constitutes a good example of very high atom efficiency reaction. Moreover, the waste material of the reactions is water, making them a very interesting process from an environmental and industrial point of view. The catalyst used is very cheap, stable, easy to handle and prepare.[19] All these facts make the $RuCl_2(DMSO)_4$-catalyzed alkylation process very interesting comparing to other protocols using expensive and difficult-to-handle catalysts.

4. Experimental

4.1. Chemicals and instrumentation

Full general statements were described elsewhere.[20] All reagents were commercially available (Acros, Aldrich, Strem) and were used as received.

4.2. General procedure for reaction of secondary alcohols with primary alcohols

To a solution of $RuCl_2(DMSO)_4$ (0.048 g, 0.1 mmol) and KOH (0.660 g, 10 mmol) in 1,4-dioxane (5 mL) was added the corresponding secondary alcohol **1** or **4** (5 mmol), followed by the addition of the corresponding primary alcohol **2** or **13** (5 mmol). In the case of using amino alcohols **13**, benzophenone (2.7 g, 15 mmol) was also added. The mixture was stirred and heated at 80 °C for a period of seven days. Then, the mixture was quenched by addition of a saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated, and removed under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using suitable mixtures of hexane/ethyl acetate to afford the corresponding product **3**, **5** or **14**. Yields are included in Tables 1–4. Compounds **3a**, **3g**, **3h**, **3l**, **5a**, **5b**, **5d**, **5e**, **14a–f**, which have been previously fully described by us,[4n] were characterized by comparison of their spectroscopic (IR, ^1H, and ^{13}C NMR, and mass spectra) and chromatographic data with those of the reported products. Physical and spectroscopic data as well as literature references follow.

4.2.1. 3-(4-Chlorophenyl)-1-phenyl-1-propanol (3b).[10] R_f 0.29 (hexane/ethyl acetate: 4/1); t_R 16.5; ν (film) 3408 (O–H), 3026, 1648 (C=CH), 1063 cm^{-1} (C–O); δ_H 1.84 (1H, s, OH), 1.90–2.15 (2H, m, CH_2CO), 2.55–2.75 (2H, m, CH_2CH_2CO), 4.65–4.70 (1H, m, CHO), 7.11, 7.23, and 7.25–7.40 (2H, 2H, and 5H, respectively, d, d, and m, respectively, J=8.5 and 8.5 Hz, respectively, ArH); δ_C 31.35, 40.30, 73.70, 125.85 (2C), 127.75, 128.45 (2C), 128.55 (2C), 129.75 (2C), 1312.55, 140.20, 144.40; *m/z* 248 (M^++2, 1%), 246 (3), 230 (21), 229 (11), 228 (61), 193 (33), 125 (12), 107 (10), 103 (15), 79 (48), 77 (33).

4.2.2. 3-(3-Chlorophenyl)-1-phenyl-1-propanol (3c). R_f 0.15 (hexane/ethyl acetate: 4/1); t_R 16.4; ν (film) 3381 (O–H), 3069, 1589, 1566 (C=CH), 1078 cm^{-1} (C–O); δ_H 1.97 (1H, s, OH), 1.90–2.15 (2H, m, CH_2CO), 2.55–2.80 (2H, m, CH_2CH_2CO), 4.65 (1H, dd, J=5.5, 7.6 Hz, CHO), 7.05–7.40 (9H, m, ArH); δ_C 31.65, 40.10, 73.65, 125.85, 126.00, 126.60, 127.75 (2C), 128.40, 128.55 (2C), 129.60, 134.05, 143.80, 144.30; *m/z* 248 (M^++2, 8%), 246 (M^+, 23), 228 (14), 126 (10), 107 (100), 103 (11), 91 (11), 79 (41), 77 (29). HRMS: M^+ found 246.0808. $C_{15}H_{15}OCl$ requires 246.0811.

4.2.3. 3-(4-Methoxyphenyl)-1-phenyl-1-propanol (3d).[10] t_R 16.9; R_f 0.7 (hexane/ethyl acetate: 4/1); ν (film) 3419 (O–H), 3028, 1622, 1513 (C=CH), 1039 cm^{-1} (C–O); δ_H 1.95 (1H, s, OH), 2.00–2.15 (2H, m, CH_2CO), 2.55–2.75 (2H, m, CH_2CH_2CO), 3.76 (3H, s, CH_3), 4.65–4.70 (1H, m, CHO), 6.80–6.85, 7.10–7.15, and 7.25–7.35 (2H, 2H, and 5H, respectively, 3m, ArH); δ_C 31.15, 40.70, 55.30, 73.85, 113.80 (2C), 125.95 (2C), 127.65, 128.55 (2C), 129.35 (2C), 133.80, 144.65, 157.80; *m/z* 242 (M^+, 28%), 225 (17), 224 (100), 223 (20), 209 (15), 193 (19), 135 (16), 133 (11), 122 (22), 121 (51), 108 (14), 107 (32), 105 (12), 91 (13), 79 (29), 78 (11), 77 (26).

4.2.4. 3-(2-Naphthyl)-1-phenyl-1-propanol (3e).[9] t_R 19.4; R_f 0.68 (hexane/ethyl acetate: 4/1); ν (film) 3375 (O–H), 3057, 1596, 1518 (C=CH), 1066 cm^{-1} (C–O); δ_H 1.95 (1H, s, OH), 2.10–2.30 (2H, m, CH_2CO), 3.05–3.15 and 3.20–3.30 (2H, m, CH_2CH_2CO), 4.75–4.80 (1H, m, CHO), 7.25–7.50, 7.70, 7.80–7.85, and 7.95–8.00 (9H, 1H, 1H, and 1H, respectively, m, d, m, and m, respectively, J=8 Hz, ArH); δ_C 29.10, 39.80, 74.15, 123.75, 125.45, 125.55, 125.80, 125.95 (2C), 126.65, 127.70, 128.55 (2C), 128.75, 131.80, 133.90, 137.95, 144.50; *m/z* 262 (M^+, 32%), 244 (24), 155 (17), 154 (11), 153 (38), 152 (14), 143 (12), 142 (100), 141 (40), 133 (11), 128 (13), 115 (22), 107 (20), 79 (22), 77 (18).

4.2.5. 1-Phenyl-3-(2-furyl)-1-propanol (3f).[21] R_f 0.23 (hexane/ethyl acetate: 4/1); t_R 13.4; ν (film) 3394 (O–H), 3021, 1597, 1514 (C=CH), 1065 cm^{-1} (C–O); δ_H 1.95 (1H, s, OH), 2.00–2.15 (2H, m, CH_2CO), 2.65–2.80 (2H, m, CH_2CH_2CO), 4.70–4.75 (1H, m, CHO), 5.95–6.00, 6.25–6.30, and 7.25–7.35 (1H, 1H, and 6H, respectively, 3m, ArH); δ_C 24.35, 37.10, 73.65, 105.00, 110.10, 125.85 (2C), 127.65, 128.50 (2C), 140.95, 144.30, 155.50; *m/z*

202 (M^+, 6%), 185 (14), 184 (100), 183 (13), 155 (27), 141 (12), 120 (12), 107 (30), 105 (17), 104 (10), 91 (12), 81 (22), 79 (40), 77 (31).

4.2.6. 1-(4-Methylphenyl)-3-phenyl-1-propanol (3i).[9] R_f 0.39 (hexane/ethyl acetate: 4/1); t_R 15.7; ν (film) 3377 (O–H), 3023, 1607, 1520 (C=CH), 1066 cm^{-1} (C–O); δ_H 1.86 (1H, s, OH), 1.95–2.20 (2H, m, CH_2CO), 2.34 (3H, s, CH_3), 2.60–2.80 (2H, m, CH_2CH_2CO), 4.60–4.65 (1H, m, CHO), 7.15–7.30 (9H, m, ArH); δ_C 21.10, 32.05, 40.30, 73.70, 125.75, 125.85 (2C), 128.35 (2C), 128.40 (2C), 129.15 (2C), 137.70, 141.55, 141.80; *m/z* 226 (M^+, 16%), 208 (21), 121 (100), 93 (27), 91 (30), 77 (17).

4.2.7. 3-(4-Chlorophenyl)-1-(4-methylphenyl)-1-propanol (3j). R_f 0.46 (hexane/ethyl acetate: 8/2); t_R 17.6; ν (film) 3377 (O–H), 3115, 3028, 1500 (C=CH), 1095 (C–O); δ_H 1.82 (1H, s, OH), 1.85–2.15 (2H, m, CH_2CO), 2.55–2.75 (2H, m, CH_2CH_2CO), 2.35 (3H, s, CH_3), 4.62 (1H, t, J=5.7 Hz, CHO), 7.05–7.3 (8H, m, ArH); δ_C 21.00, 31.40, 40.20, 73.50, 125.80, 128.40, 129.2, 129.75, 131.2, 137.2, 140.3, 141.4; *m/z* 260 (M^+, 6%), 242 (23), 121 (100), 93 (25), 91 (19), 77 (16). HRMS: M^+ found 260.0966. $C_{16}H_{17}OCl$ requires 260.0968.

4.2.8. 3-(3,4-Dimethoxyphenyl)-1-(4-methylphenyl)-1-propanol (3k). R_f 0.18 (hexane/ethyl acetate: 8/2); t_R 19.5; ν (film) 3437 (O–H), 3004, 1595 (C=CH), 2839 (MeO), 1033 cm^{-1} (C–O); δ_H 1.90 (1H, s, OH), 1.90–2.15 (2H, m, CH_2CO), 2.35 (3H, s, CH_3), 2.60–2.70 (2H, m, CH_2CH_2CO), 3.85 (6H, s, 2×MeO), 4.65 (1H, t, J=5.1 Hz, CHO), 6.70–6.80, 7.16, and 7.24 (3H, 2H, and 2H, respectively, m, d, and d, respectively, J=7.9 and 8.3 Hz, respectively, ArH); δ_C 21.00, 31.65, 40.50, 55.75, 55.85, 73.70, 111.15, 111.65, 120.15, 125.85, 129.15, 134.40, 137.30, 141.55, 147.10, 148.75; *m/z* 287 (M^++1, 13%), 286 (M^+, 66), 268 (21), 237 (21), 153 (10), 152 (100), 151 (29), 137 (18), 121 (48), 93 (16), 91 (21), 77 (16). HRMS: M^+ found 286.1563. $C_{18}H_{22}O_3$ requires 286.1569.

4.2.9. 1,7,7-Trimethyl-3-[(*E*)-1-phenylmethylidene]bicyclo[2.2.1]heptan-2-one (5c).[22] Mp 73–74 °C; R_f 0.63 (hexane/ethyl acetate: 8/2); $[\alpha]_D^{20}$ −5.2 (*c* 0.8, $CHCl_3$); t_R 15.7; ν (KBr) 3054, 1656 (C=CH), 1728 cm^{-1} (C=O); δ_H 0.80, 0.99, and 1.03 [3H each, 3s, $(CH_3)_2CCCH_3$], 1.45–1.60, 1.75–1.80, and 2.15–2.20 (2H, 1H, and 1H, respectively, 3m, CH_2CH_2), 3.10 (1H, d, J=4.3 Hz, $CHCH_2$), 7.24 (1H, s, C=CHPh), 7.30–7.50 (5H, m, Ph); δ_C 9.20, 18.20, 20.45, 25.85, 30.60, 46.60, 49.10, 57.00, 127.40, 128.55 (2C), 128.60, 129.65 (2C), 135.55, 142.00, 208.10; *m/z* 240 (M^+, 100%), 225 (31), 212 (14), 198 (12), 197 (46), 184 (12), 171 (10), 169 (21), 158 (42), 157 (51), 156 (31), 155 (26), 149 (16), 141 (30), 134 (13), 130 (12), 129 (49), 128 (47), 127 (15), 115 (23), 95 (17), 91 (28), 77 (12), 55 (12).

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Easy α-alkylation of ketones with alcohols through a hydrogen autotransfer process catalyzed by $RuCl_2(DMSO)_4$

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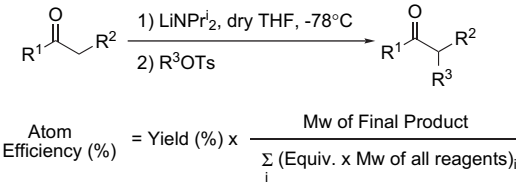
Abstract—The electrophilic α-alkylation of ketones with alcohols is accomplished by a hydrogen autotransfer process catalyzed by $RuCl_2(DMSO)_4$. The reaction can produce either simple alkylated ketones or α,β-unsaturated ketones just by choosing the appropriate starting ketones (methyl ketones or bicyclic methylenic ketones, respectively), as well as quinolines (by using 2-aminobenzyl alcohol derivatives) or the corresponding alcohol derivatives by the addition of an extra equivalent of the initial alcohol. In the last case, after the above alkylation process reduction of the carbonyl compound takes place. A mechanistic study seems to indicate that the process goes through the oxidation of the alcohols with ruthenium (after a previous deprotonation) to yield the corresponding aldehyde and a ruthenium hydride intermediate. In turn, the aldehyde suffers a classical aldol reaction with the starting ketone to form the corresponding α,β-unsaturated ketone, which finally is reduced through a Michael-type addition by the aforementioned ruthenium hydride intermediate.

1. Introduction

One of the challenges that chemists should face in this new century is to develop transformations that are not only efficient, selective and high yielding, but also environmentally benign, which could be integrated in sustainable processes.[1] There are two main strategies in order to minimize the environmental impact of a reaction: one of them involves the use of 'greener' solvents,[2] and another implies the use of less prejudicial or recyclable catalysts and reagents.[3] Some pivotal methods in organic synthesis like carbon–carbon bond formation reactions,[4] especially the electrophilic α-alkylation of carbonyl compounds,[5] are against these principles. For instance, the classical protocols for this reaction create some problems (e.g., LDA, dry THF, alkyl tosylates, etc., Scheme 1), not only from a synthetic but also from an economic and environmental point of view. The waste problems, such as the unavoidable inorganic salts derived from the leaving group and bases, make sometimes these classical alkylation methods not very practical for industrial use.[6] Another important aspect (many times forgotten) is the atom economy or efficiency,[7] which is in these cases very low (≈20%) due to the high molecular weight of strong bases as well as the leaving group of the alkylating electrophiles used.



Scheme 1. Example of classical α-alkylation of ketones.

Some of the aforementioned problems, such as the low atom efficiency or the enormous wastage of inorganic salts, have been overcome by the α-alkylation of methyl ketone derivatives with alcohols with the use of a hydrogen autotransfer process, which can be considered as a new type of domino reaction.[8] This type of process involves an initial removal of hydrogen from one of the initial reagents (R^1–H) by a catalyst (C), followed by reaction of the new reagents (R^1 and R^2) to form a new compound (P), which is in turn the hydrogen acceptor of the previously formed hydrogenated catalyst(C–H), renewing the catalyst (Scheme 2). The first catalyst used was a mixture of oxides supported in alumina ($CuO/ZnO/Al_2O_3$ 1/1/8), which gave the expected alkylated ketones with very low yields (25%).[9] Similar results were obtained with only alumina slightly doped with sodium.[10] The introduction of ruthenium complexes such as $Ru(MeCOCHCOMe)_3$[11] and $RuCl_2(PPh_3)_3$[12] improved yields up to the range of 50% and 90%, respectively, although in the last case, the addition of large amounts of 1-dodecene decreased the atom efficiency. Other different transition metal complexes such as $[IrCl(COD)]_2$[13] and palladium supported

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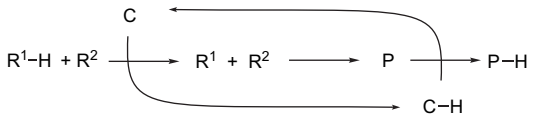
either on carbon charcoal[14] or on aluminum hydroxide[15] have been introduced as alternatives.



Scheme 2. General scheme for a hydrogen autotransfer process.

Alcohols are generally not considered as electrophiles[16] due to the high energy of the C–O bond (≈90 kcal/mol), the poor leaving group character of the OH being even increased after its deprotonation under the classical basic conditions for the alkylation reactions. However, their hypothetical use as electrophiles would have an extraordinary advantage, since the lost molecule will be water, a very small weight and environmentally friendly molecule. The reason of this contradictory behavior (being usually nucleophile but under some conditions electrophile) is based on the in situ transformation of alcohols into highly electrophilic aldehydes, which can react now with other usual nucleophiles such as phosphorous ylides[17] or α-deprotonated nitriles,[18] and even with methyl ketone derivatives, in situ formed through a Oppenauer oxidation of the corresponding secondary alcohol.[19] Not only metal complexes are the catalysts for these hydrogen autotransfer processes, but also enzymes worked nicely.[20]

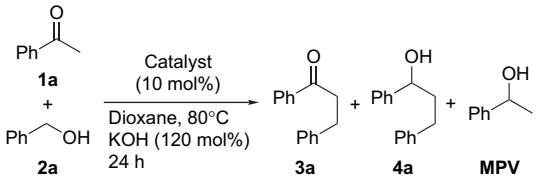
2. Results and discussion

We have recently introduced the alternative use of $RuCl_2(DMSO)_4$[21] as a cheap and easily handled complex for the regioselective α-alkylation of methyl ketone derivatives with primary alcohols.[22] This ruthenium complex possesses a Lewis acid character similar to other late transition metal chloride complexes,[23] as it was proven in the multicomponent[24] Strecker reaction.[25] Here, we report the systematic study of different parameters of the reaction and additives, which could have some impact on the reaction, as well as its application to the synthesis of the corresponding alcohols, quinolines, and α,β-unsaturated ketones of commercial interest. The reaction process has been extended for the first time to methylenic ketone derivatives. A labeling reagent–product study permitted to determine the possible reaction pathway.

2.1. α-Alkylation of methyl ketone derivatives with alcohols

The alkylation of acetophenone (**1a**) with benzyl alcohol (**2a**) to give the corresponding ketone **3a** was chosen as the reaction model in order to optimize all different parameters, studying first the nature of the catalyst (Table 1). The reaction using a typical Meerwein–Ponndorf–Verley catalyst such as aluminum triisopropoxide gave a mixture nearly equimolecular of the expected ketone **3a**, as well as the related alcohol **4a**, which came from the reduction of the above ketone, and 1-phenyl-1-ethanol (**MPV** product), which is the expected product from a classical Meerwein–Ponndorf–Verley reduction.[26] The use of transition metallic salts such as those derived from vanadium or chromium did not produce any important change in the above results (Table 1, entries 2 and 3). Iron trichloride showed more promising results with a 60% yield and 40% atom efficiency (see Scheme 1) for ketone **3a**. However, the change of the anionic ion or the oxidation state of cationic iron atom decreased the yield (Table 1, entries 4–6). Moving along the periodic table did not have any reasonable improvement (entries 7–12). To our delight, the reaction with $RuCl_2(DMSO)_4$ gave a satisfactory 80% yield and 49% atom efficiency, with only trace of 1-phenyl-1-ethanol (**MPV**). In our hands, the reaction with $RuCl_2(PPh_3)_3$ gave lower results (compare entries 13 and 14). Moving again along the periodic table did not have any reasonable improvement (entries 15 and 16). Finally, it should be pointed out that the reaction with the dimeric complex $[IrCl(COD)]_2$ gave similar yield to that obtained with $RuCl_2(DMSO)_4$ (compare entries 13 and 17) and slightly lower atom efficiency (47%, see Scheme 1).

Table 1. Catalyst optimization

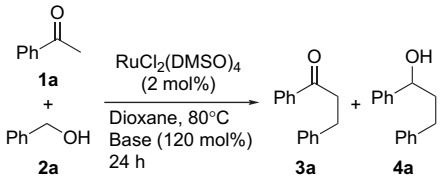


Entry	Catalyst	Yields (%)[a]		
		3a	**4a**	**MPV**
1	$Al(O^iPr)_3$	15	25	25
2	VCl_2	21	16	41
3	$CrCl_2$	26	19	32
4	$FeCl_3$	60	12	15
5	$Fe(acac)_3$	0	18	59
6	$FeCl_2$	25	21	33
7	$CoCl_2$	24	34	7
8	$NiCl_2$	16	28	22
9	$NiCl_2$[b]	0	0	16
10	$CuCl_2$	25	30	11
11	$Cu(OTf)_2$	38	23	16
12	$ZnCl_2$	16	35	10
13	$RuCl_2(DMSO)_4$	80	8	<1
14	$RuCl_2(PPh_3)_3$	61	15	7
15	$RhCl(PPh_3)_3$	49	20	10
16	$PdCl_2$	52	11	21
17	$[IrCl(COD)]_2$	82	5	<1

[a] Yields determined by ^1H NMR using *N,N*-diphenyl formamide as internal standard.
[b] A 40 mol % of $P(OEt)_3$ was added.

Once the best catalyst was found (Table 1, entry 13), other parameters of the reaction were tested (Table 2). The reaction using stoichiometric amounts of all starting reagents and only 2 mol % of catalyst in 1,4-dioxane gave the expected ketone in 72% yield after 24 h at 80 °C (entry 1). Changing the solvent by other less coordinating one, such as toluene, methylene chloride or THF, gave worse results, increasing the amount of the isolated alcohol **4a** (entries 2–4). The nature and the amount of the base were also tested, finding that the reaction failed when neither a base nor triethylamine were used. Even using substoichiometric amount of KOH (10 mol %) or CsOH gave modest results (entries 6 and 8). When the reaction was performed using only 1 mol % of the ruthenium catalyst, the yield decreased deeply (entry 9), the reaction failed when only 0.2% was

Table 2. Conditions optimization



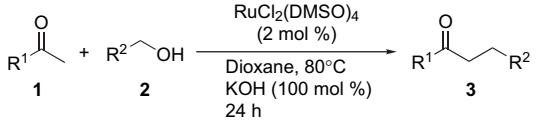
Entry	Solvent	Base	Yield **3a** (%)[a]	Yield **4a** (%)[a]
1	1,4-Dioxane	KOH	78 (72)[b]	6 (4)[b]
2	PhMe	KOH	61	18
3	CH_2Cl_2	KOH	13	10
4	THF	KOH	64	18
5	1,4-Dioxane	—	0	0
6	1,4-Dioxane	KOH[c]	12	0
7	1,4-Dioxane	Et_3N	0	0
8	1,4-Dioxane	CsOH	36	31
9[d]	1,4-Dioxane	KOH	35	3
10	1,4-Dioxane[e]	KOH	58	20
11[f]	1,4-Dioxane	KOH	77	10
12[g]	1,4-Dioxane	KOH	74	13
13[h]	1,4-Dioxane	KOH	32	54

[a] Yields determined by ^{1}H NMR using *N*,*N*-diphenyl formamide as internal standard.
[b] Isolated yields after column chromatography (silica gel: hexane/ethyl acetate).
[c] A 10 mol % of KOH was used.
[d] A 1 mol % of $RuCl_2(DMSO)_4$ was used.
[e] Reaction performed at reflux temperature.
[f] A 2 mol % of 2,6-pyridinedicarboxylic acid was added.
[g] A 4 mol % of 2,6-pyridinedicarboxylic acid was added.
[h] A 200 mol % of **2a** was used.

added. The reaction temperature had also an appreciable impact on the ratio of products, increasing the amount of alcohol **4a** when the temperature was increased (entry 10). In the last case, the GC–MS analysis of the reaction mixture at different reaction times showed the presence of benzaldehyde and chalcone as by-products, which can indicate the possible reaction pathway (vide infra). The presence of different amounts of 2,6-pyridinedicarboxylic acid, as stabilizing ruthenium ligand,[27] decreased the ratio of products. However, the increase of amount of alcohol **2a** (200 mol %, entry 13) changed the main isolated product, in this case being alcohol **4a** (vide infra).

Once the best conditions were found (Table 2, entry 1), this protocol was employed with other ketones and alcohols (Table 3). The reaction gave excellent results using methyl aryl ketones and aromatic alcohols independently of the electron character of the substituted alcohol (entries 1–3 and 12–15). In the case of using heteroaromatic alcohol derivatives, the yield decreased (entries 4 and 5), the reaction failing for aliphatic or propargyl alcohols[28] (entries 6 and 8). An especial case occurred when cinnamyl alcohol was used (entry 7), since instead of the expected δ,ε-unsaturated ketone the related saturated ketone **3g** was isolated in 48% yield, this ketone arising from the reduction of the double bond of the expected product. In order to improve the chemical yield, the reaction was repeated using a double amount of cinnamyl alcohol to ensure the total reduction of all carbon–carbon double bonds, obtaining in this case a 78% yield. Concerning the ketone scope, it should be pointed out that the alkylation process unfortunately failed for aliphatic methyl ketones (entry 6). However, the results

Table 3. α-Alkylation of methyl ketone derivatives with alcohols catalyzed by $RuCl_2(DMSO)_4$



Entry	R^1	R^2	No.	Yield (%)[a]
1	Ph	Ph	**a**	72
2	Ph	3-$PhCH_2OC_6H_4$	**b**	86
3	Ph	2-BrC_6H_4	**c**	93
4	Ph	2-Furyl	**d**	25
5	Ph	3-Indenyl	**e**	20
6	Ph	^{i}Pr	**f**	<5
7	Ph	(*E*)-PhCH=CH	**g**	48[b] (78)[b,c]
8	Ph	HC≡C	**h**	0[d]
9	*n*-C_5H_{11}	Ph	**i**	<5
10	4-MeC_6H_4	Ph	**j**	96
11[e]	4-MeC_6H_4	Ph	**j**	68
12	4-MeC_6H_4	4-$MeOC_6H_4$	**k**	92
13	4-MeC_6H_4	4-ClC_6H_4	**l**	85
14	4-MeC_6H_4	2-ClC_6H_4	**m**	92
15	4-MeC_6H_4	3,4-$(MeO)_2C_6H_3$	**n**	69
16	4-$F_3CC_6H_4$	Ph	**o**	0[f]
17	2-H_2N-4,5-$(OCH_2)C_6H_2$	Ph	**p**	55
18	2-Naphthyl	Ph	**q**	87
19	2-Thienyl	Ph	**r**	45
20	2-Thienyl	2-BrC_6H_4	**s**	41
21	*N*-Methylpyrrol-2-yl	Ph	**t**	80
22	Ferrocenyl	Ph	**u**	17[g]
23	3-Indenyl	Ph	**v**	0[h]

[a] Isolated yields after column chromatography (silica gel: hexane/ethyl acetate); yields obtained using 2 equiv of alcohols in parenthesis.
[b] The corresponding full hydrogenated ketone was the only isolated product.
[c] Cinnamyl alcohols (2 equiv) were used.
[d] The starting acetophenone (**1a**) was recovered in practically quantitative yield.
[e] KO^{t}Bu was used as base instead of KOH.
[f] The corresponding alcohol **4o** was isolated in 48–89% yield (see text).
[g] The related α,β-unsaturated ketone **6u** was isolated in 60% yield.
[h] The related α,β-unsaturated ketone **6v** was isolated in 79% yield.

obtained using different methyl aryl ketones were good independently of the electronic character of the substituent on the aromatic ring (compare entries 1, 10, and 16–18, and footnote e). The atomic efficiency reached up to 70% in the case of ketone **1j** (entry 10). It should be pointed out that changing the KOH base for a slightly stronger KO^{t}Bu as base in the reaction, the yield decreased significantly and consequently the atomic efficiency (entry 11). In the case of using *p*-trifluoromethylacetophenone, instead of the expected ketone **3o**, the only product isolated was the related alcohol **4o** (48%), which comes from the expected alkylation process followed by a reduction of the ketone **3o**. When the reaction was repeated with 2 equiv of alcohol (the source of alkylating as well as the reducing agent) the yield of **4o** increased up to 89% (entry 16).

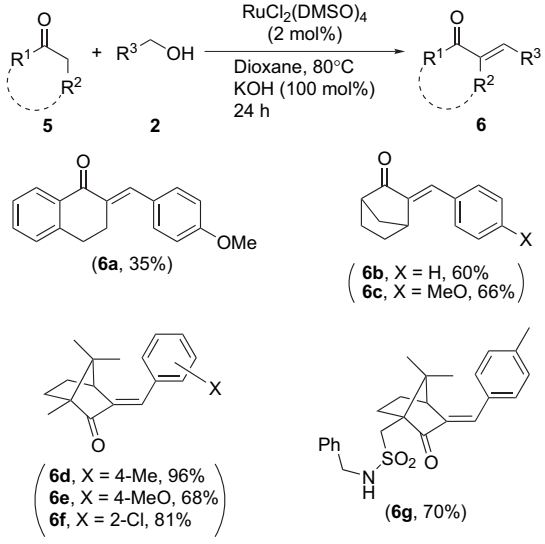
The reaction was also expanded to heteroaromatic methyl ketones (Table 3, entries 19–23), giving in these cases different results depending on the nature of the heteroaromatic system. Thus, the reaction with thiophene derivative gave the expected ketones **3r**,**s** with moderated yield, the only by-product detected being the related Meerwein–Ponndorf–Verley alcohol coming from the reduction of starting ketone. In the case of the pyrrol ketone, the result was similar to

other aryl ketones. Finally, when the reaction was performed with either ferrocenyl or indenyl ketone derivatives, the main isolated product was not the corresponding expected ketone **3u** or **3v**, but the related α,β-unsaturated ketone of type **6** (see infra). In these two cases, the final hydrogenation of the double bond failed, at least partially, but not the catalytic cycle. At this moment, we do not have any clear explanation for this behavior, but it is known that in the aerobic oxidation of amines by ruthenium complexes, oxygen[29] is the final scavenger for hydrogen, and here it could occur something similar, the direct generation of hydrogen being not excluded.[30]

The reaction of propiophenone with benzyl alcohol merits a separated comment, since this reaction gave a mixture of different products being the starting ketone the major one, followed by the Meerwein–Ponndorf–Verley alcohol derived from its reduction, the expected ketone of type **3**, and the related α,β-unsaturated ketone of type **6** being minor components of the crude mixture (estimated yields by ^{1}H NMR lower than 5% in any case). However, when the reaction was performed in the presence of equal amounts of propiophenone, acetophenone, and benzyl alcohol, the process showed a high selectivity giving ketone **3a** in a 78% yield and recovering the starting propiophenone in a higher 90% yield, the estimated yield of secondary alcohol **4a** and the Meerwein–Ponndorf–Verley alcohol (1-phenylpropanol) being less than 7% for both. This result shows the high selectivity of the alkylation process for methyl aryl ketones.

2.2. α-Alkenylation of bicyclic ketone derivatives with alcohols

As noticed in the above paragraph, the reaction with ketones different from methyl derivatives failed. In the literature, the hydrogen autotransfer strategy had been only applied with moderated success to benzofused α-tetralone (**5a**) and related systems.[12–15] The only isolated product was surprisingly ketone **6a** when the above reaction was performed using ketone **5a** and 4-methoxybenzyl alcohol, albeit with moderated yield (35%). The reaction with other bicyclic ketones **5** (not only benzofused but also aliphatic ones) gave the corresponding α,β-unsaturated ketone **6** as the only product with good to excellent yields (Scheme 3). In order to understand the catalytic turnover of ruthenium species, we hypothesize the reoxidation of the ruthenium hydride intermediate by reaction with oxygen or by direct generation of hydrogen as it was previously pointed out. The presence of functional groups on the aromatic ring of the aldehyde did not have any influence on the results, in all cases the chemical yield being good. However, the structure of the starting ketone has a higher impact on the results. It is worthy to note that synthesized chiral benzylidenecamphor derivatives **6d–f** have different applications, such as in the synthesis of second-order non-linear optical materials,[31] as chiral dopants for nematic liquid crystals which induce ordering into a helix in the nematic phase[32] or as sunscreens (**6e**).[33] The previous preparation of all this type of compounds involved the condensation between camphor and the corresponding aromatic aldehyde using anhydrous solvents and strong and expensive bases, such as $NaNH_2$ or potassium *tert*-butoxide, with the yield never being higher than 75%.[34] With this new protocol, the yields are significantly higher, avoiding the necessity of using dry solvents, special handle reagents, and aromatic aldehydes, which have stability problems with their storage (usually they are oxidized by the atmospheric oxygen).



Scheme 3. α-Alkenylation of bicyclic ketones.

The *Z*-configuration of the double bond was unambiguously determined by the X-ray of compound **6e** (Fig. 1) and by NOESY experiments of compounds **6c**, **e**, and **f**. It should be pointed out that the reaction of *N*-benzyl camphorsulfonamide[35] with 4-methylbenzyl alcohol failed under standard conditions (Scheme 3), recovering the starting ketone unchanged. We attributed this failure to the presence of an acidic proton in the ketone structure, which competed with the alcohol to be deprotonated. However, the expected ketone **6g** was obtained with a fair chemical yield when the same reaction was performed under similar conditions but using 300 mol % of KOH, this type of camphorsulfonamide derivatives having been tested as alternative sunscreen.[36]

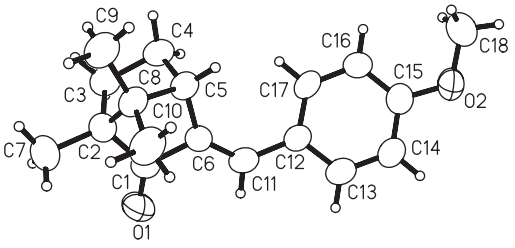
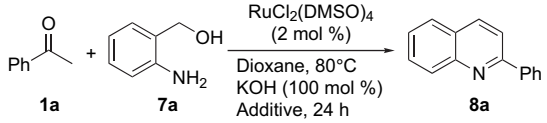


Figure 1. ORTEP drawing of compound **6e**.

2.3. Synthesis of quinolines by α-alkylation of ketones with 2-aminobenzyl alcohol derivatives

Another interesting application of this reaction appeared when it was performed using 2-aminobenzyl alcohol (**7a**) as alkylating agent and acetophenone (**1a**). In this case, quinoline **8a** was the only product isolated (Table 4), instead of the corresponding ketone of type **3**. The isolation of pure quinoline was very easy just by an acidic–basic extraction. This product arises formally from the internal condensation of the

Table 4. Optimization of the cyclization process



1a **7a** **8a**

Entry	Additive	Amount (%)	Yield (%)[a]
1	—	—	70
2	1-Hexene	200	86
3	1-Hexene	1200	75
4	Acetone	200	89
5	PhCOMe (**2a**)	200	81
6	PhCOPh	200	94

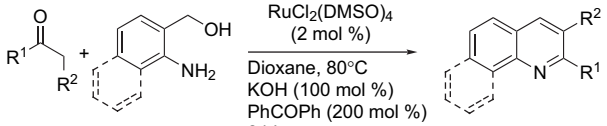
[a] Isolated yield after acidic/basic aqueous extraction.

amine moiety with the corresponding α,β-unsaturated ketone of type **6**.[37] The presence of a quinoline scaffold in the framework of various pharmacologically active compounds possessing anti-malarial, anti-inflammatory, anti-asthmatic, anti-bacterial, and anti-hypersensitive activities,[38] spurred on the optimization of this process, as well as on the study of its scope.[39] In order to improve the results, other hydrogen scavengers for the ruthenium hydride intermediate different from atmospheric oxygen such as olefins or ketones were tested, finding that all these scavengers gave better results than oxygen. It should be pointed out that it was also possible to use acetone as hydrogen scavenger, since its condensation with the corresponding in situ formed 2-aminobenzaldehyde seems to be slower than with acetophenone, so not interfering in the desired reaction. Despite all, the best result was found when benzophenone was used as hydrogen scavenger. Although the presence of these additives could be seen as an inconvenience for the isolation of quinoline, this is not true since the simple acidic–basic aqueous extraction yielded the pure compound **8a**.

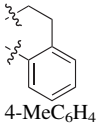
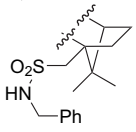
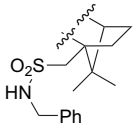
Once the best conditions were found (Table 4, entry 6), this protocol was employed with other ketones and alcohols (Table 5). The reaction gave excellent results using alcohol **7a**, not only with methyl aryl ketones but also with ketones bearing larger substituents than methyl or cyclic systems such as α-tetralone (entries 1–4). All these results, compared with those obtained previously with simple benzylic alcohols, could be an evidence that the condensation between the carbonyl group of the ketone with the amine to form the corresponding imine, takes place prior to the aldol condensation and therefore favoring it. High yields are also obtained for a broad set of different aryl methyl ketones, including heteroaromatic compounds (entries 7–10) and a ferrocenyl derivative (entry 11). In the last case, the crystallographic analysis of compound **8k** showed the co-planarity between both aromatic systems (Fig. 2) of great importance for a possible non-linear optical behavior.[40]

When the reaction was performed using camphor, together with the expected camphor-based chiral quinoline **8o**,[41] the related (*E*)-3-(2-aminophenyl)methylene-camphor (**6o**) was isolated in 20% yield. This α,β-unsaturated ketone **6o** could be easily transformed into the corresponding quinoline **8o** in quantitative yield by treatment with a catalytic amount of *para*-toluenesulfonic acid and azeotropic removal of water with benzene. Whereas the reaction using the related

Table 5. Synthesis of quinolines **8**



1 or **5** **7a**: benzyl **7b**: naphthyl **8**

Entry	Alcohol	No.	R^1	R^2	Yield (%)[a]
1	**7a**	**8a**	Ph	H	94[b]
2	**7a**	**8b**	Ph	Me	81[b]
3	**7a**	**8c**	Ph	Et	67[b]
4	**7a**	**8d**			98[b]
5	**7a**	**8e**	4-MeC_6H_4	H	96[b]
6	**7b**	**8f**	4-MeC_6H_4	H	93
7	**7a**	**8g**	2-Pyridyl	H	93
8	**7a**	**8h**	2-Furyl	H	93
9	**7a**	**8i**	2-Thienyl	H	96
10	**7a**	**8j**	*N*-Methylpyrrol-2-yl	H	76
11[d]	**7a**	**8k**	Ferrocenyl	H	88
12	**7a**	**8l**	Et	Me	96
13	**7a**	**8m**	$-(CH_2)_4-$		88
14	**7a**	**8n**			75
15	**7a**	**8o**			30[c]
16	**7a**	**8p**			65[d]
17	**7b**	**8q**			66[d]

[a] Isolated yields after column chromatography (silica gel: hexane/ethyl acetate).
[b] Isolated yields after acidic/basic aqueous extraction.
[c] A 20% yield of (*E*)-3-(2-aminophenyl)methylene-camphor (**6o**) was isolated.
[d] Yield obtained using 300 mol % of KOH.

camphorsulfonamide and 1 equiv of base failed, when the amount of base was increased up to 3 equiv, the expected quinoline **8p** was isolated in similar yield compared to other compounds **8**. The change of alcohol **7a** by the naphthyl derivative **7b** gave similar results (compare entries 5, 6, 16, and 17 in Table 5).

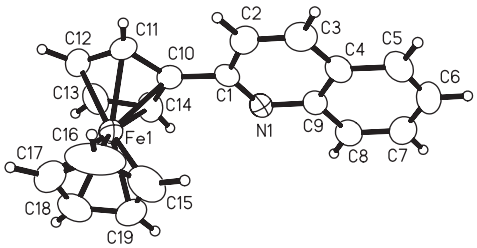


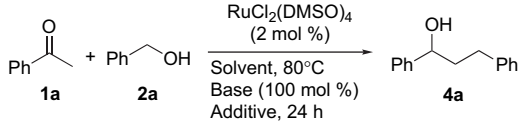
Figure 2. ORTEP drawing of compound **8k**.

2.4. Synthesis of secondary alcohols by a tandem α-alkylation of methyl ketone derivatives with alcohols and reduction

The reaction conditions shown in Table 3 could be changed to produce alcohols **4** as the main products,[42] instead of the related ketones **3**. Thus, when the reaction was performed using a double amount of alcohol **2a**, referred to ketone **1a**, under an argon atmosphere and in a pressure tube, the main isolated product was alcohol **4a** (Table 6, entry 1). This compound came formally from a α-alkylation process followed by a Meerwein–Ponndorf–Verley reduction.[26] As in previous cases of simple alkylations, lowering the amount of either catalyst or base gave poorer yield. However, the result did not improve increasing the amount of alcohol **2a** up to 6 equiv (entry 5). The nature of the initial ruthenium complex seems to be very important, since the reaction using $[RuHCl(CO)(PPh_3)_3]$ as catalyst gave very poor results (entry 2).[43] The effect of the solvent and base was also tested, the best results being obtained using dioxane and KOH (entries 1 and 6–13). Finally, we studied the influence of different additives. Thus, the reaction using a mixture of ruthenium complex and triphenyl phosphine in 1/1 molar ratio gave a slight better result. However, the increase of the phosphine/ruthenium ratio or the use of a diphosphine or nitrogenated ligands, as well as a phase transfer catalyst did not improve the previous results (entries 15–17).

The aforementioned protocol (Table 6, entry 14) was then used with other ketones and alcohols (Table 7). Unfortunately, the reaction only worked nicely when both reagents, the ketone and the alcohol, were aromatic. The reaction using isobutanol gave only 45% yield (entry 2), the same range of yield was found for the combination of aliphatic ketones with benzyl alcohol. It should be pointed out that the reaction using 2-heptanone only gave one product (entry 4), which arises from the alkylation of the methyl substituent, and not from the methylenic alkylation.

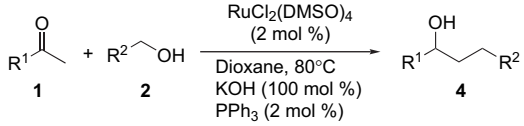
Table 6. Optimization of tandem process of α-alkylation and reduction



Entry	Solvent	Base	Additive[a]	Yield (%)[b]
1	1,4-Dioxane	KOH	—	78
2[c]	1,4-Dioxane	KOH	—	7
3	1,4-Dioxane	KOH[d]	—	0
4[e]	1,4-Dioxane	KOH	—	0
5	1,4-Dioxane	KOH	**2a** (600)	69
6	PhMe	KOH	—	61
7	CH_2Cl_2	KOH	—	10[f]
8	THF	KOH	—	72
9	DMF	KOH	—	<5
10	MeCN	KOH	—	0
11	1,4-Dioxane	CsOH	—	53
12	1,4-Dioxane	K_2CO_3	—	0
13	1,4-Dioxane	Et_3N	—	0
14	1,4-Dioxane	KOH	PPh_3 (2)	82
15	1,4-Dioxane	KOH	$Ph_2P(CH_2)_2PPh_2$ (2)	61
16	1,4-Dioxane	KOH	$Me_2N(CH_2)_2NMe_2$ (2)	72
17	1,4-Dioxane	KOH	*n*-Bu_4NBr (100)	28

[a] In parenthesis mol % of additive used.
[b] Isolated yields after column chromatography (silica gel: hexane/ethyl acetate).
[c] $RuClH(CO)(PPh_3)_3$ was used instead of $RuCl_2(DMSO)_4$.
[d] A 10 mol % of KOH was used.
[e] A 0.2 mol % of $RuCl_2(DMSO)_4$ was used.
[f] Ketone **3a** was obtained in 13% yield.

Table 7. Synthesis of alcohols **4** by a tandem process of α-alkylation and reduction



Entry	No.	R^1	R^2	Yield (%)[a]
1	**4a**	Ph	Ph	82
2	**4b**	Ph	^{i}Pr	45
3	**4c**	^{t}Bu	Ph	25
4	**4d**	*n*-C_5H_{11}	Ph	35

[a] Isolated yields after column chromatography (silica gel: hexane/ethyl acetate).

2.5. Mechanistic considerations

Although similar processes using different catalysts have been described, the possible mechanistic pathway is totally unknown, only speculative catalytic cycles having been proposed based only on by-products detected, such as aldehyde and α,β-unsaturated ketone. The last part of this study was focused on the possible catalytic pathway of the reaction, for the standard reaction between 4-methylacetophenone and benzyl alcohol. The same reaction was performed with different combinations of labeled reagents finding in all cases the product **3j** labeled in different ratio and/or positions (Table 8). Thus, the reaction using only deuterated alcohol gave the expected ketone **3j** with a poor incorporation of deuterio only at the α-position with respect to the carbonyl group (entry 1). When the same reaction was repeated using KOD, the same labeled product was obtained, only increasing the deuterium incorporation (entry 2). The reaction using d_3-4-methylacetophenone[44] as the only labeled reagent gave again the same α-deuterated ketone **3j** (entry 3) with a similar deuterium incorporation to the previous case, what could indicate the presence of several enolate equilibriums, even during the aqueous work-up. The reaction using the three previous labeled reagents gave the expected ketone **3j** with a double incorporation of deuterium at the α-position (entry 4). Finally, instead of labeling the acidic hydrogens of different reagents, we labeled the benzylic position of the

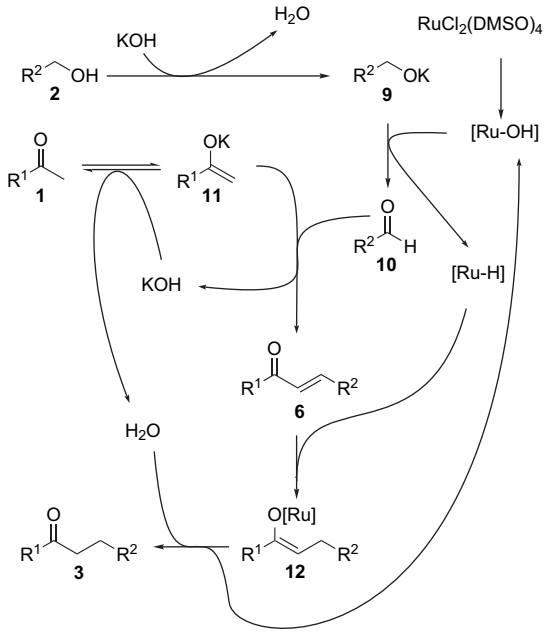
Table 8. Preparation of deuterated ketone **3j** by the use of labeled reagents

Entry	Labeled reagents	Deuterated ketone **3j**	Deuterium incorporation (%)[a]
1	$PhCH_2OD$	4-$MeC_6H_4COCDHCH_2Ph$	10
2	$PhCH_2OD$, KOD	4-$MeC_6H_4COCDHCH_2Ph$	50
3	4-$MeC_6H_4COCD_3$	4-$MeC_6H_4COCDHCH_2Ph$	50
4	4-$MeC_6H_4COCD_3$, $PhCH_2OD$, KOD	4-$MeC_6H_4COCD_2CH_2Ph$	75
5	$PhCD_2OH$	4-$MeC_6H_4COCH_2CD_2Ph$	94

[a] Isolated compound in yields higher than 85% after column chromatography (silica gel: hexane/ethyl acetate); the deuterium incorporation was estimated on the basis of ^{1}H NMR spectrum.

benzyl alcohol (prepared by reduction of methyl benzoate with $LiAlD_4$).[45] In this case, the reaction gave the product **3j** with a double deuterium incorporation in the β-position (entry 5).

All the above results, together with the observation of different by-products of the reaction, drove us to propose the mechanism pathway depicted in Scheme 4. Probably, in the reaction medium, the initial ruthenium complex evolves to form the real catalyst, which could be a polymetallic species, even bearing hydroxy groups,[46] although the permanence of chlorine ligands cannot be ruled out.[47] In turn, this species reacts with the primary alkoxide derivative to form the corresponding mono- or dihydride ruthenium catalytic active species.[47] The necessary use of stoichiometric amounts of base can indicate that its role is not only the deprotonation of the starting ketone **1** but also the deprotonation of alcohol **2** to yield water and the corresponding alkoxide **9**, which is the real substrate for the oxidation step giving the corresponding aldehyde **10** (detected in some cases by GC–MS) and a new ruthenium hydride species. The condensation of enolate **11** with the in situ formed aldehyde **10** leads to the α,β-unsaturated ketone **6**. This ketone suffers a Michael-type hydride addition by the ruthenium hydride to form the corresponding ruthenium enolate **12**, which is hydrolyzed by water to form the final ketone **3**, renewing the starting catalytic ruthenium species.[48] Water comes either from the deprotonation of alcohol **2** (α-labeling of ketone **3j** when $PhCH_2OD$ was used) or from the deprotonation of the starting ketone **1** (α-labeling of ketone **3j** when d_3-4-methylacetophenone was used), this hypothesis being confirmed by the increase of the deuterium incorporation when all these reagents were labeled. Finally, it should be pointed out that the reduction of the double bond of compound **6** seems to be a Michael-type process since only the β-position in the final ketone **3** was doubly labeled when $PhCD_2OH$ was used, no cross-over labeling occurring.



Scheme 4. Proposed catalytic cycle for the α-alkylation of ketones using alcohols as electrophiles and catalyzed by $RuCl_2(DMSO)_4$.

3. Conclusions

In summary, we have described here the use of $RuCl_2(DMSO)_4$ for a simple and direct α-alkylation of ketones with not only high yields, but also good atom efficiency, using alcohols as the electrophilic partner. The final product depends strongly on the ketone nature, obtaining either the simple alkylation for methyl ketones or α,β-unsaturated ketones (firstly described) when methylenic bicyclic ketones were used as starting materials. In this way, different quinolines could be prepared with excellent yields just by using a 2-aminoaryl alcohol derivative as alkylating agent. A labeled reagent/product study showed that the process goes through an oxidation of the alcohol, classical condensation, ruthenium hydride Michael addition, and final hydrolysis to give the final ketone, renewing the catalytic ruthenium species. It is worthy to note that this procedure constitutes an excellent example of very high atom efficiency reaction. Moreover, the waste material of the reactions is water, being a very interesting process from an environmental and industrial point of view. The catalyst used is very cheap, stable, easy to handle and to be prepared.[49] All these facts make the $RuCl_2(DMSO)_4$-catalyzed alkylation process very interesting comparing to the classical alkylation protocols, using strong bases, dry solvents, and hazardous alkylating agents, as well as other alternative expensive and difficult handle catalysts.

4. Experimental

4.1. Chemicals and instrumentation

Full general statements were described elsewhere.[50] 1-Aminonaphth-1-ylmethanol (**7b**) was prepared by standard $NaBH_4$ reduction of the corresponding aldehyde in 93% yield. In turn, the above starting aldehyde was obtained in 5% overall yield from 2-methylnaphthalene, after four synthetic steps, following the reported procedure.[51] The $RuCl_2(DMSO)_4$ complex was prepared in excellent yields (85–99%) by short time refluxing of $RuCl_3 \cdot 3H_2O$ in DMSO.[49] All other reagents were commercially available (Acros, Aldrich, Strem) and were used as received. Solvents were dried by standard procedures.[52]

4.2. General procedure for reaction of ketones with alcohols

To a solution of $RuCl_2(DMSO)_4$ (0.048 g, 0.1 mmol) and KOH (0.330 g, 5 mmol) in 1,4-dioxane (5 mL) was added the corresponding ketone **1** or **5** (5 mmol) followed by the corresponding alcohol **2** or **7** (5 mmol). In the case of using amino alcohols **7**, benzophenone (1.822 g, 10 mmol) was also added. The mixture was stirred and heated at 80 °C for a period of 24 h. Then, the mixture was quenched by the addition of a saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvents removed under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using suitable mixtures of hexane/ethyl acetate to afford the corresponding product **3**, **4**, **6** or **8**. Yields are included

in Tables 1–8 and Scheme 3. Physical and spectroscopic data as well as literature references follow.

4.2.1. 1,3-Diphenyl-1-propanone (3a).[12] t_R 15.0; R_f 0.65 (hexane/ethyl acetate: 4/1); ν (film) 3058, 3021, 1597 (C=CH), 1678 cm^{-1} (C=O); δ_H 3.00–3.05 (2H, m, PhCH_2), 3.20–3.25 (2H, m, CH_2CO), 7.15–7.50 and 7.90–7.95 (8 and 2H, respectively, 2m, 2×Ph); δ_C 29.9, 40.2, 125.95, 127.85 (2C), 128.25 (2C), 128.35 (2C), 128.4 (2C), 132.85, 136.6, 141.1, 198.9; *m/z* 210 (M^+, 59%), 105 (100), 91 (10), 77 (36).

4.2.2. 3-(3-Benzyloxyphenyl)-1-phenyl-1-propanone (3b). t_R 23.4; R_f 0.64 (hexane/ethyl acetate: 4/1); ν (film) 3065, 1602, 1492 (C=CH), 1689 (C=O), 1252, 1028 cm^{-1} (C–O); δ_H 2.95–3.05 (2H, m, CH_2CH_2CO), 3.20–3.30 (2H, m, CH_2CO), 5.00 (2H, s, CH_2O), 6.80–6.90, 7.15–7.50, and 7.90–7.95 (3, 9, and 2H, respectively, 3m, ArH); δ_C 29.95, 40.1, 69.7, 112.1, 115.0, 120.9, 127.35, 127.8, 127.9, 128.4 (2C), 128.45 (2C), 129.4, 132.9, 136.6, 136.9, 142.8, 158.8, 198.9; *m/z* 316 (M^+, 19%), 196 (11), 105 (11), 91 (100), 77 (10); HRMS: M^+ found 316.1467. $C_{22}H_{20}O_2$ requires 316.1463.

4.2.3. 3-(2-Bromophenyl)-1-phenyl-1-propanone (3c).[53] t_R 16.9; R_f 0.63 (hexane/ethyl acetate: 4/1); ν (film) 3067, 1592 (C=CH), 1692 cm^{-1} (C=O); δ_H 3.10–3.20 (2H, m, PhCH_2), 3.25–3.30 (2H, m, CH_2CO), 7.00–7.55 and 7.90–7.95 (7 and 2H, respectively, 2m, ArH); δ_C 30.6, 38.4, 124.2, 127.5, 127.85, 127.9 (2C), 128.45 (2C), 130.65, 132.7, 132.95, 136.55, 140.4, 198.65; *m/z* 288 (M^+, <0.1%), 210 (16), 209 (100), 105 (56), 77 (32).

4.2.4. 3-(2-Furyl)-1-phenyl-1-propanone (3d).[54] t_R 13.4, R_f 0.40 (hexane/ethyl acetate: 4/1); ν (film) 3060, 1603, 1506 (C=CH), 1682 cm^{-1} (C=O); δ_H 3.50–3.55 (2H, m, PhCH_2), 3.75–3.80 (2H, m, CH_2CO), 6.45–6.50, 6.70–6.75, 7.74, 7.85–8.00, and 8.35–8.45 (1, 1, 1, 3, and 2H, respectively, 2m, s, and 2m, respectively, ArH); δ_C 22.4, 36.85, 105.25, 110.2, 127.95 (2C), 128.55 (2C), 133.05, 136.65, 141.0, 154.7, 198.55; *m/z* 201 (M^++1, 11%), 200 (M^+, 76), 105 (100), 95 (32), 94 (10), 81 (37), 77 (51), 51 (12).

4.2.5. 3-(1*H*-3-Indenyl)-1-phenyl-1-propanone (3e).[55] Mp 123–125 °C; t_R 14.6; R_f 0.37 (hexane/ethyl acetate=4/1); ν (KBr) 3418 (N–H), 3058, 1597 (C=CH), 1680 cm^{-1} (C=O); δ_H 3.20–3.25 (2H, m, PhCH_2), 3.35–3.45 (2H, m, CH_2CO), 7.05–7.65 and 7.95–8.00 (9 and 2H, respectively, 2m, ArH); δ_C 19.7, 39.3, 111.15, 115.5, 118.7, 119.3, 121.55, 122.05, 127.25, 128.0 (2C), 128.55 (2C), 132.95, 136.3, 136.95, 199.9; *m/z* 250 (M^++1, 11%), 249 (M^+, 57), 144 (55), 131 (10), 130 (100), 117 (12), 105 (12), 77 (20).

4.2.6. 1,5-Diphenyl-1-pentanone (3g).[56] t_R 16.6; R_f 0.62 (hexane/ethyl acetate=4/1); ν (film) 3062, 1605 (C=CH), 1690 cm^{-1} (C=O); δ_H 1.65–1.80 (4H, m, C$H_2CH_2CH_2CO$), 2.60–2.70 and 2.95–3.05 (2 and 2H, respectively, 2m, C$H_2CH_2CH_2CH_2CO$), 7.10–7.55 and 7.90–7.95 (8 and 2H, respectively, 2m, 2×Ph); δ_C 23.9, 31.05, 35.75, 38.35, 125.7, 128.0 (2C), 128.25 (2C), 128.35 (2C), 128.5 (2C), 132.85, 137.0, 142.2, 200.2; *m/z* 238 (M^+, 15%), 147 (10), 133 (36), 129 (11), 121 (11), 120 (96), 117 (10), 105 (100), 91 (29), 77 (50).

4.2.7. 1-(4-Methylphenyl)-3-phenyl-1-propanone (3j).[12] Mp 60–62 °C; t_R 15.9; R_f 0.59 (hexane/ethyl acetate=4/1); ν (KBr) 3067, 1605 (C=CH), 1677 cm^{-1} (C=O); δ_H 2.34 (3H, s, CH_3), 3.00–3.05 (2H, m, PhCH_2), 3.20–3.25 (2H, m, CH_2CO), 7.15–7.30 and 7.81 (7 and 2H, respectively, m and d, respectively, J=8.3 Hz, ArH); δ_C 21.4, 30.0, 40.1, 125.9, 128.0 (2C), 128.25 (2C), 128.35 (2C), 129.0 (2C), 134.2, 141.25, 143.6, 198.6; *m/z* 224 (M^+, 33%), 209 (22), 119 (100), 91 (32).

4.2.8. 3-(4-Methoxyphenyl)-1-(4-methylphenyl)-1-propanone (3k).[57] Mp 57–58 °C; t_R 18.2; R_f 0.53 (hexane/ethyl acetate: 4/1); ν (KBr) 3030, 1614 (C=CH), 2837 (OCH_3), 1675 cm^{-1} (C=O); δ_H 2.39 (3H, s, C$H_3C_6H_4$), 2.95–3.00 (2H, m, CH_2CH_2CO), 3.20–3.25 (2H, m, CH_2CO), 3.77 (3H, s, CH_3O), 6.82, 7.16, 7.23, and 7.85 (2H each one, 4d, J=8.7, 8.7, 7.9, and 7.9 Hz, respectively, ArH); δ_C 21.6, 29.3, 40.55, 55.2, 113.85 (2C), 128.1 (2C), 129.2 (2C), 129.3 (2C), 133.35, 134.4, 143.75, 157.9, 199.0; *m/z* 255 (M^++1, 16%), 254 (M^+, 27), 239 (11), 135 (15), 121 (100), 120 (10), 119 (90), 108 (15), 91 (42), 65 (12).

4.2.9. 3-(4-Chlorophenyl)-1-(4-methylphenyl)-1-propanone (3l).[58] Mp 83–84 °C; t_R 17.6; R_f 0.74 (hexane/ethyl acetate: 4/1); ν (KBr) 3021, 1606 (C=CH), 1669 cm^{-1} (C=O); δ_H 2.40 (3H, s, CH_3), 3.00–3.05 (2H, m, CH_2CH_2CO), 3.20–3.25 (2H, m, CH_2CO), 7.15–7.25 and 7.84 (6 and 2H, respectively, m and d, respectively, J=8.1 Hz, ArH); δ_C 21.6, 29.4, 40.0, 128.1 (2C), 128.55 (2C), 129.3 (2C), 129.8 (2C), 131.9, 134.25, 139.8, 43.95, 198.5; *m/z* 300 (M^++2, 9%), 258 (M^+, 27), 243 (18), 119 (100), 91 (24).

4.2.10. 3-(2-Chlorophenyl)-1-(4-methylphenyl)-1-propanone (3m). t_R 17.5; R_f 0.72 (hexane/ethyl acetate: 4/1); ν (film) 3066, 2921, 1606 (C=CH), 1683 cm^{-1} (C=O); δ_H 2.40 (3H, s, CH_3), 3.10–3.20 (2H, m, CH_2CH_2CO), 3.25–3.30 (2H, m, CH_2CO), 7.10–7.35 and 7.86 (6 and 2H, respectively, m and d, respectively, J=8.3 Hz, ArH); δ_C 21.6, 28.4, 38.3, 126.9 (2C), 127.65, 128.15 (2C), 129.25, 129.5, 130.75, 133.9, 134.25, 138.9, 143.85, 198.65; *m/z* 258 (M^+, <1%), 224 (17), 223 (100), 119 (90), 91 (26); HRMS: M^+ found 258.0820. $C_{16}H_{15}OCl$ requires 258.0811.

4.2.11. 3-(3,4-Dimethoxyphenyl)-1-(4-methylphenyl)-1-propanone (3n).[59] t_R 19.7; R_f 0.28 (hexane/ethyl acetate: 4/1); ν (film) 3061, 1607 (C=CH), 2834 (CH_3O), 1678 cm^{-1} (C=O); δ_H 2.40 (3H, s, C$H_3C_6H_4$), 2.95–3.00 (2H, m, CH_2CH_2CO), 3.2–3.3 (2H, m, CH_2CO), 3.85 and 3.86 (3H each one, 2s, 2×CH_3O), 6.75–6.80, 7.24, and 7.86 (3, 2, and 2H, respectively, m and 2d, respectively, J=7.9 Hz, ArH); δ_C 21.55, 29.8, 40.5, 55.7, 55.85, 111.2, 111.7, 120.1, 128.1 (2C), 129.2 (2C), 133.9, 134.35, 143.75, 147.25, 148.8, 198.95; *m/z* 285 (M^++1, 19%), 284 (M^+, 100), 165 (50), 151 (90), 119 (49), 91 (31).

4.2.12. 1-(6-Amino-1,3-benzodioxol-5-yl)-3-phenyl-1-propanone (3p). Mp 116–118 °C; t_R 20.4; R_f 0.26 (hexane/ethyl acetate: 4/1); ν (KBr) 3481, 3345 (NH_2), 3063, 1606 (C=CH), 1647 cm^{-1} (C=O); δ_H 3.00–3.15 (4H, m, CH_2CH_2), 5.86 (2H, s, OCH_2O), 6.11 and 7.08 (1 and 1H, respectively, 2s, $NO_2C_6H_2$), 6.45 (2H, s, NH_2), 7.10–7.30 (5H, m, Ph); δ_C 30.7, 40.9, 96.8, 101.2, 107.9, 110.2,

125.95, 128.35 (2C), 128.42 (2C), 138.7, 141.5, 149.45, 152.85, 198.85; *m/z* 270 (M^++1, 17%), 269 (M^+, 100), 165 (12), 164 (10), 137 (32), 136 (20); $C_{16}H_{15}NO_3$: requires C 71.36, H 5.61, N 5.20; found C 71.39, H 5.69, N 5.17.

4.2.13. 1-(2-Naphthyl)-3-phenyl-1-propanone (3q).[60] Mp 85 °C; t_R 19.6; R_f 0.64 (hexane/ethyl acetate: 4/1); ν (KBr) 3056, 3025, 1621 (C=CH), 1678 cm^{-1} (C=O); δ_H 3.05–3.15 (2H, m, PhCH_2), 3.35–3.40 (2H, m, CH_2CO), 7.15–7.30, 7.45–7.55, 7.80–8.00, and 8.40 (5, 2, 4, and 1H, respectively, 3m and s, respectively, ArH); δ_C 30.1, 40.4, 123.7, 126.05, 126.65, 127.65, 128.3 (2C), 128.35 (2C), 128.45 (2C), 129.4, 129.55, 132.35, 134.0, 135.4, 141.25, 198.95; *m/z* 261 (M^++1, 11%), 260 (M^+, 55), 156 (15), 155 (100), 127 (48).

4.2.14. 3-Phenyl-1-(2-thienyl)-1-propanone (3r).[60] t_R 15.2; R_f 0.68 (hexane/ethyl acetate: 4/1); ν (film) 3078, 1521 (C=CH), 1666 cm^{-1} (C=O); δ_H 3.05–3.10 (2H, m, PhCH_2), 3.20–3.30 (2H, m, CH_2CO), 7.10–7.30 and 7.60–7.70 (6 and 2H, respectively, 2m, ArH); δ_C 30.35, 41.1, 126.2, 128.1 (2C), 128.4 (2C), 128.5, 131.8, 133.55, 141.0, 144.1, 192.15; *m/z* 216 (M^+, 56%), 111 (100), 105 (14), 104 (19), 91 (15).

4.2.15. 3-(2-Bromophenyl)-1-(2-thienyl)-1-propanone (3s). t_R 17.1; R_f 0.56 (hexane/ethyl acetate: 4/1); ν (film) 3093, 2913 (C=CH), 1661 cm^{-1} (C=O); δ_H 3.10–3.30 (4H, m, 2×CH_2), 7.05–7.25 (7H, m, ArH); δ_C 31.1, 39.2, 124.3, 127.65, 128.05, 128.1, 130.85, 131.95, 132.85, 133.7, 140.2, 144.05, 191.95; *m/z* 216 (15%), 215 (M^+−79, 100), 111 (49); HRMS: M^+ found 215.0522. $C_{13}H_{11}OS$ requires 215.0531.

4.2.16. 1-(*N*-Methyl-1*H*-2-pyrrolyl)-3-phenyl-1-propanone (3t). t_R 14.8; R_f 0.53 (hexane/ethyl acetate: 4/1); ν (film) 3024, 1532 (C=CH), 1652 cm^{-1} (C=O); δ_H 3.00–3.15 (4H, m, 2×CH_2), 3.95 (3H, s, CH_3), 6.79, 6.09–6.15, 6.93–6.95, 7.20–7.30 (1, 1, 1, and 5H, respectively, s and 3m, respectively, ArH); δ_C 30.85, 37.7, 40.7, 107.9, 119.0, 126.0, 128.4 (2C), 128.45 (2C), 130.55, 139.95, 141.5, 190.15; *m/z* 213 (M^+, 56%), 108 (100), 81 (61), 53 (13); HRMS: M^+ found 213.1141. $C_{14}H_{15}NO$ requires 213.1154.

4.2.17. 1-Ferrocenyl-3-phenylpropanone (3u).[61] Mp 83–85 °C; t_R 20.0; R_f 0.47 (hexane/ethyl acetate: 4/1); ν (KBr) 3092, 1600 (C=CH), 1664 cm^{-1} (C=O); δ_H 3.00–3.10 (4H, m, CH_2CH_2), 4.07 (5H, s, C_5H_5Fe), 4.45–4.50 and 4.75–4.80 (2H each one, 2m, C_5H_4Fe), 7.20–7.35 (5H, m, Ph); δ_C 30.1, 41.5, 69.25 (2C), 69.65 (5C), 72.2 (2C), 78.95, 126.15, 128.5 (2C), 128.6 (2C), 141.6, 203.1; *m/z* 319 (M^++1, 23%), 318 (M^+, 100), 253 (27), 185 (10), 129 (11), 121 (23).

4.2.18. 1,3-Diphenyl-1-propanol (4a).[12] t_R 15.18; R_f 0.5 (hexane/ethyl acetate: 4/1); ν (film) 3399 (O–H), 3100, 1616 (C=CH), 1065 cm^{-1} (C–O); δ_H 1.90 (1H, s, OH), 1.95–2.20 (2H, m, PhCH_2), 2.55–2.75 (2H, m, CH_2CO), 4.68 (1H, dd, *J*=7.6, 5.5 Hz, CHO), 7.15–7.35 (10H, m, 2×Ph); δ_C 32.0, 40.45, 73.85, 125.85, 125.9, 127.6 (2C), 128.35 (2C), 128.4 (2C), 128.5 (2C), 141.75, 144.5; *m/z* 212 (M^+, 10%), 210 (16), 207 (19), 195 (11), 194 (79), 193 (17), 179 (12), 178 (10), 170 (26), 115 (13), 108 (12), 107 (100), 106 (11), 105 (46), 104 (11), 103 (17), 92 (24), 91 (39), 79 (47), 78 (12), 77 (54), 65 (14), 51 (12).

4.2.19. 1-Phenyl-4-methyl-1-pentanol (4b).[62] t_R 10.11; R_f 0.34 (hexane/ethyl acetate: 4/1); ν (film) 3374 (O–H), 3065, 3034 cm^{-1} (C=CH); δ_H 0.86 and 0.88 [3H each one, d, *J*=1.7 Hz, CH(CH_3)$_2$], 1.15–1.20 [1H, m, CH(CH_3)$_2$], 1.25–1.35 and 1.45–1.55 (1H each one, 2m, CH_2CH), 1.65–1.80 (2H, m, CH_2CHO), 1.85 (1H, s, OH), 4.62 (1H, t, *J*=6.8 Hz, CHO), 7.20–7.40 (5H, m, Ph); δ_C 22.5, 22.6, 28.0, 34.9, 36.9, 75.0, 125.9 (2C), 127.5, 128.4 (2C), 144.9; *m/z* 178 (M^+, 2%), 117 (11), 107 (100), 79 (33), 77 (17).

4.2.20. 1-Phenyl-4,4-dimethyl-3-pentanol (4c).[63] t_R 10.57; R_f 0.24 (hexane/ethyl acetate: 10/1); ν (film) 3416 (O–H), 3062, 3027, 1604 cm^{-1} (C=CH); δ_H 0.89 (9H, s, 3×CH_3), 1.48 (1H, s, OH), 1.55–1.65, 1.80–1.90 (1H each one, 2m, PhCH_2), 2.55–2.70, 2.85–3.00 (1H each one, 2m, CH_2CHO), 3.23 (1H, d, *J*=10.4 Hz, CHO), 7.15–7.35 (5H, m, Ph); δ_C 25.6 (3C), 33.3, 33.4, 35.0, 79.4, 125.8, 128.4 (2C), 128.5 (2C), 142.4; *m/z* 192 (M^+, <1%), 118 (14), 117 (35), 104 (28), 92 (20), 91 (100), 57 (18).

4.2.21. 1-Phenyl-3-octanol (4d).[19c] t_R 12.13; R_f 0.27 (hexane/ethyl acetate: 4/1); ν (film) 3357 (O–H), 3062, 3026, 1603 cm^{-1} (C=CH); δ_H 0.85–0.95 (3H, m, CH_3), 1.20–1.55 [9H, m, $(CH_2)_4$ and OH], 1.65–1.85 and 2.65–2.80 [2H each one, 2m, Ph(CH_2)$_2$], 3.55–3.70 (1H, m, CHO), 7.15–7.35 (5H, m, Ph); δ_C 14.0, 22.6, 25.3, 31.9, 32.1, 37.6, 39.1, 71.4, 125.8, 128.35 (2C), 128.4 (2C), 142.2; *m/z* 206 (M^+, <1%), 188 (20), 117 (47), 105 (16), 104 (87), 92 (43), 91 (100), 78 (11), 55 (22).

4.2.22. 3-Phenyl-1-(4-trifluoromethylphenyl)-1-propanol (4o).[64] t_R 14.9; R_f 0.71 (hexane/ethyl acetate: 4/1); ν (film) 3370 (O–H), 3025, 1621 (C=CH), 1069 cm^{-1} (C–O); δ_H 1.90–2.10 (2H, m, CH_2CH$_2$CHO), 2.55–2.75 (2H, m, CH_2CHO), 2.79 (1H, s, OH), 4.60–4.65 (1H, m, CHO), 7.10–7.25, 7.35, and 7.53 (5, 2, and 2H, respectively, m and 2d, respectively, *J*=8.1 Hz, ArH); δ_C 31.7, 40.4, 73.0, 125.3, 124.1 (q, $J_{1,2}$=272.2 Hz, CF_3), 125.95 (2C), 126.1 (2C), 128.3 (2C), 128.4 (2C), 129.6 (q, $J_{1,3}$=31.8 Hz, CCF_3), 141.25, 148.45; *m/z* 280 (M^+, <10%), 263 (17), 262 (100), 261 (18), 193 (22), 175 (66), 127 (45), 105 (21), 92 (40), 91 (31), 78 (11), 77 (12).

4.2.23. 2-[(*E*)-1-(4-Methoxyphenyl)methylidene]-1,2,3,4-tetrahydro-1-naphthalenone (6a).[65] Mp 105–107 °C; t_R 21.2; R_f 0.74 (hexane/ethyl acetate: 1/1); ν (KBr) 3070, 1605 (C=CH), 2832 (OCH_3), 1669 cm^{-1} (C=O); δ_H 2.90–2.95 and 3.10–3.15 (2H each one, 2m, CH_2CH_2), 3.84 (3H, s, CH_3O), 6.95, 7.24, 7.30–7.50, and 8.12 (2, 1, 4, and 1H, respectively, 2d, m, and d, *J*=8.7, 8.1, and 8.1 Hz, respectively, ArH), 7.85 [1H, s, CH=C(CO)CH$_2$]; δ_C 27.15, 28.75, 55.3, 113.9 (2C), 126.9, 128.05, 128.1, 128.35, 131.7 (2C), 133.05, 133.45, 133.6, 136.65, 143.0, 159.9, 187.8; *m/z* 265 (M^++1, 12%), 264 (M^+, 67), 263 (100), 249 (22), 233 (25), 121 (12).

4.2.24. 3-[(*E*)-1-Phenylmethylidene]bicyclo[2.2.1]heptan-2-one (6b).[66] t_R 14.8; R_f 0.37 (hexane/ethyl acetate: 4/1); ν (film) 3060, 1645 (C=CH), 1727 cm^{-1} (C=O); δ_H

1.60–1.75 (4H, m, CH_2CH_2), 1.90–2.10 (2H, m, CHC*H*$_2$CH), 2.75–2.80 and 3.60–3.65 (1H each one, 2m, C*H*CH_2CH_2C*H*), 7.15 (1H, s, CH=CCO), 7.30–7.50 (5H, m, Ph); δ_C 24.25, 27.25, 37.75, 40.15, 48.5, 127.15, 128.6 (2C), 128.8, 129.65 (2C), 135.2, 141.6, 206.7; *m/z* 199 (M^++1, 15%), 198 (M^+, 100), 197 (18), 170 (14), 169 (33), 155 (31), 142 (26), 141 (38), 129 (23), 128 (32), 127 (10), 115 (25), 102 (11), 92 (14), 91 (20).

4.2.25. 3-[(*E*)-1-(4-Methoxyphenyl)methylidene]bicyclo[2.2.1]heptan-2-one (6c).[66] t_R 17.0; R_f 0.74 (hexane/ethyl acetate: 1/1); ν (film) 2871 (OCH_3), 1720 (C=O), 1643, 1605 cm^{-1} (C=CH); δ_H 1.60–1.75 (4H, m, CH_2CH_2), 1.90–2.05 (2H, m, CH_2), 2.75–2.80 and 3.60–3.65 (1H each one, 2m, C*H*CH_2CH_2C*H*), 3.83 (3H, s, CH_3), 6.92 and 7.45 (2H each one, 2d, J=8.7 Hz, ArH), 7.11 (1H, s, CH=CCO); δ_C 24.35, 27.2, 37.9, 40.1, 48.5, 55.2, 114.1 (2C), 127.1, 127.75, 131.35 (2C), 139.45, 160.15, 206.9; *m/z* 229 (M^++1, 17%), 228 (M^+, 100), 200 (32), 199 (20), 185 (35), 172 (29), 171 (15), 157 (15), 145 (12), 128 (14), 121 (16), 115 (16).

4.2.26. 1,7,7-Trimethyl-3-[(*E*)-1-(4-methylphenyl)methylidene]bicyclo[2.2.1]heptan-2-one (6d).[67] Mp 93–95 °C; t_R 16.5; R_f 0.57 (hexane/ethyl acetate: 3/2); $[\alpha]_D^{20}$ +373.8 (*c* 0.8, $CHCl_3$); ν (KBr) 3090, 1642, 1610 (C=CH), 1724 cm^{-1} (C=O); δ_H 0.79, 0.98, and 1.02 [3H each one, 3s, $(CH_3)_2CCCH_3$], 1.45–1.60, 1.70–1.80, 2.10–2.20 (2, 1, and 1H, respectively, 3m, CH_2CH_2), 2.36 (3H, s, C*H*$_3C_6H_4$), 3.05–3.10 (1H, m, C*H*CH_2), 7.15–7.20 and 7.35–7.40 (3 and 2H, respectively, 2m, C=C*H*C_6H_4); δ_C 9.2, 18.25, 20.4, 21.25, 25.8, 30.65, 46.55, 49.1, 56.95, 127.45, 129.3 (2C), 129.65 (2C), 132.7, 138.8, 141.15, 208.0; *m/z* 255 (M^++1, 20%), 254 (M^+, 100), 239 (30), 226 (12), 212 (11), 183 (28), 172 (27), 171 (36), 170 (29), 169 (28), 157 (16), 155 (26), 149 (12), 148 (10), 143 (24), 142 (12), 141 (20), 129 (16), 128 (38), 115 (22), 105 (24), 95 (11), 91 (12), 55 (10).

4.2.27. 3-[(*E*)-1-(4-Methoxyphenyl)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (6e).[68] Mp 127–129 °C; t_R 17.9; R_f 0.46 (hexane/ethyl acetate: 4/1); $[\alpha]_D^{20}$ +404 (*c* 0.8, $CHCl_3$); ν (KBr) 3026, 1637, 1615 (C=CH), 2830 (OCH_3), 1724 cm^{-1} (C=O); δ_H 0.80, 0.99, and 1.02 [3H each one, 3s, $(CH_3)_2CCCH_3$], 1.45–1.60, 1.70–1.80, and 2.10–2.20 (2, 1, and 1H, respectively, 3m, CH_2CH_2), 3.05–3.10 (1H, m, $CHCH_2$), 3.82 (3H, s, CH_3O), 6.92 and 7.44 (2H each one, 2d, J=8.7 Hz, C_6H_4), 7.19 (1H, s, CH=CCO); δ_C 9.25, 18.3, 20.45, 25.8, 30.75, 46.7, 49.1, 55.2, 56.9, 114.1 (2C), 127.25, 128.15, 131.3 (2C), 139.9, 160.0, 208.15; *m/z* 271 (M^++1, 20%), 270 (M^+, 100), 242 (16), 227 (33), 199 (13), 188 (13), 187 (22), 186 (42), 185 (19), 171 (17), 159 (12), 128 (11), 121 (26), 115 (15). Crystal data: $C_{18}H_{22}O_2$, M=270.36; Orthorhombic, a=6.519 (2), b=12.2929 (13), c=18.989 (6) Å; V=1521.7 (7) $Å^3$; space group $P2_1$ 21 21; Z=4; D_c=1.180 mg/m^3; λ=0.71073 Å; μ=0.075 mm^{-1}; $F(000)$=584; T=23±1 °C. Data collection based on three ω-scan runs (starting ω=−34°) at values ϕ=0°, 120°, 240° with the detector at 2θ=−32°. An additional run of 100 frames, at 2θ=−32°, ω=−34° and ϕ=0°, was acquired to improve redundancy. For each of these runs, 606 frames were collected at 0.3° intervals and 30 s per frame. The diffraction frames were integrated using the program SAINT and the integrated intensities were corrected for Lorentz-polarization effects with SADABS. The structure was solved by direct methods and refined to all 1581 unique F_o^2 by full matrix least squares. All of the hydrogen atoms were placed at idealized positions and retained as rigid atoms. Final $wR2$=0.1216 for all data and 185 parameters; $R1$=0.1178 for 890 $F_o>4\sigma$ (F_o).

4.2.28. 3-[(*E*)-1-(2-Chlorophenyl)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (6f).[69] Mp 85–87 °C; t_R 16.8; R_f 0.49 (hexane/ethyl acetate: 4/1); $[\alpha]_D^{20}$ +258 (*c* 0.8, $CHCl_3$); ν (KBr) 3067, 1660, 1615 (C=CH), 1728 cm^{-1} (C=O); δ_H 0.82, 0.98, and 1.04 [3H each one, 3s, $(CH_3)_2CCCH_3$], 1.45–1.65, 1.75–1.85, and 2.10–2.20 (2, 1, and 1H, respectively, 3m, CH_2CH_2), 2.90–2.95 (1H, m, C*H*CH_2), 7.20–7.30 and 7.35–7.45 (2H each one, 2m, C_6H_4), 7.50 (1H, s, CH=CCO); δ_C 9.15, 18.05, 20.45, 25.95, 30.35, 46.4, 48.7, 57.25, 123.8, 126.5, 129.45, 129.7, 129.75, 133.9, 135.1, 143.85, 207.35; *m/z* 276 (M^++2, 5%), 274 (M^+, 15), 240 (19), 239 (100), 157 (13), 128 (65), 127 (13).

4.2.29. *N*-Benzyl-7,7-dimethyl-3-[(*E*)-1-(4-methylphenyl)methylidene]-2-oxobicyclo[2.2.1]hept-1-ylmethanesulfonamide (6g). R_f 0.49 (hexane/ethyl acetate: 3/2); $[\alpha]_D^{20}$ +252.6 (*c* 17.4, $CHCl_3$); ν (film) 3296 (NH), 3032, 1634, 1609 (C=CH), 1728 cm^{-1} (C=O); δ_H 0.71 and 0.98 [3 and 3H, respectively, 2s, $C(CH_3)_2$], 1.58–1.64 and 2.00–2.25 (1 and 4H, respectively, 2m, $CHCH_2CH_2$), 2.38 (3H, s, C*H*$_3C_6H_4$), 2.94 and 3.27 (1 and 1H, respectively, 2d, J=15.1 Hz, CH_2SO_2), 3.07 (1H, d, J=2.8 Hz, C=CH), 4.39 (2H, d, J=6.4 Hz, CH_2N), 6.20 (1H, t, J=6.4 Hz, NH), 7.15–7.45 (9H, m, ArH); δ_C 18.4, 20.3, 21.25, 25.6, 27.75, 47.6, 48.4, 48.6, 50.5, 58.3, 127.55, 128.15 (2C), 128.5 (2C), 129.4 (2C), 129.7, 129.8 (2C), 131.85, 136.95, 139.2, 139.55, 205.4; *m/z* 255 (M^+−168, 18%), 254 (100), 253 (69), 252 (10), 239 (100), 237 (12), 225 (23), 211 (31), 209 (19), 197 (48), 183 (13), 171 (25), 169 (25), 155 (22), 143 (19), 141 (12), 129 (11), 128 (20), 119 (17), 115 (12), 107 (15), 106 (80), 105 (47), 91 (33), 79 (11), 77 (12); HRMS: M^+ found 423.1877. $C_{25}H_{29}SNO_3$ requires 423.1868.

4.2.30. 3-[(*E*)-1-(2-Aminophenyl)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (6o).[41] R_f 0.12 (hexane/ethyl acetate: 4/1); $[\alpha]_D^{20}$ +336.5 (*c* 1.8, $CHCl_3$); ν (film) 3454, 3364 (NH_2), 3033, 1636 (C=CH), 1716 cm^{-1} (C=O); δ_H 0.81, 0.98, and 1.02 [3H each one, 3s, $(CH_3)_2CCCH_3$], 1.45–1.65, 1.75–1.80, and 2.10–2.20 (2H, 1, and 1H, respectively, 3m, CH_2CH_2), 2.95–3.00 (1H, m, CH_2CH), 6.65–6.80 and 7.10–7.25 (2 and 3H, respectively, 2m, ArH); δ_C 9.25, 18.2, 20.55, 26.25, 30.55, 46.5, 48.85, 57.4, 115.8, 118.15, 120.6, 122.25, 129.25, 129.85, 142.65, 145.85, 208.05; *m/z* 256 (M^++1, 16%), 255 (M^+, 87), 254 (25), 240 (19), 238 (35), 212 (25), 186 (32), 184 (11), 173 (18), 172 (100), 171 (48), 170 (18), 159 (16), 156 (16), 154 (14), 144 (44), 143 (41), 130 (20), 117 (26), 115 (11), 106 (17).

4.2.31. (*E*)-1-Ferrocenyl-3-phenyl-2-propenone (6u).[69] Mp 139–141 °C; t_R 21.9; R_f 0.36 (hexane/ethyl acetate: 4/1); ν (KBr) 3092, 1600 (C=CH), 1647 cm^{-1} (C=O); δ_H 4.22 (5H, s, C_5H_5Fe), 4.55–4.60 and 4.90–4.95 (2H each

one, 2m, C_5H_4Fe), 7.13 and 7.80 (1H each one, 2d, J=15.6 Hz, CH=CHCO), 7.40–7.45 and 7.65–7.70 (3 and 2H, respectively, 2m, Ph); δ_C 69.7 (2C), 70.1 (5C), 72.75 (2C), 80.6, 122.9, 128.25 (2C), 128.9 (2C), 130.1, 135.1, 140.8, 192.9; *m/z* 317 (M^++1, 23%), 316 (M^+, 100), 251 (17), 121 (12).

4.2.32. (*E*)-1-(1*H*-3-Indolyl)-3-phenyl-2-propen-1-one (6v).[70] Mp 225–230 °C; t_R 26.4; R_f 0.57 (hexane/ethyl acetate: 1/1); ν (KBr) 3126 (N–H), 1638 (C=O), 1569 cm^{-1} (C=CH); δ_H 7.20–7.90, 8.35–8.40, and 8.70–8.75 (10, 1, and 1H, respectively, 3m, C=CH), 12.11 (1H, s, NH); δ_C 113.2, 118.85, 122.85, 122.9, 24.1, 125.7, 127.0, 129.4 (2C), 129.8 (2C), 130.7, 135.7, 136.3, 137.95, 140.55, 184.7; *m/z* 248 (M^++1, 18%), 247 (M^+, 100), 246 (50), 219 (22), 218 (50), 217 (19), 144 (46), 117 (11), 116 (18), 89 (16).

4.2.33. 2-Phenylquinoline (8a).[37c] Mp 80–82 °C; t_R 16.3; R_f 0.61 (hexane/ethyl acetate: 4/1); ν (KBr) 3053, 1601, 1546 cm^{-1} (C=CH); δ_H 7.35–7.50, 7.60–7.80, and 8.00–8.20 (4, 3, and 4H, respectively, 3m, ArH); δ_C 118.8, 126.1, 127.0, 127.3, 127.4 (2C), 128.7 (2C), 129.15, 129.5, 129.55, 136.6, 139.45, 148.1, 157.1; *m/z* 206 (M^++1, 15%), 205 (M^+, 100), 204 (95), 203 (12), 102 (15).

4.2.34. 3-Methyl-2-phenylquinoline (8b).[37b] t_R 16.4 min; R_f 0.48 (hexane/ethyl acetate: 4/1); ν (film) 3058, 1605, 1558 cm^{-1} (C=CH); δ_H 2.36 (3H, s, CH_3), 7.35–7.70 (8H, m, Ph and H_{5-7}-quinoline), 7.87 (1H, s, H_4-quinoline), 8.14 (1H, d, J=8.4 Hz, H_8-quinoline); δ_C 20.3, 126.05, 126.4, 127.2, 127.85, 127.95 (2C), 128.4, 128.55 (2C), 128.8, 128.95, 136.4, 140.5, 146.25, 160.1; *m/z* 219 (M^+, 35%), 218 (100), 217 (28), 108 (12).

4.2.35. 3-Ethyl-2-phenylquinoline (8c).[71] t_R 16.8; R_f 0.53 (hexane/ethyl acetate: 4/1); ν (film) 3058, 1626, 1592 cm^{-1} (C=CH); δ_H 1.16 (3H, t, J=7.5 Hz, CH_3), 2.77 (2H, q, J=7.5 Hz, CH_2), 7.35–7.65 (7H, m, Ph and $H_{5,7}$-quinoline), 7.75–7.80 (1H, m, H_6-quinoline), 8.01 (1H, s, H_4-quinoline), 8.14 (1H, d, J=8.4 Hz, H_8-quinoline); δ_C 14.55, 25.85, 126.2, 126.75, 127.75, 127.95, 128.15 (2C), 128.55 (2C), 128.65, 129.05, 134.8, 135.10, 140.65, 146.1, 160.4; *m/z* 233 (M^+, 43%), 232 (100), 218 (11), 217 (39), 216 (11), 108 (13).

4.2.36. 1,2-Dihydrobenzo[*c*]acridine (8d).[37c] Mp 62–64 °C; t_R 18.7; R_f 0.78 (hexane/ethyl acetate: 4/1); ν (KBr) 3038, 1601 cm^{-1} (C=CH); δ_H 2.90–2.95 and 3.00–3.05 (2H each one, 2m, CH_2CH_2), 7.15–8.15 and 8.57 (7 and 1H, respectively, m and d, respectively, J=1.2 Hz, ArH); δ_C 28.25, 28.65 125.9, 125.95, 126.8, 127.2, 127.7, 127.85, 128.55, 129.25, 129.55, 130.45, 133.6, 134.55, 139.3, 147.45, 153.2; *m/z* 232 (M^++1, 16%), 183 (M^+, 99), 230 (100), 229 (13), 228 (17), 202 (10), 115 (14), 114 (12).

4.2.37. 2-(4-Methylphenyl)quinoline (8e).[37c] Mp 80–81 °C; t_R 17.2; R_f 0.75 (hexane/ethyl acetate: 4/1); ν (KBr) 3058, 1661, 1606 cm^{-1} (C=CH); δ_H 2.36 (3H, s, CH_3), 7.25 (2H, d, J=8.1 Hz, 2×CH_3CCH), 7.35–7.45 (1H, m, H_3-quinoline), 7.60–7.75 (3H, m, H_{5-7}-quinoline), 8.00–8.05 (3H, m, H_4-quinoline and 2×CH_3CCHCH), 8.15 (1H, d, J=4.1 Hz, H_8-quinoline); δ_C 21.15, 118.55, 125.8, 126.85, 127.2, 127.25 (2C), 128.05, 129.35 (2C), 129.4, 136.4, 136.6, 139.1, 148.05, 156.95; *m/z* 220 (M^++1, 17%), 219 (M^+, 100), 218 (51), 217 (20), 204 (21), 108 (13).

4.2.38. 2-(4-Methylphenyl)benzo[*h*]quinoline (8f). Mp 79–81 °C; t_R 23.6; R_f 0.74 (hexane/ethyl acetate: 4/1); ν (KBr) 3049, 2918, 1601, 1558 cm^{-1} (C=CH); δ_H 2.39 (3H, s, CH_3), 7.28 and 8.17 (2 and 2H, 2d, J=7.8 Hz, $CH_3C_6H_4$), 7.52 (1H, d, J=8.6 Hz, H_6), 7.60–7.70 (3H, m, H_9, H_7, and H_8), 7.81 (2H, d, J=8.6 Hz, H_5 and H_3), 7.98–8.01 (1H, m, H_4), 9.47 (1H, d, J=7.8 Hz, H_{10}); δ_C 21.25, 118.45, 124.6, 124.8, 125.0, 126.65, 127.0, 127.15 (2C), 127.6, 127.9, 129.4 (2C), 131.7, 133.75, 136.25, 136.8, 139.05, 146.0, 155.25; *m/z* 270 (M^++1, 22%), 269 (M^+, 100), 268 (27), 267 (13). $C_{20}H_{15}N$: requires C 89.19, H 5.61, N 5.20; found C 89.25, H 5.70, N 5.23.

4.2.39. 2-(2-Pyridyl)quinoline (8g).[37c] Mp 95–97 °C; t_R 16.1; R_f 0.5 (hexane/ethyl acetate: 4/1); ν (KBr) 3060, 1596 cm^{-1} (C=CH); δ_H 7.25–7.35 (1H, m, H_5-Py), 7.50–7.55 (1H, m, H_6-quinoline), 7.70–7.65 (1H, m, H_7-quinoline), 7.70–7.85 (2H, m, $H_{3,4}$-Py), 8.17 (1H, d, J=8.4 Hz, H_5-quinoline), 8.23 (1H, d, J=8.7 Hz, H_4-quinoline), 8.54 (1H, d, J=8.7 Hz, H_3-quinoline), 8.64 (1H, d, J=8.1 Hz, H_8-quinoline) 8.70–8.75 (1H, m, H_6-Py); δ_C 118.85, 121.75, 123.9, 126.65, 127.5, 128.1, 129.45, 129.65, 136.7, 136.8, 147.75, 149.0, 155.95, 156.1; *m/z* 207 (M^++1, 14%), 206 (M^+, 100), 205 (73), 178 (17).

4.2.40. 2-(2-Furyl)quinoline (8h).[37c] Mp 94 °C; t_R 14.7; R_f 0.45 (hexane/ethyl acetate: 4/1); ν (KBr) 3143, 1600 cm^{-1} (C=CH); δ_H 6.54 (1H, dd, J=1.9, 3.4 Hz, H_4-furyl), 7.19 (1H, dd, J=0.6, 3.4 Hz, H_3-furyl), 7.40–7.75 (5H, m, H_5-furyl and $H_{3,5-7}$-quinoline), 8.05 (1H, d, J=4.3 Hz, H_4-quinoline), 8.13 (1H, d, J=4.2 Hz, H_8-quinoline); δ_C 110.05, 112.05, 117.25, 126.0, 126.9, 127.4, 129.0, 129.7, 136.5, 143.9, 147.8, 148.75, 153.4; *m/z* 196 (M^++1, 14%), 195 (M^+, 100), 194 (26), 167 (30), 166 (23), 140 (12), 139 (14).

4.2.41. 2-(2-Thienyl)quinoline (8i).[37c] Mp 131–133 °C; t_R 16.6; R_f 0.62 (hexane/ethyl acetate: 4/1); ν (KBr) 3103, 3053, 1615, 1597 cm^{-1} (C=CH); δ_H 7.10–7.15 (1H, m, H_4-thienyl), 7.40–7.45 (2H, m, H_3-thienyl and H_3-quinoline), 7.60–7.75 (4H, m, H_5-thienyl, $H_{3,5-7}$-quinoline), 8.05 (1H, d, J=8.4 Hz, H_4-quinoline), 8.07 (1H, d, J=7.8 Hz, H_8-quinoline); δ_C 117.15, 125.75, 125.95, 127.05, 127.4, 128.0, 128.5, 129.0, 129.7, 136.5, 145.25, 147.95, 152.2; *m/z* 212 (M^++1, 16%), 211 (M^+, 100), 210 (29).

4.2.42. 2-(1-Methyl-1*H*-2-pyrrolyl)quinoline (8j).[72] Mp 61–63 °C; t_R 16.2; R_f 0.6 (hexane/ethyl acetate: 4/1); ν (KBr) 3104, 2948, 1609, 1558 cm^{-1} (C=CH); δ_H 4.15 (3H, s, CH_3), 6.20–6.25 and 6.70–6.75 (1 and 2H, respectively, 2m, CH_3NCH=CHCH), 7.35–7.40 (1H, m, H_3-quinoline), 7.55–7.70 (3H, m, H_{5-7}-quinoline), 7.97 (1H, d, J=8.6 Hz, H_4-quinoline), 8.00 (1H, d, J=8.6 Hz, H_8-quinoline); δ_C 37.6, 107.7, 112.25, 119.95, 125.35, 125.9, 127.35, 127.55, 128.9, 129.95, 132.0, 135.75, 147.5, 152.1; *m/z* 208 (M^+, 51%), 207 (100).

4.2.43. 2-Ferrocenylquinoline (8k).[73] t_R 21.3; R_f 0.52 (hexane/ethyl acetate: 4/1); ν (KBr) 3094, 1601 cm^{-1} (C=CH); δ_H 4.05 (5H, s, C_5H_5Fe), 4.40–4.45 and 5.00–5.05 (2H each

one, 2m, C_5H_4Fe), 7.40–7.75 and 8.00–8.10 (4 and 2H, respectively, 2m, quinoline); δ_C 67.9 (2C), 69.6 (5C), 70.4 (2C), 83.75, 119.45, 125.3, 126.6, 127.45, 128.85, 129.35, 135.4, 148.1, 159.45; *m/z* 314 (M^++1, 22%), 313 (M^+, 100), 248 (35). Crystal data: $C_{19}H_{15}FeN$, M=546.77; Monoclinic, a=6.1612 (4), b=12.1309 (9), c=19.1000 (14) Å; V=1420.28 (17) Å^3; space group P 21/n; Z=4; D_c=1.465 mg/m^3; λ=0.71073 Å; μ=1.053 mm^{-1}; $F(000)$=2368; T=21±1 °C. Data collection based on three ω-scan runs (starting ω=−34°) at values ϕ=0°, 120°, 240° with the detector at 2θ=−32°. An additional run of 100 frames, at 2θ=−32°, ω=−34° and ϕ=0°, was acquired to improve redundancy. For each of these runs, 606 frames were collected at 0.3° intervals and 30 s per frame. The diffraction frames were integrated using the program SAINT and the integrated intensities were corrected for Lorentz-polarization effects with SADABS. The structure was solved by direct methods and refined to all 2518 unique F_o^2 by full matrix least squares. All of the hydrogen atoms were placed at idealized positions and retained as rigid atoms. Final $wR2$=0.1051 for all data and 190 parameters; $R1$=0.0938 for 1604 $F_o>4\sigma$ (F_o).

4.2.44. 2-Ethyl-3-methylquinoline (8l).[74] Mp 49–51 °C; t_R 12.2; R_f 0.5 (hexane/ethyl acetate: 8/2); ν (KBr) 3058, 1665, 1626, 1600 cm^{-1} (C=CH); δ_H 1.35 (3H, t, J=7.5 Hz, C*H*$_3$CH$_2$), 2.40 (3H, s, CH$_3$C), 2.95 (2H, q, J=7.5 Hz, CH$_2$CH$_3$), 7.35–7.45 and 7.55–7.65 (1 and 2H, respectively, 2m, H_{5-7}-quinoline), 7.74 (1H, s, H_4-quinoline), 8.03 (1H, d, J=8.4 Hz, H_8-quinoline); δ_C 12.7, 18.9, 29.3, 125.4, 126.5, 127.15, 128.1, 128.3, 129.2, 135.55, 146.45, 163.05; *m/z* 171 (M^+, 63%), 171 (100), 143 (27), 115 (14).

4.2.45. 1,2,3,4-Tetrahydroacridine (8m).[75] t_R 14.4; R_f 0.43 (hexane/ethyl acetate: 4/1); ν (film) 3054, 1626, 1596 cm^{-1} (C=CH); δ_H 1.80–1.90 and 1.90–2.00 [2H each one, 2m, CH$_2$(C*H*$_2$)$_2$CH$_2$], 2.90–2.95 and 3.10–3.15 [2H each one, 2m, C*H*$_2$(CH$_2$)$_2$C*H*$_2$], 7.40–7.45 and 7.55–7.65 (1 and 2H, respectively, 2m, H_{6-8}-acridine), 7.74 (1H, s, H_9-acridine), 7.98 (1H, d, J=8.4 Hz, H_5-acridine); δ_C 22.75, 23.05, 29.1, 33.35, 125.4, 126.75, 127.0, 128.05, 128.35, 130.8, 134.85, 146.35, 159.1; *m/z* 184 (M^++1, 13%), 183 (M^+, 100), 182 (95), 168 (26), 167 (28), 155 (14), 154 (18).

4.2.46. 3-Azatetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaene (8n).[76] t_R 14.7; R_f 0.35 (hexane/ethyl acetate: 4/1); ν (film) 3062, 1640 cm^{-1} (C=CH); δ_H 1.20–1.45, 1.65–1.70, and 1.88–1.92 (2, 1, and 1H, respectively, 3m, CH$_2$CH$_2$), 2.00–2.10 (2H, m, C*H*$_2$CH), 3.45–3.55 (2H, m, C*H*CH$_2$C*H*), 7.35–7.45, 7.55–7.65, 7.65–7.70, and 8.02 (1, 1, 2, and 1H, respectively, 3m and d, respectively, J=8.4 Hz, ArH); δ_C 25.5, 27.25, 41.95, 45.2, 46.55, 125.15, 125.4, 127.4, 127.6, 127.75, 128.45, 139.75, 146.45, 170.3; *m/z* 195 (M^+, 60%), 194 (51), 180 (15), 168 (16), 167 (100), 166 (18).

4.2.47. 1,15,15-Trimethyl-3-azatetracyclo-[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaene (8o).[41] t_R 15.4; R_f 0.57 (hexane/ethyl acetate: 4/1); $[\alpha]_D^{20}$ +34.9 (c 9.6, CHCl$_3$); ν (film) 3068, 1641 cm^{-1} (C=CH); δ_H 0.56, 1.05, and 1.43 [3H each one, 3s, (CH$_3$)$_2$CCCH$_3$], 1.20–1.40, 1.90–2.00, and 2.10–2.20 (2, 1, and 1H, respectively, 3m, CH$_2$CH$_2$), 2.94 (1H, d, J=4.1 Hz, CH$_2$C*H*), 7.40–7.45, 7.55–7.60, 7.65–7.70, and 8.05–8.10 (1, 1, 2, and 1H, respectively, 4m, ArH); δ_C 10.55, 18.9, 20.15, 26.35, 31.8, 51.15, 54.05, 55.2, 125.05, 125.95, 127.35, 127.5, 127.85, 128.7, 140.0, 146.7, 172.05; *m/z* 237 (M^+, 29%), 222 (21), 208 (12), 195 (19), 194 (100), 193 (14), 180 (16).

4.2.48. *N*-Benzyl-15,15-dimethyl-3-azatetracyclo-[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethanesulfonamide (8p). R_f 0.54 (hexane/ethyl acetate: 3/2); $[\alpha]_D^{20}$ +76.9 (c 8.5, CHCl$_3$); ν (film) 3068, 1634, 1581 cm^{-1} (C=CH); δ_H 0.50 and 1.01 (3 and 3H, respectively, 2s, 2×CH$_3$), 1.20–1.30, 2.00–2.05, and 2.15–2.25 (1, 1, and 2H, respectively, 3m, CH$_2$CH$_2$), 2.97 (1H, d, J=3.3 Hz, C*H*CH$_2$), 3.22 and 3.55 (1 and 1H, respectively, 2d, J=15.2 Hz, CH$_2$SO$_2$), 4.35–4.45 and 4.55–4.60 (1 and 1H, 2m, CH$_2$N), 7.25–7.45 and 7.70–7.75 (8 and 2H, respectively, 2m, ArH), 9.51 (1H, t, J=6.3 Hz, NH); δ_C 19.0, 20.4, 26.5, 30.25, 48.25, 50.55, 51.75, 55.45, 57.6, 126.15, 127.6, 127.65, 127.7, 127.75, 128.35, 128.7 (2C), 128.75 (2C), 128.8, 137.4, 139.4, 145.15, 168.45; *m/z* 238 (M^+−168, 10%), 237 (70), 236 (100), 220 (11), 209 (18), 208 (14), 195 (19), 194 (50), 193 (14), 192 (14), 180 (21); HRMS: M^+ found 406.1722. $C_{24}H_{26}SN_2O_2$ requires 406.1715.

4.2.49. *N*-Benzyl-19,19-dimethyl-3-azapentacyclo-[14.2.1.0^{4,13}.0^{5,10}]nonadeca-2(15),3,5(10),6,8,11,13-heptaen-1-ylmethanesulfonamide (8q). R_f 0.52 (hexane/ethyl acetate: 6/4); $[\alpha]_D^{20}$ +28.0 (c 13.5, CHCl$_3$); ν (film) 3295 (NH), 3060, 1613, 1563 cm^{-1} (C=CH); δ_H 0.48 and 1.04 (3 and 3H, respectively, 2s, 2×CH$_3$), 1.22–1.32, 1.95–2.00, and 2.20–2.40 (1, 1, and 2H, respectively, 3m, CH$_2$CH$_2$), 3.00 (1H, d, J=3.7 Hz, C*H*CH$_2$), 3.30 and 3.67 (2H, 2d, J=15.1 Hz, CH$_2$SO$_2$), 4.48–4.63 (2H, m, CH$_2$N), 7.15–7.40, 7.50–7.65, 7.75–7.85, and 8.78 (6, 2, 3, and 1H, respectively, 3m and d, respectively, J=8.3 Hz, ArH), 8.82 (1H, t, J=6.6 Hz, NH); δ_C 19.3, 20.15, 26.25, 29.0, 47.5, 50.5, 52.35, 55.75, 58.05, 123.35, 125.4, 125.6, 126.8, 127.05, 127.3, 127.4, 128.0 (2C), 128.2, 128.3 (2C), 128.45, 130.75, 133.25, 137.35, 139.95, 143.3, 166.85; *m/z* 288 (M^+−168, 11%), 287 (68), 286 (100), 285 (14), 258 (14), 245 (17), 244 (45), 243 (18), 242 (25), 230 (21), 106 (11), 91 (10); HRMS: M^+−$C_7H_8NO_2S$ found 286.1593. $C_{21}H_{20}N$ requires 286.1596.

CCDC-296061 and CCDC-296062 contain the supplementary crystallographic data for compounds **6e** and **7a**, respectively, reported in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Novel formation of 1,3-oxazepine heterocycles via palladium-catalyzed intramolecular coupling reaction

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Abstract—The oxazepine ring systems containing pyridazinone moiety were constructed via palladium-catalyzed intramolecular coupling reaction. The best conditions for this reaction were $Pd(OAc)_2$ as a palladium source, 1,1′-bis(diphenylphosphino)-ferrocene (DPPF) as the ligand, and K_2CO_3 as base at 80 °C in toluene. The products have potential applications as biological and medicinal relevant compounds.

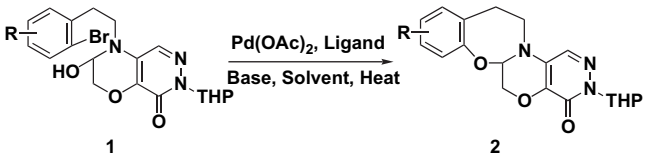
1. Introduction

The modification of the oxazepine nucleus is a versatile research area due to its presence in some natural products and biologically active substances.[1] There are many methods for the synthesis of oxazepine ring systems. However, new, simple, and efficient ways for constructing oxazepine rings are still in great demand.[2]

Palladium-catalyzed cross-coupling reactions Ar–X with carbon nucleophiles have found wide application in the synthesis of complex organic molecules due to their mild reaction conditions and high functional group compatibility.[3] Successful extension of these reactions to heteroatom nucleophiles including amines and thiols have been reported.[4] Recent advances in the Pd-catalyzed aryl aminations have extended the generality of this reaction to include a wide variety of amines. In contrast, the Pd-catalyzed coupling of Ar–X with alcohols still remains as an elusive goal in spite of its potential application in organic synthesis.[5] Aryl ethers, including oxygen heterocycles, are prominent in a large number of pharmacologically important molecules and are found in numerous secondary metabolites.[6] Available methods for the synthesis of aryl ethers via direct nucleophilic substitution of an aryl halide with an alcohol typically require harsh or restrictive conditions or a large excess of the alcohol and are limited in substrate scope.[7]

2. Results and discussion

To the best of our knowledge Buchwald and co-workers[8] have prepared a seven-membered ring via an intramolecular cycloamination, which is the first application of this cyclization to form these important tricyclic oxazepine ring systems. As a part of our continuing interest in the development of novel syntheses of heterocyclic systems,[9] we report herein our results in effecting an intramolecular Pd-catalyzed coupling reaction of an aryl halide with an alcohol (Scheme 1).



1 2

Scheme 1. The intramolecular Pd-catalyzed coupling reaction of an aryl halide with an alcohol.

Preparation of Substrate **1** is shown in Schemes 2 and 3. Substrate **1** was obtained from the corresponding pyridazino-1,4-oxazine **8** by bromination and reduction. Pyridazino-1,4-oxazine **8** was prepared by cyclization of chloroacetamide **7** with pyridazinone **6**. Chloroacetamide **7** was easily prepared by addition of various amines to 2-chloroacetyl chloride. Pyridazinone **6** was synthesized in four steps from commercially available mucochloric acid.

Treatment of mucochloric acid with hydrazine sulfate in refluxing ethanol/water (v/v = 1:1) in the presence of sodium acetate gave 4,5-dichloro-3(2*H*)-pyridazinone (**3**) in excellent yields.[10] The pyridazinone nitrogen of 4,5-dichloro-3(2*H*)-pyridazinone was protected by treatment of

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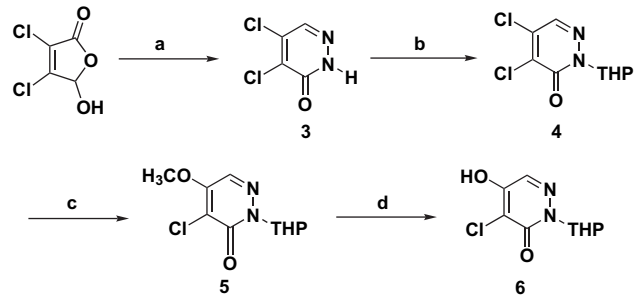
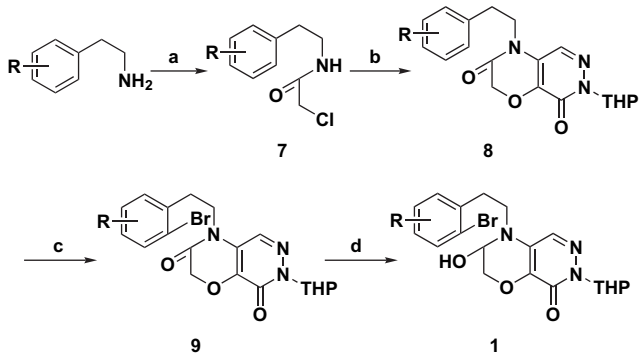
compound **3** with excess dihydropyran and *p*-toluenesulfonic acid in refluxing tetrahydrofuran to give 4,5-dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**4**).[11] The compound **4** was followed by methoxide displacement to produce 4-chloro-5-methoxy pyridazinone **5**, which was then hydrolyzed with potassium hydroxide in refluxing water to give 4-chloro-5-hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**6**) in good yield (Scheme 2).



Scheme 2. (a) H_2NNH_2–H_2SO_4, AcONa, EtOH/H_2O, reflux; (b) DHP, PTSA, THF, reflux; (c) MeONa, MeOH, rt; and (d) KOH, H_2O, reflux.

In addition, reaction of substituted phenylethyl amines with chloroacetyl chloride in the presence of potassium carbonate in refluxing dichloromethane afforded compound **7** in excellent yields (Scheme 3). The reaction occurred at room temperature for 12 h or at refluxing temperature for 2 h. The compound **8** was synthesized by the reaction of various substituted phenylethyl-2-chloroacetamides **7** with pyridazinone **6**. The cyclization occurred smoothly in the presence of cesium carbonate at refluxing acetonitrile in 63–79% isolated yields via Smiles rearrangement.[9]



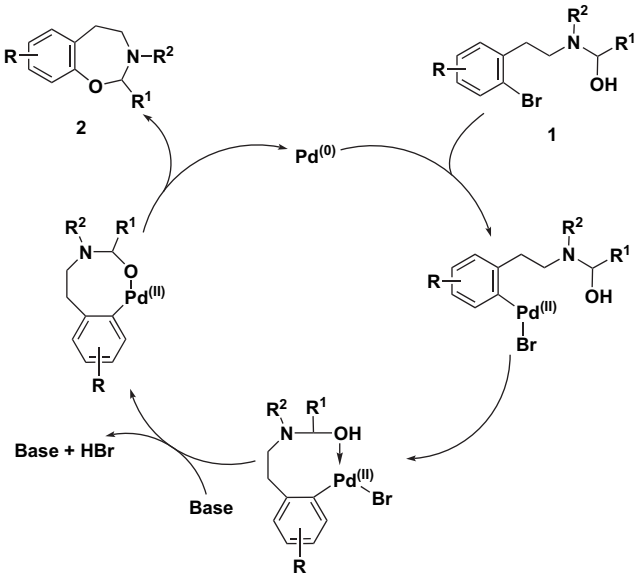
Scheme 3. (a) $ClCH_2COCl$, K_2CO_3, CH_2Cl_2, reflux; (b) **6**, Cs_2CO_3, CH_3CN, reflux; (c) NBS, DMF, rt, 100 °C; and (d) $NaBH_4$, CH_3OH, rt.

According to literature procedure,[12] bromination of **8** with NBS in *N*,*N*-dimethyl formamide gave rise to compound **9** in good yield. Toward the end of subjection, reduction of compound **9** in the present of sodium borohydride in methanol at room temperature afforded the corresponding reduced product **1**.

The different conditions reported for the intramolecular cycloamination to form seven-membered rings ($Pd(PPh_3)_4$, NaO*t*-Bu, and toluene)[8] resulted in poor yields of desired product **2**. Subjecting substrates **1** to the other reaction conditions ($Pd_2(dba)_3$, P(*o*-tolyl)$_3$, NaO*t*-Bu, and toluene) afforded no desired cyclic product. However, the use of (*S*)-(−)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-bi-naphthyl (Tol-BINAP) and 1,1′-bis(diphenylphosphino)-ferrocene (DPPF) ligands in place of P(*o*-tolyl)$_3$, either NaO*t*-Bu or K_2CO_3 as base and $Pd(OAc)_2$ as the Pd source gave the desired cyclic product **2** (Table 1).

The ligand DPPF proved to be more effective than DPPE, DPPBz, BINAP, and Tol-BINAP. Optimization of NaO*t*-Bu and K_2CO_3 as base showed that the use of a large excess of K_2CO_3 instead of NaO*t*-Bu afforded products in higher yields. Although it has been reported that the latter gives faster reactions, its high basicity often causes problems. Observed side products included dehalogenation of the aryl bromides and oxidation of the alcohol to the ketone. A steric effect was observed for Entry **g**, the increase of the steric congestion on phenyl ring with trimethoxy groups obviously reduced reaction yield. Under the conditions employed, oxazepine formation was not observed in toluene in the absence of Pd-catalyst for any of the substrates examined in Table 1.

The proposed mechanism for the intramolecular Pd-catalyzed coupling reaction of an aryl bromide with an alcohol is shown in Scheme 4. The reaction occurs by oxidative addition of the aryl bromide, subsequent generation of the palladium oxametallacycle, and C–O bond-forming reductive elimination. Although aryl bromide intermediates were generated independently and were shown to be kinetically competent to be intermediates, the oxametallacycles could not be observed or isolated.

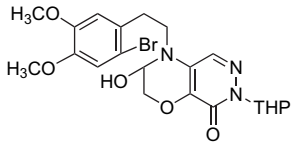
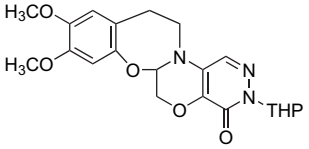
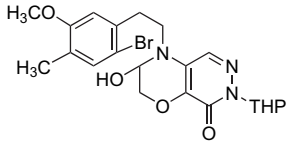
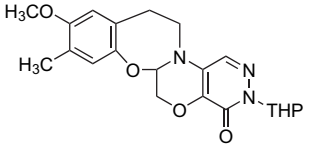
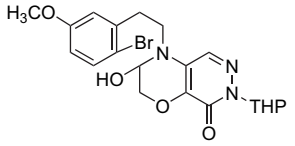
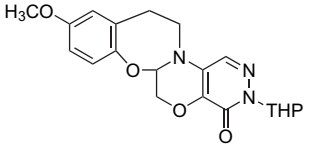
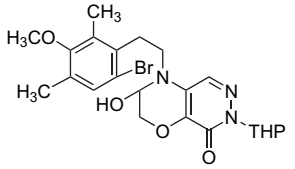
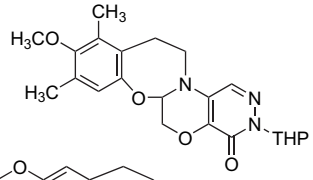
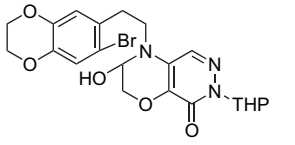
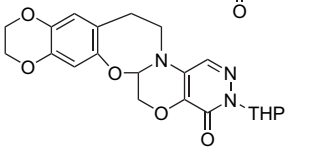
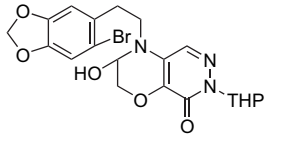
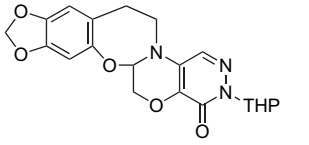
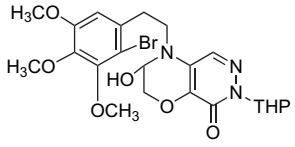
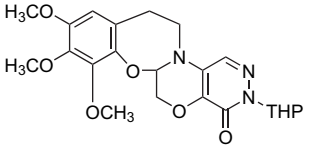
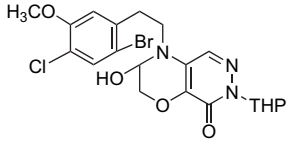
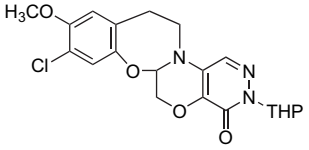
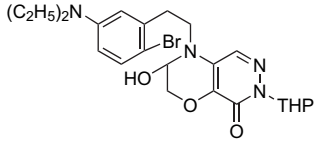
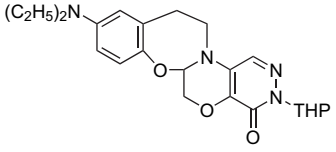
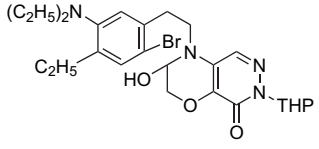
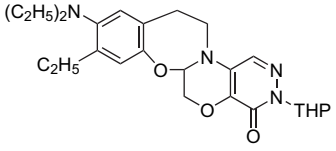


Scheme 4. The proposed mechanism for the intramolecular Pd-catalyzed coupling reaction of an aryl bromide with an alcohol.

3. Conclusion

In summary, we have developed a useful synthetic method for oxazepine ring systems. The best conditions for this reaction were $Pd(OAc)_2$ as a palladium source, 1,1′-bis(diphenylphosphino)-ferrocene (DPPF) as the ligand, and K_2CO_3 as base at 80 °C in toluene. This approach may give access to useful intermediates for the synthesis of natural products and hitherto unknown pharmaceuticals.

Table 1. Pd-catalyzed synthesis of oxazepines containing pyridazinone moiety

Entry	Substrate **1**	Ligand	Base	Product **2**	Yield (%)[a]
a		DPPF	K_2CO_3		62
b		DPPF	K_2CO_3		70
c		DPPF	K_2CO_3		65
d		DPPF	K_2CO_3		55
e		DPPF	K_2CO_3		63
f		DPPF	K_2CO_3		58
g		DPPF	K_2CO_3		26
h		DPPF	K_2CO_3		71
i		DPPF	K_2CO_3		53
j		DPPF	K_2CO_3		46

[a] Yields refer to the average of isolated yields for two or more runs.

4. Experimental

4.1. General

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and were uncorrected. ^1H and ^{13}C NMR spectra (300 MHz for ^1H and 75 MHz for ^{13}C) were recorded in $CDCl_3$ with $CHCl_3$ as an internal reference on a Varian spectrometer. IR spectra were recorded on FTIR Nicolet Impect 410 spectrophotometer. Elemental analyses were performed on a Perkin–Elmer 2400 elemental analyzer. Thin layer chromatography (TLC) was performed

on Merck silica gel plates, with the compounds being identified in one or more of the following manners: UV (UL listed 977c inspection equipment), 25% PMA solution (phosphomolybdic acid and ethanol). Column chromatography was performed on Merck D-6100 silica gel 60 (70–230 mesh, ASTM). All solvents were distilled before use. Glassware was dried in an oven at 110 °C overnight.

4.2. 4,5-Dichloro-3(2*H*)-pyridazinone (3)[9b]

To a 250-mL flask equipped with a magnetic stirrer was added sodium acetate (27.2 g, 213 mmol) and hydrazine sulfate (17.7 g, 213 mmol) in ethanol/H_2O (v/v:1/1) (120 mL). The mixture was heated to 60 °C for 1 h, then, mucochloric acid (30 g, 178 mmol) was added to the warm solution. The solution was stirred under reflux for 4 h, followed by cooling to room temperature, then, filtered. The residue was washed with water, dried at room temperature to obtain slight yellow product **3** in 92% yield. Mp 198–200 °C; IR (KBr) 3250, 3200, 3031, 2864, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.5, 137.2, 139.4, 167.5; Anal. Calcd for $C_4H_2Cl_2N_2O$: C, 29.12; H, 1.22; N, 16.98. Found: C, 29.16; H, 1.32; N, 17.06%.

4.3. 4,5-Dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (4)

4,5-Dichloro-3(2*H*)-pyridazinone (30 g, 181.8 mmol), dihydropyran (19.4 g, 230.8 mmol), *p*-toluenesulfonic acid monohydrate (2.83 g, 14.9 mmol), and 160 mL of tetrahydrofuran were added to a 500-mL round bottomed flask equipped with a beating mantle, reflux condenser, and a mechanical stirrer. The mixture was stirred at reflux for 29 h. Additional dihydropyran was added at 6 h (13.3 g, 157.9 mmol) and at 21 h (7.8 g, 92.5 mmol). The reaction mixture was allowed to cool to room temperature overnight. The mixture was concentrated in vacuo to an oily residue. The residue was taken up in 160 mL of ethyl acetate and washed with 2 N sodium hydroxide. The organic solution was dried ($MgSO_4$) and concentrated in vacuo to give 4,5-dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**4**), which was a black oily solid, which was used without further purification in the next step. The product was purified by filtration through silica gel with ethyl acetate followed by evaporation and recrystallization from ethyl acetate/cyclohexane to give a white solid. Mp 75–77 °C; IR (KBr) 3078, 2923, 2853, 1670, 1573, 1460, 1382, 1320, 1235, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 6.01 (d, J=10.8 Hz, 1H), 4.13 (d, J=13.5 Hz, 1H), 3.70–3.81 (m, 1H), 2.03–2.17 (m, 2H), 1.58–1.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 24.9, 28.0, 66.7, 73.3, 112.0, 129.7, 132.8, 155.4; Anal. Calcd for $C_9H_{10}N_2O_2Cl_2$: C, 43.40; H, 4.05; N, 11.25. Found: C, 43.28; H, 4.16; N, 11.07%.

4.4. 4-Chloro-5-methoxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (5)

4,5-Dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**4**) from the previous step and 170 mL of methanol were added to a 500-mL round bottomed flask equipped with a glycol cooling jacket and a mechanical stirrer. The resulting solution was cooled to 0 °C and 87% potassium hydroxide (11.7 g, 181.7 mmol) was added in portions over approximately 1 h. The mixture was heated to 40 °C. Following the addition, the mixture was allowed to stir for an additional 3 h at ambient temperature. The reaction mixture was partitioned with 120 mL of ethyl acetate and 120 mL of water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried ($MgSO_4$). The organic solution was clarified by filtration and concentrated to give a dark semi-solid. The crude material was equally divided and added to two 220-mL flasks. The material was suspended and stirred in 120 mL hexane/ethyl ether (2:1). The washed material was vacuum filtered on a Buchner funnel and air dried overnight to give 34.1 g (77% over two steps) of 4-chloro-5-methoxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**5**) as a dark solid suitable for further transformations. The product was purified by recrystallization from ethyl acetate/cyclohexane to give a white solid. Mp 116–118 °C; IR (KBr) 3062, 2933, 2860, 1678, 1556, 1400, 1365, 1230, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 6.08 (d, J=10.8 Hz, 1H), 4.10–4.19 (m, 1H), 4.08 (s, 3H), 3.71–3.82 (m, 1H), 2.03–2.17 (m, 2H), 1.60–1.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 25.1, 28.2, 66.8, 68.3, 73.5, 111.4, 129.2, 134.0, 155.2; Anal. Calcd for $C_{10}H_{13}N_2O_3Cl$: C, 49.09; H, 5.36; N, 11.45. Found: C, 49.23; H, 5.33; N, 11.51%.

4.5. 4-Chloro-5-hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (6)

To a 500-mL flask was added 4-chloro-5-methoxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**5**) (45 g, 184 mmol) and potassium hydroxide (12.4 g, 220.8 mmol) in water (150 mL). The mixture solution was heated to reflux for 3 h, then, cooled to room temperature and 1 N HCl aqueous solution was added dropwise to cooled solution (pH= 5–6). The mixture solution was filtered and residue was washed with water. The crude product was purified by recrystallization from methanol/hexane to give 4-chloro-5-hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**6**) as a white solid in 86.5% yield. Mp 135–137 °C; IR (KBr) 3397, 2967, 2865, 2569, 1638, 1588, 1410, 1301, 1205, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.45–7.56 (m, 1H), 6.03 (d, J=10.5 Hz, 1H), 4.12 (d, J=13.2 Hz, 1H), 3.72–3.80 (m, 1H), 2.03–2.17 (m, 2H), 1.63–1.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 24.9, 28.2, 66.7, 73.5, 111.5, 129.1, 133.8, 155.3; Anal. Calcd for $C_9H_{11}N_2O_3Cl$: C, 46.87; H, 4.81; N, 12.15. Found: C, 46.95; H, 4.78; N, 12.10%.

4.6. *N*-(3,4-Dimethoxyphenethyl)-2-chloroacetamide (7a)

A solution of chloroacetyl chloride (3.6 g, 32.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of (3,4-dimethoxyphenyl)ethyl amine (5.3 g, 29.6 mmol) and K_2CO_3 (4.5 g, 32.6 mmol) in CH_2Cl_2 (150 mL) at room temperature. The mixture solution was refluxed for 2 h, cooled to room temperature and H_2O was added. The phases were separated and aqueous layer was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash column chromatography using CH_2Cl_2 as eluent to afford

product **7** as a white solid with 92.1% yield. Mp 101–103 °C; IR (KBr) 3326, 3053, 2945, 1632, 1528, 1271, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.67–6.82 (m, 3H), 6.53 (s, 1H), 4.23 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.26 (q, J=6.6 Hz, 2H), 2.55 (t, J=6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.2, 40.4, 45.8, 57.2, 58.0, 112.7, 115.4, 120.1, 133.6, 146.3, 147.8, 166.3; Anal. Calcd for $C_{12}H_{16}ClNO_3$: C, 55.93; H, 6.26; N, 5.43. Found: C, 56.02; H, 6.19; N, 5.42%.

4.7. 4-(3,4-Dimethoxyphenethyl)-7-(tetrahydro-2*H*-pyran-2-yl)-2*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8(4*H*,7*H*)-dione (8a)

To a 250-mL flask equipped with a magnetic stirrer was added 4-chloro-5-hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**6**) (4.24 g, 18.4 mmol), *N*-(3,4-dimethoxyphenethyl)-2-chloroacetamide (**7a**) (3.6 g, 18.4 mmol), and Cs_2CO_3 (7.2 g, 22.1 mmol) in CH_3CN (100 mL). The mixture was heated to reflux for 60 h, monitored by TLC. Then CH_3CN was removed under reduced pressure and CH_2Cl_2/H_2O was added. The phases were separated and aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. The crude product was separated by flash column chromatography using EtOAc/CH_2Cl_2 (30%) as eluent to afford the product **8a** as a thin yellow solid with 83.7% yield. Mp 181–183 °C; IR (KBr) 3020, 2940, 2861, 1702, 1659, 1625, 1532, 1430, 1376, 1315, 1276, 1245, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 6.69–6.80 (m, 3H), 6.10 (d, J=10.8 Hz, 1H), 4.74–4.87 (m, 1H), 3.96–4.15 (m, 3H), 3.73–3.86 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.87 (t, J=7.2 Hz, 2H), 2.02–2.12 (m, 2H), 1.61–1.74 (m, 4H), 1.57 (d, J=4.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 24.8, 28.9, 33.7, 43.0, 55.8, 68.8, 74.3, 76.6, 82.7, 108.1, 111.3, 111.7, 120.7, 124.9, 127.2, 129.2, 147.7, 149.0, 160.2, 164.4; Anal. Calcd for $C_{21}H_{25}N_3O_6$: C, 60.71; H, 6.07; N, 10.11. Found: C, 60.62; H, 6.16; N, 10.03%.

4.8. 4-(2-Bromo-4,5-dimethoxyphenethyl)-7-(tetrahydro-2*H*-pyran-2-yl)-2*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8(4*H*,7*H*)-dione (9a)

A solution of NBS (1.78 g, 10 mmol) in dry DMF (20 mL) was added to a solution of substrate **8a** (4.15 g, 10 mmol) in dry DMF (20 mL) and stirred at room temperature for 48 h. The mixture was poured into water (100 mL) and extracted with dichloromethane (200 mL). The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to yield crude monobromide. The crude product was separated by flash column chromatography using EtOAc/CH_2Cl_2 (20%) as eluent to afford the product **9a** as a thin yellow solid with 82.2% yield. Mp 175–177 °C; IR (KBr) 3034, 2952, 2863, 1705, 1650, 1542, 1421, 1376, 1257, 1215, 1106 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.72–6.78 (m, 2H), 6.12 (d, J=10.8 Hz, 1H), 4.75–4.86 (m, 1H), 3.99–4.16 (m, 3H), 3.74–3.86 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.84 (t, J=7.5 Hz, 2H), 2.00–2.11 (m, 2H), 1.62–1.74 (m, 4H), 1.55 (d, J=5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 25.2, 28.8, 34.0, 43.2, 55.8, 68.6, 73.8, 75.5, 83.5, 106.3, 112.5, 119.8, 126.0, 128.2, 129.4, 135.6, 147.7, 148.6, 159.3, 164.8; Anal. Calcd for $C_{21}H_{24}BrN_3O_6$: C, 51.02; H, 4.89; N, 8.50. Found: C, 50.95; H, 4.97; N, 8.58%.

4.9. 4-(2-Bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1a)

To a 100-mL flask equipped with a magnetic stirrer was added compound **9a** (2.47 g, 5 mmol) in CH_3OH (50 mL). The mixture was cooled to 0 °C in an ice bath and $NaBH_4$ (0.22 g, 6 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and then CH_3OH was removed under reduced pressure. CH_2Cl_2 was added to the residue and stirred for 10 min, then filtered and washed with CH_2Cl_2. The solvent was evaporated in vacuo. The crude product was purified by flash column chromatography using EtOAc/CH_2Cl_2 as eluent to afford the product **1a** as a thin yellow solid with 89.6% yield. Mp 223–225 °C; IR (KBr) 3310, 3012, 2973, 2860, 1645, 1612, 1530, 1273, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.67–6.82 (m, 2H), 6.10 (d, J=10.8 Hz, 1H), 4.42–4.49 (m, 2H), 4.06–4.17 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.58–3.82 (m, 4H), 2.88–2.92 (m, 2H), 2.01–2.17 (m, 2H), 1.60–1.71 (m, 4H), 1.42–1.49 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 25.1, 29.1, 34.1, 43.6, 47.0, 55.8, 67.4, 69.7, 74.2, 83.6, 109.5, 112.4, 121.6, 126.3, 127.9, 129.2, 136.2, 147.5, 149.3, 163.9; Anal. Calcd for $C_{21}H_{26}BrN_3O_6$: C, 50.82; H, 5.28; N, 8.47. Found: C, 50.77; H, 5.35; N, 8.42%.

4.10. 4-(2-Bromo-5-methoxy-4-methylphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1b)

Mp 215–218 °C; IR (KBr) 3321, 3018, 2957, 2845, 1643, 1550, 1272, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 6.73–6.84 (m, 2H), 6.12 (d, J=10.8 Hz, 1H), 4.38–4.47 (m, 2H), 4.05–4.16 (m, 1H), 3.85 (s, 3H), 3.63–3.79 (m, 4H), 2.82–2.90 (m, 2H), 2.31 (s, 3H), 2.05–2.18 (m, 2H), 1.63–1.75 (m, 4H), 1.40–1.48 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 25.8, 28.4, 32.5, 36.5, 44.3, 47.6, 57.2, 67.9, 71.3, 84.1, 107.9, 115.3, 119.5, 124.8, 126.9, 129.4, 137.5, 148.1, 149.7, 162.5; Anal. Calcd for $C_{21}H_{26}BrN_3O_5$: C, 52.51; H, 5.46; N, 8.75. Found: C, 52.54; H, 5.51; N, 8.67%.

4.11. 4-(2-Bromo-5-methoxyphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1c)

Mp 219–221 °C; IR (KBr) 3332, 3026, 2961, 2845, 1631, 1547, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 6.64–6.81 (m, 3H), 6.04 (d, J=10.5 Hz, 1H), 4.35–4.46 (m, 2H), 4.11–4.18 (m, 1H), 3.87 (s, 3H), 3.60–3.78 (m, 4H), 2.85–2.94 (m, 2H), 1.97–2.13 (m, 2H), 1.65–1.72 (m, 4H), 1.44–1.52 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 24.1, 30.6, 34.3, 44.2, 47.7, 56.4, 65.1, 74.8, 85.0, 110.6, 113.9, 121.3, 127.0, 129.1, 131.2, 135.5, 146.3, 148.7, 164.2; Anal. Calcd for $C_{20}H_{24}BrN_3O_5$: C, 51.51; H, 5.19; N, 9.01. Found: C, 51.61; H, 5.22; N, 8.93%.

4.12. 4-(6-Bromo-3-methoxy-2,4-dimethylphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1d)

Mp 210–212 °C; IR (KBr) 3301, 3014, 2961, 2849, 1637, 1540, 1273, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.80 (s, 1H), 6.12 (d, J=10.2 Hz, 1H), 4.43–4.52 (m, 2H), 4.12–4.19 (m, 1H), 3.85 (s, 3H), 3.61–3.75 (m, 4H), 2.80–2.91 (m, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 2.07–2.15 (m, 2H), 1.63–1.74 (m, 4H), 1.42–1.49 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 26.4, 29.1, 32.3, 33.6, 38.2, 43.8, 47.5, 59.7, 68.3, 71.8, 82.9, 109.1, 116.6, 118.9, 125.0, 127.2, 133.4, 137.2, 147.2, 148.6, 163.7; Anal. Calcd for $C_{22}H_{28}BrN_3O_5$: C, 53.45; H, 5.71; N, 8.50. Found: C, 53.39; H, 5.72; N, 8.44%.

4.13. 4-(2-(6-Bromo-2,3-dihydrobenzo[*b*][1,4]dioxin-7-yl)ethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1e)

Mp 220–222 °C; IR (KBr) 3296, 3021, 2963, 2842, 1633, 1614, 1537, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 6.72–6.82 (m, 2H), 6.14 (d, J=10.8 Hz, 1H), 4.40–4.48 (m, 2H), 4.06–4.28 (m, 5H), 3.62–3.80 (m, 4H), 2.87–2.96 (m, 2H), 2.05–2.16 (m, 2H), 1.63–1.73 (m, 4H), 1.42–1.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 25.4, 28.6, 34.7, 44.7, 47.2, 57.9, 68.3, 69.9, 76.1, 84.6, 107.8, 111.6, 120.5, 127.2, 127.8, 131.5, 136.1, 145.4, 148.0, 163.5; Anal. Calcd for $C_{21}H_{24}BrN_3O_6$: C, 51.02; H, 4.89; N, 8.50. Found: C, 50.95; H, 4.96; N, 8.45%.

4.14. 4-(2-(5-Bromobenzo[*d*][1,3]dioxol-6-yl)ethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1f)

Mp 223–225 °C; IR (KBr) 3282, 3027, 2953, 2849, 1621, 1604, 1538, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 6.73–6.82 (m, 2H), 6.10 (d, J=10.5 Hz, 1H), 4.37–4.46 (m, 2H), 4.14–4.27 (m, 3H), 3.55–3.72 (m, 4H), 2.83–2.95 (m, 2H), 2.02–2.15 (m, 2H), 1.63–1.71 (m, 4H), 1.38–1.46 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 25.2, 28.7, 35.3, 46.0, 47.7, 56.1, 72.4, 76.5, 83.6, 108.5, 113.0, 121.3, 126.1, 127.9, 132.8, 135.9, 146.2, 148.6, 164.4; Anal. Calcd for $C_{20}H_{22}BrN_3O_6$: C, 50.01; H, 4.62; N, 8.75. Found: C, 50.10; H, 4.61; N, 8.63%.

4.15. 4-(2-Bromo-3,4,5-trimethoxyphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1g)

Mp 225–226 °C; IR (KBr) 3332, 3017, 2946, 2862, 1640, 1617, 1535, 1275, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 6.86 (s, 1H), 6.13 (d, J=10.5 Hz, 1H), 4.43–4.52 (m, 2H), 4.07–4.16 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.62–3.80 (m, 4H), 2.87–2.95 (m, 2H), 2.00–2.14 (m, 2H), 1.62–1.71 (m, 4H), 1.41–1.51 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 25.6, 30.2, 34.5, 42.2, 47.9, 54.4, 67.5, 69.9, 71.6, 73.8, 84.0, 108.6, 112.2, 122.7, 127.3, 128.5, 129.8, 135.5, 146.1, 148.8, 163.3; Anal. Calcd for $C_{22}H_{28}BrN_3O_7$: C, 50.20; H, 5.36; N, 7.98. Found: C, 50.33; H, 5.47; N, 7.91%.

4.16. 4-(2-Bromo-4-chloro-5-methoxyphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1h)

Mp 211–213 °C; IR (KBr) 3322, 3016, 2965, 2855, 1638, 1546, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.64–6.78 (m, 2H), 6.06 (d, J=10.5 Hz, 1H), 4.30–4.41 (m, 2H), 4.13–4.20 (m, 1H), 3.89 (s, 3H), 3.60–3.73 (m, 4H), 2.88–2.97 (m, 2H), 1.99–2.13 (m, 2H), 1.62–1.71 (m, 4H), 1.45–1.54 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 24.3, 30.1, 35.2, 45.6, 46.7, 57.7, 65.2, 75.1, 84.6, 110.8, 114.9, 121.4, 126.8, 129.3, 134.5, 135.8, 145.3, 147.9, 164.6; Anal. Calcd for $C_{20}H_{23}BrClN_3O_5$: C, 47.97; H, 4.63; N, 8.39. Found: C, 48.05; H, 4.65; N, 8.48%.

4.17. 4-(2-Bromo-5-(diethylamino)phenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1i)

Mp 202–204 °C; IR (KBr) 3309, 3036, 2951, 2855, 1636, 1542, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.67–6.84 (m, 3H), 6.04 (d, J=10.5 Hz, 1H), 4.30–4.41 (m, 2H), 4.10–4.19 (m, 1H), 3.62–3.77 (m, 4H), 2.74–2.99 (m, 6H), 1.98–2.14 (m, 2H), 1.65–1.75 (m, 4H), 1.43–1.55 (m, 3H), 1.19 (t, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.7, 25.0, 31.8, 34.6, 43.1, 48.4, 56.7, 65.2, 73.3, 85.5, 112.6, 113.2, 123.0, 127.8, 131.1, 132.5, 135.2, 146.2, 148.6, 164.6; Anal. Calcd for $C_{23}H_{31}BrN_4O_4$: C, 54.44; H, 6.16; N, 11.04. Found: C, 54.28; H, 6.19; N, 10.87%.

4.18. 4-(2-Bromo-5-(diethylamino)-4-ethylphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1j)

Mp 196–199 °C; IR (KBr) 3317, 3024, 2956, 2847, 1628, 1544, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.72–6.86 (m, 2H), 6.08 (d, J=10.5 Hz, 1H), 4.31–4.44 (m, 2H), 4.05–4.13 (m, 1H), 3.64–3.77 (m, 4H), 2.72–2.95 (m, 6H), 1.99–2.23 (m, 4H), 1.63–1.75 (m, 4H), 1.46–1.56 (m, 3H), 1.16–1.23 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 14.4, 23.9, 25.6, 29.4, 32.3, 34.2, 41.7, 48.1, 57.5, 67.3, 72.8, 85.4, 111.5, 113.0, 122.6, 127.9, 131.5, 133.4, 136.1, 145.2, 147.9, 164.3; Anal. Calcd for $C_{25}H_{35}BrN_4O_4$: C, 56.08; H, 6.59; N, 10.46. Found: C, 56.13; H, 6.45; N, 10.40%.

4.19. 9,10-Dimethoxy-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2a)

A round bottom flask was flushed with nitrogen and charged with 5 mol % $Pd(OAc)_2$, 10 mol % DPPF, and toluene. The mixture was stirred under nitrogen for 10 min. In another round bottom flask substrate **1** and K_2CO_3 were weighed. Then, $Pd(OAc)_2$/DPPF solution was added, and the flask was rinsed with an additional toluene. The resulting mixture was heated to 80 °C under N_2 with vigorous stirring until the starting substrate **1** had disappeared as judged by TLC. After cooling down, the solid material was filtered off and washed with CH_2Cl_2. The solvent was evaporated and the crude product was purified by flash column chromatography using EtOAc/CH_2Cl_2 (30%) as eluent to afford the

product as a white solid in 62% yield. Mp 195–197 °C; IR (KBr) 3069, 2980, 2938, 2860, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 6.82 (s, 1H), 6.67 (s, 1H), 6.17–6.25 (m, 1H), 6.08 (d, J=10.8 Hz, 1H), 4.40–4.46 (m, 2H), 4.10–4.15 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.73–3.78 (m, 1H), 3.58–3.67 (m, 2H), 2.87 (t, J=7.2 Hz, 2H), 2.08–2.17 (m, 2H), 1.61–1.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 24.8, 28.9, 33.7, 43.0, 55.8, 68.8, 74.3, 76.6, 82.7, 85.3, 111.3, 111.7, 120.7, 124.9, 127.2, 129.2, 148.0, 148.7, 155.2, 167.4; Anal. Calcd for $C_{21}H_{25}N_3O_6$: C, 60.71; H, 6.07; N, 10.11. Found: C, 60.76; H, 6.11; N, 10.02%.

4.20. 10-Methoxy-9-methyl-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2b)

Prepared as a thin yellow solid in 70% yield. Mp 189–191 °C; IR (KBr) 3067, 2983, 2945, 2862, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 6.85 (s, 1H), 6.68 (s, 1H), 6.14–6.23 (m, 1H), 6.04 (d, J=10.2 Hz, 1H), 4.37–4.45 (m, 2H), 4.11–4.15 (m, 1H), 3.87 (s, 3H), 3.70–3.76 (m, 1H), 3.60–3.68 (m, 2H), 2.86 (t, J=7.2 Hz, 2H), 2.31 (s, 3H), 2.05–2.16 (m, 2H), 1.64–1.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 24.7, 28.7, 33.7, 42.6, 56.3, 68.9, 75.1, 76.3, 82.6, 85.4, 111.8, 111.9, 122.3, 124.7, 126.7, 129.2, 148.0, 148.7, 154.9, 167.5; Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 63.26; H, 6.32; N, 10.45%.

4.21. 10-Methoxy-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]-cyclohepta[1,2-*a*]naphthalen-4-one (2c)

Prepared as a white solid in 65% yield. Mp 202–205 °C; IR (KBr) 3072, 2985, 2947, 2870, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 6.71–6.85 (m, 3H), 6.18–6.27 (m, 1H), 6.10 (d, J=10.5 Hz, 1H), 4.40–4.47 (m, 2H), 4.08–4.14 (m, 1H), 3.86 (s, 3H), 3.71–3.77 (m, 1H), 3.59–3.69 (m, 2H), 2.83 (t, J=6.9 Hz, 2H), 2.10–2.18 (m, 2H), 1.60–1.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 24.7, 29.1, 34.0, 42.7, 56.3, 68.8, 75.8, 82.5, 84.2, 111.5, 112.4, 115.4, 121.6, 124.95, 127.3, 128.3, 147.9, 148.7, 156.4, 168.0; Anal. Calcd for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.01; N, 10.90. Found: C, 62.38; H, 6.07; N, 10.79%.

4.22. 10-Methoxy-9,11-dimethyl-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2d)

Prepared as a white solid in 55% yield. Mp 192–194 °C; IR (KBr) 3062, 2955, 2857, 1631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 6.82 (s, 1H), 6.22–6.31 (m, 1H), 6.11 (d, J=10.5 Hz, 1H), 4.36–4.43 (m, 2H), 4.10–4.15 (m, 1H), 3.88 (s, 3H), 3.68–3.75 (m, 1H), 3.60–3.67 (m, 2H), 2.84 (t, J=7.5 Hz, 2H), 2.33 (s, 3H), 2.26 (s, 3H), 2.06–2.16 (m, 2H), 1.67–1.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 24.8, 25.7, 29.5, 34.6, 42.7, 55.9, 68.8, 75.3, 76.3, 83.2, 85.4, 111.7, 122.2, 124.9, 126.6, 128.0, 135.3, 148.3, 149.5, 155.1, 167.7; Anal. Calcd for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16. Found: C, 63.82; H, 6.62; N, 10.11%.

4.23. 3-(Tetrahydro-pyran-2-yl)-6,6a,10,11,14,15-hexahydro-3*H*-5,7,9,12-tetraoxa-2,3,15a-triaza-cyclohepta[1,2-*a*;4,5-*b*']dinaphthalen-4-one (2e)

Prepared as a white solid in 63% yield. Mp 205–207 °C; IR (KBr) 3066, 2983, 2948, 2849, 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 6.80 (s, 1H), 6.71 (s, 1H), 6.19–6.27 (m, 1H), 6.09 (d, J=10.2 Hz, 1H), 4.22–4.45 (m, 6H), 4.08–4.15 (m, 1H), 3.73–3.80 (m, 1H), 3.56–3.65 (m, 2H), 2.85 (t, J=6.9 Hz, 2H), 2.10–2.19 (m, 2H), 1.60–1.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 24.8, 28.9, 34.1, 43.3, 56.2, 68.3, 74.1, 76.0, 82.1, 84.7, 111.4, 111.7, 121.3, 125.6, 127.3, 129.9, 146.3, 149.6, 155.1, 167.5; Anal. Calcd for $C_{21}H_{23}N_3O_6$: C, 61.01; H, 5.61; N, 10.16. Found: C, 60.95; H, 5.71; N, 10.13%.

4.24. 9,10-Methylenedioxy-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2f)

Prepared as a white solid in 58% yield. Mp 209–211 °C; IR (KBr) 3058, 2976, 2943, 2862, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.8 (s, 1H), 6.82 (s, 1H), 6.67 (s, 1H), 6.16–6.25 (m, 1H), 6.08 (d, J=10.8 Hz, 1H), 4.95 (s, 2H), 4.39–4.46 (m, 2H), 4.07–4.13 (m, 1H), 3.71–3.79 (m, 1H), 3.60–3.68 (m, 2H), 2.92 (t, J=7.5 Hz, 2H), 2.05–2.15 (m, 2H), 1.60–1.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 24.7, 28.4, 33.5, 42.2, 56.7, 68.4, 76.2, 83.1, 85.3, 111.7, 112.5, 122.0, 124.4, 127.6, 130.2, 147.7, 150.2, 154.8, 167.6; Anal. Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 60.15; H, 5.43; N, 10.37%.

4.25. 8,9,10-Trimethoxy-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2g)

Prepared as a white solid in 26% yield. Mp 212–215 °C; IR (KBr) 3062, 2971, 2943, 2848, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 6.68 (s, 1H), 6.15–6.23 (m, 1H), 6.06 (d, J=10.2 Hz, 1H), 4.41–4.48 (m, 2H), 4.13–4.19 (m, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.70–3.76 (m, 1H), 3.53–3.62 (m, 2H), 2.85 (t, J=7.5 Hz, 2H), 2.08–2.16 (m, 2H), 1.58–1.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 24.9, 29.1, 33.5, 43.7, 57.0, 69.4, 71.2, 74.6, 77.3, 82.7, 85.1, 111.4, 121.8, 125.4, 128.0, 131.6, 138.3, 148.0, 149.6, 154.4, 167.7; Anal. Calcd for $C_{22}H_{27}N_3O_7$: C, 59.32; H, 6.11; N, 9.43. Found: C, 59.46; H, 6.17; N, 9.38%.

4.26. 9-Chloro-10-methoxy-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2h)

Prepared as a white solid in 71% yield. Mp 202–204 °C; IR (KBr) 3053, 2948, 2855, 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 6.82 (s, 1H), 6.65 (s, 1H), 6.23–6.30 (m, 1H), 6.05 (d, J=10.8 Hz, 1H), 4.41–4.48 (m, 2H), 4.14–4.19 (m, 1H), 3.87 (s, 3H), 3.62–3.67 (m, 1H), 3.50–3.58 (m, 2H), 2.72 (t, J=7.5 Hz, 2H), 2.04–2.12 (m, 2H), 1.57–1.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 27.9, 34.2, 42.3, 58.1, 65.8, 74.3, 76.5, 81.4, 84.2, 111.5, 113.7, 121.8, 124.5, 128.2, 130.8, 146.1, 148.8, 155.0,

166.4; Anal. Calcd for $C_{20}H_{22}ClN_3O_5$: C, 57.21; H, 5.28; N, 10.01. Found: C, 57.26; H, 5.32; N, 10.08%.

4.27. 10-Diethylamino-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2i)

Prepared as a thin yellow solid in 53% yield. Mp 182–184 °C; IR (KBr) 3058, 2961, 2945, 2850, 1638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 6.72–6.83 (m, 3H), 6.14–6.21 (m, 1H), 6.06 (d, J=10.2 Hz, 1H), 4.36–4.41 (m, 2H), 4.06–4.12 (m, 1H), 3.70–3.77 (m, 1H), 3.56–3.65 (m, 2H), 3.32 (q, J=6.6 Hz, 4H), 2.83 (t, J=6.9 Hz, 2H), 2.10–2.18 (m, 2H), 1.60–1.70 (m, 4H), 1.22 (t, J=6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.3, 24.8, 28.9, 33.8, 42.7, 45.7, 56.6, 75.4, 82.0, 83.9, 111.6, 112.1, 116.4, 122.7, 124.8, 127.4, 128.3, 146.7, 148.3, 158.2, 167.3; Anal. Calcd for $C_{23}H_{30}N_4O_4$: C, 64.77; H, 7.09; N, 13.14. Found: C, 64.67; H, 7.07; N, 13.02%.

4.28. 10-Diethylamino-9-ethyl-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2j)

Prepared as a thin yellow solid in 46% yield. Mp 186–187 °C; IR (KBr) 3046, 2957, 2843, 1636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.79 (s, 1H), 6.67 (s, 1H), 6.16–6.26 (m, 1H), 6.04 (d, J=9.9 Hz, 1H), 4.37–4.44 (m, 2H), 4.05–4.11 (m, 1H), 3.68–3.76 (m, 1H), 3.55–3.63 (m, 2H), 3.36 (q, J=6.6 Hz, 4H), 2.86 (t, J=6.9 Hz, 2H), 2.43 (q, J=5.4 Hz, 2H), 2.11–2.18 (m, 2H), 1.62–1.71 (m, 4H), 1.25 (t, J=6.3 Hz, 6H), 1.15 (t, J=5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 14.2, 17.6, 22.9, 24.7, 29.8, 35.2, 42.7, 46.3, 57.8, 74.3, 82.1, 84.2, 111.3, 117.1, 122.4, 125.7, 127.7, 129.7, 133.5, 145.3, 148.0, 157.8, 167.4; Anal. Calcd for $C_{25}H_{34}N_4O_4$: C, 66.06; H, 7.54; N, 12.33. Found: C, 65.95; H, 7.49; N, 12.36%.

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Preparation of *N*-arylpiperazines and other *N*-aryl compounds from aryl bromides as scaffolds of bioactive compounds

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Abstract—Aryl bromides are coupled with *N*-compounds to give the corresponding arylamines in the presence of a palladium catalyst, a suitable ligand, and a weak base. The catalysts perform well for a large number of different starting material combinations at 100–150 °C with drops of toluene or without solvent, and with low catalyst levels (0.12 mol % Pd). The low catalyst amount makes the process environment friendly.

In the course of our work aimed at obtaining new compounds with biological activity, we required an easy source of *N*-aryl derivatives to serve as precursors. *N*-arylpiperazines, *N*-arylindoles, *N*-arylpyrroles, and substituted anilines are important compounds, particularly in pharmaceutical research and also as intermediates of synthesis. The *N*-arylpiperazine subunit is embedded in several pharmacologically interesting targets such as compounds related to the serotonine ligands,[1] calcium blockers,[2] antipsychotic drugs,[3] antihypertensive,[4] and acetylcholinesterase inhibitory activity.[5] For these reasons significant efforts have gone into the development of efficient methods for their preparation.

In the last decade, several research groups such as Buchwald et al.[6–10] and Hartwig et al.[11–14] reported the palladium-catalyzed coupling of aryl halides with several amino-derivatives. This important reaction opens a new way for synthesizing several pharmaceutical molecules that are otherwise difficult to prepare.

This direct N-arylation is an alternative to classical S_NAr reactions for the preparation of arylamines. Compared to analogous C–C bond-forming such as Suzuki, Stille, and Heck coupling reactions, the cross-coupling methodology to form C–N bonds is more limited.

Recent reports from several research groups on the palladium-catalyzed cross coupling of aryl halides with *N*-derivatives have furnished interesting results but have revealed the need to find more general conditions or the optimization of each process is strongly recommended. Moreover, efficient conditions for the arylation of piperazines have not been reported up to now.

The synthesis of arylpiperazines by palladium-catalyzed amination reaction from unprotected piperazine has been previously reported.[15,16] The results clearly indicate that the piperazine arylation was successful only in low to moderate yields. Fort and co-workers[17] reported a nickel-catalyzed method for the synthesis of *N*,*N*′-diarylpiperazines from aryl chlorides and Zhao et al. described first the use of Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$ catalyst for the arylation of piperazines.[16]

This work was initiated by searching efficient methods for the preparation of scaffolds for potential bioactive compounds, and intends to develop general reaction conditions for the palladium-catalyzed formation of these anilines. Herein we describe our results and details (Tables 1 and 2).

We have prepared arylamines from interesting substrates using Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$ as catalyst, chelating ligand such as 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) or triphenylphosphine (PPh_3), and cesium carbonate base without solvent or few drops of toluene were added when the starting material were solid compounds. The reagents can be weighed and manipulated in contact with air facilitating the industrial use. This is a fast and clean reaction and the results showed that it is possible to replace the expensive BINAP by PPh_3 more readily available than other classic used ligands. This is a modified Buchwald–Hartwig amination of aryl bromides using different substrates and

Keywords: *N*-Arylpiperazines; *N*-Arylindoles; Substituted anilines; Palladium catalyst; N-Arylation; Aryl halides.
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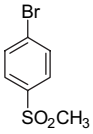
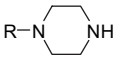
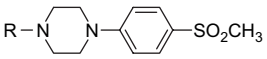
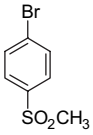
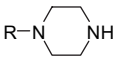
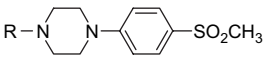
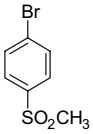
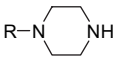
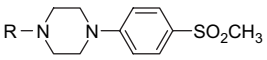
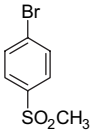
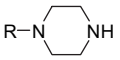
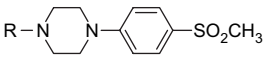
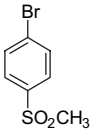
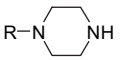
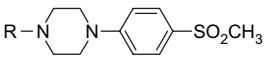
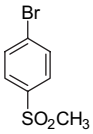
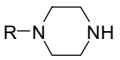
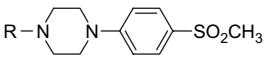
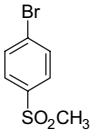
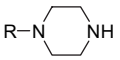
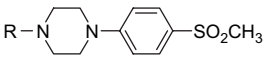
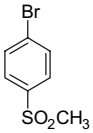
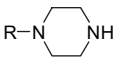
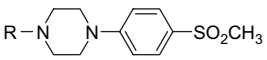
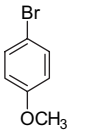
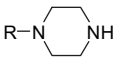
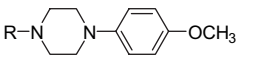
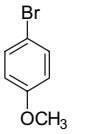
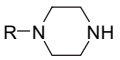
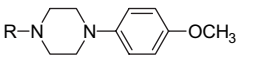
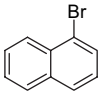
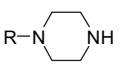
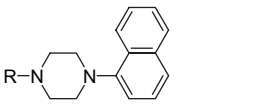
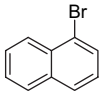
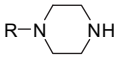
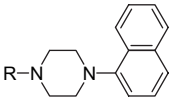
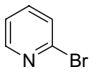
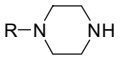
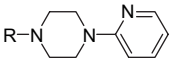
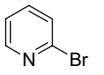
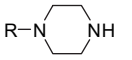
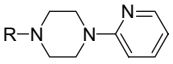
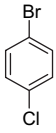
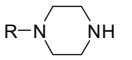
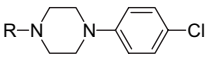
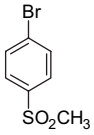
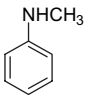
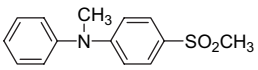
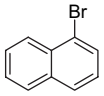
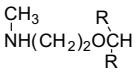
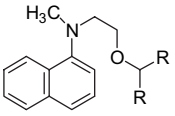
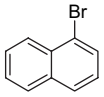
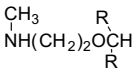
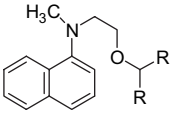
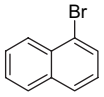
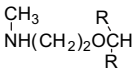
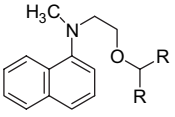
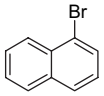
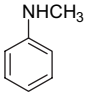
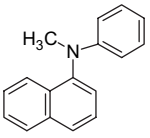
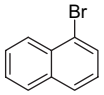
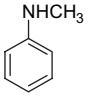
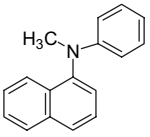
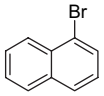
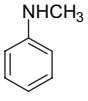
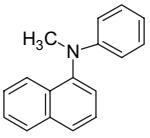
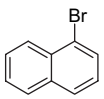
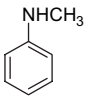
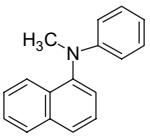
Table 1. Palladium-catalyzed formation of tertiary amines

Entry	Ar-X	R_1R_2NH	Product	Yield (%)[a]	Conditions
1		 R=4-fluorophenyl	 R=4-fluorophenyl	92 (75)	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (±)/Cs_2CO_3
2		 R=4-fluorophenyl	 R=4-fluorophenyl	91	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs_2CO_3
3		 R=4-fluorophenyl	 R=4-fluorophenyl	88	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/PPh_3/Cs_2CO_3
4		 R=4-fluorophenyl	 R=4-fluorophenyl	0	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/Cs_2CO_3 without ligand
5		 R=4-fluorophenyl	 R=4-fluorophenyl	23	Pd(OAc)$_2$/BINAP (+)/Cs_2CO_3
6		 R=4-fluorophenyl	 R=4-fluorophenyl	81 (78)	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (±)/KO*t*-Bu
7		 R=4-fluorophenyl	 R=4-fluorophenyl	55	Cu/K_2CO_3
8		 R=4-fluorophenyl	 R=4-fluorophenyl	0	BINAP (+)/Cs_2CO_3 without catalyst
9		 R=4-fluorophenyl	 R=4-fluorophenyl	43 (47)	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (±)/Cs_2CO_3
10		 R=4-fluorophenyl	 R=4-fluorophenyl	32	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/PPh_3/Cs_2CO_3
11		 R=4-fluorophenyl	 R=4-fluorophenyl	81 (68)	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs_2CO_3

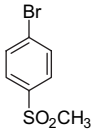
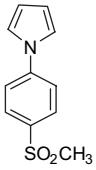
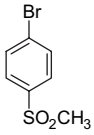
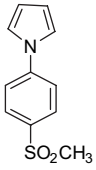
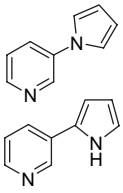
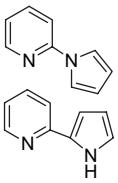
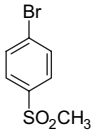
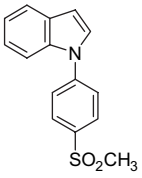
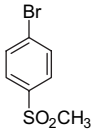
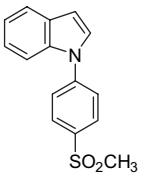
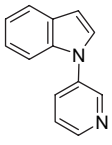
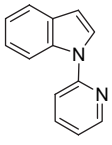
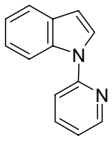
(*continued*)

Table 1. (*continued*)

Entry	Ar-X	R_1R_2NH	Product	Yield (%)[a]	Conditions
12		 R=4-fluorophenyl	 R=4-fluorophenyl	78	$Pd[P(o\text{-tolyl})_3]_2Cl_2/PPh_3/Cs_2CO_3$
13		 R=4-fluorophenyl	 R=4-fluorophenyl	41	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (±)/$Cs_2CO_3$
14		 R=4-fluorophenyl	 R=4-fluorophenyl	45 (48)	$Pd[P(o\text{-tolyl})_3]_2Cl_2/PPh_3/Cs_2CO_3$
15		 R=4-fluorophenyl	 R=4-fluorophenyl	79	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (±)/$Cs_2CO_3$
16				90	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (+)/$Cs_2CO_3$
17		 R=4-fluorophenyl	 R=4-fluorophenyl	85 (87)	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (±)/$Cs_2CO_3$
18		 R=4-fluorophenyl	 R=4-fluorophenyl	87	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (+)/$Cs_2CO_3$
19		 R=4-fluorophenyl		86	$Pd[P(o\text{-tolyl})_3]_2Cl_2/PPh_3/Cs_2CO_3$
20				78 (69)	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (±)/$Cs_2CO_3$
21				79	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (+)/$Cs_2CO_3$
22				76	$Pd[P(o\text{-tolyl})_3]_2Cl_2/PPh_3/Cs_2CO_3$
23				5	$Pd(OAc)_2$/BINAP (+)/Cs_2CO_3

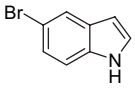
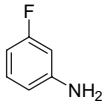
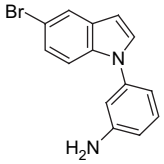
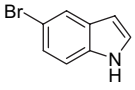
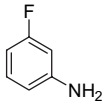
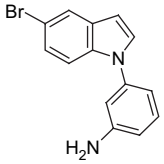
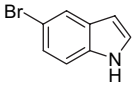
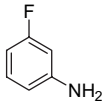
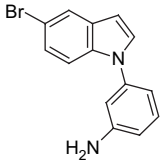
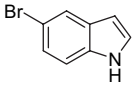
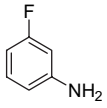
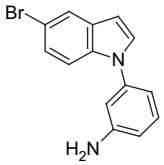
[a] Yields reported correspond to analytically pure isolated compounds (average of two or three runs). All the reactions were conducted at 120 °C for 2 h except for entries 7 (120 h) and 8 (24 h). Compounds of entries 1, 6, 9, 11, 14, 17, and 20 have been prepared on a 1-g scale and the yields are indicated in brackets.

Table 2. Palladium-catalyzed N-arylation of pyrrole and indole

Entry	Ar-X	R_1R_2NH	Product	Yield (%)	Conditions
1				75 (69)	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (+)/$Cs_2CO_3$
2				72	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/$PPh_3$/$Cs_2CO_3$
3				21[a] 46[a]	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (+)/$Cs_2CO_3$
4				72 18	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (+)/$Cs_2CO_3$
5				87 (82)	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (+)/$Cs_2CO_3$
6				90	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/$PPh_3$/$Cs_2CO_3$
7				48	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (+)/$Cs_2CO_3$
8				86 (81)	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (+)/$Cs_2CO_3$
9				88	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/$PPh_3$/$Cs_2CO_3$

(*continued*)

Table 2. (*continued*)

Entry	Ar-X	R_1R_2NH	Product	Yield (%)	Conditions
10				0[b]	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs_2CO_3
11				30[c]	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs_2CO_3
12				65[d]	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs_2CO_3
13				0[e]	BINAP (+)/Cs_2CO_3 without catalyst

Compounds of entries 1, 5, and 8 have been prepared on a 1-g scale and the yields are indicated in brackets.
Yields reported correspond to analytically pure isolated compounds (average of two or three runs). All the reactions were conducted at 120 °C for 2 h. Except the indicated cases.
[a] 4 h at 150 °C.
[b] 24 h at 130 °C.
[c] 6 h at 150 °C.
[d] 24 h at 150 °C.
[e] 24 h at 180 °C without catalyst.

optimized conditions, which allows the synthesis of precursors of bioactive compounds. Aryl bromides were chosen as starting compounds because they are readily available and more reactive than aryl chlorides and triflates.[18] Furthermore, the preparation of functionalized aryl iodides was more difficult.[19]

According to Buchwald and co-workers[8] and Ma and co-workers,[20] the acyclic secondary amines are usually problematic substrates for the coupling reactions, probably due to steric hindrance, high nucleophilicity, and basicity and also the possibility of β-elimination hydrogen can be considered. The preparation of hindered *N*,*N*-dialkylarylamines was successful in these conditions giving the corresponding disubstituted anilines (Table 1). Acyclic secondary amine substrates (Table 1, entry 18) gave a lower yield of coupled product than those obtained with cyclic secondary amines and electron poor aryl bromide (Table 1, entry 1), but better than cyclic secondary amines and electron rich aryl bromide (Table 1, entry 9). Electron poor aryl bromides containing a sulfone group afforded the expected products with excellent yields within 2 h (Table 1, entry 1). The reaction was shown to tolerate the naphthyl group with good yield of 76–87% (Table 1, entries 17–22). Another interesting observation was the regioselective reaction of 1-bromo-4-chlorobenzene with the substituted piperazine under the same reaction conditions (Table 1, entry 15). Changing the chelating ligand from BINAP to triphenylphosphine (PPh_3), which is less expensive, resulted in non-significant modification of yields (Table 1, compare entry 1 vs entry 3; entry 9 vs entry 10; entry 13 vs entry 14; entry 17 vs entry 19). In the same way, both racemic and non-racemic BINAP ((*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) gave similar results in all the tested transformations (Table 1, compare entry 1 vs entry 2; entry 17 vs entry 18; entry 20 vs entry 21). Moreover addition of a large excess of BINAP did not modify the yields under our experimental conditions and also was determined that the order of addition of reagents was not important. The experiments carried out from 1 g of substrate provide the desired compounds in acceptable yields using a minimal amount of catalyst (see Tables 1 and 2, the yields of 1-g scale reactions were indicated in brackets).

No reaction occurred without addition of ligand BINAP or triphenylphosphine to Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$, substrate, and cesium carbonate (Table 1, entry 4). The results showed that P(*o*-tolyl)$_3$ present in the catalyst system was ineffective, even for the N-arylation of the activated substrates. The use of $Pd(OAc)_2$ as a precatalyst was found to be less efficient than Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$ in the tested substrates (Table 1, entries 5 and 23). When strongly basic KO*t*-Bu was used instead of Cs_2CO_3 the expected piperazine was obtained in a good yield (Table 1, entry 6).

On the other hand the Ullmann-type coupling using Cu/K_2CO_3 gave the desired product in 55% yield and starting

aryl bromide remained unreacted after 120 h of reaction (Table 1, entry 7). In this study the Pd catalyst revealed superiority over the Cu system.

When $Pd_2(dba)_3$ was used as catalyst under conditions presented by Verkade and Urgaonkar the aryl bromide reacted very slowly and the reaction was not complete after 3 days.[21]

In the same way, the synthesis of *N*-arylpyrrole or indole has been achieved by using the same conditions. Hartwig et al. have reported previously the preparation of *N*-arylazoles using the combination of $Pd(dba)_2$ and dppf in the presence of NaO*t*-Bu or Cs_2CO_3.[11] The $Pd(dba)_2$ is a good catalyst but difficult the purification of products. More late the same authors have optimized the reaction conditions using $Pd(dba)_2$/$P(t\text{-}Bu)_3$.[22] When 5-bromoindole was treated with 3-fluoroaniline, both possessing two reactive positions, the arylation took place exclusively at the 1-position over the N-atom, giving the corresponding *N*-arylindole as a single isomeric product at temperature near to 150 °C (Table 2, entries 11 and 12), and the expected 5-(3-fluorophenylamino)indole was not detected under these conditions. In contrast, the reaction was unsuccessful at 130 °C after more than 24 h (Table 2, entry 10). Thus, this method allowed the synthesis of *N*-(3-aminophenyl)-5-bromoindole from 5-bromoindole and 3-fluoroaniline under severe reaction conditions (Table 2, entry 12). The 3-fluoroaniline was the choice thinking that the arylation will take place at the amine group. The displacement of fluoride (3-fluoroaniline) instead of bromine (5-bromoindole) is not clear; aryl fluorides have long been considered inert to Pd-catalyzed coupling reactions,[22] and only aryl fluorides with strong electron-withdrawing substituents give coupling reactions.[23] Only the high temperatures can explain this behavior. Attempts at the same temperature in the absence of Pd catalyst were unsuccessful (Table 2, entry 13), result that corroborate the radical mechanism of this reaction.

The pyridinylation of indole was also conducted in the same manner as described above using 3-bromopyridine and indole but the intended coupled product was obtained in low yield (Table 2, entry 7). Nevertheless, the 2-bromopyridine in the same conditions gives the *N*-arylpyrrole in excellent yield (Table 2, entry 8). It is interesting the reactivity of pyrrole with heteroaromatic substrates such as the 2- and 3-bromopyridine. In all cases, mixtures of two isomers were obtained. The reaction of 3-bromopyridine with pyrrole gave the *N*-arylpyrrole (21%) and the nornicotyrine (46%) (Table 2, entry 3). Whereas the treatment of pyrrole with 2-bromopyridine afforded the 2-(1-pyrrolyl) pyridine (72%) and the 2,2′-pyrrolylpyridine (18%) (Table 2, entry 4). The reaction of 2-bromopyridine with the pyrrole and indole rings proceeded with more yield and selectivity than the reaction of 3-bromopyridine. Our hypothesis is that the 2-bromopyridine facilitates the complexation with the catalyst system and N-arylation of the azole was preferable as expected (Table 2, entries 4 and 8). Recently, Doucet et al. reported the significant effect of the position and the nature of the halide on the heteroaromatic nuclei on catalyzed palladium reactions.[24]

The substitution of the two different positions of the pyrrole by the reaction of the pyrrole with the bromopyridine is dependent on the position of the bromine atom over the pyridine nucleus (Table 2, entries 3 and 4). So, it is know that the 2-position of bromopyridines is most susceptible to do oxidative addition to palladium than the 3-position. Moreover, due to pyrrole electronic distribution, it might be involved in two different arylation mechanisms, as suggested by the ab initio computational data included in Supplementary material. Pyrrole and indole react readily with electron poor aryl bromide and give *N*-arylpyrrole (Table 2, entry 1) and *N*-arylindole (Table 2, entry 5) in good yield.

The N-arylation of pyrrole and indole can be obtained at 100 °C, but a significant amount of starting material remained unreacted after a long reaction time at this temperature. Considering these results, the process was optimized at a higher temperature (130–150 °C). In general, this coupling reaction was found to be temperature dependent, higher reaction temperatures increases the yield, but by raising the temperature to 180 °C, the ratio of side products was increased.

In summary, we report new conditions for the palladium-catalyzed amination of aryl bromides, which do not require the use of solvent or few drops of toluene (exceptional cases), and need low catalyst amounts. The direct N-arylation of substituted piperazines was an interesting aspect of this strategy. This developed methodology was efficient on a 1-g scale for coupling aryl and aliphatic amines. This protocol will be applied to the preparation of more complex and interesting nitrogen containing compounds and these studies will be reported in due course.

Amination of aryl halides (Tables 1 and 2). General procedure. A flask was charged with aryl halide (1.0 mmol), amine (1.2 mmol), cesium carbonate (1.0 mmol), $Pd[P(o\text{-}tolyl)_3]_2Cl_2$ (0.12 mol % Pd), and BINAP (0.0075 mmol) under argon without addition of solvent (just drops of toluene was added only in exceptional cases when both starting compounds were solids). The flask was hermetically closed and the mixture was heated at 100–130 °C (after the substrate and all reagents have been added without any period of incubation) with stirring until the starting material has been completely consumed as analyzed by TLC. The mixture was then allowed to cool to room temperature and the crude product was directly purified further by flash chromatography on silica gel, eluting with mixtures of hexane/ethyl acetate. All the commercially available reagents used were purchased from Aldrich Chemical Co. and were used without previous purification. The catalyst was acquired from Strem (Chemicals for Research). Yields reported correspond to analytically pure isolated compounds.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.011

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Reactivity of unsaturated sultones synthesized from unsaturated alcohols by ring-closing metathesis. Application to the racemic synthesis of the originally proposed structure of mycothiazole

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Abstract—Unsaturated sultones have been synthesized from various primary or secondary alkenols by ring-closing metathesis of the corresponding unsaturated sulfonates. By treatment with a strong base, β,γ-unsaturated sultones can be metalated and subsequently alkylated with electrophiles. When iodomethylmagnesium chloride was selected as the electrophile, seven-membered ring β,γ-unsaturated sultones were converted into homoallylic conjugated (*Z*)-dienols. This methodology was applied to the racemic synthesis of the originally proposed structure of the marine natural product mycothiazole.

1. Introduction

Homoallylic conjugated (*Z*)-dienols of type **A** (Fig. 1) and their derivatives are present in a variety of biologically active natural products such as palytoxin,[1] ostreocin,[2] discodermolide,[3] dictyostatin,[4] neodihydrohistrionicotoxin,[5] and mycothiazole.[6] As illustrated in the total synthesis of some of these natural products or in synthetic approaches, various strategies have been developed to synthesize conjugated (*Z*)-dienols of type **A** in a stereoselective manner (Scheme 1).

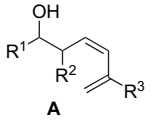

Figure 1. Structure of the homoallylic conjugated (*Z*)-dienols of type **A**.

A first approach involves palladium- or nickel-catalyzed cross-coupling reactions[7] between (*Z*)-alkenyl iodides (X=I)[8,9] or enol carbamates and triflates [X=OCON(*i*-Pr_2) or OTf][10] of type **B**, respectively, with an alkenyl metal of type **C** [route (a), Scheme 1]. The (*Z*)-alkenyl iodides of type **B** (X=I) can also undergo a Nozaki–Hiyama–Kishi coupling with an aldehyde (R^3CHO) followed by oxidation of the resulting allylic alcohol and subsequent methylenation of the carbonyl group [route (b), Scheme 1].[11] The (*Z*)-alkenyl iodides of type **B** are generally prepared from the aldehydes of type **D** by a Wittig olefination with (iodomethylene)triphenylphosphorane,[12] but the direct conversion of these latter aldehydes to the conjugated (*Z*)-dienols of type **A** can also be achieved by reaction with allylic organometallic species of type **E** such as an allyltitanium bearing a diphenylphosphanyl group (Z=PPh_2) and subsequent elimination of phosphine oxide,[13] or an allylchromium[14] or an allylborane[15] bearing a trimethylsilyl group (Z=$SiMe_3$) followed by Peterson elimination [route (c), Scheme 1].[16] Another strategy relies on a copper-promoted coupling of the alkynylsilane moiety in the homopropargylic alcohols of type **F** with vinyl iodide, followed by an intramolecular hydrosilylation of the carbon–carbon triple bond [route (d), Scheme 1].[17] As the reduction of lactones of type **G** followed by Wittig methylenation can provide access to subunits of type **A**, an alternative route has been developed from homoallylic alcohols of type **H** that relies on a ring-closing metathesis reaction (RCM) of the corresponding derived acrylates [route (e), Scheme 1].[18] Whereas a R^3 substituent ($R^3 \neq H$) can be introduced in the first two routes [routes (a) and (b), Scheme 1], the other strategies have only been reported for the synthesis of subunits of type **A** bearing a terminal olefin (R^3=H).

The development of an alternative complementary route to subunits of type **A** from homoallylic alcohols of type **H**[19] was considered that would rely on an unsaturated heterocyclic intermediate generated by RCM for the control of (*Z*) configuration of the α,β-disubstituted double bond and

Keywords: Ring-closing metathesis; Sultones; Conjugated dienes; Natural products.
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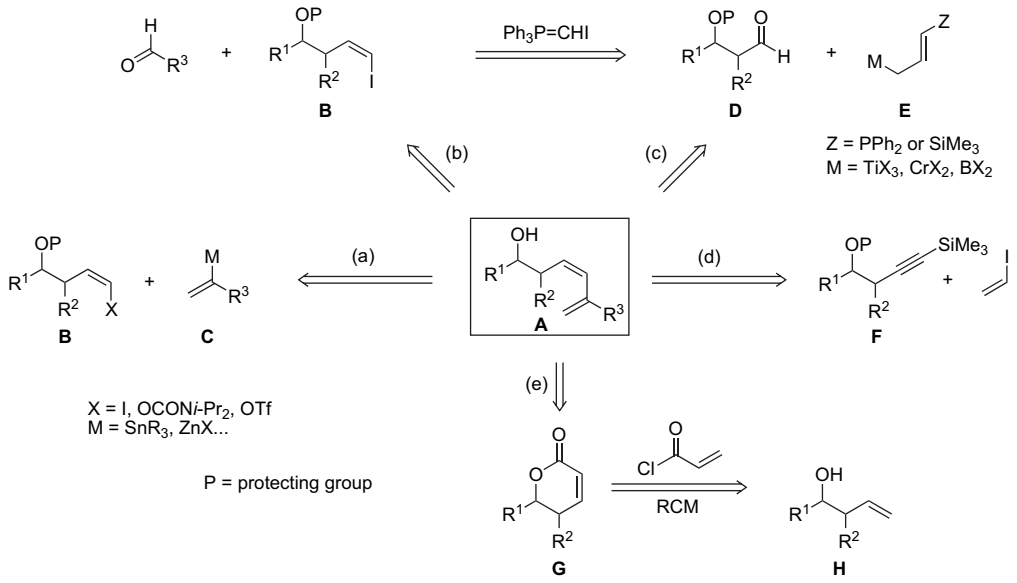
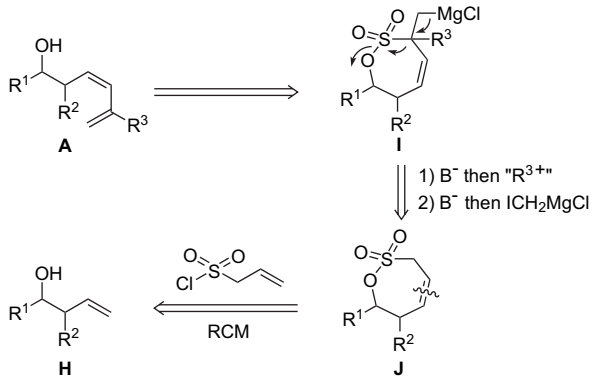


Scheme 1. Synthetic approaches toward homoallylic conjugated (*Z*)-dienols of type **A**.

would enable the introduction of a R^3 substituent. Based on literature precedents, subunits of type **A** should be generated from the β-metalated sultones of type **I** by β-elimination of the sulfonyl moiety and loss of sulfur dioxide.[20,21] Such intermediates of type **I** should be accessible from the unsaturated sultones of type **J** by sequential metalation and electrophilic trapping, first by an appropriate alkylating reagent containing the R^3 moiety and then with the carbenoid reagent ICH_2MgCl.[21] A RCM could be used to elaborate the unsaturated sultones of type **J** from the corresponding unsaturated sulfonates derived from homoallylic alcohols of type **H** (Scheme 2).



Scheme 2. Synthesis of subunits of type **A** from unsaturated sultones.

Herein, we would like to report a full account of our results concerning the synthesis of unsaturated sultones by RCM, their subsequent transformation to homoallylic conjugated (*Z*)-dienols of type **A** as well as the application of this methodology to the racemic synthesis of the originally proposed structure of the marine natural product mycothiazole.

2. Synthesis of unsaturated sultones by RCM

The RCM catalyzed by ruthenium–carbene complexes is a particularly attractive strategy for the synthesis of unsaturated carbocycles as well as oxygen, nitrogen, or phosphorous containing heterocycles that would be difficult to obtain by other routes.[22] When we initially started our investigations on this subject, the preparation of unsaturated sultones by RCM had not been described, although the synthesis of sulfur-containing heterocycles by this strategy had already been the subject of several reports.[23] Thus, it was initially reported that, unlike the more reactive Schrock's molybdenum carbene catalyst, the ruthenium–carbene complex **I**,[24] the so-called first generation Grubbs' catalyst (Fig. 2) was not suitable for the generation of cyclic sulfides due to its poisoning by low-valent organosulfur compounds.[25,26] However, it was later demonstrated that the second generation ruthenium catalysts bearing an *N*-heterocyclic carbene (such as **II** or its dehydro analogue) could be used successfully in some cases, depending on the substitution pattern of the substrates.[27] However, the ruthenium catalysts are compatible with the higher oxidation states of the sulfur atom as illustrated by the numerous reports concerning the synthesis of unsaturated sulfoxides,[28] sulfones,[29] sulfonamides,[30] and sulfamides[31] by RCM using the ruthenium–carbene catalysts **I** or **II** (Fig. 2).

In order to demonstrate that a variety of sultones could be generated by RCM, and not only those of type **J** required for our synthetic approach toward homoallylic conjugated (*Z*)-dienols of type **A**, a variety of primary alkenols were treated with vinyl-, allyl-, or homoallylsulfonyl chlorides[32] in the presence of Et_3N (CH_2Cl_2, 0 °C to rt) to generate the corresponding primary unsaturated sulfonates **1a–f** (40–90%). These sulfonates underwent a RCM in the

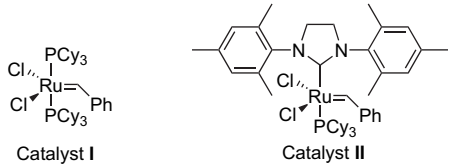
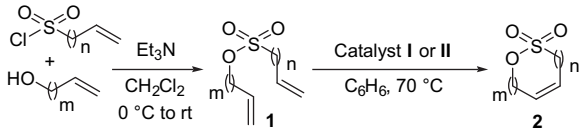


Figure 2. RCM catalysts.

Table 1. Synthesis of unsaturated sultones from primary alkenols

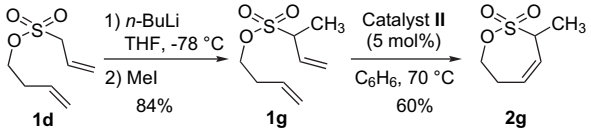


m	*n*	Sulfonate **1** (yield%)	Sultone **2** (yield%)
1	0	**1a** (40)	**2a** (100)
2	0	**1b** (87)	**2b** (90)
1	1	**1c** (76)	**2c** (51)[a] (99)
2	1	**1d** (90)	**2d** (60)[a] (100)
3	1	**1e** (83)	**2e** (94)[a]
2	2	**1f** (90)	**2f** (99)[a] (51)

[a] Yields refer to the use of catalyst **I**.

presence of catalyst **I** or **II** (C_6H_6, 70 °C) and the corresponding unsaturated sultones **2a–f** were obtained in good to virtually quantitative yields (Table 1). The second generation catalyst **II**, which is less sensitive to steric and electronic effects compared to catalyst **I**,[24] was used to achieve the RCM of the unsaturated sulfonates **1a** and **1b**, which provided the corresponding α,β-unsaturated five- and six-membered ring sultones **2a** (100%) and **2b** (90%), respectively. It was observed that catalyst **I** was considerably less efficient than catalyst **II** for the formation of the six- and seven-membered ring β,γ-unsaturated sultones **2c** (51% compared to 99%) and **2d** (60% compared to 100%), respectively. Similar results were disclosed, prior to our first report, by Metz and co-workers who achieved the formation of five- to nine-membered and fifteen-membered ring sultones from primary unsaturated sulfonates using catalyst **II** in refluxing CH_2Cl_2.[33] Despite the well-known difficulties associated with the formation of medium-size rings by RCM, we observed that the less reactive catalyst **I** was particularly efficient in promoting the RCM reaction of the unsaturated sulfonates **1e** and **1f** leading to the eight-membered ring sultones **2e** (94%) and **2f** (99%), respectively, whereas the latter was obtained in considerably lower yield (51%) when catalyst **II** was employed (Table 1).[34]

It was also demonstrated that primary unsaturated sulfonates could be substituted prior to RCM. Thus, the sulfonate **1d** was metalated by treatment with *n*-BuLi in THF at −78 °C[35] and subsequent addition of methyl iodide regioselectively afforded the α-substituted sulfonate **1g** in good yield (84%). After treatment with catalyst **II** (C_6H_6, 70 °C), the α-methyl-β,γ-unsaturated seven-membered ring sultone **2g** (60%) was produced (Scheme 3).

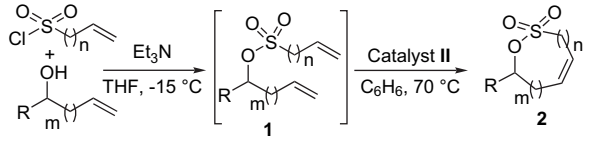


Scheme 3. Alkylation of acyclic unsaturated sulfonates.

The synthesis of unsaturated sultones derived from secondary alkenols was next investigated. It turned out that the sulfonates **1h–l** derived from secondary allylic or homoallylic alcohols were considerably less stable than those derived from primary ones, but their preparation could be achieved by reaction with vinyl or allylsulfonyl chlorides in the presence of Et_3N in THF at −15 °C.[36] The latter solvent provided better results than CH_2Cl_2 presumably because of the lower solubility of triethylamine hydrochloride, which may be responsible for side reactions. Nevertheless, the crude intermediate secondary sulfonates **1h–l** were not purified and immediately treated with catalyst **II** in C_6H_6 at 70 °C. Under these conditions, the corresponding functionalized α,β- or β,γ-unsaturated sultones **2h–l** were obtained in satisfactory overall yields (54–76%) from the corresponding secondary alkenols (Table 2).

These results demonstrate that a wide variety of sultones can be easily synthesized by RCM of the corresponding sulfonates derived from either primary or secondary alkenols.[33,34] The unsaturated sultones **2** should constitute interesting heterocyclic building blocks in organic synthesis since they possess multiple sites of reactivity.[37,38]

Table 2. Synthesis of unsaturated sultones from secondary alkenols

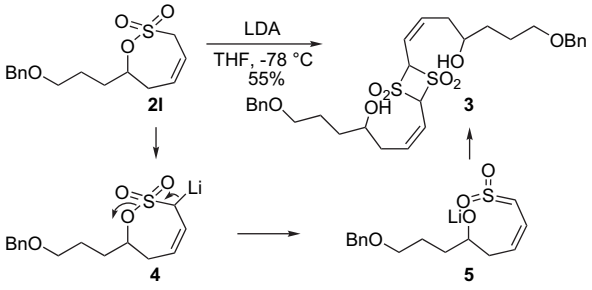


m	*n*	R	Sultones **2** (yield%)
1	0	$(CH_2)_3OBn$	**1h** **2h** (76)
1	0	CO_2Et	**1i** **2i** (54)
0	1	CH_2OPiv	**1j** **2j** (74)
0	1	$CH_2OTBDPS$	**1k** **2k** (65)
1	1	$(CH_2)_3OBn$	**1l** **2l** (65)

Following our initial goal, the transformation of the β,γ-unsaturated seven-membered ring sultones of type **J** such as **2d** and **2l** into homoallylic conjugated (*Z*)-dienols of type **A** was investigated (Scheme 2). This operation implies that these unsaturated sultones should be metalated at the α-position of the sulfonyl moiety and functionalized by reaction with appropriate electrophiles.

3. Synthesis of conjugated (*Z*)-dienols of type A

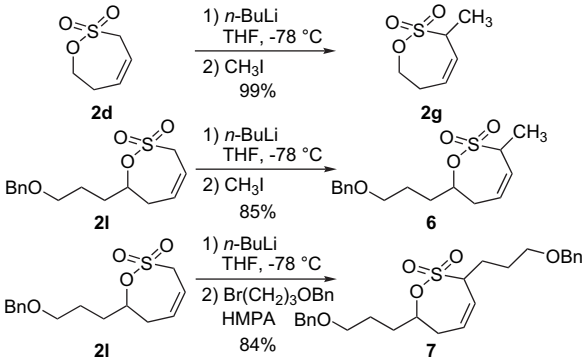
Sultones can be metalated at the α-position of the sulfonyl group using a strong base such as an alkyllithium reagent.[39] In the case of β,γ-unsaturated sultones of type **J**, the acidity of the hydrogens at the α-position should be improved compared to the saturated analogues, and the use of a milder base such as LDA was considered for achieving the metalation. However, when sultone **2l** was treated with LDA in THF at −78 °C, the formation of the 1,3-dithietane tetraoxide **3** took place rapidly prior to the introduction of any electrophilic agent. The latter compound was isolated in 55% yield in the apparent form of a 60:40 mixture of *trans*/*cis*-diastereomers (unassigned relative configuration) bearing double bonds of (*Z*) configuration, as indicated by the analysis of the ^{1}H NMR spectrum. The formation of **3** may be explained by the transformation of the α-lithiated sultone **4** into the corresponding sulfene **5** that dimerized under these conditions to **3** (Scheme 4).[40]



Scheme 4. Metalation of sultone **2l** with LDA.

Fortunately, this side-reaction was not observed when sultone **2l** was metalated with *n*-BuLi in THF at −78 °C and subsequent addition of methyl iodide cleanly provided the α-methyl β,γ-unsaturated seven-membered ring sultone **6** in 85% yield as a single diastereomer (unassigned relative configuration) (Scheme 5). Although, the different behavior of the α-lithiated sultone **4** under these two sets of experimental conditions has not been fully elucidated, it appeared obvious that the presence of excess LDA and/or diisopropylamine modified the reactivity of the carbon–lithium bond in the latter species and was responsible for its transformation to sulfene **5**. Indeed, when **2l** was metalated with an excess of *n*-BuLi, the subsequent addition of diisopropylamine also triggered the formation of 1,3-dithietane tetraoxide **3**.

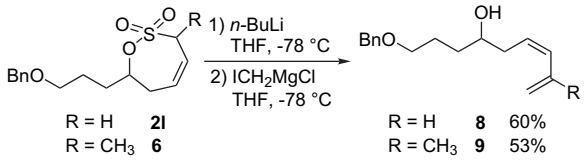
Metalation of sultone **2d** derived from a primary alkenol with *n*-BuLi in THF at −78 °C followed by addition of methyl iodide afforded α-methylated sultone **2g**, a substrate that was previously synthesized by alkylation of the acyclic sulfonate **1d** and subsequent RCM (Scheme 3). Besides methyl iodide, other less reactive alkylating agents such as the alkyl bromide $Br(CH_2)_3OBn$ could be used successfully



Scheme 5. Alkylation of sultones **2d** and **2l**.

provided that the polar co-solvent HMPA was added. Under these conditions, sultone **2l** was effectively converted into the α-alkylated sultone **7** (84%, single diastereomer of unassigned relative configuration) (Scheme 5).

In order to demonstrate that conjugated (*Z*)-dienols of type **A** could be generated from unsaturated sultones of type **J**, substrates **2l** and **6** were metalated with *n*-BuLi in THF at −78 °C and the resulting organolithium reagents were alkylated with ICH_2MgCl[41] (generated from CH_2I_2 and *i*-PrMgCl, THF, −78 °C). As anticipated, this carbenoid reagent behaved as an electrophilic species and the Grignard reagents initially generated by this alkylation reaction underwent β-elimination and loss of sulfur dioxide to deliver the homoallylic alcohols **8** (60%) and **9** (53%) bearing a 1,3-diene unit with an internal (*Z*)-disubstituted double bond and either a terminal or an α,α-disubstituted olefin, respectively (Scheme 6).



Scheme 6. Synthesis of the conjugated (*Z*)-dienols of type **A**.

Having demonstrated that conjugated (*Z*)-dienols of type **A** could be synthesized from homoallylic alcohols, we envisaged to highlight the interest of this methodology by its application to the total synthesis of biologically active natural products. In order to fully benefit from the intermediacy of an unsaturated sultone in this strategy, natural products bearing a subunit of type **A** with an α,α-disubstituted double bond appeared rather interesting targets and the marine natural product mycothiazole was selected.

4. Total synthesis of the originally proposed structure of mycothiazole

Over the past few years, natural products of marine origin have continued to be of interest due to their wide spectrum of biological and pharmacological properties. Mycothiazole was first isolated in 1988 from the marine sponge *Spongia mycofijiensis* collected from the Vanuatu islands.[6] Its presence was also detected recently in the extracts of another

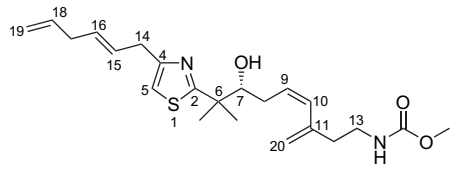


Figure 3. Originally proposed structure of (−)-mycothiazole.

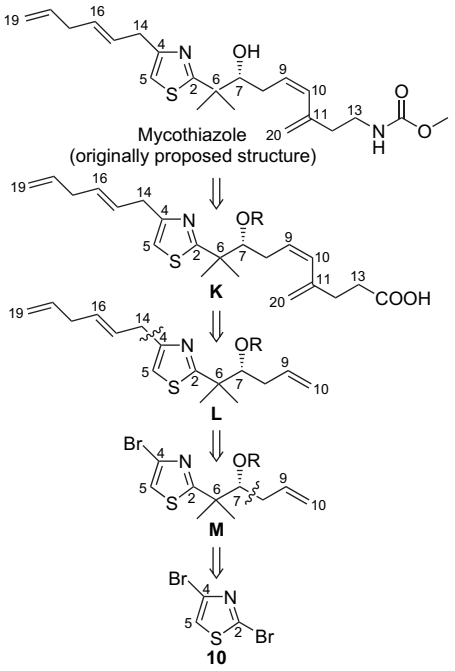
marine sponge of the genus *Dactylospongia*.[42] Mycothiazole was found to exhibit an antihelminthic activity in vitro.[6] Moreover, screening assays by the National Cancer Institute (NCI) in the United States indicated that mycothiazole exhibits a rather selective toxicity against a small cell lung cancer line.[43] The originally proposed structure of mycothiazole was established after extensive NMR analysis and confirmed by the exhaustive interpretation of a HREIMS spectrum (Fig. 3).[6] The synthesis and biological evaluation of simplified analogues of mycothiazole are still currently being investigated.[44]

The main structural feature of this natural product is a 2,4-disubstituted thiazole ring, which is embedded between two acyclic dienic side chains. The C2 side-chain includes a nitrogen substituent at C13 (methyl carbamate), a conjugated diene moiety consisting of a (*Z*)-disubstituted double bond (C9–C10) and a methylene group (C11–C20), a quaternary carbon at C6 substituted by a *gem*-dimethyl group, and a secondary alcohol at C7 that constitutes the unique stereocenter of mycothiazole having a (*R*) configuration. The C4 substituent is a 2,5-hexadienyl chain containing a disubstituted double bond (C15–C16) to which an (*E*) configuration was originally assigned and a terminal olefin (C18–C19). A conjugated (*Z*)-dienol subunit of type **A** is easily recognized in the C7–C11 fragment of this natural product.[45]

The first total synthesis of the proposed structure of mycothiazole features the formation of the thiazole ring by condensation of L-cysteine methyl ester with a carboxylic acid followed by oxidation with activated MnO_2 to form the 2,4-disubstituted thiazole, an enantioselective aldol condensation for the control of configuration at the C7 stereocenter, and the stepwise construction of the 2,5-hexadienyl side-chain at C4 by two sequential Stille coupling reactions (C15–C14 and C17–C18 bond formation). A third Stille coupling enabled the construction of the C10–C11 bond and hence the elaboration of the subunit of type **A** [according to route (a), Scheme 1].[9] The assignment of the (*R*) absolute configuration to mycothiazole was based on the comparison of the signs of optical rotations of the synthetic sample and the natural product. The discrepancies observed between the values were attributed to the lability of mycothiazole upon storage.[9] Synthetic approaches have also been reported toward a C4–C7 subunit containing the 2,4-disubstituted thiazole[46] and the C8–C13 fragment containing the conjugated diene by an ene–yne cross-metathesis, which occurred without stereoselectivity.[47,48]

4.1. Retrosynthetic analysis

In our retrosynthetic analysis of the originally proposed structure of mycothiazole, the installation of the methyl carbamate at C13 was envisaged by a Schmidt reaction applied to the carboxylic acid of type **K**. The key stage would be the elaboration of the conjugated (*Z*)-dienol moiety in compound **K** from the corresponding homoallylic alcohol derivative of type **L**, through an intermediate sultone, using the previously described strategy. The introduction of the side-chain at C4 in compound **L** should be achieved from the substituted 4-bromothiazole of type **M**. In this latter compound, the secondary homoallylic alcohol at C7 would be created by allylation of an intermediate aldehyde whose preparation was envisaged from the readily available 2,4-dibromothiazole **10**[49] (Scheme 7).



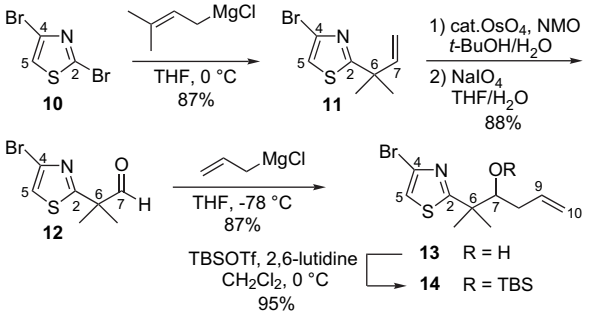
Scheme 7. Retrosynthetic analysis.

The selection of this latter compound as a starting material would also be potentially attractive for the synthesis of structural analogues of the natural product bearing a different side-chain at C4.

4.2. Synthesis of the C4–C10 subunit

Our synthesis of the originally proposed structure of mycothiazole first required the chemoselective substitution of bromine at C2 in 2,4-dibromothiazole **10**. Prenylmagnesium chloride chemoselectively reacted with **10** in THF at 0 °C with complete allylic transposition (S_E2' process)[50] to produce 2,4-disubstituted thiazole **11** (87%). The terminal olefin in compound **11** was subjected to a dihydroxylation (cat. OsO_4, NMO, *t*-BuOH/H_2O) and the resulting intermediate 1,2-diol was not purified but underwent an oxidative cleavage with $NaIO_4$ in THF/H_2O to afford aldehyde **12** (88%). This compound was treated with allylmagnesium bromide and the resulting secondary alcohol **13** (87%) was protected as a *tert*-butyldimethylsilyl ether (TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C) to produce compound **14** (95%) containing the C4–C10 subunit of mycothiazole (Scheme 8).

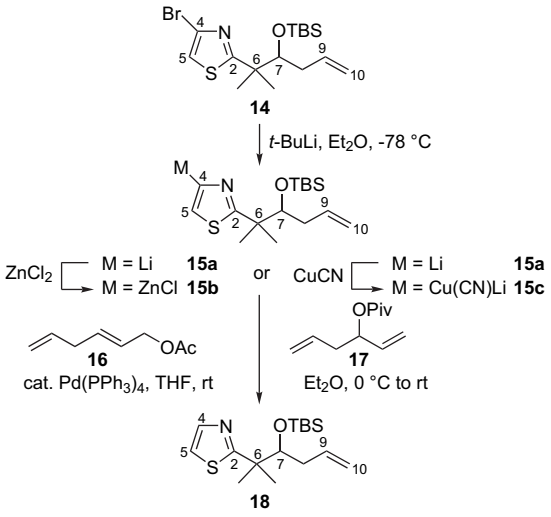
The next task was to install the 2,5-hexadienyl side-chain at C4 on the thiazole ring.



Scheme 8. Synthesis of the C4–C10 subunit.

4.3. Installation of the unsaturated side-chain at C4

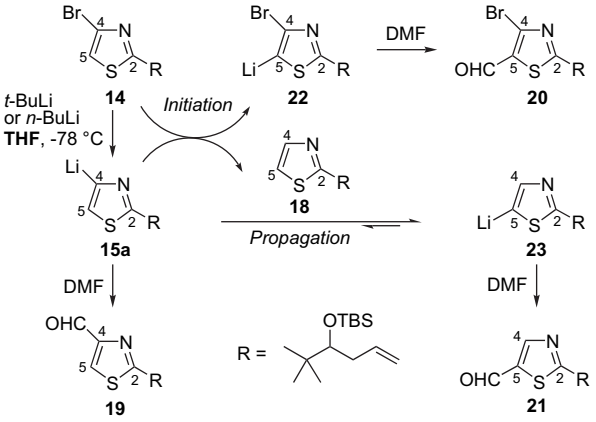
Our initial plan was to create the C4–C14 bond by a cross-coupling reaction. Thus, the substituted 4-bromothiazole **14** underwent lithium–bromine exchange with *tert*-butyllithium in ether at −78 °C.[51] The corresponding organolithium reagent **15a** was transmetalated with zinc chloride, but the resulting organozinc reagent **15b** did not react with the allylic acetate **16**[52] in the presence of a catalytic amount of $Pd(PPh_3)_4$ in THF.[53] A transmetalation of **15a** with copper cyanide was also attempted but the resulting lower order cyanocuprate **15c** did not achieve the S_N2' substitution of the allylic ester **17**[54] and presumably decomposed upon warming to rt. In both cases, only the mono-substituted thiazole **18** resulting from the protonation of the carbon–metal bond at C4 was recovered after hydrolysis of the reaction mixture (Scheme 9).



Scheme 9. Attempts to form the C4–C14 bond.

These two initial unsuccessful attempts of introducing the side-chain at C4 by direct formation of the C4–C14 bond, although not optimized, led us to consider an alternative plan in which the 2,5-hexadienyl side-chain at C4 would be installed by the formation of the C14–C15 bond. This strategy required at first the homologation of the substituted 4-bromothiazole **14** and this operation was envisaged by the introduction of a formyl group at C4.

The substituted 4-bromothiazole **14** was subjected to lithium–bromine exchange with *tert*-butyllithium or *n*-butyllithium[51] but these reactions were initially inadverently carried out in THF as the solvent. In this case, subsequent formylation with DMF afforded mixtures of products containing the desired disubstituted thiazole **19** formylated at C4 as the minor component, the mono-substituted thiazole **18**, the substituted 4-bromo-5-formylthiazole **20** as well as the corresponding regioisomeric thiazole **21** formylated at C5. The relative proportions of these compounds differ considerably from one experience to another and were presumably affected by the rate of addition of alkyllithium as well as the reaction time at −78 °C before DMF was introduced, although the aldehyde **21** (formyl group at C5) was clearly the major component (43–72% isolated yields) (Scheme 10).

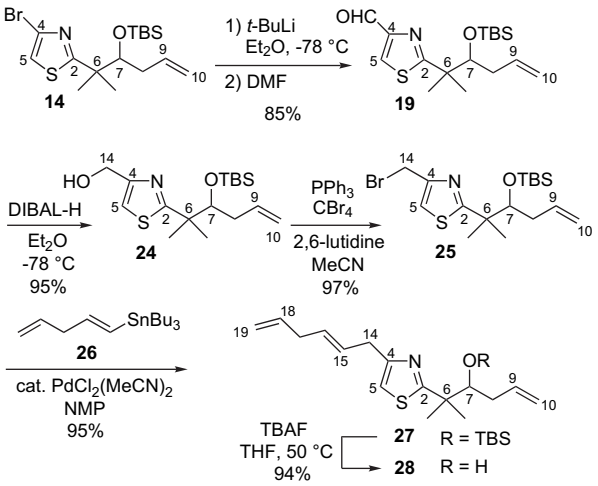


Scheme 10. Lithium–bromine exchange of **14** carried out in THF.

Indeed, the order of acidity of the hydrogens on thiazoles is H2>H5>H4 and it is well-known that thiazol-4-yl metals are destabilized by the adjacent nitrogen atom's lone-pair effect, as in the imidazole series.[55] Thus, as the organolithium **15a** was gradually generated by lithium–bromine exchange of **14**, it may abstract a hydrogen at C5 on the parent bromide **14** and generate the protonated compound **18**, as well as the substituted 4-bromothiazol-5-yllithium **22**, which accounted for the formation of **20** after addition of DMF. The small amount of **18** generated during this initiation phase is then able to subsequently catalyze the equilibration of the organolithium **15a** at C4 to the thermodynamically more stable regioisomeric thiazol-5-yllithium **23** (Scheme 10).[56] This mechanism shares some similarities with the so-called 'halogen dance reaction' observed when 2-trimethylsilyl-4-bromothiazole was deprotonated with LDA, the propagation being ensured in this case by a 4,5-dibrominated thiazole preferentially undergoing Br–Li exchange at C5.[57] However, such an equilibration does not take place in ether as the organolithium **15a** displays a lower basic character in this less-coordinating solvent compared to THF. In fact, examination of literature results indicates that halogen–metal exchange reactions on 4-halothiazoles have been generally carried out in ether.[51]

Thus, the substituted 4-bromothiazole **14** underwent a clean lithium–bromine exchange with *tert*-butyllithium in ether at −78 °C[51] and subsequent formylation with DMF cleanly afforded aldehyde **19** (85%). Subsequent reduction (DIBAL-H, Et_2O, −78 °C) afforded the primary alcohol **24** (95%), which was treated with PPh_3 and CBr_4 in THF.[9] Under these conditions, the corresponding bromide **25** was

obtained in modest yield (52%) due to a slow and incomplete reaction, despite the use of a large excess of reagents. When carried out in acetonitrile in the presence of 2,6-lutidine,[58] bromination of **20** proceeded considerably faster and led to **25** in excellent yield (97%). With the aim of installing the unsaturated side-chain of the originally proposed structure of mycothiazole at C4 in a single operation, the bromide **25** was subjected to a Stille coupling with (*E*)-1-tributylstannylpenta-1,4-diene **26**[59] in the presence of a catalytic amount of $PdCl_2(MeCN)_2$ in *N*-methylpyrrolidinone (NMP)[9] and the 1,4-diene **27** was obtained in 95% yield. Subsequent deprotection of the hindered hydroxyl group at C7 with TBAF in THF at 50 °C finally afforded the homoallylic alcohol **28** (94%) (Scheme 11).



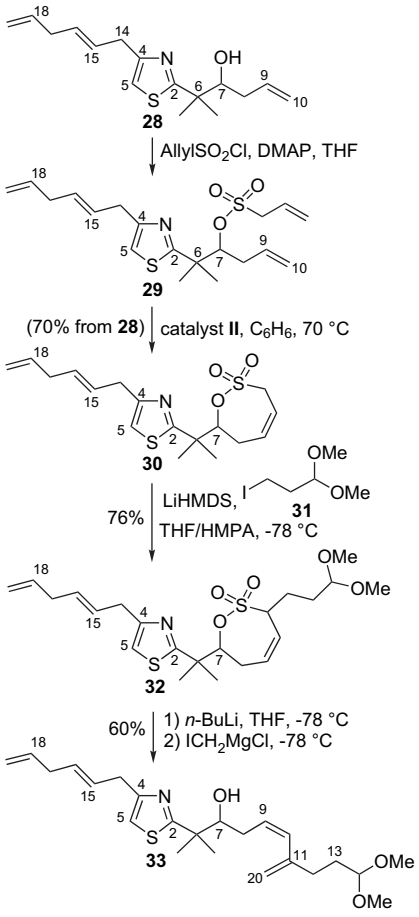
Scheme 11. Synthesis of the C10–C19 subunit.

With compound **28** in hand, the formation of the conjugated (*Z*)-dienol moiety (C9–C13 subunit), that constitutes the pivotal stage of our synthetic approach toward mycothiazole, could be tested.

4.4. Formation of the conjugated (*Z*)-dienol moiety

Following our synthetic plan, the elaboration of the conjugated (*Z*)-dienol moiety of mycothiazole from the homoallylic alcohol **28** required at first the preparation of the key intermediate unsaturated sultone **30**. The sterically hindered secondary alcohol **28** did not react with allylsulfonyl chloride in the presence of triethylamine in THF at rt, but switching to DMAP as the base enabled the synthesis of intermediate sulfonate **29**. The latter compound was not purified and underwent RCM by treatment with catalyst **II** (C_6H_6, 70 °C). Under these conditions, the unsaturated sultone **30** was obtained in 70% yield (two steps from alcohol **28**).

The next task was to alkylate the unsaturated sultone **30** with an appropriate electrophile, precursor of the (*N*-carbomethoxyamino)ethyl substituent (C12–C13) of mycothiazole. We selected the readily available 1,1-dimethoxy-3-iodopropane **31**[60] as the alkylating agent since the acetal moiety could then be deprotected to the aldehyde and the latter could be oxidized to the carboxylic acid required for the subsequent Schmidt reaction. The alkylation of sultone **30** with the functionalized alkyl iodide **31** turned out to be difficult to achieve since dialkylation was often observed as a side-reaction. After optimization, it was discovered that addition of LiHMDS to a mixture of sultone **30** and iodide **31** in the presence of HMPA (THF, −78 °C) cleanly afforded monoalkylated sultone **32** (76%) as a 1:1 mixture of diastereomers.[61] The sultone **32** was then efficiently deprotonated with *n*-butyllithium in THF at −78 °C and subsequent addition of ICH_2MgCl provided the desired conjugated (*Z*)-dienol **33** in 60% yield (Scheme 12).



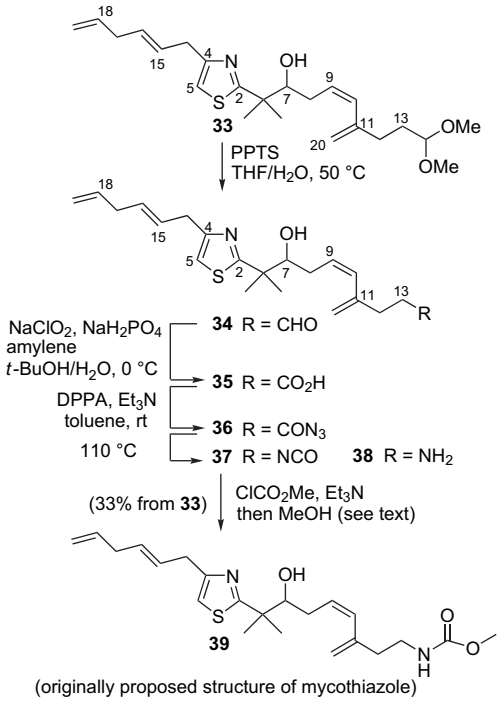
Scheme 12. Elaboration of the homoallylic conjugated (*Z*)-dienol.

Having successfully accomplished the key transformation of our synthesis, only functional group manipulations were required in order to complete the total synthesis of the originally proposed structure of mycothiazole.

4.5. Completion of the synthesis of the originally proposed structure of mycothiazole

Hydrolysis of the dimethyl acetal in compound **33** (PPTS, THF/H_2O, 50 °C) quantitatively afforded aldehyde **34**, which was not purified but directly chemoselectively oxidized by $NaClO_2$ in the presence of amylene and excess NaH_2PO_4 in *t*-BuOH/H_2O.[62] However, upon completion of the oxidation, acidification of the reaction mixture with hydrochloric acid should be absolutely avoided as the decomposition of the resulting carboxylic acid **35** occurred. This extremely sensitive compound could be in fact directly extracted from the reaction mixture with EtOAc and immediately treated with diphenylphosphoryl azide (DPPA) and Et_3N in toluene.[63] After formation of the acylazide **36**, the

reaction mixture was heated at reflux in order to induce Curtius rearrangement to the corresponding isocyanate **37**. As the latter was apparently not readily converted into the proposed structure of mycothiazole when MeOH was added to the reaction mixture at reflux, we initially thought that **37** had probably accidentally hydrolyzed to amine **38**. However, the compound obtained after purification by preparative TLC on silica gel did not react with $ClCO_2Me$ in the presence of Et_3N. This result suggested that the rather robust isocyanate **37** had been isolated and therefore, the reaction mixture was treated with an excess of MeOH. Under these conditions, a surprisingly smooth methanolysis took place,[64] which produced compound **39** in 33% overall yield from dimethyl acetal **33** (four steps) (Scheme 13).



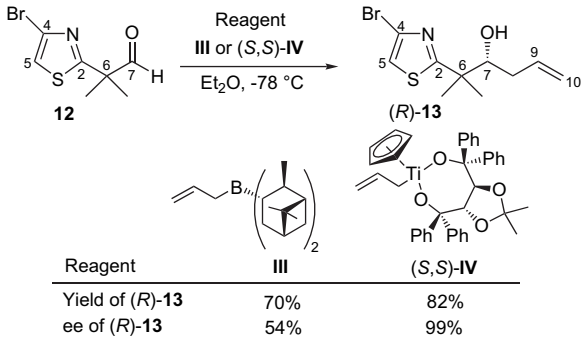
Scheme 13. Completion of the synthesis of the originally proposed structure of mycothiazole.

Although the ^1H NMR data of compound **39** were in good agreement with those previously reported for natural mycothiazole,[6] as well as for the synthetic material corresponding to the originally proposed structure [compound (−)-**39**],[9] the ^{13}C NMR data were only in perfect agreement with those of the synthetic material. Indeed, some discrepancies were noted between the chemical shifts of some carbons of the 2,5-hexadienyl side-chain at C4 and those reported for the natural product. In particular, signals corresponding to C14 and C17 (present numbering system) in compound **39** appeared significantly upfield. Differences between the observed analytical data of mycothiazole and the synthetic sample were initially attributed to the lability of the natural product,[6,9] but recently the configuration of the C14–C15 disubstituted double bond was reassigned to (*Z*) on the basis of a 600 MHz ^1H NMR spectrum and NOE experiments.[65]

We had thus completed a racemic synthesis of the originally proposed structure of mycothiazole and not of the natural product itself.[66]

4.6. Formal enantioselective approach

As mycothiazole contains a single stereocenter at C7, we investigated a formal enantioselective approach relying on the preparation of the optically active alcohol (*R*)-**13**. Thus, addition of the chiral allylic borane **III** [generated from allylmagnesium bromide and (+)-*B*-chlorodiisopinocampheyl borane ((+)-DIPCl)][67] to aldehyde **12** in ether at −78 °C led to the corresponding secondary homoallylic alcohol (*R*)-**13** (70%) with low optical purity (ee=54%). Although this result could have been probably optimized by modifying the reaction conditions, an enantioselective allyltitanation of aldehyde **12** with the allyltitanium complex (*S*,*S*)-**IV** [generated from allylmagnesium chloride and the corresponding ((*S*,*S*)-TADDOL)CpTiCl complex][68] in THF/Et_2O at −78 °C afforded (*R*)-**13** in much better yield and enantiomeric excess (82% yield, ee=99%) (Scheme 14).



Scheme 14. Formal enantioselective approach.

The (*R*) configuration of the homoallylic alcohol **13** obtained from these reactions was attributed on the basis of the known face-selectivities of the chiral allylating reagents and particularly the allyltitanium complex **IV**, which displays an extremely high face-selectivity regardless of the nature of the aldehydes.[68]

5. Conclusion

In summary, unsaturated sultones have been generated from primary or secondary unsaturated alcohols by RCM of the corresponding unsaturated sulfonates. The β,γ-unsaturated seven-membered ring sultones have been converted to homoallylic conjugated (*Z*)-dienols by sequential metalation and electrophilic trapping, first with an alkyl halide and then with the carbenoid ICH_2MgCl. This methodology has been applied to the synthesis of originally proposed structure of (±)-mycothiazole, which has been achieved in 18 steps from 2,4-dibromothiazole with an overall yield of 5%. The side-chain at C2 was introduced in a stepwise fashion by using a chemoselective prenylation, an aldehyde allylation, a chain-extension of a homoallylic alcohol to a conjugated (*Z*)-dienol, proceeding through an intermediate unsaturated sultone, and a Curtius rearrangement. The installation of the side-chain at C4 was based on a one carbon homologation followed by a Stille coupling. A formal enantioselective approach has also been demonstrated with the preparation of the secondary homoallylic alcohol **13** in high enantiomeric purity (ee=99%). In principle, we could effectively access to mycothiazole by a similar strategy described herein, using

(*Z*)-1-tributylstannylpenta-1,4-diene[69] instead of its (*E*) geometric isomer in Stille coupling that served to elaborate the 2,5-hexadienyl side-chain at the C4 position of the thiazole ring.

6. Experimental

6.1. General procedures

IR spectra were recorded on a Perkin–Elmer 298. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ and data were reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet or overlap of nonequivalent resonances), integration. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ and data were reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s=quaternary C, d=CH, t=CH_2, q=CH_3). THF and diethyl ether were distilled from sodium/benzophenone. CH_2Cl_2, benzene, toluene, Et_3N, NMP, *i*-Pr_2NEt, DMF, and HMPA were distilled from CaH_2. Other reagents were obtained from commercial suppliers and used as received. TLC was performed on silica gel plates visualized either with a UV lamp (254 nm), or by using solutions of *p*-anisaldehyde/sulfuric acid/acetic acid in EtOH or $KMnO_4/K_2CO_3$ in water followed by heating. Flash chromatography was performed on silica gel (230–400 mesh).

6.2. Synthesis of unsaturated sultones by RCM

6.2.1. Synthesis of unsaturated sulfonates derived from primary alcohols.

6.2.1.1. General procedure. To a solution of an unsaturated primary alcohol (1.0–1.1 equiv) and Et_3N (1.1–1.2 equiv) in CH_2Cl_2 (1 M) at 0 °C was added dropwise a solution of an unsaturated sulfonyl chloride (1.0 equiv) in CH_2Cl_2 (1 M). After 0.5 to 1 h at rt, the reaction mixture was diluted with pentane and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel.

6.2.1.2. Allyl vinylsulfonate (1a). This compound was prepared from allyl alcohol (300 μL, 4.35 mmol, 1.1 equiv), Et_3N (610 μL, 4.35 mmol, 1.1 equiv), and vinylsulfonyl chloride (500 mg, 3.95 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography, (petroleum ether/EtOAc 80:20), 150 mg (40%) of **1a** were obtained as a colorless oil; IR 3060, 1650, 1610, 1360, 1175, 940 (br), 920, 845, 810, 740 cm^{-1}; ^{1}H NMR δ 6.52 (dd, *J*=16.5, 9.5 Hz, 1H), 6.37 (d, *J*=16.5 Hz, 1H), 6.12 (d, *J*=9.5 Hz, 1H), 5.89 (ddt, *J*=17.3, 10.3, 5.9 Hz, 1H), 5.38 (dq, *J*=17.3, 1.5 Hz, 1H), 5.31 (dq, *J*=10.3, 1.5 Hz, 1H), 4.57 (dt, *J*=5.9, 1.5 Hz, 2H); ^{13}C NMR δ 132.5 (d), 130.2 (t), 130.1 (d), 120.5 (t), 71.0 (t).

6.2.1.3. But-3-enyl vinylsulfonate (1b). This compound was prepared from but-3-en-1-ol (360 μL, 4.15 mmol, 1.05 equiv), Et_3N (610 μL, 4.35 mmol, 1.1 equiv), and vinylsulfonyl chloride (500 mg, 3.95 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography (petroleum ether/EtOAc 80:20), 650 mg (87%) of **1b** were obtained as a colorless oil; IR 3060, 1640, 1360, 1175, 960, 910, 835, 800, 735 cm^{-1}; ^{1}H NMR δ 6.50 (dd, *J*=16.6, 9.9 Hz, 1H), 6.34 (d, *J*=16.6 Hz, 1H), 6.11 (d, *J*=9.9 Hz, 1H), 5.71 (ddt, *J*=16.9, 10.3, 6.6 Hz, 1H), 5.15–5.04 (m, 2H), 4.09 (t, *J*=6.6 Hz, 2H), 2.43 (apparent q, *J*=6.6 Hz, 2H); ^{13}C NMR δ 132.3 (d), 132.2 (d), 130.2 (t), 118.2 (t), 69.7 (t), 33.0 (t); EIMS *m/z* (relative intensity) 121 (M−$C_3H_5^{\ddagger}$, 31), 91 (100), 55 (13), 54 (69). Anal. Calcd for $C_6H_{10}O_3S$: C, 44.43; H, 6.21. Found: C, 44.26; H, 6.35.

6.2.1.4. Allyl allylsulfonate (1c). This compound was prepared from allyl alcohol (380 μL, 5.60 mmol, 1.05 equiv), Et_3N (820 μL, 5.90 mmol, 1.1 equiv), and allylsulfonyl chloride (750 mg, 5.30 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography (petroleum ether/EtOAc 70:30), 660 mg (76%) of **1c** were obtained as a colorless oil; IR 1640, 1355, 1160, 960, 940, 925, 880, 825 cm^{-1}; ^{1}H NMR δ 6.01–5.82 (m, 2H), 5.50–5.43 (m, 2H), 5.45 (dq, *J*=17.0, 1.5 Hz, 1H), 5.36 (dq, *J*=10.3, 1.1 Hz, 1H), 4.71 (dt, *J*=5.9, 1.5 Hz, 2H), 3.86 (dt, *J*=7.4, 1.1 Hz, 2H); ^{13}C NMR δ 130.4 (d), 124.3 (t and d, 2C), 120.4 (t), 70.9 (t), 55.0 (t); EIMS *m/z* (relative intensity) 121 (M−$C_3H_5^{\ddagger}$, 3), 106 (21), 97 (8), 83 (29), 81 (16), 80 (21), 79 (14), 69 (59), 67 (57), 57 (80), 56 (44), 55 (64), 54 (100). Anal. Calcd for $C_6H_{10}O_3S$: C, 44.43; H, 6.21. Found: C, 44.45; H, 6.24.

6.2.1.5. But-3-enyl allylsulfonate (1d). This compound was prepared from but-3-en-1-ol (485 μL, 5.60 mmol, 1.05 equiv), Et_3N (825 μL, 5.86 mmol, 1.1 equiv), and allylsulfonyl chloride (750 mg, 5.33 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography (petroleum ether/EtOAc 75:25), 850 mg (90%) of **1d** were obtained as a colorless oil; IR 3080, 1640, 1360, 1170, 960, 910, 820, 740, 640 cm^{-1}; ^{1}H NMR δ 5.88 (ddt, *J*=16.2, 10.6, 7.3 Hz, 1H), 5.76 (ddt, *J*=17.2, 10.3, 6.6 Hz, 1H), 5.48–5.40 (m, 2H), 5.19–5.09 (m, 2H), 4.25 (t, *J*=6.6 Hz, 2H), 3.82 (dt, *J*=7.3, 1.5 Hz, 2H), 2.47 (apparent qt, *J*=6.6, 1.3 Hz, 2H); ^{13}C NMR δ 132.3 (d), 124.3 (d), 124.0 (t), 118.0 (t), 69.4 (t), 54.3 (t), 33.2 (t). Anal. Calcd for $C_7H_{12}O_3S$: C, 47.71; H, 6.86. Found: C, 47.81; H, 6.94.

6.2.1.6. Pent-4-enyl allylsulfonate (1e). This compound was prepared from pent-4-en-1-ol (400 μL, 3.92 mmol, 1.1 equiv), Et_3N (600 μL, 4.27 mmol, 1.2 equiv), and allylsulfonyl chloride (500 mg, 3.56 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography (petroleum ether/EtOAc 90:10 to 80:20), 560 mg (83%) of **1e** were obtained as a colorless oil; IR 3070, 1640, 1350, 1160, 970, 920, 830, 640 cm^{-1}; ^{1}H NMR δ 5.86 (ddt, *J*=16.9, 9.9, 7.3 Hz, 1H), 5.74 (ddt, *J*=16.9, 10.3, 6.6 Hz, 1H), 5.42 (dq, *J*=10.3, 1.5 Hz, 1H), 5.41 (dq, *J*=16.9, 1.5 Hz, 1H), 5.05–4.95 (m, 2H), 4.19 (t, *J*=6.6 Hz, 2H), 3.79 (dt, *J*=7.0, 1.1 Hz, 2H), 2.13 (m, 2H), 1.79 (m, 2H); ^{13}C NMR δ 136.5 (d), 124.4 (d), 124.1 (t), 115.7 (t), 69.9 (t), 54.5 (t), 29.2 (t), 28.2 (t). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.42. Found: C, 50.36; H, 7.48.

6.2.1.7. But-4-enyl but-3-ene-1-sulfonate (1f). This compound was prepared from but-3-en-1-ol (0.85 mL,

9.8 mmol, 1.0 equiv), Et_3N (1.5 mL, 11 mmol, 1.1 equiv), and (but-3-enyl)sulfonyl chloride (1.5 g, 9.8 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography (petroleum ether/EtOAc 70:30), 1.7 g (90%) of **1f** were obtained as a colorless oil; IR 3080, 1640, 1360, 1170, 1160, 955, 905, 825 cm^{-1}; ^1H NMR δ 5.84–5.67 (m, 2H), 5.16–5.04 (m, 4H), 4.20 (t, J=6.6 Hz, 2H), 3.15–3.09 (m, 2H), 2.58–2.49 (m, 2H), 2.49–2.40 (m, 2H); ^{13}C NMR δ 133.6 (d), 132.4 (d), 118.2 (t), 117.1 (t), 68.6 (t), 49.4 (t), 33.3 (t), 27.5 (t); EIMS m/z (relative intensity) 136 ($M-C_4H_6^+$, 0.5), 119 (6), 108 (3), 93 (4), 79 (3), 67 (5), 55 (100), 54 (80). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.41. Found: C, 50.20; H, 7.61.

6.2.2. Synthesis of unsaturated sultones derived from primary alcohols.

6.2.2.1. General procedure. To a degassed solution of an unsaturated sulfonate **1a–f** in C_6H_6 (0.05–0.01 M) (argon bubbling, 15 min) was added catalyst **I** or catalyst **II** (0.015–0.05 equiv) and the resulting solution was heated at 70 °C. After 0.5 to 3 h, the reaction mixture was cooled to rt, concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel.

6.2.2.2. 5*H*-[1,2]Oxathiole-2,2-dioxide (2a). This compound was prepared from **1a** (150 mg, 1.03 mmol) by using catalyst **II** (21 mg, 0.025 mmol, 0.025 equiv) in C_6H_6 (33 mL) at 70 °C for 1 h. After purification by flash chromatography (petroleum ether/EtOAc 70:30), 121 mg (100%) of **2a** were obtained as pale brown solid; mp 85 °C; IR 1610, 1345, 1180, 1090, 1000, 920, 870, 750 cm^{-1}; ^1H NMR δ 7.03 (dt, J=6.6, 2.0 Hz, 1H), 6.81 (dt, J=6.6, 2.4 Hz, 1H), 5.11 (dd, J=2.4, 2.0 Hz, 2H); ^{13}C NMR δ 136.8 (d), 124.3 (d), 72.2 (t); EIMS m/z (relative intensity) 120 (M^+, 40), 91 (24), 66 (100), 65 (28), 56 (10), 55 (11). Anal. Calcd for $C_3H_4O_3S$: C, 29.99; H, 3.36. Found: C, 30.10; H, 3.47.

6.2.2.3. 5,6-Dihydro-[1,2]oxathiine-2,2-dioxide (2b). This compound was prepared from **1b** (400 mg, 2.47 mmol) by using catalyst **II** (42 mg, 0.049 mmol, 0.02 equiv) in C_6H_6 (50 mL) at 70 °C for 3 h. After purification by flash chromatography (petroleum ether/EtOAc 60:40), 300 mg (90%) of **2b** were obtained as pale brown solid; mp 90 °C; IR 1620, 1355, 1345, 1180, 970, 920, 860, 825 cm^{-1}; ^1H NMR δ 6.60–6.49 (m, 2H), 4.79 (t, J=5.7 Hz, 2H), 2.57–2.51 (m, 2H); ^{13}C NMR δ 137.0 (d), 126.7 (d), 69.4 (t), 24.4 (t); EIMS m/z (relative intensity) 134 (M^+, 50), 104 (100), 76 (23), 70 (15), 69 (39), 68 (11), 55 (100). Anal. Calcd for $C_4H_6O_3S$: C, 35.81; H, 4.51. Found: C, 35.86; H, 4.65.

6.2.2.4. 3,6-Dihydro-[1,2]oxathiine-2,2-dioxide (2c). This compound was prepared from **1c** (400 mg, 2.50 mmol) by using catalyst **II** (52 mg, 0.06 mmol, 0.025 equiv) in C_6H_6 (82 mL) for 3 h at 70 °C. After purification by flash chromatography (petroleum ether/EtOAc 60:40), 335 mg (99%) of **2c** were obtained as a waxy beige solid; mp<50 °C; IR 1640, 1360, 1170, 1130, 1030, 940, 885, 860, 800, 720 cm^{-1}; ^1H NMR δ 5.95–5.88 (m, 1H), 5.84–5.77 (m, 1H), 5.07–5.03 (m, 2H), 3.82–3.78 (m, 2H); ^{13}C NMR δ 123.6 (d), 119.0 (d), 72.5 (t), 46.6 (t); EIMS m/z (relative intensity) 134 (M^+, 1), 70 ($M-SO_2^+$, 100), 69 (33), 65 (10), 54 (22), 53 (13); HRMS (CI^+, CH_4) calcd for $C_4H_7O_3S$ ($M+H^+$): 135.0116. Found: 135.0118.

6.2.2.5. 2,7-3*H*-Dihydro-[1,2]oxathiepine-2,2-dioxide (2d). This compound was prepared from **1d** (100 mg, 0.568 mmol) by using catalyst **II** (24 mg, 0.028 mmol, 0.02 equiv) in C_6H_6 (57 mL) for 2 h at 70 °C. After purification by flash chromatography (petroleum ether/EtOAc 75:25), 84 mg (100%) of **2d** were obtained as a pale brown solid; mp 78 °C; IR 1650, 1370, 1270, 1160, 975, 910, 880, 840, 805, 740 cm^{-1}; ^1H NMR δ 6.25–6.16 (m, 1H), 5.80–5.71 (m, 1H), 4.52–4.48 (m, 2H), 4.02 (apparent br d, J=6.2 Hz, 2H), 2.65 (m, 2H); ^{13}C NMR δ 134.8 (d), 119.4 (d), 72.5 (t), 51.1 (t), 28.8 (t); EIMS m/z (relative intensity) 148 (M^+, 1), 83 (4), 67 (100), 55 (18), 54 (87), 53 (14). Anal. Calcd for $C_5H_8O_3S$: C, 40.53; H, 5.44. Found: C, 40.61; H, 5.60.

6.2.2.6. 3,4,7,8-Tetrahydro-[1,2]oxathiocine-2,2-dioxide (2e). This compound was prepared from **1e** (150 mg, 0.788 mmol) by using catalyst **I** (33 mg, 0.040 mmol, 0.05 equiv) in C_6H_6 (75 mL) for 3 h at 70 °C. After purification by flash chromatography (petroleum ether/ether 95:5 to 90:10), 120 mg (94%) of **2e** were obtained as a pale brown waxy solid; mp<50 °C; IR 1650, 1380, 1275, 1265, 1250, 1150, 1060, 990, 945, 930, 820, 790, 760 cm^{-1}; ^1H NMR δ 6.03–5.93 (m, 1H), 5.77–5.69 (m, 1H), 4.36 (t, J=5.9 Hz, 2H), 3.91 (apparent dd, J=7.7, 0.8 Hz, 2H), 2.42–2.32 (m, 2H), 1.99–1.91 (m, 2H); ^{13}C NMR δ 136.6 (d), 118.6 (d), 71.0 (t), 48.5 (t), 26.6 (t), 22.9 (t); EIMS m/z (relative intensity) 162 (M^+, 3), 98 ($M-SO_2^+$, 74), 97 (52), 80 (35), 67 (87), 57 (31), 56 (100), 53 (32); HRMS (CI^+, CH_4) calcd for $C_6H_{11}O_3S$ ($M+H^+$): 163.0429. Found: 163.0427.

6.2.2.7. 3,4,7,8-Tetrahydro-[1,2]oxathiocine-2,2-dioxide (2f). This compound was prepared from **1f** (650 mg, 3.42 mmol) by using catalyst **I** (140 mg, 0.170 mmol, 0.05 equiv) in C_6H_6 (350 mL) for 4 h at 70 °C. After purification by flash chromatography (petroleum ether/ether 50:50), 550 mg (99%) of **2f** were obtained as a pale brown solid; mp 62 °C; IR 1350, 1165, 1010, 980, 965, 920, 880, 770, 740 cm^{-1}; ^1H NMR δ 5.97–5.79 (m, 2H), 4.25 (t, J=5.9 Hz, 2H), 3.31–3.27 (m, 2H), 2.63–2.52 (m, 4H); ^{13}C NMR δ 130.4 (d), 127.8 (d), 68.9 (t), 53.7 (t), 26.9 (t), 20.8 (t); EIMS m/z (relative intensity) 162 (M^+, 2), 80 (66), 79 (13), 68 (78), 67 (100), 53 (26). Anal. Calcd for $C_6H_{10}O_3S$: C, 44.43; H, 6.21. Found: C, 44.55; H, 6.30.

6.2.3. Preparation of sultone 2g from 1d.

6.2.3.1. But-3-enyl but-1-ene-3-sulfonate (1g). To a solution of sulfonate **1d** (1.0 g, 5.7 mmol) in THF (30 mL) at −78 °C was added *n*-BuLi (2.3 mL, 2.5 M in hexanes, 5.7 mmol, 1.0 equiv). After 1.5 h at −78 °C, CH_3I (1.1 mL, 17 mmol, 3.0 equiv) was added. After a further 1.5 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. After purification by flash chromatography (petroleum ether/EtOAc 80:20), 900 mg (84%) of **1g** were obtained as a colorless oil; IR 3080, 1640, 1350, 1170, 960, 910, 820, 790, 650 cm^{-1}; ^1H NMR δ 5.88 (ddd, J=17.3, 10.3, 7.7 Hz, 1H), 5.74

(ddt, J=17.0, 10.0, 6.6 Hz, 1H), 5.38 (dt, J=17.0, 1.1 Hz, 1H), 5.37 (dt, J=10.0, 1.1 Hz, 1H), 5.16–5.07 (m, 2H), 4.22 (t, J=6.6 Hz, 2H), 3.80 (m, 1H), 2.44 (apparent qt, J=6.6, 1.5 Hz, 2H), 1.50 (d, J=7.0 Hz, 3H); ^{13}C NMR δ 132.4 (d), 130.9 (d), 121.3 (t), 118.1 (t), 69.3 (t), 60.1 (d), 33.5 (t), 14.2 (q); EIMS m/z (relative intensity) 148 (M^+, 0.1), 136 (4), 81 (2), 71 (3), 56 (5), 55 (100), 54 (22), 53 (6). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.42. Found: C, 50.15; H, 7.63.

6.2.3.2. 3-Methyl-6,7-dihydro-3*H*-[1,2]oxathiepine-2,2-dioxide (2g). To a solution of **1g** (900 mg, 4.74 mmol) in C_6H_6 (100 mL) was added catalyst **II** (10 mg, 0.12 mmol, 0.025 equiv). After 2 h at 70 °C, the reaction mixture was cooled to rt, concentrated under reduced pressure, and the crude material was purified by flash chromatography (petroleum ether/ether 70:30) to afford 450 mg (60%) of **2g** as a colorless oil; IR 3030, 1460, 1355, 1275, 1170, 1005, 975, 950, 890, 840, 780, 750 cm^{-1}; ^{1}H NMR δ 6.11 (dddd, J=11.2, 7.7, 5.9, 1.8 Hz, 1H), 5.55 (ddd, J=11.2, 5.1, 1.8 Hz, 1H), 4.60–4.53 (m, 1H), 4.46–4.39 (m, 1H), 4.19–4.09 (m, 1H), 2.73–2.60 (m, 1H), 2.52–2.42 (m, 1H), 1.60 (d, J=7.4 Hz, 3H); ^{13}C NMR δ 132.8 (d), 127.5 (d), 72.7 (t), 57.3 (d), 28.4 (t), 15.3 (q); EIMS m/z (relative intensity) 162 (M^+, 0.5), 120 (10), 97 (17), 83 (36), 81 (28), 80 (16), 69 (18), 68 (100), 67 (60), 55 (16), 53 (24).

6.2.4. Synthesis of unsaturated sultones derived from secondary alcohols.

6.2.4.1. General procedure. To a solution of the unsaturated secondary alcohols **1h–l** and Et_3N (1.1–2.0 equiv) in THF at −15 °C was added dropwise a solution of the appropriate sulfonyl chloride (1.1–1.5 equiv) in THF. After 1 h at −15 °C, an additional quantity of sulfonyl chloride (0.2–0.5 equiv) was generally added to ensure complete conversion. After 1 h at −15 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was filtered through a short plug of silica gel (Et_2O) and the filtrate was evaporated under reduced pressure. The crude sulfonates **2h–l** were dissolved in benzene (0.08–0.06 M) and to the resulting degassed solution (argon bubbling, 15 min) was added catalyst **II** (0.01–0.05 equiv). After 1 h at 70 °C, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel.

6.2.4.2. 6-[(3-Benzyloxy)propyl]-5,6-dihydro-[1,2]oxathiine-2,2-dioxide (2h). This compound was synthesized according to the general procedure from 7-benzyloxyhept-1-en-4-ol (2.0 g, 9.0 mmol), Et_3N (1.5 mL, 11 mmol, 1.2 equiv), and vinylsulfonyl chloride (1.40+0.28 g, 11.0+2.2 mmol, 1.2+0.2 equiv) in THF (30 mL). The crude sulfonate was then treated with catalyst **II** (55 mg, 0.070 mmol, 0.011 equiv) in C_6H_6 (150 mL). After purification by flash chromatography (petroleum ether/EtOAc 70:30), 1.60 g (65%) of **2h** were obtained as a pale brown waxy solid; IR 3030, 1615, 1330, 1170, 1150, 1090, 880, 820, 735, 700 cm^{-1}; ^{1}H NMR δ 7.40–7.26 (m, 5H), 6.54 (ddd, J=10.7, 2.6, 1.3 Hz, 1H), 6.47 (ddd, J=10.7, 4.4, 2.3 Hz, 1H), 4.98 (m, 1H), 4.51 (s, 2H), 3.60–3.48 (m, 2H), 2.51–2.29 (m, 2H), 1.97–1.68 (m, 4H); ^{13}C NMR δ 138.2 (s), 136.6 (d), 128.3 (d, 2C), 127.5 (d, 3C), 126.0 (d), 82.0 (d), 72.8 (t), 70.0 (t), 31.5 (t), 30.1 (t), 24.7 (t); EIMS m/z (relative intensity) 282 (M^+, 4), 173 (4), 161 (5), 107 (50), 105 (12), 91 (100), 79 (12), 65 (10). Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43. Found: C, 59.39; H, 6.59.

6.2.4.3. Ethyl (2,2-dioxo-5,6-dihydro-2λ^6-[1,2]oxathiine-6-yl)formate (2i). This compound was synthesized according to the general procedure from ethyl 2-hydroxypent-4-enoate (1.75 g, 12.2 mmol), Et_3N (1.88 mL, 13.4 mmol, 1.1 equiv), and vinylsulfonyl chloride (1.69+0.31 g, 13.4+2.4 mmol, 1.1+0.2 equiv) in THF (30 mL). The crude sulfonate was then treated with catalyst **II** (200 mg, 0.235 mmol, 0.02 equiv) in C_6H_6 (120 mL). After purification by flash chromatography (petroleum ether/EtOAc 80:20), 1.35 g (54%) of **2i** were obtained as a pale brown oil; IR 3060, 1750, 1360, 1330, 1305, 1230, 1180, 1155, 1030, 950, 910, 835, 730, 685 cm^{-1}; ^{1}H NMR δ 6.64–6.51 (m, 2H), 5.36 (dd, J=9.2, 6.6 Hz, 1H), 4.29 (q, J=7.2 Hz, 2H), 2.73 (m, 2H), 1.31 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 165.7 (s), 135.9 (d), 126.2 (d), 76.2 (d), 62.5 (t), 27.0 (t), 13.9 (q); EIMS m/z (relative intensity) 178 ($M-Et^+$, 2), 161 ($M-OEt^+$, 4), 134 (12), 133 ($M-CO_2Et^+$, 100), 125 (33), 115 (10), 106 (6), 97 (45), 89 (22), 87 (12), 85 (11), 69 (22), 68 (29), 57 (9); HRMS (CI^+, CH_4) calcd for $C_7H_{11}O_5S$ ($M+H^+$): 207.0327. Found: 207.0327.

6.2.4.4. (2,2-Dioxo-3,6-dihydro-2*H*-2λ^6-[1,2]oxathiine-6-yl)methyl-2,2-dimethyl propanoate (2j). This compound was synthesized according to the general procedure from 2-hydroxybut-3-enyl 2,2-dimethyl propanoate (2.10 g, 12.2 mmol), Et_3N (3.4 mL, 24.4 mmol, 2.0 equiv), and allylsulfonyl chloride (1.9+0.34 g, 13.5+2.4 mmol, 1.1+0.2 equiv) in THF (30 mL). The crude sulfonate was then treated with catalyst **II** (49 mg, 0.057 mmol, 0.05 equiv) in C_6H_6 (120 mL). After purification by flash chromatography (petroleum ether/EtOAc 80:20), 2.24 g (74%) of **2j** were obtained as a colorless oil; IR 1730, 1625, 1480, 1360, 1280, 1160, 915, 805, 770, 740, 680, 630 cm^{-1}; ^{1}H NMR δ 5.94–5.81 (m, 2H), 5.38 (m, 1H), 4.43 (dd, J=12.3, 6.0 Hz, 1H), 4.29 (dd, J=12.3, 3.5 Hz, 1H), 3.91–3.80 (m, 1H), 3.78–3.66 (m, 1H), 1.20 (s, 9H); ^{13}C NMR δ 177.8 (s), 124.0 (d), 120.9 (d), 82.1 (d), 63.1 (t), 46.0 (t), 38.7 (s), 26.9 (q, 3C); EIMS m/z (relative intensity) 249 ($M+H^+$, 0.1), 233 ($M-Me^+$, 0.1), 218 (1), 146 ($M-t$-$BuCO_2H^+$, 14), 128 (5), 85 (31), 81 (6), 69 (12), 67 (9), 57 (100); HRMS (CI^+, CH_4) calcd for $C_{10}H_{17}O_5S$ ($M+H^+$): 249.0797. Found: 249.0798.

6.2.4.5. 6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2,2-dioxo-3,6-dihydro-2*H*-2λ^6-[1,2]oxathiine (2k). This compound was synthesized according to the general procedure from 1-(*tert*-butyldimethylsilyloxy)but-3-en-2-ol (1.6 g, 4.9 mmol), Et_3N (1.4 mL, 10 mmol, 2.05 equiv), and allylsulfonyl chloride (0.78+0.34 g, 5.5+2.5 mmol, 1.1+0.5 equiv) in THF (22 mL). The crude sulfonate was then treated with catalyst **II** (42 mg, 0.05 mmol, 0.01 equiv) in C_6H_6 (75 mL). After purification by flash chromatography (petroleum ether/EtOAc 90:10 to 85:15), 1.3 g (65%) of **2k** were obtained as a white solid; mp 106–108 °C; ^{1}H NMR δ 7.71–7.66 (m, 4H), 7.50–7.39 (m, 6H), 5.97–5.91 (m, 1H), 5.89–5.82 (m, 1H), 5.27 (m, 1H), 3.95 (dd, J=11.4,

5.1 Hz, 1H), 3.89 (dd, J=11.4, 5.1 Hz, 1H), 3.83 (m, 1H), 3.74–3.65 (m, 1H), 1.09 (s, 9H); ^{13}C NMR δ 135.4 (d, 4C), 132.6 (s, 2C), 129.9 (d, 2C), 127.7 (d, 4C), 125.4 (d), 119.7 (d), 84.3 (d), 64.1 (t), 46.2 (t), 26.6 (q, 3C), 19.1 (s); EIMS m/z (relative intensity) 266 (24, M−SO_2−$C_4H_8^+$), 265 (M−SO_2−t-Bu$^+$, 100), 247 (6), 237 (11), 199 (43), 197 (12), 187 (42), 183 (12), 181 (10). Anal. Calcd for $C_{21}H_{26}O_4SSi$: C, 62.65; H, 6.51. Found: C, 62.49; H, 6.68.

6.2.4.6. 7-[3-(Benzyloxy)propyl]-6,7-dihydro-3*H*-[1,2]oxathiepine-2,2-dioxide (2l). This compound was synthesized according to the general procedure from 7-benzyloxy-hept-1-en-3-ol (1.0 g, 4.5 mmol), Et_3N (1.3 mL, 9.2 mmol, 2.0 equiv), and allylsulfonyl chloride (1.0+0.34 g, 7.1+2.4 mmol, 1.5+0.5 equiv) in THF (21 mL). The crude sulfonate was treated with catalyst **II** (98 mg, 0.12 mmol, 0.025 equiv) in C_6H_6 (75 mL). After purification by flash chromatography (petroleum ether/EtOAc 70:30), 0.88 g (65%) of **2l** were obtained as a colorless oil; IR 3030, 1495, 1450, 1360, 1180, 1160, 1100, 965, 905, 820, 740, 705, 700 cm^{-1}; ^{1}H NMR δ 7.39–7.26 (m, 5H), 6.13 (dddd, J=11.0, 8.8, 4.8, 2.4 Hz, 1H), 5.74 (dddd, J=11.0, 8.1, 4.8, 2.6 Hz, 1H), 4.84–4.76 (m, 1H), 4.50 (s, 2H), 4.16–4.08 (m, 1H), 3.83 (dd, J=15.8, 8.5 Hz, 1H), 3.57–3.45 (m, 2H), 2.74–2.62 (m, 1H), 2.39 (ddd, apparent br d, J=16.6, 8.5, 1.1 Hz, 1H), 1.88–1.68 (m, 4H); ^{13}C NMR δ 138.3 (s), 133.9 (d), 128.3 (d, 2C), 127.5 (d, 2C), 127.4 (d), 119.3 (d), 85.1 (d), 72.8 (t), 69.1 (t), 50.5 (t), 34.2 (t), 32.2 (t), 25.2 (t); EIMS m/z (relative intensity) 296 (M$^+$, 3), 215 (M−SO_3−H$^+$, 16), 173 (4), 161 (4), 160 (4), 131 (4), 117 (3), 108 (11), 107 (46), 92 (16), 91 (10), 80 (12), 79 (17), 71 (20), 67 (11), 54 (10). Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.74; H, 6.94.

6.3. Synthesis of conjugated (*Z*)-dienols of type A

6.3.1. *trans*- and *cis*-2,4-Bis((1*Z*)-7-benzyloxy-4-hydroxy-hept-1-enyl)[1,3]dithietane-1,1,3,3-tetroxide (3). To a solution of i-Pr_2NH (0.14 mL, 1.0 mmol, 3.0 equiv) in THF (2 mL) at −78 °C was added n-BuLi (0.40 mL, 2.5 M in hexanes, 1.0 mmol, 3.0 equiv). After 15 min at 0 °C, the resulting LDA solution was cooled to −78 °C and a solution of sultone **2l** (100 mg, 0.337 mmol) in THF (2 mL) was added. After 1 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 60:40 to 50:50) to afford 55 mg (55%) of **3** as a colorless oil and as an apparent 60:40 mixture of diastereomers; IR 3400 (br), 3020, 1640, 1450, 1350, 1155, 1080, 845, 740, 700 cm^{-1}; MS (CI$^+$, NH_3) m/z (relative intensity) 610 (M+NH_4^+, 77), 548 (10), 482 (22), 431 (20), 252 (16), 196 (100), 141 (13), 102 (55).

Major diastereomer: ^{1}H NMR δ 7.38–7.25 (m, 10H), 6.70 (d, J=9.6 Hz, 2H), 6.27 (dd, J=11.0, 7.7 Hz, 2H), 5.89 (dd, apparent br t, J=11.0, 9.6 Hz, 2H), 4.51 (s, 4H), 3.70–3.61 (m, 2H), 3.55–3.44 (m, 4H), 3.16 (br s, 2H, OH), 2.33–2.22 (m, 4H), 1.78–1.45 (m, 8H); ^{13}C NMR δ 140.0 (d, 2C), 137.8 (s, 2C), 128.3 (d, 6C), 127.7 (d, 4C), 113.3 (d, 2C), 97.0 (d, 2C), 73.0 (t, 2C), 70.2 (d, 2C), 69.8 (t, 2C), 36.4 (t, 2C), 34.7 (t, 2C), 26.2 (t, 2C).

Minor diastereomer: ^{1}H NMR δ 7.38–7.25 (m, 10H), 6.45 (d, J=9.9 Hz, 2H), 6.25 (dd, J=10.7, 7.7 Hz, 2H), 6.06 (dd, apparent br t, J=10.7, 9.9 Hz, 2H), 4.51 (s, 4H), 3.70–3.61 (m, 2H), 3.55–3.44 (m, 4H), 3.16 (br s, 2H, OH), 2.33–2.22 (m, 4H), 1.78–1.45 (m, 8H); ^{13}C NMR δ 140.4 (d, 2C), 137.8 (s, 2C), 128.3 (d, 6C), 127.7 (d, 4C), 114.7 (d, 2C), 98.8 (d, 2C), 73.0 (t, 2C), 70.1 (d, 2C), 69.8 (t, 2C), 36.2 (t, 2C), 34.6 (t, 2C), 26.2 (t, 2C).

6.3.2. (3*R or *S**,7*S**)-7-[(3-Benzyloxy)propyl]-3-methyl-3*H*-[1,2]oxathiepine-2,2-dioxide (6).** To a solution of sultone **2l** (100 mg, 0.336 mmol) in THF (5 mL) at −78 °C was added n-BuLi (200 μL, 2.5 M in hexanes, 0.500 mmol, 1.5 equiv). After 1 h at −78 °C, CH_3I (84 μL, 1.34 mmol, 4.0 equiv) was added. After 15 min at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ether 80:20) to afford 87 mg (85%) of **6** as a colorless oil and as a single diastereomer (unassigned relative configuration); IR 3020, 1450, 1340, 1170, 1160, 1100, 945, 910, 810, 740, 700 cm^{-1}; ^{1}H NMR δ 7.39–7.26 (m, 5H), 5.92 (ddd, J=12.0, 7.7, 4.4 Hz, 1H), 5.69 (ddd, J=12.0, 7.0, 2.0 Hz, 1H), 4.82 (m, 1H), 4.50 (s, 2H), 3.97 (apparent quintet, J=7.2 Hz, 1H), 3.59–3.41 (m, 2H), 2.64 (m, 1H), 2.44–2.34 (m, 1H), 1.90–1.67 (m, 4H), 1.62 (d, J=7.4 Hz, 3H); ^{13}C NMR δ 138.3 (s), 130.8 (d), 128.2 (d, 2C), 127.5 (d, 2C), 127.4 (d), 125.6 (d), 83.6 (d), 72.8 (t), 69.1 (t), 56.3 (d), 34.3 (t), 32.1 (t), 25.3 (t), 14.9 (q); EIMS m/z (relative intensity) 310 (M$^+$, 2), 229 (M−SO_3H^+, 13), 160 (8), 123 (14), 107 (40), 95 (11), 94 (12), 93 (12), 92 (15), 91 (100), 81 (16), 79 (15), 71 (18), 68 (18), 67 (16), 65 (10).

6.3.3. 3-Methyl-6,7-dihydro-3*H*-[1,2]oxathiepine-2,2-dioxide (2g). To a solution of sultone **2d** (150 mg, 1.01 mmol) in THF (15 mL) at −78 °C, was added dropwise n-BuLi (425 μL, 2.5 M in hexanes, 1.06 mmol, 1.05 equiv). After 1 h at −78 °C, CH_3I (190 μL, 3.03 mmol, 3.0 equiv) was added. After 15 min at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ether 80:20) to afford 162 mg (92%) of **2g** as a colorless oil. This compound has previously been synthesized from sulfonate **1d** by methylation and subsequent RCM, see Section 6.2.3.

6.3.4. (3*R or *S**,7*R**)-3,7-Bis[(3-benzyloxy)propyl]-6,7-dihydro-3*H*-[1,2]oxathiepine-2,2-dioxide (7).** To a solution of sultone **2l** (150 mg, 0.507 mmol) in THF (10 mL) at −78 °C was added n-BuLi (250 μL, 2.5 M in hexanes, 0.625 mmol, 1.25 equiv). After 1 h at −78 °C, a solution of 3-benzyloxy-1-bromopropane (130 μL, 0.760 mmol, 1.5 equiv) and HMPA (350 μL, 2.03 mmol, 4.0 equiv) in THF (2 mL) was added dropwise. After 1.5 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ether

80:20 to 75:25) to afford 188 mg (84%) of **7** as a colorless oil and as a single diastereomer (unassigned relative configuration); IR 3030, 1495, 1450, 1360, 1160, 1100, 910, 740, 705, 690 cm^{-1}; ^1H NMR δ 7.89–7.28 (m, 10H), 5.96 (ddd, J=12.0, 7.5, 4.4 Hz, 1H), 5.68 (ddd, J=12.0, 7.5, 2.2 Hz, 1H), 4.80 (m, 1H), 4.49 (s, 4H), 3.92 (m, 1H), 3.57–3.47 (m, 4H), 2.68–2.56 (m, 1H), 2.44–2.22 (m, 2H), 2.18–2.04 (m, 1H), 1.88–1.68 (m, 6H); ^{13}C NMR δ 138.3 (s), 138.1 (s), 131.4 (d), 128.3 (d, 2C), 128.2 (d, 2C), 127.5 (d, 4C), 127.4 (d, 2C), 124.6 (d), 83.6 (d), 72.9 (t), 72.8 (t), 69.4 (t), 69.1 (t), 60.7 (d), 34.4 (t), 32.1 (t), 26.8 (t, 2C), 25.3 (t).

6.3.5. (6*Z*)-1-(Benzyloxy)nona-6,8-dien-4-ol (8). To a solution of sultone **2l** (157 mg, 0.531 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (320 μL, 2.5 M in hexanes, 0.796 mmol, 1.5 equiv). After 1 h at −78 °C, a solution of iodomethylmagnesium chloride [prepared from CH_2I_2 (150 μL, 1.86 mmol, 3.5 equiv) and *i*-PrMgCl (930 μL, 2 M in THF, 1.86 mmol, 3.5 equiv) in THF (3 mL), −78 °C, 1 h] was transferred via a cannula into the reaction mixture. After 1 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 80:20) to afford 79 mg (60%) of **8** as a colorless oil; IR 3400, 3030, 1495, 1450, 1365, 1270, 1205, 1095, 1030, 910, 740, 705 cm^{-1}; ^1H NMR δ 7.48–7.27 (m, 5H), 6.65 (dddd, J=16.9, 11.0, 10.3, 1.1 Hz, 1H), 6.16 (dd, apparent t, J=11.0 Hz, 1H), 5.53 (m, 1H), 5.24 (dd, J=16.9, 1.8 Hz, 1H), 5.15 (br d, J=10.3 Hz, 1H), 4.53 (s, 2H), 3.68 (m, 1H), 3.52 (t, J=5.9 Hz, 2H), 2.59 (br s, 1H, OH), 2.41–2.36 (m, 2H), 1.82–1.62 (m, 3H), 1.58–1.43 (m, 1H); ^{13}C NMR δ 138.1 (s), 132.0 (d), 131.6 (d), 128.3 (d, 2C), 128.1 (d), 127.6 (d, 2C), 127.5 (d), 117.7 (t), 72.9 (t), 71.1 (d), 70.3 (t), 35.6 (t), 34.0 (t), 26.1 (t).

6.3.6. (6*Z*)-1-Benzyloxy-8-methylnona-6,8-dien-4-ol (9). To a solution of sultone **6** (130 mg, 0.419 mmol) in THF (4 mL) at −78 °C was added *n*-BuLi (252 μL, 2.5 M in hexanes, 0.629 mmol, 1.5 equiv). After 1 h at −78 °C, a solution iodomethylmagnesium chloride [prepared from CH_2I_2 (120 μL, 1.46 mmol, 3.5 equiv) and *i*-PrMgCl (730 μL, 2M in THF 1.46 mmol, 3.5 equiv) in THF (3 mL), −78 °C, 1 h] was transferred via a cannula into the reaction mixture. After 1 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 85:15) to afford 58 mg (53%) of **9** as a colorless oil; IR 3400, 1595, 1580, 1490, 1450, 1360, 1275, 1205, 1175, 1100, 910, 740, 705 cm^{-1}; ^1H NMR δ 7.39–7.27 (m, 5H), 6.00 (dd, J=11.8, 1.1 Hz, 1H), 5.49 (dt, J=11.8, 7.4 Hz, 1H), 4.98 (br s, 1H), 4.89 (br s, 1H), 4.53 (s, 2H), 3.71–3.64 (m, 1H), 3.52 (t, J=5.9 Hz, 2H), 2.56–2.39 (m, 3H), 1.90 (s, 3H), 1.79–1.50 (m, 4H); ^{13}C NMR δ 141.4 (s), 138.1 (s), 133.1 (d), 128.3 (d, 2C), 127.6 (d, 2C), 127.5 (d), 127.1 (d), 115.6 (t), 72.9 (t), 71.5 (d), 70.3 (t), 36.4 (d), 34.1 (d), 26.1 (d), 23.2 (q); EIMS m/z (relative intensity) 260 (M^+, 1), 259 (45), 152 (16), 137 (37), 105 (100), 95 (22), 93 (12), 82 (53), 79 (17), 71 (15), 67 (32).

6.4. Total synthesis of the originally proposed structure of mycothiazole

6.4.1. Synthesis of the C4–C10 subunit.

6.4.1.1. 2,4-Dibromothiazole (10). A mixture of thiazolidine-2,4-dione (3.4 g, 29 mmol) and phosphorous oxybromide (25 g, 87 mmol, 3.0 equiv) was heated at 110 °C. After 3 h, the reaction mixture was cooled to rt and cautiously hydrolyzed with crushed ice. The resulting mixture was extracted with ether and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by chromatography (pentane/ether 99.5:0.5) to afford 4.8 g (68%) of **10** as a white solid; mp 80–84 °C; IR 3120, 1460, 1390, 1240, 1070, 1020, 880, 820, 740 cm^{-1}; ^1H NMR δ 7.22 (s, 1H); ^{13}C NMR δ 136.2 (s), 124.1 (s), 120.7 (d); EIMS m/z (relative intensity) 245 ($M[^{81}Br_2]^+$, 52), 243 ($M[^{79}Br^{81}Br]^+$, 100), 241 ($M[^{79}Br]^+$, 52), 138 (30), 136 (30), 13 (30), 83 (13), 57 (27).

6.4.1.2. 4-Bromo-2-(1,1-dimethylallyl)thiazole (11). To a suspension of magnesium turnings (3.46 g, 142 mmol, 5.7 equiv) in THF (20 mL) was added dropwise a solution of prenyl chloride (8.0 mL, 71 mmol, 2.9 equiv) in THF (150 mL) (internal temperature maintained between 5–10 °C). After a further 0.5 h stirring at rt, the resulting solution of prenylmagnesium chloride was transferred via a cannula to a solution of **10** (6.00 g, 24.7 mmol) in THF (20 mL) at 0 °C. After 1 h at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 99.5:0.5) to afford 4.98 g (87%) of **11** as a volatile colorless liquid; IR 3120, 3080, 1640, 1480, 1460, 1395, 1260, 1240, 1080, 1020, 920, 890, 840, 820, 740 cm^{-1}; ^1H NMR δ 7.09 (s, 1H), 6.13 (dd, J=17.3, 10.5 Hz, 1H), 5.17 (dd, J=17.3, 0.7 Hz, 1H), 5.14 (dd, J=10.5, 0.7 Hz, 1H), 1.54 (s, 6H); ^{13}C NMR δ 179.8 (s), 154.0 (s), 144.4 (d), 116.0 (d), 113.3 (t), 45.6 (s), 27.8 (q, 2C); EIMS m/z (relative intensity) 233 ($M[^{81}Br]^+$, 3), 232 ($M[^{81}Br]-H^+$, 3), 231 ($M[^{79}Br]^+$, 4), 230 ($M[^{79}Br]-H^+$, 3), 218 ($M[^{81}Br]-Me^+$, 99), 216 ($M[^{79}Br]-Me^+$, 100), 203 (13), 201 (12), 192 (3), 190 (4), 152 (2), 138 (4), 137 (6), 136 (8).

6.4.1.3. 2-(4-Bromothiazol-2-yl)-2-methylpropanal (12). To a solution of **11** (3.80 g, 16.3 mmol) in *t*-BuOH/H_2O (1:1, 60 mL) at rt were successively added OsO_4 (4.0 mL, 4% in water, 0.65 mmol, 0.04 equiv) and NMO (2.10 g, 17.9 mmol, 1.1 equiv). After stirring overnight at rt, a mixture of powdered $Na_2S_2O_3$ (7.5 g) and Celite (15 g) was added. After 0.5 h, the resulting mixture was filtered through Celite (EtOAc). The organic layer was separated and the aqueous phase was extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude resulting 1,2-diol was dissolved in THF/H_2O (1:1, 300 mL) and $NaIO_4$ (8.70 g, 40.8 mmol, 2.5 equiv) was added to the resulting solution. After 1 h at rt, the reaction mixture was filtered through Celite (EtOAc). The filtrate was extracted

with EtOAc and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by filtration through a short plug of silica gel (petroleum ether/ether 90:10) to afford 3.37 g (88%) of aldehyde **12** as a pale yellow oil, which was directly engaged in the next step; ^{1}H NMR δ 9.67 (s, 1H), 7.25 (s, 1H), 1.40 (s, 6H); ^{13}C NMR δ 199.0 (d), 172.8 (s), 125.2 (s), 117.1 (d), 51.7 (s), 22.6 (q, 2C).

6.4.1.4. 2-(4-Bromothiazol-2-yl)-2-methylhex-5-en-3-ol (13). To a solution of **12** (3.34 g, 14.3 mmol) in THF (25 mL) at −78 °C was added a solution of allylmagnesium bromide (21.5 mL, 1 M in ether, 21.5 mmol, 1.5 equiv) in ether (30 mL). After 1 h at rt, the reaction mixture was hydrolyzed with a 1 M solution of hydrochloric acid and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/ether 85:15 to 80:20) to afford 3.47 g (87%) of **13** as a colorless oil; IR 3420, 3130, 1640, 1470, 1370, 1260, 1080, 1055, 920, 890, 845, 740 cm^{-1}; ^{1}H NMR δ 7.14 (s, 1H), 5.86 (dddd, J=17.6, 9.6, 7.7, 6.3 Hz, 1H), 5.13–5.06 (m, 2H), 3.80 (m, 1H), 3.05 (m, 1H, OH), 2.31 (m, 1H), 1.98 (m, 1H), 1.45 (s, 6H); ^{13}C NMR δ 179.6 (s), 135.5 (d), 124.0 (s), 117.4 (t), 115.9 (d), 77.2 (d), 45.2 (s), 36.5 (t), 26.0 (q), 24.0 (q); EIMS m/z (relative intensity) 277 (M[^{81}Br]$^+$, 0.4), 275 (M[^{79}Br]$^+$, 0.4), 236 (M[^{81}Br]−$C_3H_5^+$, 13), 234 (M[^{79}Br]−$C_3H_5^+$, 13), 207 (100), 206 (39), 205 (98), 204 (32), 192 (41), 190 (36).

6.4.1.5. 4-Bromo-2-{2-[(*tert*-butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazole (14). To a solution of **13** (700 mg, 2.54 mmol) and 2,6-lutidine (740 μL, 6.35 mmol, 2.5 equiv) in CH_2Cl_2 (15 mL) at 0 °C was added dropwise TBSOTf (1.2 mL, 5.1 mmol, 2.0 equiv). After 3 h at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 99:1) to give 940 mg (95%) of **14** as a colorless oil; IR 3120, 3080, 1640, 1465, 1390, 1365, 1255 (br), 1090, 915, 840, 780 cm^{-1}; ^{1}H NMR δ 7.09 (s, 1H), 5.71 (m, 1H), 4.96–4.88 (m, 2H), 4.02 (t, J=5.3 Hz, 1H), 2.35–2.25 (m, 1H), 2.16–2.06 (m, 1H), 1.44 (s, 3H), 1.36 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), −0.10 (s, 3H); ^{13}C NMR δ 179.6 (s), 135.8 (d), 123.8 (s), 116.2 (t), 115.9 (d), 78.7 (d), 46.6 (s), 38.6 (t), 26.0 (q, 3C), 25.3 (q), 24.9 (q), 18.1 (s), −3.6 (q), −4.8 (q); EIMS m/z (relative intensity) 376 (M[^{81}Br]−Me$^+$, 3), 374 (M[^{79}Br]−Me$^+$, 3), 350 (M[^{81}Br]−$C_3H_5^+$, 13), 348 (M[^{79}Br]−$C_3H_5^+$, 12), 335 (M[^{81}Br]−$C_4H_8^+$, 19), 334 (M[^{81}Br]−t-Bu$^+$, 100), 333 (M[^{79}Br]−$C_4H_8^+$, 19), 332 (M[^{79}Br]−t-Bu$^+$, 96), 186 (12), 185 (70), 129 (10), 127 (13), 115 (14), 99 (12), 75 (31), 73 (61). Anal. Calcd for $C_{16}H_{28}BrNOSSi$: C, 49.22; H, 7.23; N, 3.59. Found: C, 49.32; H, 7.23; N, 3.72.

6.4.2. Br–Li exchange of 14 with *n*-BuLi in THF and subsequent formylation. To a solution of *n*-BuLi (1.1 mL, 2.5 M in hexanes, 2.8 mmol, 1.5 equiv) in THF (10 mL) at −78 °C was added dropwise a solution of **14** (730 mg, 1.88 mmol) in THF (10 mL). After 15 min at −78 °C, freshly distilled DMF (295 mL, 3.76 mmol, 2.0 equiv) was added. After 0.5 h, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/ether 97:3 to 85:15) to afford 175 mg (22%) of **20**, 200 mg (34%) of **18**, 92 mg (14%) of **19**, and 90 mg (14%) of **21** as pale yellow oils.

6.4.2.1. 2-{2-[(*tert*-Butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazole (18). IR 3080, 1705, 1680, 1640, 1470, 1390, 1360, 1260, 1090, 1060, 1040, 1005, 910, 840, 770, 740, 725 cm^{-1}; ^{1}H NMR δ 7.66 (d, J=3.3 Hz, 1H), 7.14 (d, J=3.3 Hz, 1H), 5.63 (dddd, J=16.5, 10.3, 7.7, 6.6 Hz, 1H), 4.89–4.80 (m, 2H), 3.99 (dd, J=6.3, 4.6 Hz, 1H), 2.26–2.16 (m, 1H), 2.09–1.99 (m, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 0.85 (s, 9H), 0.02 (s, 3H), −0.06 (s, 3H); ^{13}C NMR δ 178.3 (s), 141.5 (d), 135.9 (d), 117.8 (d), 115.8 (t), 78.9 (d), 46.0 (s), 38.5 (t), 26.0 (q), 25.9 (q, 3C), 24.5 (q), 18.0 (s), −3.7 (q), −4.8 (q); EIMS m/z (relative intensity) 311 (M$^+$, 1), 296 (M−Me$^+$, 5), 270 (M−$C_3H_5^+$, 16), 256 (10), 254 (100), 198 (12), 185 (35), 180 (11), 138 (8), 127 (31), 115 (7), 99 (6), 75 (11), 73 (39).

6.4.2.2. 2-{2-[(*tert*-Butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazole-4-carboxaldehyde (19). IR 3080, 1710, 1640, 1485, 1470, 1390, 1365, 1260, 1135, 1090, 1055, 1005, 915, 840, 780, 700 cm^{-1}; ^{1}H NMR δ 10.0 (s, 1H), 8.08 (s, 1H), 5.67 (dddd, J=16.9, 10.3, 7.7, 6.6 Hz, 1H), 4.93–4.84 (m, 2H), 3.99 (dd, apparent t, J=5.1 Hz, 1H), 2.36–2.26 (m, 1H), 2.15–2.05 (m, 1H), 1.49 (s, 3H), 1.40 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), −0.08 (s, 3H); ^{13}C NMR δ 184.9 (d), 179.4 (s), 153.9 (s), 135.4 (d), 127.4 (d), 116.2 (t), 78.7 (d), 46.7 (s), 38.5 (t), 26.1 (q), 25.9 (q, 3C), 25.2 (q), 18.1 (s), −3.7 (q), −4.8 (q); EIMS m/z (relative intensity) 324 (M−Me$^+$, 3), 298 (M−$C_3H_5^+$, 21), 284 (10), 283 (20), 282 (100), 213 (13), 212 (76), 185 (34), 166 (5), 155 (5), 115 (6), 75 (10), 73 (38).

6.4.2.3. 4-Bromo-2-{2-[(*tert*-butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazole-5-carboxaldehyde (20). IR 3080, 1675, 1640, 1480, 1460, 1365, 1250, 1090, 1005, 915, 840, 780, 740, 680 cm^{-1}; ^{1}H NMR δ 9.94 (s, 1H), 5.70 (dddd, J=16.9, 10.7, 7.7, 6.4 Hz, 1H), 4.97–4.88 (m, 2H), 4.03 (t, J=5.2 Hz, 1H), 2.36–2.26 (m, 1H), 2.19–2.09 (m, 1H), 1.45 (s, 3H), 1.37 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), −0.10 (s, 3H); ^{13}C NMR δ 186.9 (s), 182.8 (d), 135.1 (d), 133.6 (s), 131.7 (s), 116.5 (t), 78.3 (d), 47.6 (s), 38.5 (t), 25.8 (q, 3C), 25.4 (q), 24.3 (q), 18.0 (s), −3.8 (q), −4.9 (q); EIMS m/z (relative intensity) 404 (M[^{81}Br]−Me$^+$, 2), 402 (M[^{79}Br]−Me$^+$, 2), 378 (M[^{81}Br]−$C_3H_5^+$, 14), 376 (M[^{79}Br]−$C_3H_5^+$, 13), 363 (M[^{81}Br]−$C_4H_8^+$, 21), 362 (M[^{81}Br]−t-Bu$^+$, 100), 361 (M[^{79}Br]−$C_4H_8^+$, 20), 360 (M[^{79}Br]−t-Bu$^+$, 96), 185 (48), 127 (20), 115 (11), 99 (14), 75 (25), 73 (60).

6.4.2.4. 2-{2-[(*tert*-Butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazole-5-carboxaldehyde (21). IR 3080, 1680, 1640, 1510, 1470, 1420, 1390, 1360, 1260, 1100, 1040, 1005, 910, 840, 780 cm^{-1}; ^{1}H NMR δ 9.98 (s, 1H), 8.29 (s, 1H), 5.66 (dddd, J=16.9, 10.3, 7.4, 6.6 Hz, 1H), 4.94–4.84 (m, 2H), 4.03 (dd, apparent t, J=5.3 Hz, 1H), 2.27 (m, 1H), 2.11 (m, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), −0.08 (s, 3H); ^{13}C NMR δ 187.3 (s), 182.1 (d), 150.6 (d), 138.6 (s), 135.4 (d), 116.3

(t), 78.5 (d), 47.3 (s), 38.6 (t), 25.8 (q, 3C), 25.4 (q), 25.0 (q), 18.0 (s), −3.8 (q), −4.8 (q); EIMS *m/z* (relative intensity) 324 ($M-Me^+$, 4), 298 ($M-C_3H_5^+$, 16), 283 ($M-C_4H_8^+$, 21), 282 ($M-t\text{-}Bu^+$, 100), 269 (6), 256 (3), 226 (8), 185 (29), 166 (6), 156 (4), 127 (9), 115 (7), 99 (7), 75 (14), 73 (46), 59 (8).

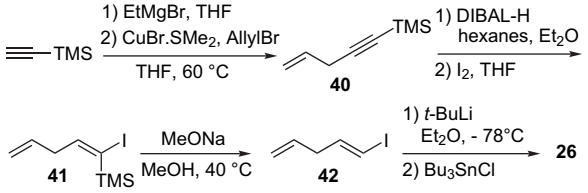
6.4.3. Installation of the unsaturated side-chain at C4.

6.4.3.1. Br–Li exchange of 14 with *t*-BuLi in ether and subsequent formylation. To a solution of *t*-BuLi (3.1 mL, 1.7 M in pentane, 5.3 mmol, 3.0 equiv) in ether (17 mL) at −78 °C was added dropwise a solution of **14** (676 mg, 1.74 mmol) in ether (17 mL). After 5 min at −78 °C, freshly distilled DMF (410 μL, 5.22 mmol, 3.0 equiv) was added dropwise. After 0.5 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/Et_2O: 90:10) to afford 500 mg (85%) of **19** as a yellow oil, see Section 6.4.2.2.

6.4.3.2. ({2-[2-(*tert*-Butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazol-4-yl)methanol (24). To a solution of aldehyde **19** (960 mg, 2.83 mmol) in ether (35 mL) at −78 °C was added DIBAL-H (4.75 mL, 1 M in hexanes, 4.75 mmol, 1.7 equiv). After 0.5 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of Rochelle's salt and diluted with ether. After 2 h at rt, the organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 910 mg (95%) of **24** as a colorless oil, which was directly engaged in the next step without purification; IR 3300, 3070, 1640, 1470, 1390, 1365, 1260, 1100, 1040, 910, 840, 780 cm^{-1}; ^1H NMR δ 7.04 (s, 1H), 5.68 (m, 1H), 4.93–4.86 (m, 2H), 4.73 (br d, J=5.0 Hz, 2H), 4.00 (dd, J=5.9, 4.8 Hz, 1H), 3.38 (t, J=5.0 Hz, 1H, OH), 2.31–2.21 (m, 1H), 2.14–2.04 (m, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), −0.09 (s, 3H); ^{13}C NMR δ 179.3 (s), 155.3 (s), 136.1 (d), 116.0 (t), 113.7 (d), 78.9 (d), 60.8 (t), 46.4 (s), 38.6 (t), 26.0 (q, 3C), 25.8 (q), 24.8 (q), 18.3 (s), −3.6 (q), −4.7 (q); EIMS *m/z* (relative intensity) 341 (M^+, 1), 300 ($M-C_3H_5^+$, 33), 285 (22), 284 (100), 262 (64), 214 (49), 192 (23), 185 (100), 183 (28), 168 (40), 157 (22), 140 (29), 115 (22), 75 (31), 73 (79). Anal. Calcd for $C_{17}H_{31}NO_2SSi$: C, 59.77; H, 9.15; N, 4.10. Found: C, 59.66; H, 9.30; N, 4.14.

6.4.3.3. 4-Bromomethyl-2-{2-[(*tert*-butyldimethylsilyl)-oxy]-1,1-dimethylpent-4-enyl}thiazole (25). To a solution of **24** (640 mg, 1.92 mmol), 2,6-lutidine (92 μL, 0.79 mmol, 0.4 equiv), and PPh_3 (830 g, 3.21 mmol, 1.7 equiv) in MeCN (16 mL) at rt was added portionwise CBr_4 (1.1 g, 3.2 mmol, 1.7 equiv). After 0.5 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/ether 95:5) to afford 740 mg (97%) of **25** as a colorless oil; IR 3070, 1640, 1470, 1385, 1365, 1255, 1085, 1040, 1000, 910, 835, 775 cm^{-1}; ^1H NMR δ 7.17 (s, 1H), 5.71 (dddd, J=16.9, 10.3, 7.3, 6.6 Hz, 1H), 4.95–4.87 (m, 2H), 4.57 (s, 2H), 4.04 (dd, J=5.9, 4.8 Hz, 1H), 2.34–2.24 (m, 1H), 2.17–2.06 (m, 1H), 1.44 (s, 3H), 1.38 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), −0.09 (s, 3H); ^{13}C NMR δ 179.2 (s), 151.1 (s), 136.0 (d), 117.0 (d), 116.0 (t), 78.9 (d), 46.4 (s), 38.6 (t), 27.6 (t), 26.0 (q, 3C), 25.5 (q), 25.0 (q), 18.3 (s), −3.6 (q), −4.6 (q); EIMS *m/z* (relative intensity) 364 ($M[^{81}Br]-C_3H_5^+$, 12), 362 ($M[^{79}Br]-C_3H_5^+$, 12), 348 ($M[^{81}Br]-t\text{-}Bu^+$, 87), 346 ($M[^{79}Br]-t\text{-}Bu^+$, 83), 324 (2), 252 (7), 192 (30), 186 (17), 185 (100), 168 (31), 140 (10), 139 (13), 129 (13), 115 (15), 95 (17), 75 (14), 73 (56).

6.4.4. Preparation of organostannane 26.



6.4.4.1. Trimethylpent-4-en-1-ylsilane (40). To a solution of EtMgBr (34 mL, 3 M in THF, 102 mmol, 1.2 equiv) in THF (120 mL) was slowly added trimethylsilylacetylene (12 mL, 85 mmol) (exothermic reaction, internal temperature between 25 and 30 °C). The resulting mixture was heated at 50 °C for 2 h and cooled to rt. To the reaction mixture was added $CuBr\cdot SMe_2$ (1.75 g, 8.49 mmol, 0.1 equiv) in one portion followed by allyl bromide (11.0 mL, 127 mmol, 1.5 equiv) dropwise (exothermic reaction, internal temperature 50 °C). After 2 h at 60 °C, the reaction mixture was hydrolyzed with a 1 M aqueous solution of hydrochloric acid and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by distillation under reduced pressure to afford 9.2 g (79%) of **40** as a colorless oil; bp 45 °C/15 mmHg; IR 2180, 1640, 1420, 1250, 1030, 1000, 915, 890, 840, 700 cm^{-1}; ^1H NMR δ 5.82 (ddt, J=17.0, 10.3, 5.2 Hz, 1H), 5.34 (dq, J=17.0, 1.7 Hz, 1H), 5.13 (dq, J=10.3, 1.7 Hz, 1H), 3.01 (dt, J=5.2, 1.7 Hz, 2H), 0.17 (s, 9H); ^{13}C NMR δ 132.1 (d), 116.1 (t), 103.3 (s), 87.0 (s), 24.1 (t), 0.00 (q, 3C).

6.4.4.2. (*E*)-1-Iodo-1-trimethylsilylpenta-1,4-diene (41). A solution of DIBAL-H (70 mL, 1 M in hexanes, 70 mmol, 1.2 equiv) was diluted with ether (7.2 mL, 70 mmol, 1.2 equiv) and a solution of **40** (8.00 g, 58.0 mmol) in ether (145 mL) was slowly added at 0 °C. After 1.5 h at rt and 2 h at 40 °C, the reaction mixture was cooled to −78 °C and a solution of iodine (36.8 g, 145 mmol, 2.5 equiv) in THF (150 mL) was added dropwise. The reaction mixture was warmed to rt, hydrolyzed with a 1 M aqueous solution of hydrochloric acid, and extracted with ether. The combined organic extracts were successively washed with a saturated aqueous solution of $NaHCO_3$ and a 25% aqueous solution of $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by distillation under reduced pressure (in the presence of a small amount of Cu powder) to afford 11.3 g (73%) of **41** as a colorless oil; bp 85 °C/10 mmHg; IR 3070, 1640, 1580, 1250, 990, 915,

840, 760, 690 cm^{-1}; ^1H NMR δ 7.16 (t, J=8.0 Hz, 1H), 5.77 (ddt, J=17.3, 9.6, 6.1 Hz, 1H), 5.11–5.03 (m, 2H), 2.83 (ddt, J=8.0, 6.1, 1.5 Hz, 2H), 0.29 (s, 9H); ^{13}C NMR δ 152.7 (d), 134.6 (d), 116.0 (t), 107.8 (s), 38.8 (t), 1.0 (q, 3C); EIMS *m/z* (relative intensity) 266 (M^+, 21), 185 (80), 139 ($M-I^+$, 4), 83 (11), 73 (100).

6.4.4.3. (*E*)-1-Iodopenta-1,4-diene (42). To a solution of MeONa [prepared by portionwise addition of sodium pieces (3.85 g, 167 mmol, 4.0 equiv) in MeOH (100 mL), 20–45 °C] at rt was added a solution of **41** (11.1 g, 41.7 mmol) in MeOH (30 mL). After 4 h at 40 °C, the reaction mixture was hydrolyzed with H_2O (100 mL) and extracted with pentane. The combined organic extracts were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by distillation under reduced pressure (in the presence of a small amount of Cu powder) to afford 6.0 g (74%) of **42** as a slightly yellow oil; bp 60–70 °C/35 mmHg; IR 1640, 1605, 1430, 1250, 1230, 1175, 1115, 990, 950, 915, 860, 840 cm^{-1}; ^1H NMR δ 6.55 (dt, J=14.3, 6.4 Hz, 1H), 6.07 (dt, J=14.3, 1.5 Hz, 1H), 5.79 (ddt, J=17.3, 10.3, 6.4 Hz, 1H), 5.12–5.05 (m, 2H), 2.81 (ddq, apparent tq, J=6.4, 1.5 Hz, 2H); ^{13}C NMR δ 143.6 (d), 134.2 (d), 116.5 (t), 72.8 (d), 39.7 (t).

6.4.4.4. (*E*)-1-Tributylstannylpenta-1,4-diene (26). To a solution of **42** (580 mg, 3.00 mmol) in ether (15 mL) at −78 °C was added *t*-BuLi (4.0 mL, 1.7 M in pentane, 6.8 mmol, 2.3 equiv). After 0.5 h at −78 °C, the reaction mixture was warmed to 0 °C and *n*-Bu_3SnCl (0.89 mL, 3.3 mmol, 1.1 equiv) was added rapidly. After 0.5 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude alkenylstannane **26** was directly engaged in the next step without further purification (purification by flash chromatography on silica gel resulted in extensive protodestannylation). An analytical sample of **26** was obtained by rapid filtration on silica gel (pentane); ^1H NMR δ 6.11–5.96 (m, 2H), 5.87 (ddt, J=16.9, 10.3, 6.6 Hz, 1H), 5.05 (dq, J=17.0, 1.5 Hz, 1H), 5.03 (dq, J=10.3, 1.5 Hz, 1H), 2.94–2.89 (m, 2H), 1.58–1.46 (m, 6H), 1.40–1.26 (m, 6H), 0.95–0.86 (m, 15H); ^{13}C NMR δ 146.4 (d), 136.7 (d), 129.0 (d), 115.2 (t), 41.9 (t), 29.3 (t, 3C), 27.4 (t, 3C), 13.7 (q, 3C), 9.4 (t, 3C).

6.4.4.5. 2-{2-[(*tert*-Butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}-(2*E*)-4-(hexa-2,5-dienyl)thiazole (27). To a degassed solution of bromide **25** (65 mg, 0.16 mmol) and stannane **26** (72 mg, 0.20 mmol, 1.25 equiv) in freshly distilled NMP (2.5 mL) (argon bubbling, 10 min) at rt was added $PdCl_2(CH_3CN)_2$ (4 mg, 0.02 mmol, 0.1 equiv). After 0.5 h at rt, the reaction mixture was hydrolyzed with a 20% aqueous solution of NH_4OH, stirred for 0.5 h and extracted with ether. The combined organic extracts were washed with a 1 M aqueous solution of $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/ether 95:5) to afford 62 mg (95%) of **27** as a colorless oil; IR 3070, 1640, 1515, 1470, 1460, 1430, 1385, 1360, 1255, 1090, 1040, 1000, 970, 910, 835, 775, 740 cm^{-1}; ^1H NMR δ 6.74 (s, 1H), 5.86 (ddt, J=16.6, 10.2, 6.4 Hz, 1H), 5.77–5.52 (m, 3H), 5.10–4.98 (m, 2H), 4.96–4.85 (m, 2H), 4.07 (dd, J=6.0, 4.5 Hz, 1H), 3.50 (br d, J=6.4 Hz, 2H), 2.81 (apparent br t, J=6.4 Hz, 2H), 2.28 (m, 1H), 2.10 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), −0.11 (s, 3H); ^{13}C NMR δ 178.2 (s), 155.1 (s), 136.8 (d), 136.3 (d), 129.8 (d), 128.0 (d), 115.8 (t), 115.0 (t), 112.0 (d), 78.9 (d), 46.1 (s), 38.5 (t), 36.5 (t), 34.8 (t), 25.9 (q, 3C), 25.6 (q), 24.4 (q), 18.1 (s), −3.7 (q), −4.8 (q); EIMS *m/z* (relative intensity) 391 (M^+, 3), 376 ($M-Me^+$, 4), 350 ($M-C_3H_5^+$, 15), 336 (12), 335 (27), 334 ($M-t$-Bu^+, 100), 260 (20), 207 (41), 186 (12), 185 (72), 129 (13), 115 (14), 75 (10), 73 (54).

6.4.4.6. 2-[((2*E*)-4-Hexa-2,5-dienyl)thiazol-2-yl]-2-methylhex-5-en-3-ol (28). To a solution of **27** (300 mg, 0.777 mmol) in THF (10 mL) at rt was added *n*-Bu_4NF (2.3 mL, 1 M in THF, 2.3 mmol, 3.0 equiv). After 1.5 h at 50 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/Et_2O 75:25) to give 200 mg (94%) of **28** as a colorless oil; IR 3400 (br), 3070, 1640, 1520, 1470, 1430, 1365, 1050, 990, 970, 910, 740 cm^{-1}; ^1H NMR δ 6.75 (s, 1H), 5.91 (ddt, J=17.0, 10.2, 6.8 Hz, 1H), 5.82 (ddt, J=16.9, 10.2, 6.4 Hz, 1H), 5.72–5.50 (m, 2H), 5.10–4.96 (m, 4H), 4.52 (br d, J=5.7 Hz, 1H), 3.73 (m, 1H), 3.46 (br d, J=6.0 Hz, 2H), 2.78 (apparent br t, J=6.4, 2H), 2.32–2.24 (m, 1H), 2.05–1.94 (m, 1H), 1.44 (s, 3H), 1.40 (s, 3H); ^{13}C NMR δ 178.9 (s), 155.4 (s), 136.8 (d), 136.3 (d), 130.3 (d), 127.7 (d), 116.5 (t), 115.2 (t), 111.9 (d), 77.9 (d), 44.6 (s), 36.6 (t, 2C), 34.7 (t), 26.9 (q), 24.3 (q); EIMS *m/z* (relative intensity) 277 (M^+, 1), 236 ($M-C_3H_5^+$, 19), 208 (19), 207 (100), 206 (21), 192 (16), 166 (9), 139 (11), 138 (12), 126 (9), 97 (6), 71 (10); HRMS (CI^+, CH_4) calcd for $C_{16}H_{24}NOS$ ($M+H^+$): 278.1579. Found: 278.1575.

6.4.5. Synthesis of the originally proposed structure of mycothiazole.

6.4.5.1. 2-[1-(2,2-Dioxo-2,3,6,7-tetrahydro-2λ⁶-[1,2]-oxathiepin-7-yl)-1-methylethyl]-4-((2*E*)-hexa-2,5-dienyl)-thiazole (30). To a solution of **28** (110 g, 0.405 mmol) and DMAP (97 mg, 0.80 mmol, 2.0 equiv) in THF (3 mL) at rt was added dropwise a solution of allylsulfonyl chloride (84 mg, 0.60 mmol, 1.5 equiv) in THF (2 mL). After 2 h at rt, a solution of DMAP (97 mg, 0.80 mmol, 2.0 equiv) and allylsulfonyl chloride (84 mg, 0.60 mmol, 1.5 equiv) in THF (2 mL) was added. After 1 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined organic extracts were washed with an aqueous solution of $CuSO_4$, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was filtered through silica gel (ether) and after evaporation of the solvent under reduced pressure, the crude sulfonate **29** was dissolved in C_6H_6 (40 mL). To the resulting degassed solution (argon bubbling, 15 min) at 70 °C was added catalyst **II** [(51 mg, 0.06 mmol, 0.15 equiv) in three portions at 1 h interval]. After a further 1 h at 70 °C, the reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 70:30) to afford 98 mg (70%) of **30** as a colorless oil; IR

3080, 3015, 3030, 1640, 1515, 1430, 1360, 1170, 1055, 970, 910, 875, 830, 740, 700, 690 cm^{-1}; ^1H NMR δ 6.85 (s, 1H), 6.09 (m, 1H), 5.87 (ddt, J=17.3, 10.2, 6.4 Hz, 1H), 5.80–5.52 (m, 3H), 5.12–5.00 (m, 3H), 4.14 (m, 1H), 3.90 (apparent br dd, J=15.5, 8.1 Hz, 1H), 3.58–3.48 (m, 2H), 2.84 (apparent br t, J=6.4 Hz, 2H), 2.59 (m, 1H), 2.42 (dd, J=16.2, 8.5 Hz, 1H), 1.55 (s, 3H), 1.54 (s, 3H); ^{13}C NMR δ 174.5 (s), 156.0 (s), 136.9 (d), 134.5 (d), 130.3 (d), 127.8 (d), 119.1 (d), 115.2 (t), 113.1 (d), 90.1 (d), 50.5 (t), 44.6 (s), 36.6 (t), 34.8 (t), 29.8 (t), 26.9 (q), 22.4 (q); EIMS m/z (relative intensity) 353 (M^+, 39), 338 ($M-Me^+$, 7), 324 (10), 313 (19), 312 ($M-C_3H_5^+$, 100), 272 ($M-[CH_2{=}CH{-}CH_2{-}CH{=}CH]^+$, 12), 218 (37), 207 (58), 206 (95), 192 (22), 164 (28), 152 (22), 139 (28), 138 (58), 97 (19), 71 (23), 55 (21).

6.4.5.2. 2-{1-[3-(3,3-Dimethoxypropyl)-2,2-dioxo-2,3,6,7-tetrahydro-2λ⁶-[1,2]oxathiepin-7-yl]-1-methylethyl}-4-((2*E*)-hexa-2,5-dienyl)thiazole (32). To a solution of **30** (142 mg, 0.402 mmol), iodide **31** (111 mg, 0.482 mmol, 1.2 equiv), and HMPA (280 μL, 1.61 mmol, 4.0 equiv) in THF (10 mL) at −78 °C was added dropwise LiHMDS (0.48 mL, 1 M in THF, 0.48 mmol, 1.2 equiv). After 20 min at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 65:35) to afford 139 mg (76%) of **30** as a colorless oil and as a nearly 1:1 mixture of diastereomers. In order to facilitate characterization, the two diastereomers were partially separated by resubjecting an analytical sample of the mixture to purification by flash chromatography.

First eluting diastereomer: IR 1640, 1520, 1460, 1360, 1170, 1130, 1055, 970, 905, 740, 690 cm^{-1}; ^1H NMR δ 6.82 (s, 1H), 6.08 (m, 1H), 5.94–5.47 (m, 4H), 5.18–4.96 (m, 3H), 4.38 (apparent td, J=5.5, 2.0 Hz, 1H), 4.09 (m, 1H), 3.49 (br d, J=6.4 Hz, 2H), 3.33 (s, 6H), 2.81 (apparent br t, J=6.4 Hz, 2H), 2.57–2.15 (m, 4H), 2.08–1.67 (m, 2H), 1.51 (s, 6H); ^{13}C NMR δ 174.6 (s), 155.9 (s), 136.9 (d), 133.8 (d), 130.3 (d), 127.8 (d), 126.9 (d), 115.2 (t), 113.0 (d), 104.0 (d), 91.4 (d), 61.0 (d), 53.2 (q, 2C), 44.7 (s), 36.6 (t), 34.8 (t), 29.7 (t), 29.1 (t), 27.0 (q), 24.6 (t), 22.5 (q); EIMS m/z (relative intensity) 424 ($M-OMe^+$, 10), 423 (38), 382 (31), 344 (20), 326 (12), 316 (15), 288 (13), 235 (13), 218 (12), 208 (15), 207 (70), 206 (57), 194 (13), 192 (15), 139 (15), 138 (27), 97 (13), 91 (14), 79 (14), 77 (13), 71 (100); HRMS (CI^+, CH_4) calcd for $C_{22}H_{34}NO_5S_2$ ($M+H^+$): 456.1878. Found: 456.1875.

Second eluting diastereomer: IR 1640, 1520, 1460, 1420, 1360, 1170, 1125, 1060, 970, 905, 740, 690 cm^{-1}; ^1H NMR δ 6.82 (s, 1H), 5.95–5.77 (m, 2H), 5.74–5.50 (m, 3H), 5.17–4.97 (m, 3H), 4.38 (br t, J=5.5 Hz, 1H), 3.96 (m, 1H), 3.50 (br d, J=6.4 Hz, 2H), 3.34 (s, 3H), 3.33 (s, 3H), 2.81 (apparent br t, J=6.4 Hz, 2H), 2.56 (m, 1H), 2.39–2.17 (m, 2H), 2.00 (m, 1H), 1.80–1.69 (m, 2H), 1.55 (s, 3H), 1.52 (s, 3H); ^{13}C NMR δ 174.5 (s), 156.0 (s), 136.9 (d), 132.2 (d), 130.3 (d), 127.8 (d), 124.1 (d), 115.2 (t), 113.1 (d), 104.0 (d), 88.2 (d), 60.4 (d), 53.2 (q), 53.1 (q), 44.5 (s), 36.6 (t), 34.8 (t), 29.7 (t), 29.6 (t), 27.0 (q), 25.0 (t), 22.5 (q); EIMS m/z (relative intensity) 384 (21), 383 (16), 336 (20), 168 (13), 167 (75), 166 (100), 97 (13), 75 (31), 71 (64); HRMS (CI^+, CH_4) calcd for $C_{22}H_{34}NO_5S_2$ ($M+H^+$): 456.1878. Found: 456.1875.

6.4.5.3. (5*Z*)-2-[(4-(2*E*)-Hexa-2,5-dienyl)thiazol-2-yl]-10,10-dimethoxy-2-methyl-7-methylenedec-5-en-3-ol (33). To a solution of **32** (139 mg, 0.305 mmol) in THF (10 mL) at −78 °C was added a solution of *n*-BuLi (0.25 mL, 2.5 M in hexanes, 0.625 mmol, 2.5 equiv). After 0.5 h at −78 °C, a solution of ICH_2MgCl [prepared from CH_2I_2 (576 mg, 2.15 mmol, 7 equiv) and *i*-PrMgCl (1.1 mL, 2 M in THF, 2.2 mmol, 7 equiv) in THF (10 mL), −80 °C, 1 h] was added via a cannula to the reaction mixture. After 15 min at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/ether 70:30) to afford 74 mg (60%) of **33** as a colorless oil; IR 3420, 1640, 1520, 1450, 1380, 1365, 1125, 1055, 970, 910 cm^{-1}; ^1H NMR δ 6.77 (s, 1H), 5.92–5.53 (m, 5H), 5.18–4.98 (m, 2H), 4.98 (br s, 1H), 4.85 (br s, 1H), 4.63 (m, 1H), 4.35 (apparent t, J=5.8 Hz, 1H), 3.73 (m, 1H), 3.47 (apparent br d, J=6.4 Hz, 2H), 3.32 (s, 6H), 2.80 (apparent br t, J=6.4 Hz, 2H), 2.49 (m, 1H), 2.24–2.09 (m, 3H), 1.75–1.66 (m, 2H), 1.44 (s, 3H), 1.40 (s, 3H); ^{13}C NMR δ 179.0 (s), 155.4 (s), 144.7 (s), 136.9 (d), 131.0 (d), 130.4 (d), 129.7 (d), 127.7 (d), 115.2 (t), 113.7 (t), 111.9 (d), 104.1 (d), 78.7 (d), 52.8 (q, 2C), 44.7 (s), 36.6 (t), 34.7 (t), 32.2 (t), 31.2 (t), 31.1 (t), 27.0 (q), 24.2 (q); MS (CI^+, CH_4) m/z (relative intensity) 406 ($M+H^+$, 74), 390 ($M-Me^+$, 64), 374 (37), 368 (38), 358 (35), 318 (30), 280 (26), 236 (36), 183 (28), 169 (33), 127 (29), 70 (100); HRMS (CI^+, CH_4) calcd for $C_{23}H_{36}NO_3S$ ($M+H^+$): 406.2416. Found: 406.2422.

6.4.5.4. (4*Z*)-8-[((2*E*)-4-Hexa-2,5-dienyl)thiazol-2-yl]-7-hydroxy-8-methyl-3-methylenenon-4-enylmethyl carbamate (39) (originally proposed structure of mycothiazole). To a solution of **33** (15 mg, 37 μmol) in THF/H_2O (1:1, 6 mL) at rt was added PPTS (19 mg, 74 μmol, 2.0 equiv). After 18 h at 50 °C, the reaction mixture was hydrolyzed with water and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude aldehyde **34** was dissolved in *t*-BuOH/H_2O (3:1, 2 mL) and to the resulting solution at 0 °C were successively added 2-methylbut-2-ene (43 μL, 0.41 mmol, 11 equiv), $NaH_2PO_4 \cdot H_2O$ (69 mg, 0.44 mmol, 12 equiv), and $NaClO_2$ (24 mg, 0.22 mmol, 6 equiv). After 1 h at 0 °C, the reaction mixture was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude highly sensitive carboxylic acid **35**, which was immediately dissolved in toluene (5 mL). To the resulting solution at rt were successively added Et_3N (20 μL, 0.14 mmol, 3.9 equiv) and diphenylphosphoryl azide (24 μL, 0.11 mmol, 3.0 equiv). After 1 h at rt, the reaction mixture was heated at 110 °C. After 1 h, MeOH (3 mL) was added and the reaction mixture was further heated at reflux for 1 h. After concentration under reduced pressure, the residue was purified by preparative chromatography on silica gel (pentane/ether 50:50) to afford 10 mg of the isocyanate **37**. This compound (which was initially mistaken with the amine **38**) was dissolved in CH_2Cl_2 (3 mL), and to the resulting solution at rt were successively

added Et_3N (20 μL, 0.14 mmol) and $ClCO_2Me$ (8 μL, 0.10 mmol). After 0.5 h, additional quantities of Et_3N (50 μL, 0.36 mmol) and $ClCO_2Me$ (28 μL, 0.36 mmol) were added. As no reaction apparently occurred, MeOH (2 mL) was added to the reaction mixture. After 1 h at rt, the reaction mixture was concentrated under reduced pressure and the residue was purified by preparative chromatography on silica gel (petroleum ether/EtOAc 50:50) to afford 5 mg (33%) of **39**; R_f (petroleum ether/EtOAc) 0.5; ^{1}H NMR δ 6.77 (s, 1H), 5.92–5.52 (m, 5H), 5.43 (br s, 1H, NH), 5.09–4.86 (m, 4H+OH), 3.79 (br d, J=9.8 Hz, 1H), 3.63 (s, 3H), 3.46 (d, J=6.4 Hz, 2H), 3.35–3.14 (m, 2H), 2.80 (t, J=6.0 Hz, 2H), 2.48–2.17 (m, 4H), 1.43 (s, 3H), 1.39 (s, 3H); EIMS 404 (M^+, 5), 373 ($M-OMe^+$, 2), 316 (21), 236 (42), 208 (15), 207 (100), 206 (10), 192 (6), 138 (5), 105 (8), 88 (9); HRMS (EI) calcd for $C_{22}H_{32}N_2O_3S$ (M^+): 404.2134. Found: 404.2133.

6.5. Comparison of the ^{1}H and ^{13}C NMR data

See Tables 3 and 4.

6.6. Formal enantioselective approach

6.6.1. Synthesis of (*R*)-13 by an enantioselective allylboration. To a solution of (+)-DIPCl (390 mg, 1.20 mmol, 1.2 equiv) in ether (10 mL) at −78 °C was added dropwise allylmagnesium bromide (1.1 mL, 1 M in ether, 1.1 mmol, 1.1 equiv). After 3 h at −78 °C, a solution of aldehyde **12** (230 mg, 1.00 mmol) in ether (2 mL) was added. After 2 h at −78 °C, the reaction mixture was warmed to rt and hydrolyzed by addition of a 3 M aqueous solution of NaOH (2 mL) and a 30% aqueous solution of H_2O_2 (1 mL). After 1 h at 40 °C, the resulting mixture was filtered through Celite (ether) and the filtrate was extracted with EtOAc. The

Table 3. Table of comparison of the ^{1}H NMR data

H	Synthetic compound **39** present study 300 MHz, $CDCl_3$	Synthetic compound (−)-**39**[9] previous total synthesis 270 MHz, $CDCl_3$	(−)-Mycothiazole natural product[6] 300 MHz, $CDCl_3$
H5	6.77 (s)	6.77 (s)	6.73 (t)
H7	3.79 (br d, J=9.8 Hz)	3.78 (dd, J=9.6, 3.0 Hz)	3.74 (dd, J=10.2, 3.0 Hz)
H8	2.48–2.17 (m)	2.43–2.18 (m)	2.39 (m), 2.24 (m)
H9	5.92–5.52 (m)	5.91–5.52 (m)	5.65 (m)
H10	5.92–5.52 (m)	5.91–5.52 (m)	5.83 (m)
H12	2.48–2.17 (m)	2.43–2.18 (m)	2.29 (m), 2.18 (m)
H13	3.35–3.14 (m)	3.33–3.16 (m)	3.23 (m), 3.14 (m)
H14	3.46 (d, J=6.4 Hz)	3.46 (d, J=5.6 Hz)	3.46 (d, J=7.2 Hz)
H15	5.92–5.52 (m)	5.91–5.52 (m)	5.68 (br m)
H16	5.92–5.52 (m)	5.91–5.52 (m)	5.50 (m)
H17	2.80 (br t, J=6.0 Hz)	2.80 (t, J=6.0 Hz)	2.84 (dt, J=6.3, 1.5 Hz)
H18	5.92–5.52 (m)	5.91–5.52 (m)	5.73 (m)
H19	5.09–4.86 (m)	5.09–4.88 (m)	4.96 (m), 4.96 (m)
H20	5.09–4.86 (m)	5.09–4.88 (m)	4.96 (m), 4.83 (m)
H21	1.43 (s)	1.43 (s)	1.39 (s)
H22	1.39 (s)	1.39 (s)	1.35 (s)
H24	3.63 (s)	3.63 (s)	3.56 (s)
NH	5.43 (br s)	5.43 (br s)	Not indicated
OH	5.09–4.86 (m)	5.09–4.88 (m)	Not indicated

Table 4. Table of comparison of the ^{13}C NMR data

C	Synthetic compound **39** present study 75 MHz, $CDCl_3$	Synthetic compound (−)-**39** previous total synthesis[9] 67.5 MHz, $CDCl_3$	(−)-Mycothiazole natural product[6] 75 MHz, $CDCl_3$
C2	Not accurately assigned (low signal/noise ratio)	179.4	179.4
C4	155.4	155.4	154.9
C5	112.0	112.0	111.8
C6	44.6	44.5	44.5
C7	78.1	78.1	78.1
C8	30.6	30.6	30.6
C9	130.6	130.6	130.8
C10	130.9	130.9	130.8
C11	Not accurately assigned (low signal/noise ratio)	142.5	142.4
C12	37.1	37.1	37.1
C13	39.4	39.4	39.4
C14	**34.7**	**34.7**	29.4
C15	**127.6**	**127.6**	126.7
C16	**130.5**	**130.4**	128.8
C17	**36.6**	**36.6**	31.5
C18	136.8	136.8	136.4
C19	115.2	115.2	115.0
C20	115.9	115.8	115.8
C21	26.7	26.7	26.6
C22	23.9	23.9	23.9
C23	157.2	157.1	157.1
C24	51.8	51.8	51.8

combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 90:10 to 85:15) to afford 190 mg (70%) of (*R*)-**13** as a colorless oil. The ee value (ee=54%) was determined by HPLC: Chiral OD-H column, elution rate: 1 mL/min, eluent: hexane, detection: 230–260 nm, injection: 10 μL (of a 2 mg/mL solution), retention times: (*S*)-enantiomer, 48.4 min; (*R*)-enantiomer, 55.5 min.

6.6.2. Synthesis of (*R*)-13 by an enantioselective allyltitanation. To a solution of ((*S*,*S*)-TADDOL)CpTiCl (980 mg, 1.60 mmol, 1.6 equiv) in ether (16 mL) at 0 °C was added dropwise allylmagnesium chloride (650 μL, 2 M in THF, 1.30 mmol, 1.3 equiv). After 3 h at 0 °C, a solution of aldehyde **12** (230 mg, 1.00 mmol) in ether (4 mL) was added at −78 °C. After 5 h at −78 °C, the reaction mixture was warmed to rt and hydrolyzed with a 45% aqueous solution of NH_4F. After stirring overnight at rt, the resulting mixture was filtered through Celite (ether). The organic layer was separated and washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was taken-up in pentane and the precipitated (*S*,*S*)-TADDOL (634 mg, 1.36 mmol, 85% recovery) was separated by filtration. The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography (pentane/ether 90:10 to 85:15) to afford 226 mg (82%) of (*R*)-**13** as a colorless oil. The ee value (ee=99%) was determined by HPLC with chiral OD-H column; $[\alpha]_D^{20}$ +20.2 (*c* 1.0, MeOH).

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Unexpected reactions of ferrocene acetal derived from tartaric acid with alkyllithium: competition between proton abstraction and nucleophilic attack

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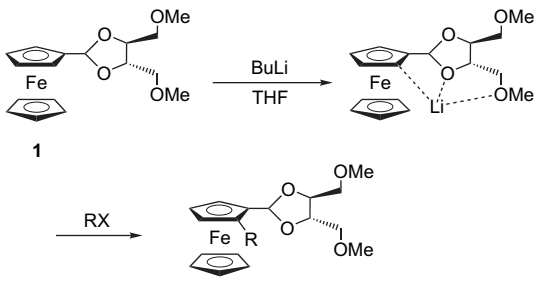
Abstract—We wished to prepare planar chiral compounds by the lithiation of acetal 2-ferrocenyl-(4*S*,5*S*)-bis(methoxymethyl)-1,3-dioxolane (**1**) with butyllithium followed by the reaction with an electrophile. However, the desired products were not observed and two unexpected products, 1-ferrocenyl-1-pentanol (**4**) of the nucleophilic attack product and 2-ferrocenyl-4,5-dimethylene-1,3-dioxolane (**5**) of the proton abstraction product, were isolated. Because the nucleophilic attack on acetal carbon is rarely reported so far and both products **4** and **5** may have some potential uses in organic synthesis, these unexpected reactions are investigated in detail. The mechanisms of these reactions are discussed.

1. Introduction

In recent years, ferrocene ligands with planar chirality have been studied and showed high activities and selectivities in many kinds of asymmetric reactions.[1] Currently there is much effort devoted to their design and synthesis. Ugi method[2] has been widely applied to prepare ferrocenyl compounds with planar chirality, and the strategy using *ortho*-directing groups as the attached chirality auxiliary is a key process for the creation of planar chirality.[3–11] A number of chiral *ortho*-directing substituents, such as sulfoxides,[3] acetals,[4] oxazolines,[5] hydrazones,[6] azepines,[7] sulfoximines,[8] pyrrolidine,[9] *O*-methyl ephedrine derivatives,[10] and oxazaphospholidine-oxide,[11] have been studied. Some of these *ortho*-directing groups, such as oxazoline moiety, can be used as ligands as it is. Some cannot be used directly, and need to be modified further. On the other hand, the ferrocenyl ligands with only planar chirality as chiral element have attracted the interest of many chemists for their excellent asymmetric catalytic activity.[12] To synthesize such ligands, it is necessary to remove central chirality or to destroy the *ortho*-directing chiral groups. Since acetal group as the *ortho*-directing auxiliary can be removed under mild conditions,[4] we set up a new route to introduce a planar chirality element to 2-ferrocenyl-(4*S*,5*S*)-bis(methoxymethyl)-1,3-dioxolane (**1**), which could be readily prepared from ferrocenecarboxaldehyde and available dimethyl L-tartrate, and transformation of which to an achiral aldehyde derivative would occur under mild conditions as known. Then, it should be rationalized that by coordination of the organolithium species to acetal oxygen, diastereoselective *ortho*-lithiation of **1**, followed by the reaction with electrophilic reagents such as chlorodiphenylphosphine, would result in the introduction of planar chirality (Scheme 1). However, different from our expectation, the lithiation of ferrocene acetal **1** with butyllithium did not occur at the Cp ring of the ferrocene, and two competitive reactions, proton abstraction and nucleophilic attack at the acetal group, were observed. Here we want to report this unexpected result of the lithiation of ferrocene acetal **1**.



1

Scheme 1.

Keywords: Lithiation; *ortho*-Directing groups; Ferrocene; Butyllithium; Dimethyl L-tartrate; Ferrocene acetal; Ferrocene alcohol.
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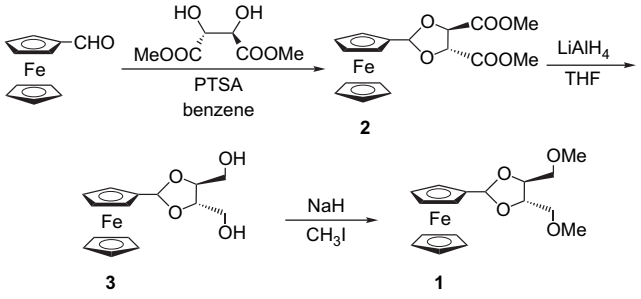
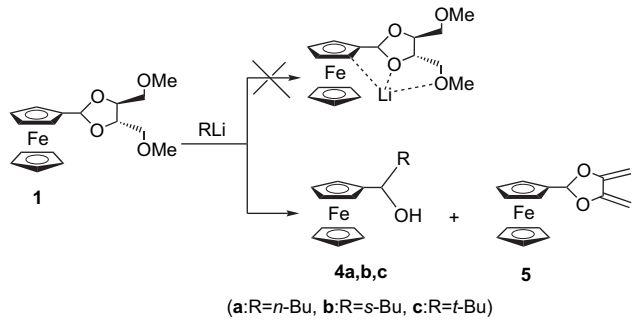
2. Results and discussion

As shown in Scheme 2, ferrocene acetal **1** was readily prepared from ferrocenecarboxaldehyde and commercially available dimethyl L-tartrate in three steps. A benzene solution of ferrocenecarboxaldehyde and 1 equiv dimethyl L-tartrate was heated to reflux in the presence of 0.1 equiv *p*-toluenesulfonic acid monohydrate for 13 h under simultaneous azeotropic removal of the resulting water. After work-up, an acetal intermediate **2** was obtained in 60% isolated yield. Then **2** was reduced by lithium aluminum hydride in THF to acetal diol intermediate **3** in the isolated yield of 51%. Next, diol **3** was treated with sodium hydride in THF and then reacted with iodomethane to afford acetal **1** in 96% isolated yield.



Scheme 2.

Then, attempt to prepare the planar chiral compounds, the lithiation of acetal **1** followed by the reaction with an electrophile, was undertaken. However, the desired products were not observed and two unexpected products, ferrocenyl alcohol **4** of the nucleophilic attack product and ferrocenyl diene **5** of the proton abstraction product, were isolated (Scheme 3). Because the nucleophilic attack on acetal carbon is rarely reported so far,[13] and ferrocene alcohol **4** and diene **5** may have some potential uses in organic synthesis, particularly, **4** has been used in investigations of the stereochemistry of nucleophilic substitution reactions at the chiral center and so on,[14] these unexpected reactions were then examined in detail.



Scheme 3.

First, the effects of the additive, the solvent, and the kind of butyllithium on the yields of the two products were investigated using **1**. The results are summarized in Table 1.

The results indicate that all of the above factors have effect on the two competitive reactions, namely the proton abstraction and nucleophilic attack reactions. When **1** was treated with *n*-butyllithium in ether, the proton abstraction reaction predominated and **5** was isolated as the main product (entry 1). When TMEDA was added to the above reaction system, the reaction became slower and nucleophilic attack product **4** was isolated as the main product (entry 2). The change of solvents from ether to THF and toluene also slows down the reactions and **4** was isolated as the main product (entries 3 and 4). We may also conclude that higher yield of **4** could be achieved with a bulkier alkyllithium (entries 1, 5, and 6). *s*-Butyllithium also afforded **5** as the main product. However, *tert*-butyllithium provided **4** as the main product in 53% yield. The ee of **4c** in entry 6 was determined as 54% by an ^{1}H NMR analysis using Eu(hfc)$_3$ as chiral shift reagent and the optical rotation of **4c** was determined to be +43°, by which the main enantiomer of **4c** was deduced to have an *S*-configuration.[14a]

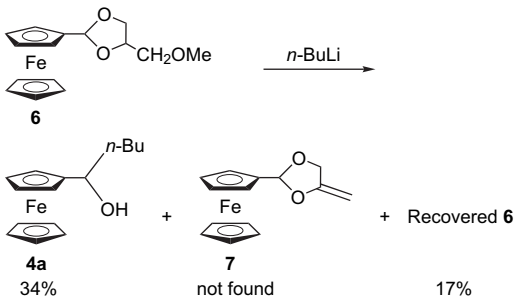
Table 1. Competition of proton abstraction and nucleophilic attack toward acetal **1** with butyllithiums[a]

Entry	BuLi	Solvent	Time (h)	Yield (%)[b]		
				4	**5**	Recovered **1**
1	*n*-BuLi	Ether	5.5	6	52	Trace
2	*n*-BuLi	Ether[c]	12	31	14	31
3	*n*-BuLi	THF	12	16	6	34
4	*n*-BuLi	Toluene	12	22	18	25
5	*s*-BuLi	Ether	1	14	52	Trace
6	*t*-BuLi	Ether	6	53	22	Trace

[a] Reactions were conducted at rt, except entry 6, which was carried out at −78 °C. The ratio of acetal **1**/butyllithium is 1:2.4.
[b] Isolated yield.
[c] TMEDA added (1 equiv to butyllithium).

Next, in order to investigate the reaction mechanism, the isolated diene **5** was treated with *n*-butyllithium in ether at room temperature for 10 h. No reaction was observed. This showed that the alcohol product **4** is not produced via diene **5**.

Then, ferrocene acetal **6** was prepared as a mixture of two diastereomers via the condensation of ferrocenecarboxaldehyde with glycerol followed by a methylation with iodomethane. The reaction of acetal **6** with *n*-butyllithium also afforded nucleophilic attack product **4a**, but no proton abstraction product **7** was observed (Scheme 4). This result, as well as the fact that **5** is inert toward *n*-butyllithium, indicates that for nucleophilic attack on acetal carbon, the chelation of two molecules of butyllithium with the oxygen atoms in acetal ring and methoxy groups is necessary. Therefore, a plausible mechanism for nucleophilic attack reaction of **6** and **1** can be elucidated as in Figures 1 and 2, respectively, although no reasonable by-product for identification was obtained. For the lithiation of **1**, the nucleophilic attack on acetal carbon would be suggested to occur on the side of acetal ring by butyllithium chelated with the methoxy oxygen on the bottom face of acetal ring trans to ferrocene, where it would be less hindered than from the top face of acetal ring (Fig. 2). The (*S*)-product of **4** obtained with *tert*-butyllithium also supported this postulation.



Scheme 4.

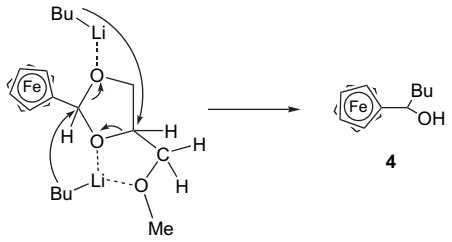


Figure 1.

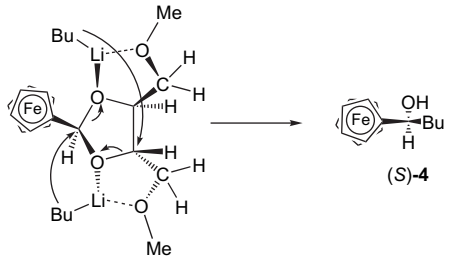


Figure 2.

Since no proton abstraction product **7** was afforded from the reaction of acetal **6** with *n*-butyllithium, a plausible mechanism for the reaction of proton abstraction is presented as shown in Figure 3. The two butyllithium molecules are chelated with two methoxy groups simultaneously, and the two protons are pulled out by each butyl anion nearby. With the butyllithium bearing a bulkier group or *n*-butyllithium combined with TMEDA, it would be more difficult for Li(I) to be chelated with two methoxy groups simultaneously.

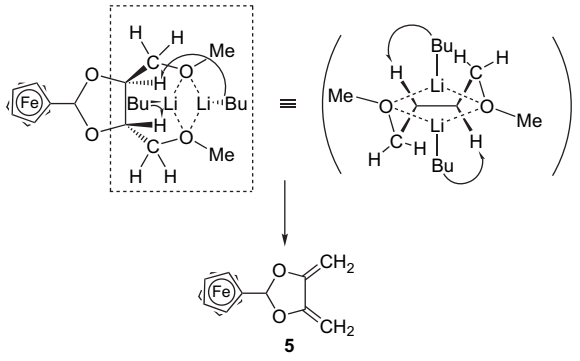


Figure 3.

The experimental results strongly supported this proposed mechanism (entries 1, 5, and 6 in Table 1).

3. Conclusions

In summary, for the preparation of planar chiral compounds, the lithiation of acetal **1** followed by the reaction with electrophile was conducted. However, the desired products were not found and two unexpected products, ferrocenyl alcohol **4** of the nucleophilic attack product and ferrocenyl diene **5** of the proton abstraction product, were isolated. It is clear that the nucleophilic attack and proton abstraction reactions occurred competitively, since the ratio of the two products changes with the change of reaction conditions. Their plausible mechanisms were proposed.

4. Experimental

4.1. General

Optical rotations were measured on a DIP-181 digital polarimeter. ^{1}H NMR spectra were recorded on a JEOL GSX-400 spectrometer and the chemical shifts were referenced to $CHCl_3$ (δ 7.27) in $CDCl_3$. The fast atom bombardment mass spectra (FAB-MS) and high-resolution mass spectra (HRMS) were obtained on a JEOL JMS-DX303HF spectrometer.

THF, ether, and toluene were freshly distilled from sodium and TMEDA from CaH_2 before use. All of the other chemicals used in synthetic procedures were of reagent grade. Merck 70–230 mesh silica gel was used for column chromatography. TLC plastic sheet (Silica gel 60 F_{254}) was used for the determination of R_f. All of the reactions were carried out under an argon atmosphere.

4.1.1. 2-Ferrocenyl-(4*S*,5*S*)-bis(methoxycarbonyl)-1,3-dioxolane 2. A solution of ferrocenecarboxaldehyde (3.9 g, 18.0 mmol), dimethyl L-tartrate (3.2 g, 18.0 mmol), and *p*-toluenesulfonic acid monohydrate (0.034 g, 0.18 mmol) in benzene (20 mL) was heated to reflux for 13 h under simultaneous azeotropic removal of the resulting water. The mixture was diluted with benzene, and neutralized with Na_2CO_3 powder. The neutralized solution was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The resulting residue was purified by chromatography (ethyl acetate–hexane 1:5) to provide the desired compound **2** (4.10 g, 60%). R_f=0.07 (ethyl acetate–hexane 1:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 1H), 4.92 (d, J 3.7 Hz, 1H), 4.79 (d, J 4.0 Hz, 1H), 4.50 (br, 1H), 4.39 (br, 1H), 4.24 (s, 5H), 4.21 (br, 2H), 3.88 (s, 3H), 3.82 (s, 3H).

4.1.2. 2-Ferrocenyl-(4*S*,5*S*)-bis(hydroxymethyl)-1,3-dioxolane 3. To a suspension of $LiAlH_4$ (0.82 g, 22 mmol) in dry THF (60 mL) was added **2** (4.1 g, 11 mmol) in dry THF (40 mL) within 35 min at 0 °C. The reaction mixture was heated to reflux for 3 h. To the reaction mixture, water (3.2 mL) and 4 M NaOH (1.2 mL) were added successively and slowly at 0 °C to quench the reaction. The solvent was evaporated and the residue was dissolved in dichloromethane (20 mL), and dried over $MgSO_4$. After

filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by chromatography (ethyl acetate) to provide the desired compound **3** as a yellow solid (1.7 g, 51%). R_f=0.30 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94 (s, 1H), 4.37–4.33 (m, 2H), 4.22–4.20 (m, 2H), 4.21 (s, 5H), 4.13–4.10 (m, 2H), 3.89–3.73 (m, 4H), 2.06–1.99 (m, 2H).

4.1.3. 2-Ferrocenyl-(4*S*,5*S*)-bis(methoxymethyl)-1,3-dioxolane 1. To a suspension of sodium hydride (0.40 g, 17 mmol) in dry THF (16 mL) was added **3** (1.7 g, 5.5 mmol) in dry THF (30 mL) at 0 °C and stirred for 0.5 h. To the mixture was added iodomethane (1.30 mL, 21 mmol) at 0 °C, then, the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane, then washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The resulting residue was purified by chromatography (ethyl acetate–hexane 1:2) to provide the desired compound **1** (1.8 g, 96%). R_f=0.30 (ethyl acetate–hexane 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (s, 1H), 4.35 (br m, 2H), 4.20 (s, 5H), 4.16 (br m, 2H), 4.14–4.09 (m, 1H), 4.06–4.01 (m, 1H), 3.63–3.52 (m, 4H), 3.45 (s, 3H), 3.43 (s, 3H). HRMS (FAB) calcd for $C_{17}H_{22}O_4Fe$: 346.0868, found: 346.0869. $[\alpha]_D^{14}$ +7.29 (*c* 1.10, $CHCl_3$).

4.1.4. 2-Ferrocenyl-4-methoxymethyl-1,3-dioxolane 6. A solution of ferrocenecarboxaldehyde (1.5 g, 7.0 mmol), glycerol (0.7 g, 7.6 mmol), *p*-toluenesulfonic acid monohydrate (0.070 g, 0.37 mmol) in benzene (20 mL) was heated to reflux for 6 h under simultaneous azeotropic removal of the resulting water. The mixture was diluted with ether, washed with brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (ethyl acetate–hexane 1:2) to provide the desired corresponding acetal compound (1.10 g). To a suspension of sodium hydride (0.28 g, 12 mmol) in dry THF (16 mL) was added the above acetal compound (1.10 g) in dry THF (40 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. To the mixture, iodomethane was added, and the reaction mixture was stirred for 20 min at 0 °C and then for 1.5 h at room temperature. Methanol was added to quench the reaction. The reaction mixture was diluted with ether, washed with brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure. The resulting residue was purified by chromatography (ethyl acetate–hexane 1:2) to provide the desired compound **6** (0.39 g, 18% for two steps). But the two diastereomers of **6** could not be separated. The ^{1}H NMR of **6** showed two sets of signals in a ratio of 1:1 and some of the signals are overlapped. R_f=0.33 (ethyl acetate–hexane 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (s, 1H), 5.75 (s, 1H), 4.36–4.34 (m, 2H), 4.34–4.28 (m, 4H), 4.21 (s, 5H), 4.20 (s, 5H), 4.19–4.16 (m, 5H), 4.03 (dd, *J* 8.4, 7.0 Hz, 1H), 3.88 (dd, *J* 8.1, 5.5 Hz, 1H), 3.77 (dd, *J* 8.1, 6.2 Hz, 1H), 3.59–3.43 (m, 4H), 3.44 (s, 3H), 3.41 (s, 3H). HRMS (FAB) calcd for $C_{15}H_{18}O_3Fe$: 302.0605, found: 302.0603.

4.2. General procedure for treatment of compound 1 with butyllithium

In a typical run, to a solution of acetal compound **1** (0.91 g, 2.6 mmol) in dry ether (30 mL) was added slowly 1.56 M *n*-butyllithium (4.1 mL, 6.3 mmol) within 60 min and the mixture was then stirred for 5.5 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane. The solution was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The resulting residue was subjected to chromatography (ethyl acetate–hexane 1:20) to provide compound **4a** (dark yellow oil, 0.042 g, 6%) and **5** (dark yellow oil, 0.381 g, 52%) (entry 1 in Table 1).

4.2.1. 1-Ferrocenylpentan-1-ol 4a. R_f=0.07 (ethyl acetate–hexane 1:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.34–4.29 (m, 1H), 4.26–4.24 (m, 1H), 4.21 (s, 5H), 4.20–4.15 (m, 3H), 1.93 (d, *J* 3.7 Hz, 1H), 1.73–1.53 (m, 2H), 1.49–1.25 (m, 4H), 0.91 (t, *J* 7.3 Hz, 3H). HRMS (FAB) calcd for $C_{15}H_{20}OFe$: 272.0864, found: 272.0864.

4.2.2. 2-Methyl-1-ferrocenylbutan-1-ol 4b. R_f=0.23 (ethyl acetate–hexane 1:10). There are two sets of signals with a rate of 1:1 in the spectrum of ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27–4.14 (m, 10H), 4.22 (s, 5H), 4.21 (s, 5H), 2.14 (d, *J* 1.5 Hz, 1H), 2.05 (d, *J* 1.8 Hz, 1H), 1.61–1.38 (m, 4H), 1.15–0.81 (m, 11H), 0.73 (d, *J* 7.0 Hz, 3H). HRMS (FAB) calcd for $C_{15}H_{20}OFe$: 272.0864, found: 272.0879.

4.2.3. 2,2-Dimethyl-1-ferrocenylpropan-1-ol 4c. R_f=0.14 (ethyl acetate–hexane 1:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.38–4.09 (m, 9H), 3.97 (s, 1H), 0.88 (s, 9H). HRMS (FAB) calcd for $C_{15}H_{20}OFe$: 272.0864, found: 272.0845. $[\alpha]_D^{15}$ +43 (*c* 0.5, $CHCl_3$), 54% ee, mp 78.0–82.0 °C.

4.2.4. 2-Ferrocenyl-4,5-dimethylene-1,3-dioxolane 5. R_f=0.31 (ethyl acetate–hexane 1:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.31 (s, 1H), 4.52 (d, *J* 2.9 Hz, 2H), 4.49 (d, *J* 2.9 Hz, 2H), 4.34 (m, 2H), 4.25 (s, 5H), 4.23 (m, 2H). HRMS (FAB) calcd for $C_{15}H_{14}O_2Fe$: 282.0343, found: 282.0343.

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Total syntheses of crinine and related alkaloids

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Abstract—Cyclizations of a bicyclic amine via an intramolecular Heck reaction followed by an oxidation reaction generated a tetracyclic spirocyclohexadione. From this useful intermediate, different crinine alkaloids such as crinine, buphanisine, flexinine, and augustine could be synthesized. Dienol/benzene or dienone/phenol rearrangement of this tetracyclic spirodienone afforded apogalanthamine analogs.

1. Introduction

The 2,3,4,4a-tetrahydro-1H,6H-5,10b-ethanophenanthridine (*cis*-3a-aryloctahydroindole nucleus) skeleton characterizes the crinine alkaloids such as crinine **1**, buphanisine **2**, flexinine **3**, and augustine **4**, which represent an important sub-class within the large family of *Amaryllidaceae* alkaloids (Fig. 1).[1] Many members of this sub-class display interesting biological properties including immuno-stimulatory,[2] cytotoxic,[3] antimalarial,[4] and anticholinergic activities.[5]

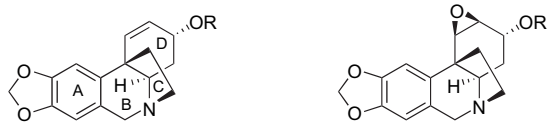

Figure 1. Structures of *Amaryllidaceae* alkaloids.

Several approaches have been developed to synthesize this skeleton, which includes a quaternary carbon. The incorporation of this sterically congested quaternary center is the critical element in the total synthesis of crinine-type alkaloids and numbers of synthetic efforts have emerged to solve this challenging problem.

The most common and generally useful syntheses developed thus far may be classified into four principal types based on the sequence of ring construction: AB→BD (biogenetic), A→C→B→D, A→C→D→B, A→D→C→B.[1,6] In the biosynthetic approach, amino spirodienones are the key intermediates, and an internal Michael cyclization serves as the main step for the construction of the skeleton by simultaneous creation of the B and D rings. The approach involving the sequence A→C→B→D requires the construction of an angular substituted phenanthridine, and the elaboration of the pyrrolidine D ring is achieved by the formation of a carbon/nitrogen bond via alkylation.

The key intermediates in the A→C→D→B and A→D→C→B approaches are 3a-arylhydroxyindoles and the formation of the B ring is generally achieved by using a Pictet–Spengler reaction.

The biomimetic approach is based on an intramolecular oxidative phenolic coupling of norbelladine analogs using vanadium oxyfluoride,[7] vanadium oxytrichloride,[8] thallium(III) trifluoroacetate,[9] anodic oxidation,[10] hypervalent iodine reagent (PIFA)[11] or on photolysis of bromophenolic compounds.[12]

An alternate synthetic route could in principle be based on intramolecular Heck cyclization.[6b,13] Our approach derives from a general program underway in the laboratory by which application of the Heck reaction followed by an oxidative step to produce spiro tricyclic dienones.[14,15] The intramolecular Heck reaction leading to 7-*exo*-trigonal cyclization has not often been described and ipso facto has rarely been used for the creation of a spiro quaternary center.

2. Results and discussions

Our synthesis started from the known aldehyde **5**[16] and amine **6**.[17] Reductive amination of these two components followed by functional transformation of the enol ether gave the amine **8**. Subsequent protection of the amine function with di-*tert*-butyl dicarbonate furnished compound **9** (75%), the precursor for the intramolecular Heck reaction

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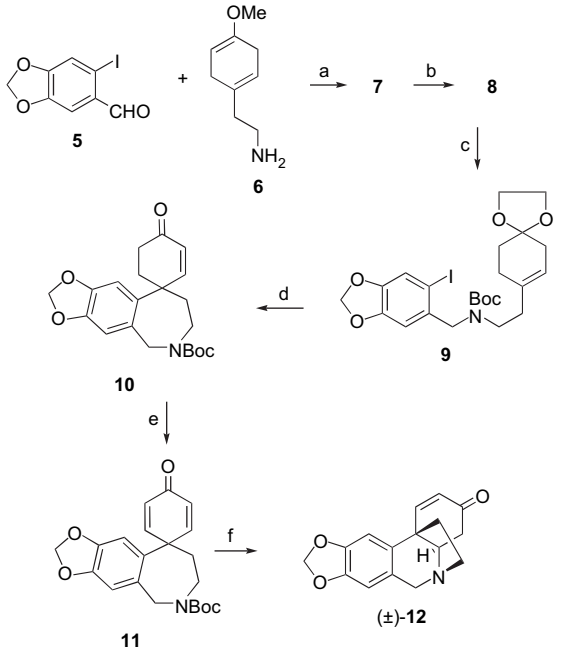
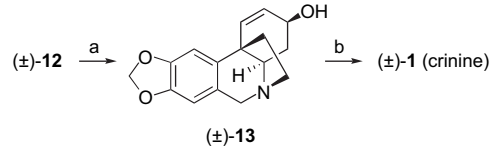
(Scheme 1). The key carbon bond-forming reaction was achieved by heating **9**, catalytic amounts of 10% [$Pd_2(dba)_3$], 20% dppe, and thallium acetate (1.2 equiv) in acetonitrile. After removal of the dioxolane group with hydrochloric acid to give **10** (56% for both steps), oxidation of the α,β-unsaturated ketone function of the latter to the corresponding dienone **11** was accomplished in 79% yield by using selenium dioxide and acetic acid in *t*-BuOH. Removal of the *N*-Boc group of **11** with trifluoroacetic acid resulted in spontaneous Michael addition to afford oxocrinine **12** (65%) (Scheme 1). A direct diastereoselective reduction of **12** to crinine **1** was not possible. However, enone **12** was stereoselectively reduced with the Luche reagent[18] to give epicrinine **13** (94%). Finally, Mitsunobu inversion of the C-3 hydroxyl provided (±)-crinine **1** (63%), which had spectral data in accordance with published values (Scheme 2).[19]

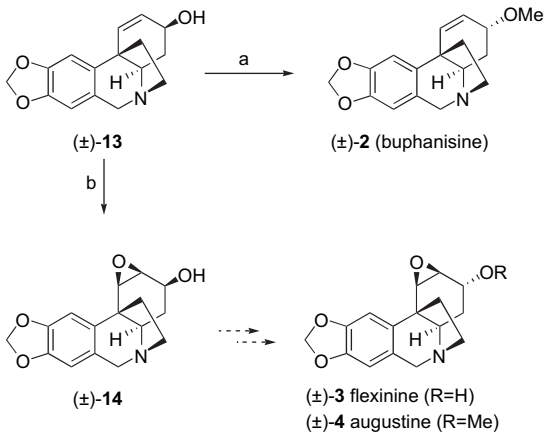


Scheme 1. Synthetic route of oxocrinine **12**: (a) MeOH, Δ, 1 h then $NaBH_4$, MeOH, AcOH, 0 °C–rt (100%); (b) $(CH_2OH)_2$, $BF_3{\cdot}Et_2O$, THF, rt (93%); (c) Boc_2O, NaOH, *t*-BuOH/H_2O, rt (75%); (d) (i) $Pd_2(dba)_3$, dppe, TIOAc, MeCN, D, 3 days; (ii) 1 N HCl, THF, rt (56%); (e) SeO_2, AcOH, *t*-BuOH, Δ, 27 h (79%); (f) TFA, CH_2Cl_2, rt then NaOH, MeOH, rt (65%).



Scheme 2. Synthetic route of (±)-crinine **1**: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, rt (94%); (b) DEAD, PPh_3, HCO_2H, THF, 3 days then 2 N NaOH, THF, rt (63%).

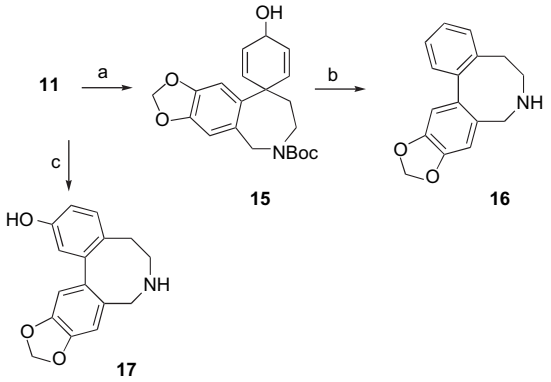
We next attempted to synthesize (±)-buphanisine **2**, which has been previously prepared via an A→C→D→B, sequence.[20] It should be noted that diastereoselective reduction of an enone function (precursor of the allylic methoxy) present in the *N*-benzyl indolone is not possible.[19] Buphanisine **2** was thus prepared by methanolysis of the allylic mesylate of (±)-epicrinine **13** with concomitant inversion of stereochemistry in 41% yield (Scheme 3).



Scheme 3. Synthetic route of buphanisine **2**, flexinine **3**, and augustine **4**: (a) (i) MsCl, NEt_3, CH_2Cl_2, rt; (ii) MeOH, rt, 40 h (41%); (b) CCl_3CN, H_2O_2 (3 equiv), TFA/CH_2Cl_2 (1/5), 24 h (42%).

Compound **12** also proved to be a valuable precursor for the synthesis of flexinine **3** and augustine **4**. These alkaloids have never been synthesized but have been isolated from different plants.[21,22] The antimalarial activities of (−)-augustine **4** in both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* are probably due to the presence of the epoxide functionality. Epoxidation of epicrinine **13** was performed with peroxymidic acid in the presence of trifluoroacetic acid to avoid oxidation of the nitrogen atom. The epoxide **14** was obtained only as the expected isomer (42%).

Finally, the synthesis of apogalanthamine analogs from spirodienone **11** via dienol/benzene[23] or dienone/phenol[24] rearrangement was examined. Reduction of **11** affords dienol **15**, which undergoes acid-catalyzed rearrangement to **16**.[25] In the same way, the dienone **11** was treated with HCl to convert it to the new biaryl **17** by dienone/phenol rearrangement (Scheme 4).



Scheme 4. Synthetic route of apogalanthamine analogs **16** and **17**: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 2 h, rt (68%); (b) concd HCl, MeCN, 95 °C, 24 h (65%); (c) concd HCl, MeCN, 1.5 h, rt (73%).

3. Conclusion

In summary, an intramolecular Heck reaction followed by a dehydrogenation reaction provided the key intermediate spirocyclohexanone **11** and an efficient strategy for the

construction of numerous alkaloids in the crinine and apogalanthamine series. An asymmetric route to these alkaloids from the valuable prochiral dienone intermediate **11** is in progress.

4. Experimental

4.1. General

NMR spectra were determined on Brucker Avance-300 with tetramethylsilane as internal reference. HMRS mass spectra were obtained on a MALDI-TOF spectrometer. Infrared (IR) spectra were recorded on a Fourier Perkin–Elmer Spectrum BX FT-IR. Elemental analyses were performed by the 'Service de microanalyses' (ICSN, CNRS, Gif-sur-Yvette).

4.2. Materials

THF was distilled from sodium/benzophenone, CH_3CN from CaH_2, MeOH from Mg/I_2, CH_2Cl_2 from P_2O_5, and NEt_3 from KOH. All separations were carried out under flash chromatographic conditions on Merck silica gel 60 (70–230 mesh) at medium pressure (200 mbar). TLC was done on Merck silica gel plates (60 F_{254}) with a fluorescent indicator.

4.2.1. [2-Iodo-4,5-methylenedioxybenzyl]-[2-(4-methoxycyclohexa-1,4-dienyl)-ethyl]amine (7). A solution of **5** (1.45 g, 5.25 mmol) and amine **6** (813.5 mg, 5.32 mmol) in dry MeOH (80 ml) was refluxed for 1 h. The solution was cooled at room temperature, then $NaBH_4$ (397 mg, 10.5 mmol, 2 equiv) was added and the pH was adjusted to 4–5 using acetic acid. The reaction mixture was stirred at room temperature for 30 min. The solvent was removed in vacuo. The residue was diluted with AcOEt and washed with saturated aqueous Na_2CO_3. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Compound **7** (2.34 g, 100%) was isolated as a yellow oil. HRMS (ESI, *m/z*) calcd for $C_{17}H_{21}NIO_3$ (MH^+): 414.0553, found: 414.0542. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.23 (1H, s), 6.91 (1H, s), 5.95 (2H, s), 5.46 (1H, s), 4.61 (1H, s), 3.78 (2H, s), 3.72 (3H, s), 2.71 (6H, m), 2.22 (2H, t, J=6.8). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 153.0, 148.5, 147.5, 135.8, 133.1, 119.3, 118.6, 110.0, 101.6, 90.4, 87.1, 58.1, 53.9, 46.6, 37.0, 29.2. IR ($CHCl_3$) ν (cm^{-1}): 2962, 2831, 1697, 1664, 1504, 1261, 1234, 1099, 1040, 1015.

4.2.2. [2-(1,4-Dioxa-spiro[4,5]dec-7-en-8-yl)-ethyl]-[2-iodo-4,5-methylenedioxybenzyl]amine (8). To a solution of **7** (2.28 g, 5.53 mmol) in dry THF (160 ml) were added at 0 °C ethylene glycol (0.62 ml, 0.11 mmol, 2 equiv) and $BF_3\cdot OEt_2$ (0.72 ml, 5.53 mmol, 1 equiv). After being stirred for 12 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and evaporated. Compound **8** (2.33 g, 93%) was isolated as a yellow oil. HRMS (ESI, *m/z*) calcd for $C_{20}H_{23}NIO_4$ (MH^+): 444.0671, found: 444.0672. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.23 (1H, s), 6.91 (1H, s), 5.95 (2H, s), 5.30 (1H, s), 3.98 (4H, s), 3.72 (2H, s), 2.69 (2H, t, J=6.6), 2.26–2.14 (6H, m), 1.76 (2H, t, J=6.6). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 148.5, 147.5, 135.8, 135.1, 120.1, 118.6, 110.0, 108.0, 101.6, 87.0, 64.4, 58.0, 46.6, 37.3, 35.7, 31.2, 27.4. IR ($CHCl_3$) ν (cm^{-1}): 2958, 2927, 1503, 1476, 1261, 1234, 1102, 1040.

4.2.3. [2-(1,4-Dioxa-spiro[4,5]dec-7-en-8-yl)-ethyl]-[2-iodo-4,5-methylenedioxybenzyl]carbamic acid *tert*-butyl ester (9). To a solution of **8** (2.15 g, 4.86 mmol) in 1/1 mixture of *t*-BuOH/H_2O (260 ml) were added Boc_2O (1.27 g, 5.84 mmol, 1.2 equiv) and 1 N aqueous NaOH (6.8 ml, 1.4 equiv). After being stirred at room temperature for 4 h, the solvents were evaporated. The residue was extracted with AcOEt. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (elution with heptane/AcOEt 90/10, 80/20, 70/30) to give **9** (1.98 g, 75%) (rotamers) as a pale yellow oil. HRMS (ESI, *m/z*) calcd for $C_{23}H_{30}NIO_6Na$ (MNa^+): 566.1004, found: 566.1016. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.22 (1H, s), 6.72 (1H, m), 5.95 (2H, s), 5.30 (1H, s, $H_{7'}$), 4.39 and 4.32 (2H, s), 3.93 (4H, s), 3.29 and 3.19 (2H, m), 2.23–2.20 (6H, m), 1.78–1.72 (2H, m), 1.54 and 1.43 (9H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.8, 155.3, 148.8, 147.6, 134.7, 133.8, 120.6, 120.4, 118.5, 108.2, 107.9, 107.7, 101.6, 86.0, 79.9, 64.4, 55.3, 54.7, 46.0, 45.4, 35.9, 35.2, 35.7, 31.2, 28.4, 27.5. IR ($CHCl_3$) ν (cm^{-1}): 2957, 1685, 1503, 1477, 1234, 1157, 1107, 1040.

4.2.4. *tert*-Butyl-7,8-(methylenedioxy)-4′-oxo-2,3,4,5-tetrahydro-1H-[2]-benzazepine-5-spiro-1′-cyclohexa-2′-ene-2-carboxylate (10). A mixture of $Pd_2(dba)_3$ (218.5 mg, 0.24 mmol, 0.1 equiv) and dppe (190.1 mg, 0.48 mmol, 0.2 equiv) in dry CH_3CN (30 ml) was stirred at room temperature for 1 h. Then TlOAc (753.6 mg, 2.86 mmol, 1.2 equiv) and **9** (1.29 g, 2.38 mmol) in CH_3CN (50 ml) were added. After being stirred at 90 °C for 72 h, the reaction mixture was filtered through Celite (elution with AcOEt) and evaporated. The residue was dissolved in THF (60 ml), then 1 N aqueous HCl (32 ml) was added. After being stirred at room temperature for 12 h, the solvent was evaporated and the residue was extracted with AcOEt. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue (elution with heptane/AcOEt 90/10, 80/20, 70/30) afforded **10** (494.3 mg, 56%) (rotamers) as a pale yellow solid. HRMS (ESI, *m/z*) calcd for $C_{21}H_{25}NO_5Na$ (MNa^+): 394.1602, found: 371.4269. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.79 (1H, d, J=10.4), 6.72 (1H, s), 6.64 (1H, s), 6.09 (1H, d, J=10.2), 5.93 (2H), 4.48, 4.41 (2H, s), 3.74 (2H, m), 2.42–2.17 (3H, m), 1.92 (1H, m), 1.43, 1.37 (9H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 199.1, 157.7, 154.9, 154.6, 146.8, 146.1, 145.9, 135.9, 135.4, 132.0, 131.7, 127.3, 111.0, 110.5, 109.7, 101.3, 80.0, 50.4, 49.7, 44.7, 44.0, 43.5, 36.4, 35.9, 34.1, 33.3, 33.0, 28.4. IR ($CHCl_3$) ν (cm^{-1}): 2961, 2930, 1682, 1506, 1488, 1261, 1162, 1041.

4.2.5. *tert*-Butyl-7,8-(methylenedioxy)-4′-oxo-2,3,4,5-tetrahydro-1H-[2]-benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-2-carboxylate (11). A mixture of α,β-unsaturated ketone **10** (1.03 g, 2.78 mmol), SeO_2 (1.24 g, 11.1 mmol, 4 equiv), acetic acid (5.6 ml) in *t*-BuOH (76 ml) was heated at reflux for 27 h. After cooling at room temperature, the

reaction mixture was filtered through Celite (elution with AcOEt) and extracted with AcOEt. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue (elution with heptane/AcOEt 90/10, 80/20, 70/30) yielded **11** (806.8 mg, 79%) (rotamers) as a yellow solid. HRMS (ESI, *m/z*) calcd for $C_{21}H_{23}NO_5Na$ (MNa^+): 392.1471, found: 392.1474. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.97 (2H, d, J=10.1), 6.74, 6.62 (1H, s), 6.54 (1H, s), 6.28 (2H, d, J=10.1), 5.94 (2H), 4.57, 4.48 (2H, s), 3.73 (2H, m), 2.27 (2H, t, J=6.1), 1.47 and 1.39 (9H, s). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 185.6, 155.0, 154.7, 153.8, 147.0, 146.9, 132.7, 132.3, 129.3, 126.8, 110.5, 110.0, 109.6, 101.5, 80.4, 80.2, 48.9, 48.6, 47.8, 44.5, 43.6, 35.8, 35.5, 28.5, 28.4. IR ($CHCl_3$) ν (cm^{-1}): 2981, 2930, 1686 (C═O), 1665 (C═O), 1624 (C═C), 1487, 1234, 1040.

4.2.6. (±)-Oxocrinine (12). To a solution of **11** (602.3 mg, 1.63 mmol) in CH_2Cl_2 (45 ml) was added trifluoroacetic acid (14 ml). After 30 min at room temperature, the mixture was basified with solid NaOH and dissolved in aqueous MeOH. After 1 h, the solvents were evaporated and the residue was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography (elution with CH_2Cl_2/MeOH 95/5) yielded **12** (286.3 mg, 65%) as white powder. HRMS (ESI, *m/z*) calcd for $C_{16}H_{16}NO_3$ (MH^+): 270.1133, found: 270.1130. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.61 (1H, d), 6.9 (1H, s), 6.51 (1H, s), 6.08 (1H, d, J=10.4), 5.91 (2H, ABq), 4.39 (1H, d, J=16.9), 3.79 (1H, d, J=16.9), 3.63 (1H, dd, J_1=5.6, J_2=13.0), 3.53 (1H, ddd, J_1=3.8, J_2=10.4, J_3=13.7), 3.00 (1H, ddd, J_1=6.2, J_2=8.8, J_3=13.3), 2.68 (1H, dd, J_1=5.6, J_2=16.8), 2.46 (1H, dd, J_1=13.0, J_2=16.8), 2.36 (1H, ddd, J_1=3.8, J_2=8.8, J_3=12.8), 2.16 (1H, ddd, J_1=6.2, J_2=10.4, J_3=12.8). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 198.2, 149.5, 146.6, 146.4, 136.0, 128.8, 126.4, 107.3, 102.5, 101.0, 68.9, 61.9, 54.1, 44.8, 44.7, 40.2. IR ($CHCl_3$) ν (cm^{-1}): 2929, 2890, 1682, 1505, 1484, 1248, 1234, 1042.

4.2.7. (±)-Epicrinine (13). To a solution of (±)-oxocrinine **12** (50.5 mg, 0.188 mmol) in dry MeOH (5 ml) were added $NaBH_4$ (14.9 mg, 0.394 mmol, 2.1 equiv) and $CeCl_3 \cdot 7H_2O$ (146.9 mg, 0.394 mmol, 2.1 equiv). After 1 h at room temperature, the mixture was filtered through Celite (elution with MeOH) and evaporated. The residue was dissolved in CH_2Cl_2, washed twice with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and evaporated. (±)-Epicrinine **13** (48.1 mg, 94%) was isolated as a white powder. HRMS (ESI, *m/z*) calcd for $C_{16}H_{18}NO_3$ (MH^+): 272.1282, found: 272.1287. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.77 (1H, s), 6.44 (1H, s), 6.36 (1H, dd, J_1=2.3, J_2=10.2), 5.77 (2H, s), 5.66 (1H, d, J=10.4), 4.26 (1H, d, J=16.8), 3.71 (1H, m), 3.31 (1H, ddd, J_1=4.7, J_2=10.4, J_3=14.3), 3.17 (1H, dd, J_1=3.8, J_2=13.4), 2.87 (1H, ddd, J_1=6.4, J_2=8.5, J_3=14.7), 2.13–1.94 (3H, m), 1.51 (1H, ddd, J_1=10.7, J_2=11.9, J_3=13.2). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 147.9, 147.4, 139.6, 132.8, 129.3, 126.3, 107.9, 103.9, 102.1, 68.1, 62.6, 53.7, 46–50, 45.8, 35.1. IR ($CHCl_3$) ν (cm^{-1}): 3603, 2956, 2856, 1504, 1483, 1250, 1236, 1041.

4.2.8. (±)-Crinine (1). To a solution of **13** (40.2 mg, 0.148 mmol) in dry THF (1.5 ml) were added PPh_3 (78.0 mg, 0.297 mmol, 2 equiv), distilled formic acid (25 µl, 0.663 mmol, 4.5 equiv), and DEAD (55 µl, 0.302 mmol, 2 equiv). The reaction was allowed to proceed under argon at room temperature for 3 days, while adding every 24 h extra portions of PPh_3 (78.0 mg), formic acid (25 µl), and DEAD (55 µl). The reaction mixture was then evaporated. Flash chromatography (elution with CH_2Cl_2/MeOH 97/3, 92/8, 90/10) yielded 3-*O*-formyl epicrinine (11.4 mg, 26%) as a white powder, a mixture (5.9 mg, 3-*O*-formyl epicrinine/3-*O*-formyl-crinine 35/65), and 3-*O*-formyl-crinine (28.9 mg, 65%) as a white powder. To a solution of 3-*O*-formyl-crinine (28.9 mg, 0.097 mmol) in THF (3 ml) was added 2 N aqueous NaOH (2.2 ml). After 1.5 h at room temperature, the solvent was evaporated. The residue was dissolved in $CHCl_3$, washed with 33% aqueous NH_3, and extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. (±)-Crinine **1** (25.3 mg, 97%) was yielded as a white powder. HRMS (ESI, *m/z*) calcd for $C_{16}H_{18}NO_3$ (MH^+): 272.1287, found: 272.1287. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.78 (1H, s), 6.59 (1H, d, J=9.8), 6.42 (1H, s), 5.97 (1H, dd, J_1=5.1, J_2=9.8), 5.83 (2H, ABq), 4.42 (1H, d, J=16.8), 4.36 (1H, m), 3.75 (1H, d, J=16.8), 3.39–3.27 (2H, m), 2.85 (1H, ddd, J_1=5.9, J_2=8.9, J_3=13.9), 2.19 (1H, ddd, J_1=4.2, J_2=9.0, J_3=12.7), 1.97–1.88 (2H, m), 1.75 (1H, ddd, J_1=4.2, J_2=J_3=13.6). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 146.2, 145.8, 138.2, 132.3, 127.5, 126.2, 107.0, 102.9, 100.8, 64.2, 62.9, 62.1, 53.6, 44.3, 44.2, 32.8. IR ($CHCl_3$) ν (cm^{-1}): 3690, 3343, 2853, 1602, 1504, 1262, 1004, 938.

4.2.9. (±)-Buphanisine (2). To a solution of **13** (45.1 mg, 0.17 mmol) in dry CH_2Cl_2 (4.4 ml) were added Et_3N (60 µl, 0.43 mmol, 2.5 equiv) and MsCl (33 µl, 0.43 mmol, 2.5 equiv). After 2 h at room temperature, the solvent was evaporated, and the residue was dissolved in dry MeOH (5 ml). After 40 h at room temperature, the solvent was evaporated, the residue was dissolved in $CHCl_3$, washed with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Preparative thin-layer chromatography (elution with CH_2Cl_2/MeOH 9/1) yielded (±)-buphanisine **2** (19.6 mg, 41%) as a white powder. HRMS (ESI, *m/z*) calcd for $C_{17}H_{20}NO_3$ (MH^+): 286.1438; found: 286.1443. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.81 (1H, s), 6.59 (1H, d, J=10.0), 6.45 (1H, s), 5.94 (1H, ddd, J_1=1.0, J_2=5.1, J_3=10.0), 5.86 (2H, d, J=1.3), 4.38 (1H, d, J=16.9), 3.81 (1H, m), 3.75 (1H, d, J=16.9), 3.34 (3H, s), 3.39–3.29 (2H, m), 2.87 (1H, ddd, J_1=5.8, J_2=9.2, J_3=12.8), 2.19–2.03 (2H, m), 1.89 (1H, ddd, J_1=5.8, J_2=10.6, J_3=12.0), 1.58 (1H, ddd, J_1=4.0, J_2=J_3=13.6). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.0, 145.6, 138.5, 133.0, 126.4, 125.3, 106.9, 102.9, 100.7, 72.7, 63.0, 62.4, 56.4, 53.6, 44.3, 28.9. IR ($CHCl_3$) ν (cm^{-1}): 2962, 2930, 1602, 1505, 1261, 1092, 1041, 1014.

4.2.10. (±)-1β,2β-Epoxy-epicrinine (14). A solution of CCl_3CN (26 µl, 0.26 mmol, 3 equiv) and 30% aqueous H_2O_2 (30 µl, 0.26 mmol, 3 equiv) in dry CH_2Cl_2 (0.5 ml) was stirred at room temperature for 1.5 h. Then, the solution

was transferred via syringe to a flask containing **13** (23.5 mg, 0.09 mmol, 1 equiv) in a mixture of CH_2Cl_2/TFA (1.1 ml/0.3 ml). After 24 h at room temperature, the reaction mixture was basified with 33% aqueous NH_3 (pH 10) and extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Preparative thin-layer chromatography (elution with CH_2Cl_2/MeOH 9/1) yielded **14** (10.4 mg, 42%) as a white powder. HRMS (ESI, *m/z*) calcd for $C_{16}H_{17}NO_4$ (MH^+): 288.1236; found: 288.1225. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.89 (1H, s), 6.49 (1H, s), 5.91 (2H, s), 4.38 (1H, d, J=16.9), 4.14 (1H, ddd, J_1=10.6, J_2=5.4, J_3=1.6), 3.84 (1H, d, J=3.8), 3.72 (1H, d, J=16.9), 3.46 (1H, d, J=3.8), 3.30 (1H, ddd, J_1=4.5, J_2=10.9, J_3=15.3), 2.91 (1H, dd, J_1=3.1, J_2=13.3), 2.84 (1H, ddd, J_1=5.8, J_2=9.2, J_3=13.0), 2.48 (1H, ddd, J_1=5.8, J_2=10.9, J_3=13.4), 2.0 (1H, ddd, J_1=4.7, J_2=9.2, J_3=13.4), 1.84 (1H, ddd, J_1=3.4, J_2=4.5, J_3=12.1), 1.39 (1H, ddd, J_1=10.9, J_2=J_3=12.1). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.5, 146.1, 137.1, 126.0, 107.2, 102.7, 101.0, 68.2, 67.5, 62.0, 58.5, 55.1, 52.5, 41.4, 38.7, 30.5. IR ($CHCl_3$) ν (cm^{-1}): 3690, 2926, 1505, 1483, 1314, 1262, 1002, 938.

4.2.11. *tert*-Butyl-7,8-(methylenedioxy)-4′-hydroxy-2,3,4,5-tetrahydro-1H-[2]-benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-2-carboxylate (15). To a solution of **11** (104.4 mg, 0.283 mmol) in dry MeOH (7 ml) were added $CeCl_3 \cdot 7H_2O$ (221.3 mg, 0.594 mmol, 2.1 equiv) and $NaBH_4$ (22.5 mg, 0.595 mmol, 2.1 equiv). After 1 h at room temperature, the mixture was filtered though Celite (elution with MeOH) and evaporated. The residue was diluted with $CHCl_3$, washed with 33% aqueous NH_3, and extracted with $CHCl_3$. The combined organic layers were washed saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Preparative thin-layer chromatography (elution: heptane/AcOEt 1/1) yielded a 1/1 separable diastereoisomeric mixture **15** (74.0 mg, 71%) (rotamers) as a white solid. HRMS (ESI, *m/z*) calcd for $C_{21}H_{28}NO_5Na$ (MNa^+): 394.1626; found: 394.1630. IR ($CHCl_3$) ν (cm^{-1}): 3691, 3586, 2959, 1684, 1602, 1505, 1416, 1261, 1099 (C–O), 1011 (C–O). Fraction 1: **15a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.60, 6.57 (1H, s), 6.65, 6.53 (1H, s), 5.9–5.86 (6H, m), 4.61 (1H, m), 4.47, 4.39 (2H, s), 3.63 (2H, m), 2.09 (2H, m), 1.42, 1.34 (9H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.1, 146.7, 145.6, 136.1, 135.8, 135.7, 135.3, 131.5, 131.2, 125.3, 125.1, 110.9, 110.6, 109.9, 109.5, 101.2, 79.8, 62.2, 49.0, 48.1, 45.1, 43.8, 43.5, 37.9, 37.8, 28.5, 28.4. Fraction 2: **15b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.74, 6.70 (1H, s), 6.67, 6.55 (1H, s), 5.9–5.87 (6H, m), 4.54 (1H, m), 4.49, 4.40 (2H, s), 3.63 (2H, m), 2.04 (2H, m), 1.44, 1.36 (9H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.0, 146.5, 145.6, 135.6, 131.5, 131.1, 125.4, 111.1, 110.7, 109.9, 109.4, 101.2, 79.8, 61.7, 49.0, 48.1, 45.4, 43.3, 42.5, 38.2, 38.0, 28.5, 28.4.

4.2.12. 2,3-Methylenedioxy-5,6,7,8-tetrahydrodibenzo[*c*,*e*]-azocine (16). To a solution of **15** (37.3 mg, 0.10 mmol) in dry CH_3CN (5 ml) was added 35% aqueous HCl. After 1.5 h at room temperature, the reaction mixture was basified with 33% aqueous NH_3 (pH 10) and extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Preparative thin-layer chromatography (elution: CH_2Cl_2/MeOH 9/1) afforded **16** (18.6 mg, 73%) as a white solid. HRMS (ESI, *m/z*) calcd for $C_{16}H_{16}NO_2$ (MH^+): 254.1187; found: 254.1183. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.37–7.22 (4H, m), 6.88 (1H, s), 6.80 (1H, s), 6.00 (2H, ABq, J=1.0), 3.87 (1H, d, J=13.9), 3.42 (1H, dd, J_1=6.8, J_2=13.9), 3.11 (1H, d, J=13.9), 2.86–2.78 (2H, m), 2.41 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 147.6, 146.7, 140.7, 139.9, 133.4, 133.1, 129.4, 129.3, 128.1, 126.1, 109.5, 109.4, 101.2, 50.2, 49.0, 36.3. IR ($CHCl_3$) ν (cm^{-1}): 3064, 2928, 1702, 1675 (Ar), 1601 (Ar), 1504, 1262, 1011.

4.2.13. 2,3-Methylenedioxy-5,6,7,8-tetrahydrodibenzo-[*c*,*e*]-azocin-11-ol (17). To a solution of **11** (50.5 mg, 0.188 mmol) in dry CH_3CN (7 ml) was added 35% aqueous HCl (4.6 ml) at room temperature. After 24 h at 95 °C, the reaction mixture was cooled at room temperature, basified with 33% aqueous NH_3 (pH 10), and extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Flash chromatography (alumina, elution: CH_2Cl_2, CH_2Cl_2/MeOH 97.5/2.5, 96/4, 90/10) afforded **17** (49.9 mg, 62%) as a white powder. HRMS (ESI, *m/z*) calcd for $C_{16}H_{16}NO_3$ (MH^+): 270.1120, found: 270.1130. ^{1}H NMR (CD_3OD, 300 MHz) δ (ppm): 7.04 (1H, d, J=8.3), 6.85 (1H, s), 6.75 (1H, dd, J_1=2.6, J_2=8.3), 6.70 (1H, s), 6.63 (1H, d, J=2.6), 5.95 (2H, ABq, J=1.0), 3.73 (1H, d, J=13.8), 3.23 (1H, dd, J_1=7.0, J_2=13.8), 3.02 (1H, d, J=13.8), 2.74–2.59 (2H, m), 2.20 (1H, dd, J_1=10.0, J_2=14.0). ^{13}C NMR (CD_3OD, 75.5 MHz) δ (ppm): 156.6, 149.0, 148.3, 142.1, 135.6, 133.6, 133.2, 131.5, 116.7, 116.3, 110.7, 109.9, 101.2, 50.7, 50.2, 35.6. IR ($CHCl_3$) ν (cm^{-1}): 3691 (O–H), 3599 (O–H), 3290 (NH), 2961, 2855, 1604 (Ar), 1572 (Ar), 1503, 1261, 1040 (C–O), 1015 (C–O).

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Synthesis of *ortho*-perfluoroalkyl phenones from hemifluorinated enones as key building blocks

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Abstract—The title compounds are prepared by cycloaddition of perfluoroalkenyl ketones and 1,3-dienes, with a subsequent aromatization by basic dehydrofluorination. The perfluoroalkenyl ketones were prepared by the reaction of perfluoroorganometallic reagents with acylsilanes. The transformation may be performed more efficiently in a simplified process without purification of the intermediate cycloadducts. The overall methodology is an interesting entry to *ortho*-perfluoroalkyl phenones with the possibility to vary the substitution at the acyl and on the ring moiety.

1. Introduction

In recent years, the synthesis of fluorinated organic compounds has become an important field in organic chemistry due to the unique properties of the fluorine atom able to significantly modify their physico-chemical and biological properties.[1] Substitution of a hydrogen atom by a fluorine or introduction of a trifluoromethyl group may improve the pharmacodynamic and the pharmacokinetic profiles of a bioactive molecule by concomitant alteration of its electronic, steric, lipophilic, or metabolic characteristics. In particular, considerable efforts have been devoted to the introduction of a trifluoromethyl group into organic molecules.[2]

Among these fluorinated molecules, fluorinated aromatics and especially trifluoromethylated ones have been extensively developed in the pharmaceutical and agrochemical fields.[3] Structures of some examples of such molecules are presented in Figure 1.

Aromatics bearing a longer *F*-alkyl chain have also been extensively studied for their applications as amphiphilic molecules or as fluorous catalysts in asymmetric catalysis.[4]

We have recently reported an exploratory study of the [4+2] cycloaddition reactions with hemifluorinated enones.[5] These substrates, in contrast to simple fluorovinylic derivatives,[6] behave as excellent dienophiles in normal electron-demand Diels–Alder reactions, due to the additive withdrawing

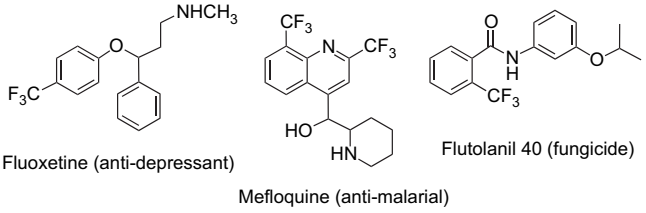

Figure 1. Some selected trifluoromethyl aromatic compounds with biological activities.

effects of the vicinal perfluoroalkyl and acyl groups. Recently, the application of vinyl fluorides in cycloadditions has been reviewed.[7] The polyfluorinated dienophiles used in this work were of variable structure (aromatic, aliphatic, carbohydrate-derived) and were prepared by our general method starting from acylsilanes and perfluoroorganometallic reagents.[8] This methodology was carried out with various dienes such as cyclopentadienes or buta-1,3-dienes and gave access to polyfluorinated norbornenes and cyclohexenes.[5] The polyfluorinated cycloalkenes thus obtained are original compounds, which deserved to be considered as elaborated intermediates for further transformations. In particular, one could expect an easy aromatization under basic conditions owing to the vicinal difluoro pattern present in their structures. Thus, hemifluorinated enones should be building blocks of choice toward *ortho*-perfluoroalkyl phenones.

We report here the synthesis of polysubstituted *ortho*-perfluoroalkyl phenones in a simple two-step process: a [4+2] cycloaddition between a diene and a hemifluorinated enone followed by a double HF elimination under basic conditions as shown in the following retrosynthetic scheme (Scheme 1).

Keywords: Organofluorine compounds; Aromatics; Enones; Diels–Alder reactions; Fluorinated phenones.
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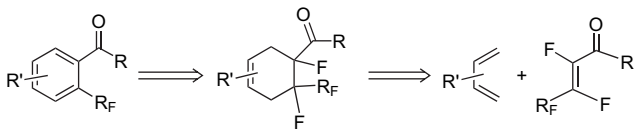


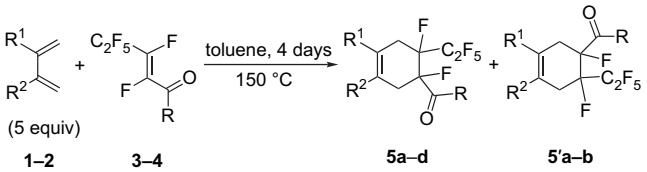
Scheme 1.

2. Results and discussion

As previously reported, the cyclohexenes were prepared in 64–77% isolated yields by heating for several days the dienes **1** and **2** and the enones **3** and **4** in toluene at 150 °C in a sealed tube (Table 1).[5] The reaction with isoprene gave a mixture of isomers in the ratio 60/40. The poor regioselectivity observed could be attributed to a weak polarization of the enone due to the presence of an electron withdrawing group at each carbon of the double bond (CO group and *F*-alkyl chain). The regioisomers were not separated and the assignment of their structure was deduced from the subsequent aromatic derivatives.

Treatment of these cycloadducts by potassium hydroxide in methanol induced the double elimination of hydrogen fluoride[9] and led to the expected *ortho*-perfluoroalkylated phenones **6** in 66–82% isolated yields (Table 2). Compounds **5** and **5′** were converted into the corresponding phenones **6** and **6′** with a similar regioisomeric ratio.

Table 1. Diels–Alder reactions of buta-1,3-dienes and hemifluorinated enones

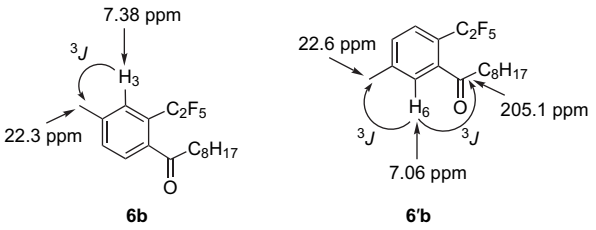


(5 equiv)

1–2 **3–4** **5a–d** **5′a–b**

Entry[a]	Diene	R^1	R^2	Enone	R	Product	Ratio **5/5′**[b]	Yield (%)
1	**1**	Me H	H Me	**3**	Ph	**5a** **5′a**	62/38	64
2	**1**	Me H	H Me	**4**	C_8H_{17}	**5b** **5′b**	51/49	65
3	**2**	Me	Me	**3**	Ph	**5c**	—	76
4	**2**	Me	Me	**4**	C_8H_{17}	**5d**	—	77

[a] Reaction conditions: 5.0 equiv of diene, toluene 10 mL at 150 °C (oil bath) in a sealed tube.
[b] Determined by ^{19}F NMR.



6b **6′b**

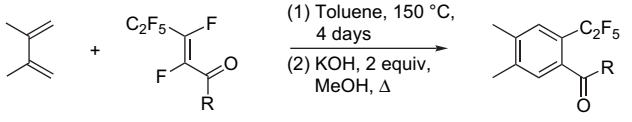
Figure 2. Determination of the structures of the aromatic regioisomers.

Although the compounds were not separated, the determination of the structure of the two regioisomers **6b** and **6′b** was performed using a ^1H–^{13}C HMBC NMR sequence. The two singlets corresponding to H-3 for the regioisomer **6b** and H-6 for the regioisomer **6′b** were attributed according to long-distance coupling constants ^3J between these two hydrogen atoms, the carbonyl group, and the methyl group as shown in Figure 2.

The same result was obtained with the regioisomers **6a** and **6′a**.

Interestingly, synthesis of the aromatic compounds can be readily achieved in a 'one-pot' sequence without isolation of the intermediate cycloadducts. After completion of the Diels–Alder reaction (GC monitoring), toluene was evaporated and the crude mixture dissolved in methanol with subsequent addition of potassium hydroxide. This process allowed a significant improvement of the yields (91–95%) of the fluorinated aromatics (Table 3).

Table 3. 'One-pot' synthesis of the *ortho*-perfluoroalkyl phenones



2 **3–4** **6c–d**

Entry	Enone	R	Product	Yield (%)
1	**3**	Ph	**6c**	91
2	**4**	C_8H_{17}	**6d**	95

Table 2. Synthesis of the *ortho*-perfluoroalkyl phenones

5a–d **5′a–b** **6a–d** **6′a–b**

Entry	Cycloadduct	R^1	R^2	R	Product	Ratio **6/6′**[b]	Yield (%)
1	**5a** **5′a**	Me H	H Me	Ph	**6a** **6′a**	62/38	66[a]
2	**5b** **5′b**	Me H	H Me	C_8H_{17}	**6b** **6′b**	51/49	75[a]
3	**5c**	Me	Me	Ph	**6c**	—	75
4	**5d**	Me	Me	C_8H_{17}	**6d**	—	82

[a] Obtained as a mixture of non-separated regioisomers.
[b] Determined by ^{19}F NMR.

3. Conclusion

Hemifluorinated enones proved to be good dienophiles for [4+2] cycloaddition reactions with buta-1,3-dienes. Basic treatment of the cycloadducts leads to the formation of *ortho*-(perfluoroethyl)phenones with good yields. These fluorinated aromatic compounds were also synthesized without isolation of the intermediate cyclohexene derivatives. Although it is limited to a few examples exhibiting the feasibility of the transformation, this paper discloses a potentially versatile methodology allowing to introduce structural diversity at the acyl moiety (structure of the starting acylsilane) and at the aryl substitution pattern (structure of the diene and length of the perfluoroalkyl chain).

4. Experimental

4.1. General methods

All air- and moisture-sensitive reactions were carried out under an argon atmosphere. Diethyl ether was distilled over Na/benzophenone before use. All reported NMR spectra were recorded with a Bruker AC 250. Chemical shifts are reported as δ values relative to $CHCl_3$ peak defined at δ=7.27 (^{1}H NMR) or δ=77.0 (^{13}C NMR). IR spectra were recorded using NaCl film or KBr pellets on an Avatar 320 FT-IR (Nicolet) spectrometer. Mass spectra (MS) were obtained on a Thermoquest Trace GC 2000 Series instrument. Elementary analyses were taken on a Perkin–Elmer CHN 2400 elementary analysis instrument. Analytical TLC was performed on Merck 60 PF_{254} silica gel pre-coated plates. Preparative flash silica gel chromatography was performed using Merck Kieselgel 60 (40–63 μm). Petroleum ether refers to the fraction with bp 40–65 °C.

All commercially available chemicals were used as received unless otherwise noted. Hemifluorinated enones **3** and **4** were obtained as previously described.[8]

4.2. General procedure for the synthesis of cycloadducts 5 and 5′

A solution of the dienes **1** and **2** (5 mmol) and the hemifluorinated enones **3** and **4** (1 mmol) was warmed in toluene (15 mL) in an oil bath at 150 °C in a sealed tube. After completion of the reaction (4 days), the reaction mixture was cooled to room temperature and toluene was evaporated. The crude mixture was purified by flash chromatography over silica gel (petroleum ether/EtOAc 99:1) to afford pure cycloadducts.

4.2.1. Mixture of non-separated regioisomers 5a/5′a (59/41). Orange oil. Yield: 65%. IR (film) ν_{max} cm^{-1}: 2925, 2858, 1698 (CO), 1579, 1448, 1383; EIMS *m/z* (%): 354 (M$^+$, 1), 334 (M−20), 295, 257, 237, 215, 137, 105 (100). Anal. Calcd for $C_{16}H_{13}F_7O$: C, 54.25; H, 3.70. Found: C, 54.33; H, 3.82.

4.2.1.1. 1-(1,6-Difluoro-4-methyl-6-pentafluoroethyl-cyclohex-3-enyl)-phenone 5a. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.74 (s, 3H, CH_3), 2.36–2.61 (m, 2H, H-5, H-2), 2.90–3.10 (m, 2H, H-5′, H-2′), 5.37 (br s, 1H, H-3), 7.37 (t, 2H, *J*=7.6 Hz, H-arom. *meta*), 7.49 (t, 1H, *J*=7.6 Hz, H-arom. *para*), 7.89 (d, 2H, *J*=7.6 Hz, H-arom. *ortho*); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.6 (CH_3), 34.7 (C-2), 35.0 (C-5), 115.8 (C-4), 128.2–129.8 (CH-arom.), 129.9 (C-3), 133.1 (C_q-arom.), 192.8 (CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −79.8 (d, 3F, *J*=13.3 Hz, CF_3), −117.1 (ddd, 1F, $^2J_{F,F}$=284.2 Hz, *J*=17.1, 11.4 Hz, CF_2), −119.1 (dd, 1F, $^2J_{F,F}$=284.2 Hz, *J*=19.1 Hz, CF_2), −166.2 (dt, 1F, *J*=38.2, 19.1 Hz, F-6), −171.9 (m, 1F, F-1).

4.2.1.2. 1-(1,6-Difluoro-3-methyl-6-pentafluoroethyl-cyclohex-3-enyl)-phenone 5′a. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.70 (s, 3H, CH_3), 2.71–2.90 (m, 2H, H-5′, H-2′), 5.33 (br s, 1H, H-4); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.3 (CH_3), 33.8 (C-2), 33.9 (C-5), 114.1 (C-4), 128.2–129.8 (CH-arom.), 129.7 (C-3), 133.1 (C_q-arom.), 192.9 (CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −79.9 (d, 3F, *J*=13.3 Hz, CF_3), −117.1 (ddd, 1F, $^2J_{F,F}$=284.2 Hz, *J*=19.1, 11.4 Hz, CF_2), −119.2 (dd, 1F, $^2J_{F,F}$=284.2 Hz, *J*=19.1 Hz, CF_2), −165.0 (dt, 1F, *J*=38.2, 19.1 Hz, F-6), −173.4 (m, 1F, F-1).

4.2.2. Mixture of non-separated regioisomers 5b/5′b (62/38). Orange oil. Yield: 64%. IR (film) ν_{max} cm^{-1}: 2928, 2857, 1732 (CO), 1445, 1205; EIMS *m/z* (%): 390 (M$^+$, 18), 370, 350, 280, 272, 230 (100). Anal. Calcd for $C_{18}H_{25}F_7O$: C, 56.38; H, 6.45. Found: C, 56.46; H, 6.60.

4.2.2.1. (1,6-Difluoro-4-methyl-6-pentafluoroethyl-cyclohex-3-enyl)-nonan-1-one 5b. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J*=6.9 Hz, CH_3), 1.23–1.33 (m, 10H, CH_2), 1.60 (m, 2H, CH_2), 1.77 (s, 3H, CH_3), 2.10–2.98 (m, 6H, CH_2CO, H-2, H-2′, H-5, H-5′), 5.39 (br s, 1H, H-3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.3 (CH_3), 22.6 (CH_2), 22.9 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 32.0 (CH_2), 34.8 (C-2), 35.2 (C-5), 38.3 (CH_2CO), 114.3 (C-4), 130.5 (C-3), 204.2 (CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −79.7 (d, 3F, *J*=11.4 Hz, CF_3), −118.5 (dm, 1F, $^2J_{F,F}$=284.2 Hz, CF_2), −120.3 (dd, 1F, $^2J_{F,F}$=284.2 Hz, *J*=21.0 Hz, CF_2), −170.5 (dt, 1F, *J*=38.2, 19.1 Hz, F-6), −174.1 (dt, 1F, *J*=26.6, 13.3 Hz, F-1).

4.2.2.2. (1,6-Difluoro-3-methyl-6-pentafluoroethyl-cyclohex-3-enyl)-nonan-1-one 5′b. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.74 (s, 3H, CH_3), 5.34 (br s, 1H, H-4); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 31.8 (CH_2), 34.9 (C-2), 35.1 (C-5), 38.4 (CH_2CO), 116.0 (C-4), 129.9 (C-3), 204.4 (CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −79.8 (d, 3F, *J*=13.3 Hz, CF_3), −118.5 (d, 1F, $^2J_{F,F}$=284.2 Hz, CF_2), −120.5 (dd, 1F, $^2J_{F,F}$=284.2 Hz, *J*=22.9 Hz, CF_2), −169.3 (dt, 1F, *J*=38.2, 19.1 Hz, F-6), −175.6 (dt, 1F, *J*=26.6, 13.3 Hz, F-1).

4.2.3. (1,6-Difluoro-3,4-dimethyl-6-pentafluoroethyl-cyclohex-3-enyl)-phenone 5c. Yellow oil. Yield: 76%. IR (film) ν_{max} cm^{-1}: 2922, 2865, 1688 (CO), 1598, 1579, 1448, 1421, 1387, 1203, 748, 691; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.71 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.42–2.57 (m, 2H, H-5, H-2), 2.77–3.17 (m, 2H, H-5′, H-2′), 7.44 (t, 2H, *J*=7.6 Hz, H-arom. *meta*), 7.56 (t, 1H, *J*=7.6 Hz, H-arom. *para*), 7.96 (d, 2H, *J*=7.6 Hz, H-arom. *ortho*); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 18.1 (CH_3), 18.3 (CH_3), 33.0 (dd, $^2J_{C,F}$=21.7 Hz, $^3J_{C,F}$=2.4 Hz, C-2 or C-5), 38.6

(dd, $^2J_{C,F}$=21.7 Hz, $^3J_{C,F}$=2.4 Hz, C-2 or C-5), 93.6 (dm, $^1J_{C,F}$=196.3 Hz, C-6), 97.2 (dd, $^1J_{C,F}$=196.4 Hz, $^2J_{C,F}$= 22.9 Hz, C-1), 117.6 (C-4), 118.4 (tq, $^1J_{C,F}$=288.3 Hz, $^2J_{C,F}$=34.5 Hz, CF_3), 119.3 (C-3), 126.3–127.9 (CH-arom.), 133.7 (C_q-arom.), 195.6 (d, $^2J_{C,F}$=27.3 Hz, CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −79.9 (d, 3F, J=13.3 Hz, CF_3), −117.3 (ddd, 1F, $^2J_{F,F}$=284.2 Hz, J=11.4, 7.6 Hz, CF_2), −119.5 (dd, 1F, $^2J_{F,F}$=284.2 Hz, J=17.2 Hz, CF_2), −165.2 (dt, 1F, J=38.1, 19.1 Hz, F-6), −172.2 (ddtt,1F, J=38.1, 13.3, 5.7 Hz, F-1); EIMS m/z (%): 368 (M^+, 2), 348 (M−20, 100), 328, 295, 271, 251, 229. Anal. Calcd for $C_{17}H_{15}F_7O$: C, 55.44; H, 4.11. Found: C, 55.59; H, 4.12.

4.2.4. 1-(1,6-Difluoro-3,4-dimethyl-6-pentafluoroethyl-cyclohex-3-enyl)-nonan-1-one 5d. Yellow oil. Yield: 77%. IR (film) ν_{max} cm^{-1}: 2927, 2858, 1733 (CO), 1460, 1421, 1221; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.89 (t, 3H, J=6.9 Hz, CH_3), 1.23–1.35 (m, 10H, CH_2), 1.61 (quint., 2H, CH_2), 1.68 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.12–2.50 (m, 2H, H-2, H-5), 2.59–2.99 (m, 4H, CH_2CO, H-2′, H-5′); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0 (CH_3), 18.1 (CH_3), 18.3 (CH_3), 22.6 (CH_2), 22.8 (CH_2), 22.9 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 34.6 (dm, $^2J_{C,F}$=21.7 Hz, C-5), 38.4 (dd, $^2J_{C,F}$=21.7 Hz, $^3J_{C,F}$= 2.0 Hz, C-2), 38.5 (d, $^3J_{C,F}$=3.2 Hz, CH_2CO), 119.2 (C-4), 121.0 (C-3), 206.6 (d, $^2J_{C,F}$=29.3 Hz, CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −79.8 (d, 3F, J=11.4 Hz, CF_3), −118.6 (ddd, 1F, $^2J_{F,F}$=284.2 Hz, $^3J_{F,F}$=11.4, 5.7 Hz, CF_2), −120.4 (dd, 1F, $^2J_{F,F}$=284.2 Hz, J=22.9 Hz, CF_2), −169.5 (dt, 1F, J=40.0, 19.0 Hz, F-6), −174.4 (dt, 1F, J=40.0, 13.3 Hz, F-1); EIMS m/z (%): 404 (M^+, 4), 384, 364, 314, 286, 229. Anal. Calcd for $C_{19}H_{27}F_7O$: C, 56.43; H, 6.73. Found: C, 56.58; H, 6.81.

4.3. General procedure for the synthesis of *ortho*-perfluoroalkyl phenones 6 and 6′

Method A: to a solution of the fluorinated cycloadduct **5** or the mixture of cycloadducts **5**–**5′** (1 mmol) in methanol (5 mL) was added potassium hydroxide (2 mmol). The solution was refluxed for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature and methanol was evaporated. The crude mixture was dissolved in diethyl ether (50 mL) and extracted twice with a saturated NaCl solution. The organic layer was then dried over $MgSO_4$ and the organic solvent was evaporated. The crude mixture was purified by flash chromatography over silica gel (petroleum ether/EtOAc 99:1) to afford pure aromatic compounds.

Method B: to a solution of the dienes **1** and **2** (5 mmol) and the hemifluorinated enones **3** and **4** (1 mmol) in toluene (15 mL) in an oil bath at 150 °C in a sealed tube. After completion of the reaction (4 days), the reaction mixture was cooled to room temperature and toluene was evaporated. The crude residue was dissolved in methanol and potassium hydroxide (2 mmol) was added. After completion of the reaction (24 h), the reaction mixture was cooled to room temperature and methanol was evaporated. The crude mixture was dissolved in diethyl ether (50 mL) and extracted twice with brine. The organic layer was then dried over $MgSO_4$ and the organic solvent was evaporated. The crude mixture was purified by flash chromatography over silica gel (petroleum ether/EtOAc 99:1) to afford pure aromatic compounds.

4.3.1. Mixture of non-separated regioisomers 6a/6′a (61/39). Yellow oil. Yield: 75%. IR (film) ν_{max} cm^{-1}: 2969, 1681 (CO), 1597, 1450, 1332, 1212, 1082, 998.

4.3.1.1. (4′-Methyl-2′-pentafluoroethyl)phenyl-phenone 6a. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 7.15 (d, 1H, J=7.9 Hz, H-6′), 7.32–7.40 (m, 3H, H-arom. *meta*, H-3′, H-5′), 7.48 (t, 1H, J=7.6 Hz, H-arom. *para*), 7.65 (d, 2H, J=7.6 Hz, H-arom. *ortho*); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.0 (CH_3), 124.0 (t, $^2J_{C,F}$=30.0 Hz, C-2′), 126.6 (C-6′), 128.4–130.1 (C-3′, CH-arom.), 132.0 (C-5′), 133.2 (C_q-arom.), 139.7 (C-4′), 139.9 (C-1′), 195.9 (CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −83.8 (s, 3F, CF_3), −107.7 (s, 2F, CF_2).

4.3.1.2. (5′-Methyl-2′-pentafluoroethyl)phenyl-phenone 6′a. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 7.07 (s, 1H, H-6′), 7.32–7.40 (m, 3H, H-arom. *meta*, H-3′, H-4′), 7.48 (t, 1H, J=7.6 Hz, H-arom. *para*), 7.65 (d, 2H, J=7.6 Hz, H-arom. *ortho*); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.2 (CH_3), 121.7 (t, $^2J_{C,F}$=30.0 Hz, C-2′), 126.9 (C-6′), 128.4–130.1 (C-3′, CH-arom.), 133.3 (C_q-arom.), 135.7 (C-4′), 144.0 (C-1′), 144.2 (C-5′), 196.1 (CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −84.0 (s, 3F, CF_3), −107.7 (s, 2F, CF_2).

4.3.2. Mixture of non-separated regioisomers 6b/6′b (60/40). Yellow oil. Yield: 66%. IR (film) ν_{max} cm^{-1}: 2958, 2928, 2857, 1713 (CO), 1612, 1572, 1459, 1333, 1205, 1086, 857; EIMS m/z (%): 350 (M^+, 8), 330, 302, 252, 237 (100), 219, 164, 159.

4.3.2.1. 1-(4′-Methyl-6′-pentafluoroethyl)phenyl-nonan-1-one 6b. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (t, 3H, J=6.9 Hz, CH_3), 1.23–1.33 (m, 10H, CH_2), 1.68 (quint., 2H, J=6.9 Hz, CH_2), 2.43 (s, 3H, CH_3), 2.76 (t, 2H, J= 6.9 Hz, CH_2), 7.17 (d, 1H, J=8.3 Hz, H-6′), 7.38 (s, 1H, H-3′), 7.39 (d, 1H, J=8.3 Hz, H-5′); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.6 (CH_2), 23.5 (CH_3), 23.6 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 44.0 (CH_2), 124.5 (t, $^2J_{C,F}$=29.0 Hz, C-2′), 126.5 (C-6′), 129.8 (C-3′), 132.4 (C-5′), 139.6 (C-4′), 139.8 (C-1′), 205.1 (CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −83.6 (s, 3F, CF_3), −107.8 (s, 2F, CF_2).

4.3.2.2. 1-(4′-Methyl-2′-pentafluoroethyl)phenyl-nonan-1-one 6′b. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (t, 3H, J=6.9 Hz, CH_3), 1.23–1.33 (m, 10H, CH_2), 1.68 (quint., 2H, J=6.9 Hz, CH_2), 2.42 (s, 3H, CH_3), 2.78 (t, 2H, J=6.9 Hz, CH_2), 7.06 (s, 1H, H-6′), 7.31 (d, 1H, J= 8.0 Hz, H-4′), 7.47 (d, 1H, J=8.0 Hz, H-3′); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.6 (CH_2), 23.4 (CH_3), 23.6 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 31.9 (CH_2), 44.2 (CH_2), 121.4 (t, $^2J_{C,F}$=30.0 Hz, C-2′), 126.8 (C-6′), 128.6 (C-3′), 142.6 (C-1′), 142.9 (C-5′), 205.3 (CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −83.9 (s, 3F, CF_3), −107.8 (s, 2F, CF_2).

4.3.3. 1-(4′,5′-Dimethyl-2′-pentafluoroethyl)phenyl-phenone 6c. Yellow oil. Yields: 75% (Method A), 95% (Method B). IR (film) ν_{max} cm^{-1}: 2920, 2865, 1685 (CO), 1598, 1575, 1442, 1420, 1387, 1203, 748, 691; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 7.00 (s,

1H, H-3′), 7.35 (t, 3H, J=7.4 Hz, H-arom. *meta*, H-6′), 7.49 (t, 1H, J=7.4 Hz, H-arom. *para*), 7.67 (d, 2H, J=7.4 Hz, H-arom. *ortho*); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.6 (CH_3), 19.7 (CH_3), 127.3 (C-3), 128.4 (CH-arom.), 129.0 (CH-arom.), 129.4 (C-6), 130.1 (CH-arom.), 133.5 (CH-arom.), 136.8 (C_q-arom.), 138.4 (C-4 or C-5), 140.8 (C-4 or C-5), 196.0 (CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −83.9 (s, 3F, CF_3), −107.6 (s, 2F, CF_2); EIMS m/z (%): 328 (M^+, 31), 309, 251, 201, 173, 133, 105 (100). Anal. Calcd for $C_{17}H_{13}F_5O$: C, 62.20; H, 3.99. Found: C, 62.47; H, 4.21.

4.3.4. 1-(4′,5′-Dimethyl-2′-pentafluoroethyl)phenyl-nonan-1-one 6d. Yellow oil. Yields: 82% (Method A), 91% (Method B). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (t, 3H, J=6.9 Hz, CH_3), 1.23–1.35 (m, 10H, CH_2), 1.68 (quint., 2H, J=7.2 Hz, CH_2), 2.32 (br s, 6H, $2CH_3$), 2.75 (t, 2H, J=7.4 Hz, CH_2), 7.01 (s, 1H, H-3), 7.32 (s, 1H, H-6); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0 (CH_3), 19.5 (CH_3), 19.6 (CH_3), 22.6 (CH_2), 23.6 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 44.8 (CH_2), 127.5 (C-3), 129.0 (C-6), 138.2 (C-4 or C-5), 141.1 (C-4 or C-5), 205.3 (CO); ^{19}F NMR (235.4 MHz, $CDCl_3$): δ −83.8 (s, 3F, CF_3), −107.6 (s, 2F, CF_2); EIMS m/z (%): 364 (M^+, 8), 349, 308, 279, 251 (100), 237, 223, 177. Anal. Calcd for $C_{19}H_{25}F_5O$: C, 62.63; H, 6.91. Found: C, 62.94; H, 6.99.

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Synthesis of 6- and 7-acyl-4*H*-benzothiazin-3-ones

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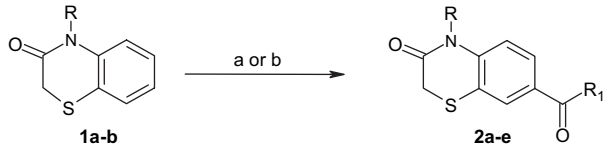
Abstract—Synthesis of 6- and 7-substituted benzoxazin-3-ones was already described in the literature by acylation of the corresponding benzoxazin-3-ones or cyclization of the corresponding 4- or 5-acyl-2-aminophenols. This paper describes original synthetic pathways to afford the 6- and 7-acyl products in the benzothiazin-3-one series, respectively, via Stille coupling reaction and by acylation.

1. Introduction

The chemistry of benzoxazin-3-one and benzothiazin-3-one heterocycles has been offering for years an attractive pathway to lots of new synthetic methods and transformations. Benzothiazin-3-ones, in fact, have gained substantial interest in the scientific community not only due to their meaningful biological activity, but also as reactive intermediates and as starting materials in a wide range of synthesis.[1–3]

Direct acylation of the benzoxazin-3-one heterocycle at the C-6 position is well described in the literature[4–7] and leads to products in accordance with theoretical study of the electronic effects.[8] Indeed, two distinct electronic effects were generated by a substituent: the mesomeric and the inductive effects. The basis of the inductive effect is probably complex but originates in part from differences in electronegativity. For the benzoxazin-3-one heterocycle, not only the withdrawing effect of the amide but also the donating and the inductive effects of the oxygen allowed the introduction of the electrophile group logically towards the *para* position of the oxygen to give 6-acylbenzoxazin-3-ones. However, the direct acylation of benzothiazin-3-one at the C-6 position is less described in the literature. We have only found some patents[9–11] describing results that are not consistent with the expected electronic effects-related reactivity.[8] In Friedel–Crafts conditions, the mesomeric effects, with benzothiazin-3-one or benzoxazin-3-one, of the amide and the sulfur or oxygen are quite identical. However, the electronegativities, implicated in the inductive effect, of oxygen and sulfur atoms are strongly different (S: 2.5, N: 3.0, O: 3.5). Therefore, the electrophile group could be introduced at the *para* position of the nitrogen affording the corresponding 7-acylbenzothiazin-3-ones.

The obvious disagreement between literature and theoretical electronic effects has prompted us to study the acylation of the benzothiazinonic ring. In the first attempt, we acylated this heterocycle directly, according to different methods, in polyphosphoric acid (PPA) and in the mixture $AlCl_3$–DMF with the corresponding carboxylic acid or acid chloride, respectively; the structures of obtained compounds **2a–d** (Scheme 1) were confirmed by full spectral data. In the second attempt, we have realized two unequivocal syntheses to afford 6- or 7-acylbenzothiazin-3-ones (Schemes 2 and 3) in order to have a reference of each position isomer.



Scheme 1. Synthesis of 7-acylbenzothiazin-3-ones **2a–e** by direct acylation. (a) PPA, R_1CO_2H; (b) $AlCl_3$–DMF, R_1COCl.

Keywords: Benzothiazin-3-one; Friedel–Crafts acylation; Stille coupling.
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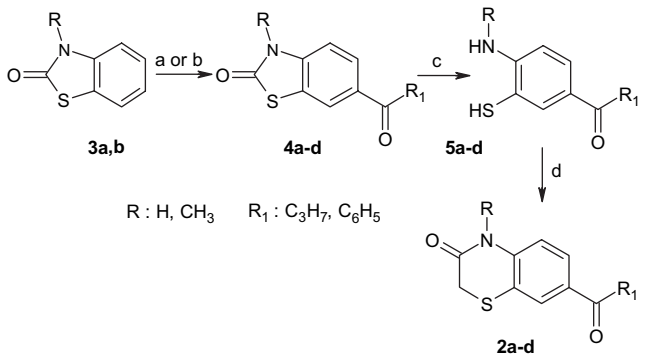
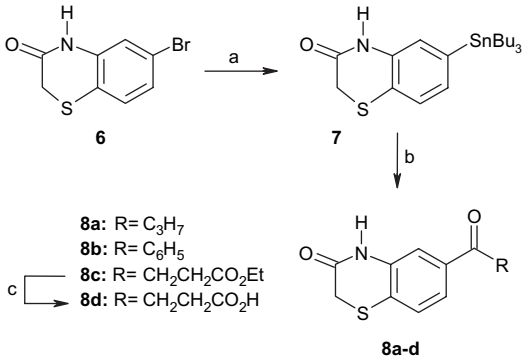


Scheme 2. Synthesis of 7-acylbenzothiazin-3-ones **2a–d** by cyclization of the 5-acyl-2-aminothiophenols **5a–d**. (a) PPA, $C_6H_5CO_2H$; (b) $AlCl_3$–DMF, $C_3H_7CO_2Cl$; (c) (i) KOH, (ii) HCl, (iii) $NaHCO_3$; (d) EtONa, $BrCH_2CO_2C_2H_5$, DMSO.



Scheme 3. Synthesis of 6-acylbenzothiazin-3-one **8a–d** via 6-tributyltin benzothiazin-3-one **7**. (a) $(Bu_3Sn)_2$, $Pd(PPh_3)_4$, toluene under argon; (b) RCOCl, $PdCl_2(PPh_3)_2$, toluene under argon; (c) (i) KOH, EtOH, H_2O, (ii) HCl.

2. Results and discussion

2.1. Synthesis of 7-acylbenzothiazin-3-ones by direct acylation

Benzothiazin-3-one derivatives **1a** and **b** were acylated by using either acyl chloride in the mixture $AlCl_3$–DMF or carboxylic acid in PPA to give the corresponding 7-acylbenzothiazin-3-one derivatives **2a–d** (Scheme 1). It was confirmed by full NMR spectral data (^{2}H COESY, ROESY, HMBC, HSQC) that compounds **2a–d** obtained by Friedel–Crafts conditions were not substituted in the C-6 position but in the C-7 position, in accordance with theoretical study of the electronic effects.

2.2. Synthesis of 7-acylbenzothiazin-3-ones 2a–d by unequivocal way

In order to confirm these structural data, we have realized the unequivocal synthesis of 7-acylbenzothiazin-3-ones **2a–d** by cyclization of the corresponding 5-acyl-2-aminothiophenols **5a–d** (Scheme 2).

6-Acylbenzothiazolin-2-ones **4a–d** were prepared according to literature procedure[12] from the corresponding benzothiazolin-2-ones **3a** and **b**. Ring opening under strong basic conditions of 6-acylbenzothiazolin-2-ones **4a–d** afforded the corresponding 5-acyl-2-aminothiophenols **5a–d** followed by cyclization using ethyl bromoacetate and sodium ethylate in DMSO,[13] which supplied compounds **2a–d** (Scheme 2) with identical physico-chemical characteristics as compounds obtained by direct acylation (Scheme 1).

6-Acylbenzothiazin-3-ones were described in the literature by cyclization of the corresponding 4-chloro-3-nitrophenylacyl derivatives.[14,15] A new approach was developed in two steps to afford original 6-acylbenzothiazin-3-ones **8a–c** (Scheme 3).

2.3. Synthesis of 6-acylbenzothiazin-3-ones 8a–c

6-Bromobenzothiazin-3-one[16] (**6**) was treated with $Pd(PPh_3)_4$ and $(Bu_3Sn)_2$ in toluene under argon to afford 6-tributyltinbenzothiazin-3-one (**7**). Reaction of derivative **7** with the corresponding acid chloride was then performed in toluene under argon with $PdCl_2(PPh_3)_2$ to give the 6-acylbenzothiazin-3-ones **8a–c**. This synthetic pathway developed, in two steps, allows access to various 6-acylbenzothiazin-3-ones (Scheme 3).

Spectral data of compounds **8a** and **b** obtained in Scheme 3 were strongly different from those found for compounds **2a** and **c** obtained by direct acylation (Scheme 1). Melting points differed for compounds **8a**, **2a** and for compounds **2c**, **8b** from 20 to 30 °C.

Combs[9,10] described the synthesis of 6-(4-oxobutyric)benzothiazin-3-one (**8d**) by acylation of the corresponding benzothiazin-3-ones in the mixture $AlCl_3$–DMF with succinic anhydride, which was not in agreement with our results. We have realized the acylation of the benzothiazin-3-one in the Combs conditions, who used ethylsuccinyl chloride and obtained derivative **2e** (Scheme 1). Full NMR spectral data confirmed that the substitution occurred at the C-7 position of the benzothiazin-3-one, as in all derivatives **2a–d** synthesized in Schemes 1 and 2. (4-Oxobutyric)benzothiazin-3-one substituted at the C-6 position was also synthesized by the unequivocal way described in Scheme 3, starting from the stannic intermediate **7** and ethylsuccinyl chloride. The 6-(ethyl-4-oxobutyrate) intermediate **8c** was obtained, followed by hydrolysis in a solution of ethanol/water with KOH leading to acid **8d** whose physico-chemical characteristics were strongly different from those for 7-(4-oxobutyric)benzothiazin-3-one **2e**.

3. Conclusion

Friedel–Crafts acylations of benzothiazin-3-ones using either $AlCl_3$–DMF mixture or PPA led to the 7-acyl derivatives **2a–d**, in accordance with the theoretical study of the electronic effects. It was confirmed by full NMR spectral data and unambiguous synthesis. In order to access 6-acylbenzothiazin-3-ones **8a–c**, we have developed a new synthetic pathway using Stille coupling with 6-tributyltinbenzothiazin-3-one intermediate. This work proves that synthesis of 6-acylbenzothiazin-3-ones from direct acylation of benzothiazin-3-one, as Combs described in the literature,[9,10] is not in agreement with our results and the electronic effect rules on this heterocycle ring.

4. Experimental

4.1. General

All compounds were purified by recrystallization in different solvents and their purity was determined by TLC. Melting points were determined by a Büchi 510 capillary apparatus and are uncorrected. Elemental analyses were performed at C.N.R.S centre Vernaison, France and were within ±0.4% of the theoretical values. Infrared spectra were obtained on a Nicolet 550-FT spectrometer on KBr paths. ^{1}H and ^{2}H NMR proton spectra were recorded on a Bruker FT-80 spectrometer and chemical shifts are in parts per million with TMS as internal standard.

4.2. General procedure for the synthesis of 7-acyl-4*H*-benzothiazin-3-one derivatives (2a–e)

The method adopted for the synthesis of 7-acyl-4*H*-benzothiazin-3-ones (**2a–e**) is described in PPA and in the mixture $AlCl_3$–DMF. Under mechanical stirring, to a mixture of benzothiazin-3-one **1a** (16.4 g, 100 mmol) in 100 g of polyphosphoric acid was added portionwise the corresponding acid (130 mmol). The resulting mixture was heated at 110 °C for 4 h. After cooling, the reaction mixture was poured into ice-water (1 L), and the resulting precipitate was filtered, washed with water, dried and recrystallized.

Reaction with $AlCl_3$–DMF: to 112 g of $AlCl_3$ (53.5 g, 400 mmol) was added dropwise anhydrous DMF (17.2 mL, 230 mmol) under stirring. To the mixture heated at 50 °C, benzothiazin-3-one **1a** (16.4 g, 100 mmol) and the corresponding acid chloride (130 mmol) were added. The mixture was heated at 90 °C for 4 h, poured into ice-water (1 L), and the resulting precipitate was filtered, washed with water, dried and recrystallized.

4.2.1. 7-Butyryl-4*H*-benzothiazin-3-one (2a). Recrystallization from acetone gave **2a** in 81% yield; mp 191–193 °C; IR (KBr, ν cm^{-1}) 3200 (NH), 1670 and 1645 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.95 (t, 3H, J=5.90 Hz, CH_3), 1.55 (m, 2H, CH_2), 2.75 (t, 2H, J=6.05 Hz, CH_2), 3.50 (s, 2H, CH_2), 6.95 (d, 1H, J=8.15 Hz, H_5), 7.55 (d, 1H, J=1.25 Hz, H_8), 7.70 (dd, 1H, J=8.15 Hz, J=1.25 Hz, H_6), 10.50 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.27; H, 5.57; N, 5.91; S, 13.61. Found: C, 61.03; H, 5.54; N, 5.74; S, 13.84.

4.2.2. 7-Butyryl-4-methyl-4*H*-benzothiazin-3-one (2b). Recrystallization from ethanol gave **2b** in 80% yield; mp 109–111 °C; IR (KBr, ν cm^{-1}) 1670 and 1640 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.00 (t, 3H, J=5.50 Hz, CH_3), 1.50 (m, 2H, CH_2), 2.80 (t, 2H, J=6.50 Hz, CH_2), 3.40 (s, 3H, CH_3), 3.50 (s, 2H, CH_2), 7.10 (d, 1H, J=8.00 Hz, H_5), 7.60 (d, 1H, J=1.40 Hz, H_8), 7.75 (dd, 1H, J=8.00 Hz, J=1.40 Hz, H_6). Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.64; H, 6.07; N, 5.62; S, 13.61. Found: C, 62.90; H, 6.02; N, 5.67; S, 12.93.

4.2.3. 7-Benzoyl-4*H*-benzothiazin-3-one (2c). Recrystallization from acetone gave **2c** in 55% yield; mp 210–212 °C; IR (KBr, ν cm^{-1}) 3196 (NH), 1694 and 1645 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.50 (s, 2H, CH_2), 7.10 (d, 1H, J=8.30 Hz, H_5), 7.50–7.60 (m, 3H, H_6, H_{Ar}), 7.70–7.80 (m, 4H, H_8, H_{Ar}), 10.50 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.91; H, 4.12; N, 5.20; S, 11.88. Found: C, 66.81; H, 4.27; N, 5.06; S, 11.23.

4.2.4. 7-Benzoyl-4-methyl-4*H*-benzothiazin-3-one (2d). Recrystallization from ethanol gave **2d** in 75% yield; mp 130–132 °C; IR (KBr, ν cm^{-1}) 1670 and 1640 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.40 (s, 3H, CH_3), 3.50 (s, 2H, CH_2), 7.10 (d, 1H, J=8.20 Hz, H_5), 7.50–7.80 (m, 7H, H_6, H_8, H_{Ar}). Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 66.44; H, 4.84; N, 5.16; S, 11.79. Found: C, 66.61; H, 4.70; N, 5.52; S, 11.70.

4.2.5. 7-(4-Oxobutyric)-4*H*-benzothiazin-3-one (2e). Recrystallization from ethanol gave **2e** in 63% yield; mp 173–174 °C; IR (KBr, ν cm^{-1}) 3189 (NH), 1701 (COO), 1678 (CON), 1647 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.60 (t, 2H, J=7.00 Hz, CH_2COO), 3.20 (t, 2H, J=7.00 Hz, CH_2CO), 2.55 (s, 2H, CH_2), 7.45 (d, 1H, J=8.20 Hz, H_5), 7.55 (d, 1H, J=1.75 Hz, H_8), 7.60 (d, 1H, J=8.20 Hz, J=1.75 Hz, H_6), 11.75 (s, 1H, NH, exchangeable with D_2O), 12.30 (br s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28; S, 12.09. Found: C, 54.64; H, 4.41; N, 5.14; S, 12.35.

4.3. General procedure for the synthesis of 5-acyl-2-aminothiophenol derivatives (5a–d)

6-Acyl-2(3*H*)-benzothiazolone (**4a–d**) (20 mmol) and KOH powder (5.6 g, 100 mmol) were heated at fusion during 1 h under nitrogen. The residue was poured into 100 mL of cold water and filtered. The aqueous solution was extracted with diethyl ether, acidified (pH=3) by 12 M HCl solution, then the pH adjusted to 8 with aqueous solution of sodium hydrogen carbonate. The precipitate was filtered, washed with water and recrystallized.

4.3.1. 5-Butyryl-2-aminothiophenol (5a). Recrystallization from acetone gave **5a** in 60% yield; mp 187–188 °C; IR (KBr, ν cm^{-1}) 3410 (NH), 3350 (SH), 1645 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.90 (t, 3H, CH_3), 1.50 (m, 2H, CH_2), 2.60 (t, 2H, CH_2), 6.25 (br s, 3H, NH_2 and SH, exchangeable with D_2O), 6.75 (d, 1H, J=7.80 Hz, H_3), 7.40 (d, 1H, J=1.10 Hz, H_6), 7.70 (dd, 1H, J=7.80 Hz, J=1.10 Hz, H_4). Anal. Calcd for $C_{10}H_{13}NOS$: C, 60.14; H, 6.81; N, 7.10; S, 16.02. Found: C, 60.42; H, 6.41; N, 6.92; S, 16.33.

4.3.2. 5-Butyryl-2-methylaminothiophenol (5b). Recrystallization from ethanol gave **5b** in 70% yield; mp 117–118 °C; IR (KBr, ν cm^{-1}) 3400 (NH), 3350 (SH), 1640 (CO), 1580 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.90 (t, 3H, J=6.20 Hz, CH_3), 2.45 (m, 2H, CH_2), 2.65 (t, 2H, J=6.05 Hz, CH_2), 2.95 (s, 3H, CH_3), 4.20–3.80 (br s, 2H, NH and SH, exchangeable with D_2O), 6.60 (d, 1H, J=8.00 Hz, H_3), 7.70 (d, 1H, J=1.20 Hz, H_6), 7.90 (dd, 1H, J=8.00 Hz, J=1.20 Hz, H_4). Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.14; H, 6.71; N, 6.69; S, 15.29. Found: C, 63.50; H, 6.71; N, 6.55; S, 15.35.

4.3.3. 5-Benzoyl-2-aminothiophenol (5c). Recrystallization from acetone gave **5c** in 60% yield; mp 208–210 °C; IR (KBr, ν cm^{-1}) 3500 (NH), 3300 (SH), 1650 (CO), 1590 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.25 (br s, 3H, NH_2 and SH, exchangeable with D_2O), 6.75 (d, 1H, J=8.30 Hz, H_3), 7.45–7.60 (m, 6H, H_6, H_{Ar}), 7.80 (dd, 1H, J=8.30 Hz, J=1.05 Hz, H_4). Anal. Calcd for $C_{13}H_{11}NOS$: C, 68.41; H, 4.83; N, 6.13; S, 14.02. Found: C, 68.32; H, 4.52; N, 6.02; S, 14.12.

4.3.4. 5-Benzoyl-2-methylaminothiophenol (5d). Recrystallization from ethanol gave **5d** in 60% yield; mp 70–71 °C; IR (KBr, ν cm^{-1}) 3400 (NH), 3350 (SH), 1650 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.95 (s, 1H, NH, exchangeable with D_2O), 3.20 (s, 3H, CH_3), 6.75 (s, 1H, SH, exchangeable with D_2O), 7.20 (d, 1H, J=8.15 Hz, H_3), 7.50 (m, 6H, H_6, H_{Ar}), 7.80 (dd, 1H, J=8.15 Hz, J=1.30 Hz, H_4). Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.12; H, 5.38; N, 5.75; S, 13.15. Found: C, 69.01; H, 5.55; N, 5.92; S, 13.02.

4.4. General procedure for the synthesis of 7-acyl-4*H*-benzothiazin-3-one derivatives (2a–d) from compounds 5a–d

The method adopted for the synthesis of 7-butyryl-4*H*-benzothiazin-3-one (**2a**) is described. To a solution of compound **5a** (3.9 g, 20 mmol) in DMSO was added sodium ethylate (1.36 g, 20 mmol). After 1 h, ethyl bromoacetate (2.45 mL, 22 mmol) was added and the mixture was stirred for 2 h at room temperature. The solution was poured into cold water and acidified with 6 M HCl solution (pH=5), filtered, washed with water and recrystallized from acetone to give **2a** in 65% yield (**2b–d**: 56–76% yield).

4.5. 6-Tributyltin-4*H*-benzothiazin-3-one (7)

To a mixture of 6-bromo-3-methyl-4*H*-benzothiazin-3-one (**6**) (4.4 g, 18 mmol) in toluene (20 mL) under argon, tetrakis(triphenyl phosphine) palladium (1.86 g, 1.8 mmol) and bis(tributyltin) (11.80 mL, 27 mmol) were added. The reaction mixture was stirred at reflux for 6 h. The solution was evaporated under reduced pressure. The oily residue was purified by flash column chromatography with petroleum ether/EtOAc (9/1) to give an oily product. Yield 53%; IR (KBr, ν cm^{-1}) 3211 (NH), 2852–2956 (CH), 1679 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.80 (t, 9H, J=5.70 Hz, $(CH_3)_3$), 1.05 (t, 6H, J=6.00 Hz, $(COCH_2)_3$), 1.30 (m, 6H, $(CH_2)_3$), 1.50 (m, 6H, $(CH_2)_3$), 3.45 (s, 2H, CH_2CO), 6.90 (d, 1H, J=0.95 Hz, H_5), 7.10 (dd, 1H, J=7.30 Hz, J=0.95 Hz, H_7), 7.30 (d, 1H, J=7.30 Hz, H_8), 8.50 (br s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{20}H_{33}NOSSn$: C, 52.88; H, 7.32; N, 3.08; S, 7.06. Found: C, 52.63; H, 7.50; N, 2.86; S, 7.32.

4.6. General procedure for the synthesis of 6-acyl-4*H*-benzothiazin-3-one derivatives (8a–c)

Compound **7** (1.04 g, 2.3 mmol) in toluene (10 mL) was placed under argon, dichlorobis(triphenyl phosphine) palladium (0.16 g, 0.23 mmol) and the corresponding acid chloride (4.6 mmol) were added. The reaction was refluxed for 2 h. The solution was evaporated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/EtOAc (9/1) and recrystallized.

4.6.1. 6-Butyryl-4*H*-benzothiazin-3-one (8a). Recrystallization from ethanol gave **8a** in 40% yield; mp 214–215 °C; IR (KBr, ν cm^{-1}) 3194 (NH), 1672 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.90 (t, 3H, J=7.00 Hz, CH_3), 1.60 (m, 2H, CH_2), 2.90 (t, 2H, J=7.00 Hz, CH_2CO), 3.55 (s, 2H, CH_2S), 7.45 (d, 1H, J=8.20 Hz, H_8), 7.50 (s, 1H, H_5), 7.55 (dd, 1H, J=8.20 Hz, J=1.75 Hz, H_7), 10.60 (br s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 61.05; H, 5.70; N, 5.68; S, 13.50.

4.6.2. 6-Benzoyl-4*H*-benzothiazin-3-one (8b). Recrystallization from ethanol gave **8b** in 69% yield, mp 180–181 °C; IR (KBr, ν cm^{-1}) 3140 (NH), 1678 and 1640 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.35 (s, 2H, CH_2CO), 7.30 (dd, 1H, J=7.90 Hz, J=1.50 Hz, H_7), 7.40 (d, 1H, J=1.50 Hz, H_5), 7.50 (d, 1H, J=7.90 Hz, H_8), 7.60 (m, 2H, H_{Ar}), 7.65–7.75 (m, 3H, H_{Ar}), 10.75 (br s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20; S, 11.91. Found: C, 66.74; H, 4.24; N, 5.03; S, 12.13.

4.6.3. 6-(Ethyl-4-oxobutyrate)-4*H*-benzothiazin-3-one (8c). Recrystallization from ethanol gave **8c** in 57% yield; mp 162–163 °C; IR (KBr, ν cm^{-1}) 3315 (NH), 1723 (COO), 1672 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.30 (t, 3H, J=7.00 Hz, CH_3), 2.80 (t, 2H, J=6.45 Hz, CH_2CO), 3.30 (t, 2H, J=6.45 Hz, CH_2COO), 3.50 (s, 2H, CH_2S), 4.20 (q, 2H, J=7.00 Hz, CH_3), 7.40 (d, 1H, J=8.20 Hz, H_7), 7.50 (d, 1H, J=1.75 Hz, H_4), 7.65 (dd, 1H, J=8.20 Hz, J=1.75 Hz, H_6), 8.50 (br s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77; S, 10.93. Found: C, 57.15; H, 5.28; N, 4.63; S, 10.78.

4.7. 6-(4-Oxobutyric)-4*H*-benzothiazin-3-one (8d)

To sodium hydroxide (0.21 g, 5.13 mmol) dissolved in a solution of ethanol/water (15/15 mL) was added compound **8c** (0.50 g, 1.71 mmol). The reaction mixture was refluxed for 2 h and then evaporated under reduced pressure. The residue was dissolved in water (30 mL). The solution was acidified with 6 N HCl to pH=1, and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The compound was recrystallized from ethanol to give **8d** in 65% yield; mp 189–190 °C; IR (KBr, ν cm^{-1}) 3254 (NH), 1701 (COO), 1669 (CON), 1650 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.60 (m, 2H, CH_2CO), 3.15 (m, 2H, CH_2COO), 3.60 (s, 2H, CH_2S), 7.40–7.60 (m, 3H, H_4, H_6, H_7), 10.60 (br s, 1H, NH, exchangeable with D_2O), 12.10 (br s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28; S, 12.09. Found: C, 54.57; H, 4.35; N, 5.08; S, 12.24.

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Synthesis and photochromic reactivity of diarylethene trimers bridged by ethenyl and ethynyl unit

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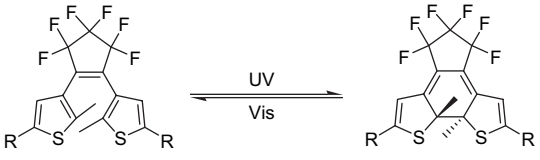
Abstract—Two diarylethene trimers bridged by ethenyl and ethynyl groups were synthesized and their photochromic behaviors were examined. Upon irradiation of the trimers **2** and **4** with UV light, one–three photoinduced cyclization reactions occur. Each isomer was isolated and analyzed by ^{1}H NMR spectrum. The quantum yield of **2** and **4** is 0.52 and 0.311, respectively.

1. Introduction

Photochromic compounds undergo reversible transformation between two distinct chemical isomers with different colors of light.[1] The photoreaction can be accompanied by changes in useful physical properties such as refractive index,[2] luminescence,[3] electronic conductance,[4] and optical rotation.[5] Photochromic diarylethene is very suitable for these purposes, due to their thermal stability and high fatigue resistance.[6] Some of these photoswitching effects are based on the changes in the extent of π-conjugation in diarylethene upon photochromic reaction (Scheme 1). Any π-electrons on the R groups can interact with each other through the π-conjugation in the ring-closed state.[7] The functionalization of the photochromic unit is a major issue because of some reasons, such as tuning the absorption wavelength or creating a system that can be used for information storage.[8] In substituted dithienylethenes some of the substituents cause a strong decrease or even a complete loss of the photochromic behavior.[9] It has been assumed that the photochromic state of one photochrome will influence the reactivity of another photochrome when they are covalently joined. Among the various types of diarylethene dimers connected with single bond,[10] phenylene,[11] ethynylene,[12] and diyne,[13] in most cases only one of the diarylethenes can convert to the closed-ring form upon UV irradiation. Even though some studies have been performed to clarify the effect of substituents,[14] a more general understanding of the way in which one photochromic unit interacts with another photochromic unit in a molecule is an important issue for practical applications. We envisioned that the strategic placement of diarylethene units within a macromolecular framework would help to understand the interaction between the diarylethene units. We now describe (i) the synthesis of macromolecules having three diarylethene units; (ii) their photochromic reactivities; (iii) the isolation of photocyclized products; (iv) the effect of bridging unit.



Scheme 1.

2. Results and discussion

2.1. Synthesis

Diarylethene trimers **2** and **4** were prepared according to the synthetic method shown in Schemes 2 and 3. Compound **2** was synthesized from 1,3,5-tris((*E*)-2-(tributylstannyl)-vinyl)benzene[15] in two steps. Stille cross coupling reaction of the stannyl with 3,5-dibromo-2-methylthiophene,[16] followed by the reaction of lithiated **1** with 4-(perfluorocyclopent-1-enyl)-2-phenylthiophene,[16] gave **2** in 50% yield. Compound **4** was synthesized in two steps from

Keywords: Photoswitch; Macromolecule; Trimer; Diarylethene.
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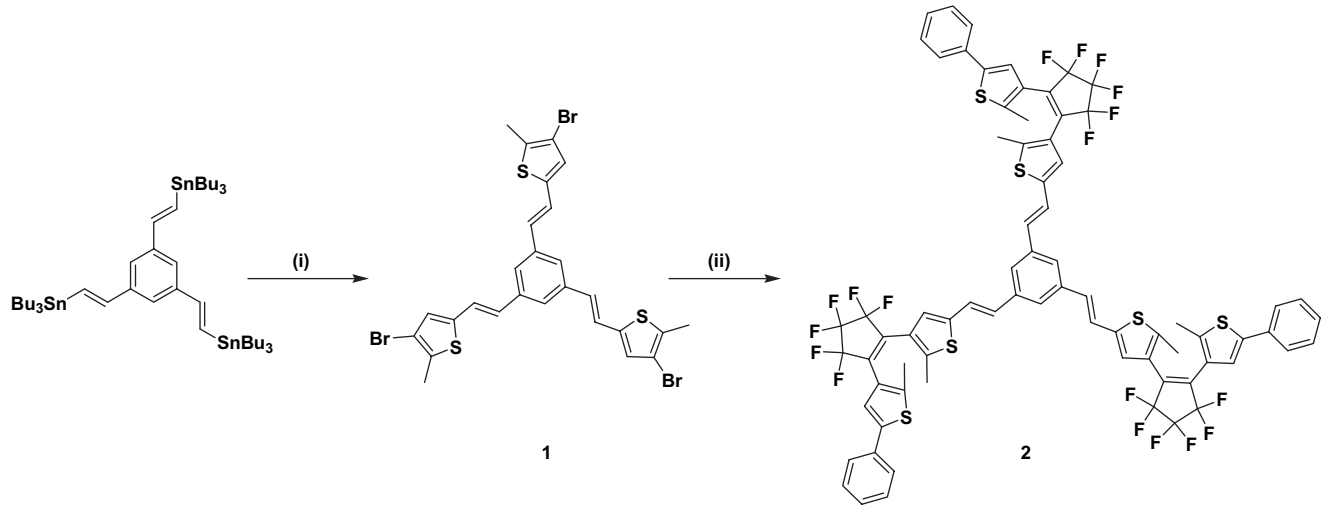
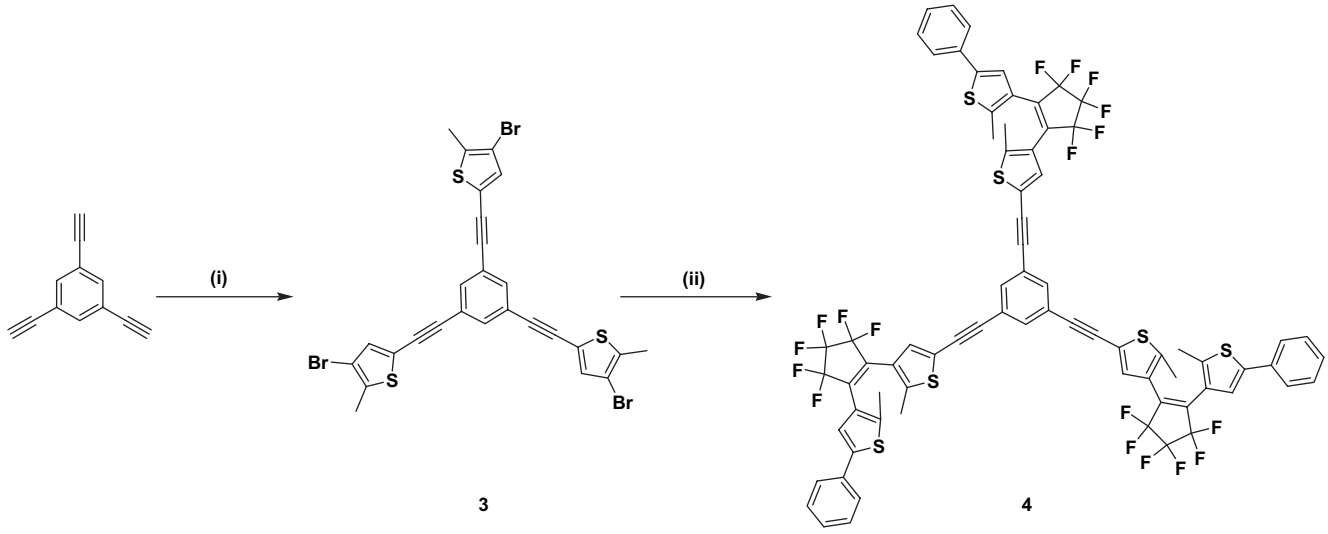


Scheme 2. (i) 3,5-Dibromo-2-methylthiophene, $Pd(PPh_3)_2Cl_2$, CsF in toluene; (ii) 4-(perfluorocyclopent-1-enyl)-2-phenylthiophene, *n*-BuLi in THF.



Scheme 3. (i) 3,5-Dibromo-2-methylthiophene, $Pd(PPh_3)_4$, CuI, NEt_3; (ii) 4-(perfluorocyclopent-1-enyl)-2-phenylthiophene, *n*-BuLi in THF.

1,3,5-triethynylbenzene.[17] Sonogashira coupling of 1,3,5-triethynylbenzene with 3,5-dibromo-2-methylthiophene followed by the reaction of lithiated **3** with 4-(perfluorocyclopent-1-enyl)-2-phenylthiophene yielded **4**. Spectroscopic data for **2** and **4** are completely consistent with their proposed structures. One resonance at 1.97 ppm for **2** and **4** in the ^1H NMR spectrum for the methyl group is observed. The mass spectra of **2** and **4** showed a molecular ion at *m*/*z* 1482 and 1476, respectively.

2.2. Photochromism of trimer 2 in chloroform

Figure 1 shows the absorption spectra of **2** in chloroform upon photoirradiation. Upon irradiation of **2** with 365 nm light, the colorless solution of the open-ring form turned blue, in which initial maximum was observed at 594 nm. It grew with shifting of the absorption maximum, and reached the photostationary state after 6 min. Upon visible light irradiation (λ>532 nm) for 2 h, the colored solution was

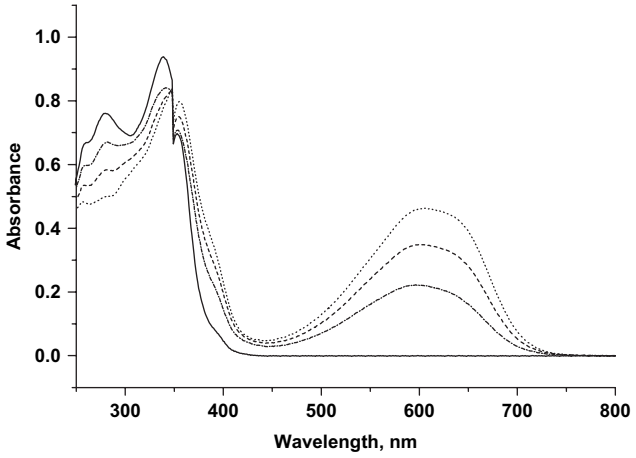
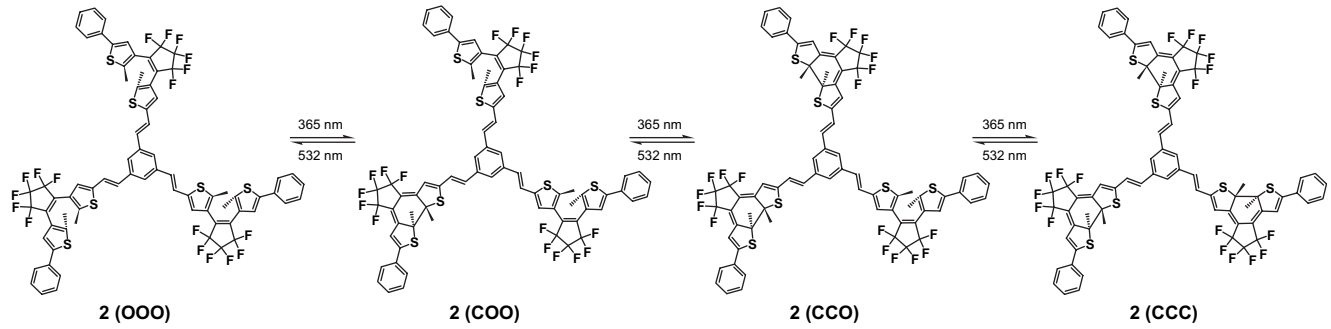


Figure 1. Absorption spectral change of the trimer **2** in chloroform upon irradiation with 365 nm light: (—) before irradiation, (-·-·-) after UV light irradiation for 2 min, (- - -) for 4 min, (···) for **8**.



Scheme 4. The photochromic reactivity of **2**.

completely bleached, indicating return to the initial open-ring isomer. In first 2 min of irradiation, an absorption band centered at 594 nm rapidly grows in as most of the **2** is converted from the colorless-open form **2** (OOO) to the blue-closed form **2** (COO) (Scheme 4). The presence of an isosbestic point at 342 nm indicates that **2** (OOO) is cleanly converted to a second photocyclized product. The closed-ring isomer **2** (COO) was isolated from the above blue colored solution by HPLC (silica gel, eluent hexane/ethyl acetate (10:1)) in 74% yield. Further irradiation (2 min) of **2** (COO) with 365 nm light afforded the anticipated red-shift of the absorption maximum at 602 nm that would have resulted from the two closed-ring isomers **2** (CCO). The photoirradiated product **2** (CCO) was analyzed with HPLC from the above solution. The fully closed-ring isomer **2** (CCC) can be achieved after an 8 min irradiation period of **2** (OOO) using 365 nm light in 52% yield. Absorption maximum of **2** (CCC) at 610 nm is shifted to longer wavelength by 8 nm in comparison with that of **2** (CCO) due to the extension of π-conjugation. The photogenerated ring-closed isomers **2** (COO), **2** (CCO), and **2** (CCC) were stable at room temperature. Figure 2 shows the ^{1}H NMR spectrum of methyl proton of **2** (OOO) in $CDCl_3$ before photoirradiation and in the ring-closed form **2** (COO), **2** (CCO), and **2** (CCC). In the ^{1}H NMR spectrum of **2** (OOO), one methyl resonance was observed at 1.97 ppm. In the blue isomer **2** (COO), one distinct new band appeared at 2.16 ppm, together with one singlet at 1.97 ppm. The integral ratio of the two signals was 1:2, indicating that the colored isomer is **2** (COO). Another key feature of **2** (COO) is the presence of four new thienyl signals at 7.28, 7.10, 6.70, and 6.42 ppm. The two new resonances at 6.70 and 6.42 ppm are significantly shifted up-field as would be expected for the ring-closed isomer. Such an up-field shift was observed in covalently linked double 1,2-dithienylethenes[10–13] and macromolecules[18] incorporating four dithienylethene units. The dissymmetric nature of the photogenerated product indicates that one of three thienyl units has cyclized to form **2** (COO). Figure 2c shows the ^{1}H NMR spectrum of methyl protons of **2** (CCO) separated from the photogenerated product by HPLC after the photoirradiation of **2** (OOO) for 4 min. Two distinct bands appeared at 2.16 and 1.97 ppm. The integral ratio of the two signals was 2:1, which indicates that the colored isomer is **2** (CCO). Figure 2d shows the ^{1}H NMR spectrum of methyl protons of **2** (CCC). One distinct band appeared at 2.16 ppm, demonstrating that **2** (OOO) was completely converted into the closed form **2** (CCC).

2.3. Photochromism of trimer 4 in chloroform

Figure 3 shows the absorption spectrum of trimer **4** in chloroform upon UV light irradiation. Irradiation of chloroform solution of **4** at 365 nm light resulted in an immediate increase in the absorption intensity at 607 nm. It grew with shifting of the absorption maximum to red-shifted region. Upon visible light irradiation (λ>532 nm) for 6 h, the blue colored solution was completely bleached. After the irradiation of **4** (OOO) for 2 min, the photogenerated products were analyzed with HPLC (silica gel, eluent hexane/ethyl acetate (9:1)). The elution peaks were detected at the isosbestic point of 342 nm. The open-ring form **4** (OOO) was eluted at 14 min. The photogenerated solution gave two peaks at

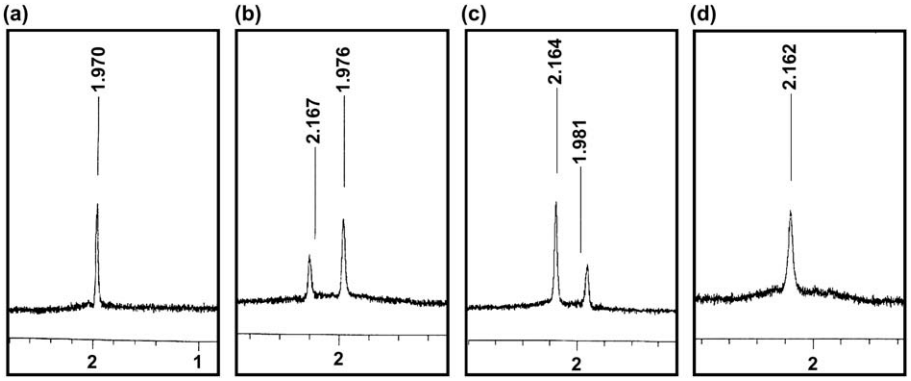


Figure 2. ^{1}H NMR methyl signals of the (a) **2** (OOO) trimer; (b) **2** (COO) trimer; (c) **2** (CCO) trimer; and (d) **2** (CCC) trimer.

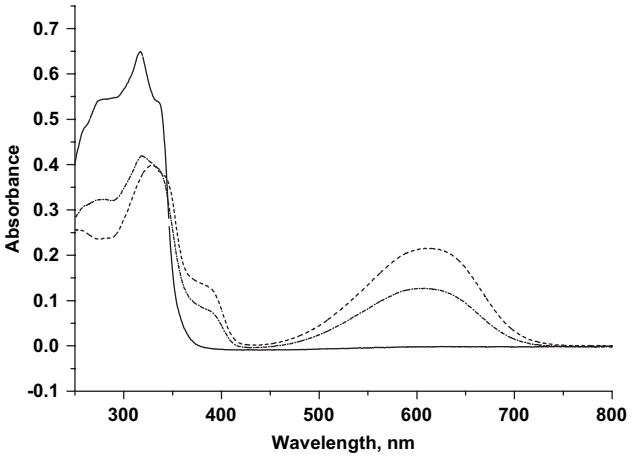


Figure 3. Absorption spectral change of the trimer **4** in chloroform upon irradiation with 365 nm light: (—) before irradiation, (-·-·-) after UV light irradiation for 2 min, (- - -) for 8 min.

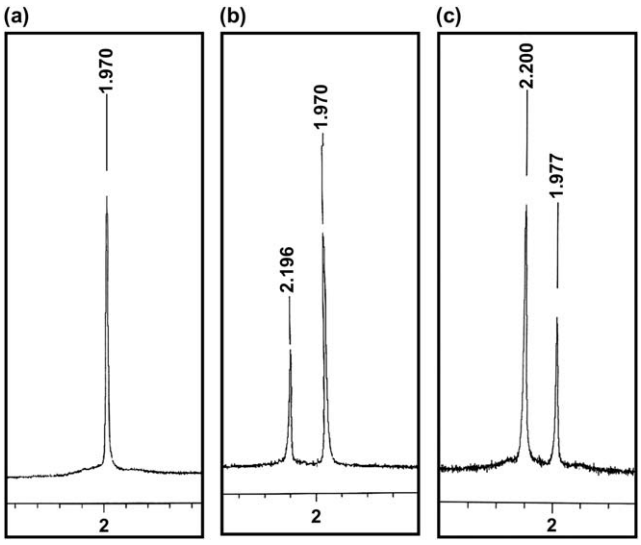
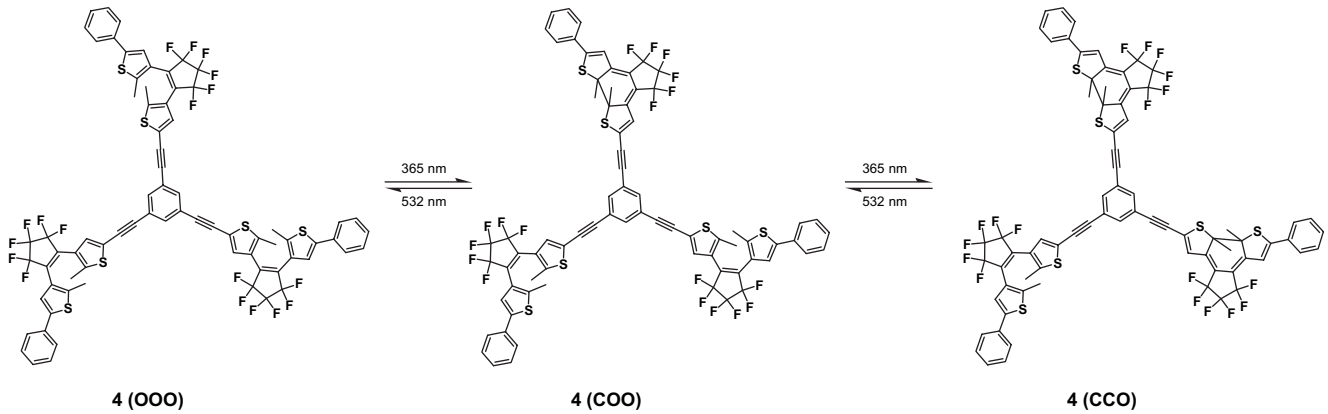


Figure 4. ^{1}H NMR methyl signals of the (a) **4** (OOO) trimer; (b) **4** (COO) trimer; and (c) **4** (CCO) trimer.

11 and 14 min. As the peak at 14 min can be assigned to be **4** (OOO), the peak at 11 min can be assigned as a photocyclized product. The ^{1}H NMR spectrum is demonstrated to be **4** (COO) (Scheme 5). Further irradiation (2 min) of **4** (COO) with 365 nm light gave the deep blue solution. The photogenerated products were analyzed with HPLC (silica gel, eluent hexane/ethyl acetate (9:1)). When monitored at the isosbestic point of 342 nm, two peaks were observed. The first peak of the isomer had an absorption maximum at 615 nm. The product was proven to be **4** (CCO) based on the ^{1}H NMR. Further irradiation of **4** (CCO) (4 min) with 365 nm light did not afforded the anticipated red-shift of the absorption maximum that would have resulted from the fully ring-closing isomer. Instead, the increase in the absorbance levels off. The ^{1}H NMR spectroscopy is a useful tool that determines the exact ratio between the open and closed forms. The most suitable signals, showing the largest shifts upon cyclization, are those of the methyl groups on the thiophene rings. Figure 4 shows the ^{1}H NMR spectrum of methyl protons **4** (OOO) in $CDCl_3$ before photoirradiation and in the ring-closed form **4** (COO) and **4** (CCO). In the ^{1}H NMR spectrum of **4** (OOO), only one methyl signal was observed at 1.97 ppm. In the ^{1}H NMR spectrum of blue isomer **4** (COO), a new methyl signal appeared at 2.20 ppm, together with one singlet at 1.97 ppm. The integral ratio of the two signals was 1:2, indicating that the colored isomer is **4** (COO). Figure 4c shows the ^{1}H NMR spectrum of methyl protons of **4** (CCO). The methyl protons show two resonances at 2.20 and 1.97 ppm with the integral ratio of 2:1. This indicates that two closed-ring forms **4** (CCO) are included in the trimer.

2.4. Quantum yield

The quantum yield of the macromolecules **2** and **4** are measured using 1,2-bis(2-methyl-3-thienyl)perfluorocyclopentene (TF_6) as a reference.[19] The cyclization quantum yield of **2** from the all open-ring form **2** (OOO) to the isomer **2** (COO), from **2** (COO) to the **2** (CCO), and **2** (CCO) to the all closed-ring form **2** (CCC) was determined to be 0.23, 0.18, and 0.11, respectively. The total cyclization quantum yield is 0.52, which is much higher than that of tridithienylethene array.[12] The quantum yield of **4** was determined to be 0.311. The cycloreversion quantum yield of **2** (CCC) and **4** (CCO) was measured to be 8.4×10^{-4} and 8.2×10^{-4}, respectively.



Scheme 5. The photochromic reactivity of **4**.

2.5. MO calculation

Our interests are focused on examining the electronic communication between three intimately connected 1,2-dithienylethene photochromes in **2** and **4**. It is assumed that the photochromic state of one photochrome will influence the reactivity of another when they are covalently joined. In compounds **2** and **4**, we wondered why three dithienylethene units in **2** (OOO) are converted into the all closed-ring form **2** (CCC), and on the other hand, only two dithienylethene units in **4** (OOO) are partially converted into **4** (CCO). To clarify the effect of bridged unit in **2** and **4**, we have carried out ab initio calculations. Molecular orbital calculation for the compounds **2** and **4** were performed using Gaussian 03 program at the B3LYP/3-21G* level. Geometry was optimized at this level. The HOMO in **2** (CCC) is delocalized over the π-conjugated systems via the two thienylethene unit (Fig. 5, **2a**). The LUMO in **2** (CCC) is delocalized through three dithienylethene units. On the other hand, the HOMO in **4** (CCC) is localized on a dithienyl unit (Fig. 5, **4a**) and the LUMO in **4** (CCC) is delocalized through two dithienyl units. Examination of the HOMO and the LUMO of **2** (CCC) and **4** (CCC) indicates that the photochromic state of one photochrome in **2** bridged by ethenyl unit influences well the reactivity of another, compared with **4** bridged by ethynyl unit resulting in the all closed-ring form.

In summary, we have prepared two macromolecules incorporating three dithienylethene units. Upon irradiation of **2** (OOO) with UV light, one, two, and three photoinduced cyclization reaction occurs. Each isomer was isolated and analyzed by ^{1}H NMR spectrum. The quantum yield of **2** and **4** are 0.52 and 0.311, respectively. The formation of all closed-ring form **2** (CCC) is due to the delocalization of the π-conjugated systems through the three dithienylethene units.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere. Solvents were distilled from appropriate reagents. Perfluorocyclopentene was purchased from Fluorochem. 1,3,5-Tris((*E*)-2-(tributylstannyl)vinyl)benzene,[15] 3,5-dibromo-2-methylthiophene,[16] and 4-(perfluorocyclopent-1-enyl)-2-phenylthiophene[16] were synthesized using previous references. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer. The absorption was recorded on a Perkin–Elmer Lambda 2S UV–vis spectrometer.

3.2. Determination of quantum yields

The quantum yield of the photochromic ring-cyclization of **2** and **4** was determined from the absorption changes at λ_{max} in UV spectra upon excitation with a UV light for ring closure and visible light for ring opening reaction. Conversion and the number of absorbed photons were determined at a given radiation power and absorbance of the sample. Then,

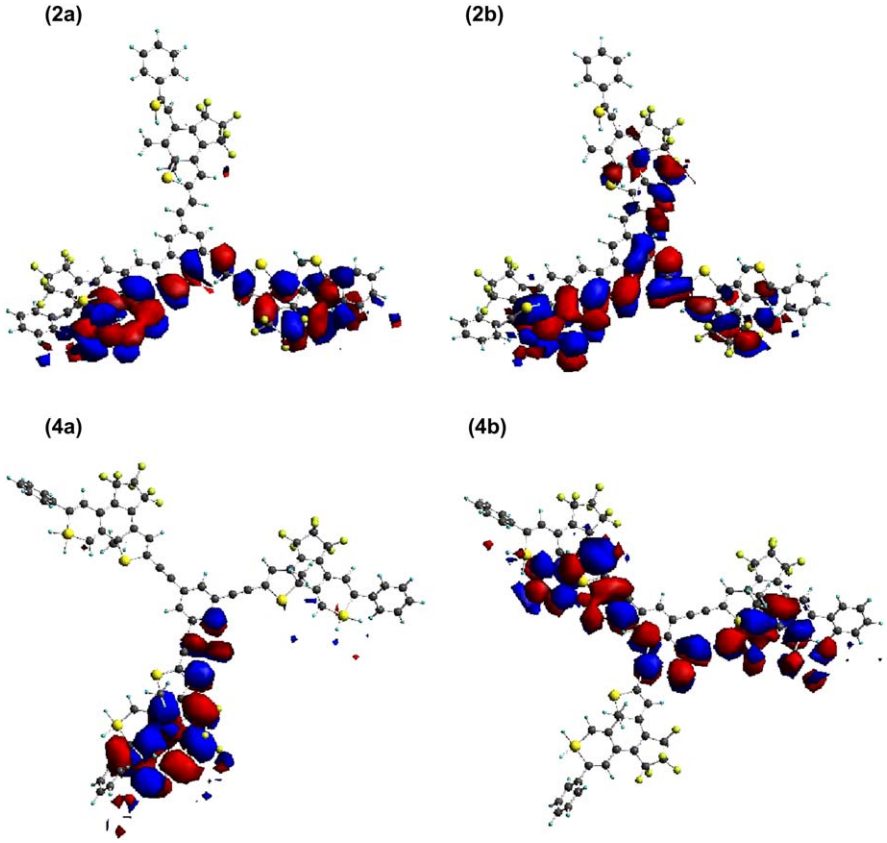


Figure 5. Representation of (a) HOMO and (b) LUMO of **2** (CCC); (a) HOMO and (b) LUMO of **4** (CCC) based on Gaussian 03 program at the B3LYP/3-21G* level.

quantum yield was determined according to the method described in Ref. 19.

3.2.1. Compound 1. To a mixture of 1,3,5-tris((*E*)-2-(tributylstannyl)vinyl)benzene (0.1 g, 0.1 mmol), $Pd(PPh_3)_2Cl_2$ (7 mg, 10 mol %), and CsF (0.027 g, 0.66 mmol) in toluene (30 mL) was added 3,5-dibromo-2-methylthiophene (84.4 mg, 0.33 mmol). The solution was refluxed for 20 h. After cooling the solution, H_2O (10 mL) and brine were added to the solution. The organic layer was separated and dried in $MgSO_4$. The solvent was removed in vacuo. The pure product **1** was obtained by chromatographic work-up (1:3 ethyl acetate/hexane, R_f=0.5) as a yellow solid in 70% yield. Mp: 176 °C. ^{1}H NMR ($CDCl_3$): δ 7.37 (s, 3H), 7.11 (d, J=16.2 Hz, 3H), 6.89 (s, 3H), 6.79 (d, J=16.2 Hz, 3H), 2.40 (s, 9H).^{13}C{^{1}H} NMR ($CDCl_3$): δ 137.5, 134.8, 133.6, 130.7, 129.2, 127.6, 126.8, 109.7, 14.5. MS: *m*/*z* 683 [M^+]. Anal. Calcd for $C_{27}H_{21}Br_3S_3$: C, 47.59; H, 3.11. Found: C, 47.46; H, 3.06.

3.2.2. Compound 2. To a stirred THF solution (50 mL) of **1** (0.31 g, 0.45 mmol) was added *n*-BuLi (1.43 mL, 2.29 mmol, 1.6 M in hexane) at −78 °C under argon atmosphere, and stirred for 1.5 h at the temperature. 4-(Perfluorocyclopent-1-enyl)-2-phenylthiophene (0.84 g, 2.29 mmol) in THF (5 mL) was slowly added to the solution at −78 °C and stirred for 3 h at the temperature. The reaction mixture was quenched by the addition of H_2O (1 mL). The product was extracted with ether. The organic layer was dried over $MgSO_4$. The pure product **2** was obtained by chromatographic work-up (1:5 ethyl acetate/hexane, R_f=0.3) as a blue solid in 70% yield. Mp: 143 °C. ^{1}H NMR ($CDCl_3$): δ 7.55 (d, J=8.1 Hz, 6H), 7.42 (s, 3H), 7.39 (t, J=6.2 Hz, 6H), 7.31 (t, J=7.1 Hz, 3H), 7.28 (s, 3H), 7.20 (d, J=16.2 Hz, 3H), 7.10 (s, 3H), 6.81 (d, J=16.2 Hz, 3H), 1.97 (s, 18H).^{13}C{^{1}H} NMR ($CDCl_3$): δ 142.3, 141.4, 140.7, 137.6, 136.4, 133.4, 129.4, 128.8, 128.4, 127.7, 126.8, 125.9, 125.7, 124.1, 122.9, 122.1, 119.7, 116.3, 112.9, 111.1, 14.8. MS: *m*/*z* 1482 [M^+]. Anal. Calcd for $C_{75}H_{48}F_{18}S_6$: C, 60.72; H, 3.26. Found: C, 60.45; H, 3.13.

3.2.3. Compound 3. To a degassed mixture of 1,3,5-triethynylbenzene (0.576 g, 3.9 mmol), $Pd(PPh_3)_4$ (0.67 g, 0.58 mmol), and CuI (0.044 g, 0.24 mmol) in Et_3N (50 mL) was added 3,5-dibromo-2-methylthiophene (5 g, 19.5 mmol). The mixture was stirred at 45 °C for 7 h. The solvent was evaporated under reduced pressure. The pure product **3** was obtained by chromatographic work-up (1:10 ethyl acetate/hexane, R_f=0.5) as a pale yellow solid in 65% yield. Mp: 165 °C. ^{1}H NMR ($CDCl_3$): δ 7.55 (s, 3H), 7.08 (s, 3H), 2.41 (s, 9H).^{13}C{^{1}H} NMR ($CDCl_3$): δ 137.2, 134.7, 133.7, 123.7, 120.2, 109.3, 91.9, 83.3, 15.1. MS: *m*/*z* 675 [M^+]. Anal. Calcd for $C_{27}H_{15}Br_3S_3$: C, 48.02; H, 2.24. Found: C, 47.75; H, 2.14.

3.2.4. Compound 4. To a stirred THF solution (50 mL) of **3** (0.2 g, 0.29 mmol) was added *n*-BuLi (0.93 mL, 1.48 mmol, 1.6 M in hexane) at −78 °C under argon atmosphere, and the solution was stirred for 1.5 h at the temperature. 4-(Perfluorocyclopent-1-enyl)-2-phenylthiophene (0.54 g, 1.48 mmol) in THF (5 mL) was slowly added to the solution at −78 °C, and stirred for 3 h at the temperature. The reaction mixture was quenched by the addition of H_2O (1 mL). The product was extracted with ether. The organic layer was dried over $MgSO_4$. The pure product **4** was obtained by chromatographic work-up (1:5 ethyl acetate/hexane, R_f=0.5) as a blue solid in 50% yield. Mp: 136 °C. ^{1}H NMR ($CDCl_3$): δ 7.60 (s, 3H), 7.55 (d, J=7.1 Hz, 6H), 7.39 (t, J=7.2 Hz, 6H), 7.33 (s, 3H), 7.32 (d, J=7.2 Hz, 3H), 7.29 (s, 3H), 1.97 (s, 18H).^{13}C{^{1}H} NMR ($CDCl_3$): δ 144.1, 142.6, 141.4, 133.8, 133.3, 132.3, 129.1, 128.5, 128.1, 125.7, 125.6, 125.3, 123.7, 122.3, 121.1, 119.5, 116.2, 113.8, 92.1, 83.2 14.6. MS: *m*/*z* 1476 [M^+]. Anal. Calcd for $C_{75}H_{42}F_{18}S_6$: C, 60.97; H, 2.87. Found: C, 60.62; H, 2.72.

3.2.5. Closed-ring isomer of 2 (COO). ^{1}H NMR ($CDCl_3$): δ 7.55 (d, J=8.1 Hz, 6H), 7.42 (s, 3H), 7.39 (t, J=6.2 Hz, 6H), 7.31 (t, J=7.1 Hz, 3H), 7.28 (s, 2H), 7.20 (d, J=16.2 Hz, 3H), 7.10 (s, 2H), 6.81 (d, J=16.2 Hz, 3H), 6.70 (s, 1H), 6.42 (s, 1H), 2.16 (s, 6H), 1.97 (s, 12H).

3.2.6. Closed-ring isomer of 2 (CCO). ^{1}H NMR ($CDCl_3$): δ 7.55 (d, J=8.1 Hz, 6H), 7.42 (s, 3H), 7.39 (t, J=6.2 Hz, 6H), 7.31 (t, J=7.1 Hz, 3H), 7.28 (s, 1H), 7.20 (d, J=16.2 Hz, 3H), 7.10 (s, 1H), 6.81 (d, J=16.2 Hz, 3H), 6.70 (s, 2H), 6.42 (s, 2H), 2.16 (s, 12H), 1.97 (s, 6H).

3.2.7. Closed-ring isomer of 2 (CCC). ^{1}H NMR ($CDCl_3$): δ 7.55 (d, J=8.1 Hz, 6H), 7.39 (t, J=6.2 Hz, 6H), 7.31 (t, J=7.1 Hz, 3H), 7.20 (d, J=16.2 Hz, 3H), 6.81 (d, J=16.2 Hz, 3H), 6.70 (s, 3H), 6.42 (s, 3H), 2.16 (s, 18H).

3.2.8. Closed-ring isomer of 4 (COO). ^{1}H NMR ($CDCl_3$): δ 7.60 (s, 3H), 7.55 (d, J=7.1 Hz, 4H), 7.42 (d, J=7.1 Hz, 2H), 7.39 (t, J=7.2 Hz, 6H), 7.33 (s, 2H), 7.32 (d, J=7.2 Hz, 3H), 7.29 (s, 2H), 6.68 (s, 1H), 6.50 (s, 1H), 2.19 (s, 6H), 1.97 (s, 12H).

3.2.9. Closed-ring isomer of 4 (CCO). ^{1}H NMR ($CDCl_3$): δ 7.60 (s, 3H), 7.55 (d, J=7.1 Hz, 2H), 7.42 (d, J=7.1 Hz, 4H), 7.39 (t, J=7.2 Hz, 6H), 7.33 (s, 1H), 7.32 (d, J=7.2 Hz, 3H), 7.29 (s, 1H), 6.68 (s, 2H), 6.51 (s, 2H), 2.19 (s, 12H), 1.97 (s, 6H).

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Wide- and narrow-rim functionalised calix[4]arenes: synthesis and characterisation

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Abstract—Functionalisation of calix[4]arene at both the wide and narrow rims leads to the formation of compounds containing bipyridyl, via an amide linkage, at the wide rim and having either a butyl chain, a benzyl group or an alkyl ester functionality at the narrow rim. All compounds were characterised using ^{1}H and ^{13}C NMR spectroscopies. Initial binding studies with $Ru(bipy)_2Cl_2$ are reported.

1. Introduction

Calix[4]arenes are macrocyclic molecules with unique three-dimensional structures. They belong to a larger family of calix[*n*]arene molecules that is relatively old, and is generated from the chemical condensation of formaldehyde and phenol.[1] When all four oxygen atoms point in the same direction, the macrocycle exhibits a bowl-shaped structure called the cone conformation. Functionalisation of the calix[4]-arene is referred to as either narrow rim (previously called lower rim), if it occurs at the phenolic oxygen, or wide rim (previously called upper rim), if it occurs at the *para* position after the removal of *p-tert*-butyl groups (see Fig. 1).

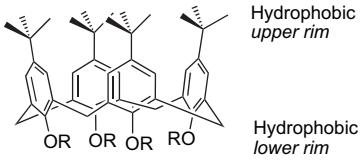

Figure 1. Structural formula of calix[4]arene.

Their controlled synthetic functionalisation and their versatile complexation properties[1] allow the use of these compounds in supramolecular chemistry as molecular scaffolds for the construction of various receptors. They are frequently employed as platforms that permit functional groups to be orientated to provide well-organised cavities. The great interest in compounds of this type is primarily motivated by the ionophoric property of the narrow rim, which leads to applications in the area of cation binding and transport, as well as highly selective receptors and novel sensors for polyanionic species.[1] This polyfunctional property stems from the fact that the narrow rim is relatively easy to chemically modify via well-established acid–base and nucleophilic reactions. The chemistry of the wide rim has not been fully exploited, and this can be explained by the relatively more difficult chemistry involved in its functionalisation; wide-rim modified derivatives are, for the most part, di-1,3- and tetrasubstituted species.

Furthermore, the functionalisation of calix[4]arenes at both the wide and narrow rims has not been widely discussed in the literature,[1] though such molecules are desirable in the development of calixarene-based supramolecular structures. As part of a broad study of the interactions of various functional groups at both the wide and narrow rims, we have prepared and characterised some dipyridyl calix[4]arenes and their copper(I/II) complexes.[2] This paper describes the functionalisation of the narrow rim with either *n*-butyl, benzyl or ester groups and the subsequent wide-rim derivatisation via amide groups containing a bipyridyl group.

2. Results and discussion

Both NMR and IR spectroscopies were used to characterise all the products synthesised. The NMR signals for the

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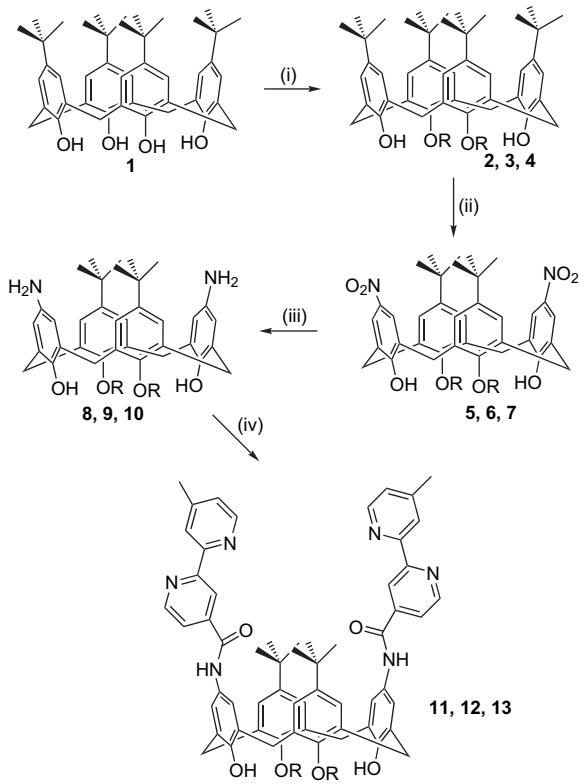
Table 1. Selected ^{1}H NMR data for compounds **1–13**

Compound	Ar-H	–CH_2–	*t*-Bu
1	7.04	4.23, 3.49	1.21
2	7.03, 6.84	4.31, 3.28	1.26, 1.00
3	7.03, 6.83	4.25, 3.29	1.27, 0.98
4	7.02, 6.85	4.43, 3.30	1.25, 1.00
5	8.03, 6.96	4.30, 3.49	1.06
6	8.03, 6.89	4.23, 3.40	1.01
7	8.02, 7.07	4.54, 3.50	1.11
8	6.90, 6.45	4.25, 3.20	1.15
9	6.84, 6.42	4.25, 3.18	1.04
10	6.97, 6.32	4.50, 3.24	1.16
11	7.40, 7.00	4.40, 3.49	1.10
12	7.40, 6.96	4.36, 3.41	1.06
13	7.39, 7.01	4.55, 3.39	1.12

methylene bridges, aromatic protons and *tert*-butyl groups for all of the calix[4]arene derivatives are summarised in Table 1; complete data for all compounds are given in Section 4. Scheme 1 shows the synthetic approach chosen for the *n*-butyl, benzyl and ester derivatives.



Scheme 1. Reagents and conditions: (i) K_2CO_3, appropriate halo-compound, MeCN, reflux 18 h; (ii) HNO_3, acetic acid, DCM, reflux 3 h; (iii) $SnCl_2$, EtOH, reflux 12 h; (iv) 4-methyl-4′-carboxylic acid-2,2′-bipyridine, DMT-MM, MeOH, reflux 4 h. R=*n*-C_4H_9, benzyl or CH_2CO_2Et.

The parent calix[4]arene **1** was reacted with potassium carbonate and the appropriate halo-compound (benzyl chloride, 1-bromo-butane or ethyl bromoacetate) in acetonitrile at reflux temperature to give the narrow-rim 1,3-disubstituted compounds **2**, **3** and **4** in good yields. Compounds **2–4** show the expected NMR pattern, with two signals being observed for both the aromatic protons of the calix[4]arene and the *tert*-butyl groups, indicative of 1,3-disubstitution on the narrow rim of the calix[4]arene. Furthermore, the cone conformation of the derivatised calix[4]arenes is also confirmed by the presence of two sharp doublets at approximately 4.3 and 3.3 ppm in each case.

The diprotected-calix[4]arene, with either the benzyl group (**2**), the *n*-butyl group (**3**) or the ester group (**4**), was then treated with concentrated nitric acid in acetic acid to give the dinitro-diprotected-calix[4]arenes **5**, **6** and **7**. In all cases, the nitro group replaces the *tert*-butyl group opposite the free OH group. The ^{1}H NMR spectra of compounds **5–7** showed several characteristic signals. The signal for the OH group shifts downfield from δ 8.00 (**3**) and 7.15 (**4**) to δ 8.66 (**5**), 9.44 (**6**) and 8.94 (**7**); the OH signal for compound **2** is hidden under the signal for one of the benzyl protons at δ 7.35. A large downfield shift is also observed for the aromatic proton on the phenyl ring to which the nitro group becomes attached (see Table 1). The signal for one of the *tert*-butyl groups is also lost, confirming the replacement of the *tert*-butyl group by the nitro group. Finally, the cone conformation of each calix[4]arene is also retained. Reinhoudt et al. describe similar shifts for the OH signals in their paper on the nitration of calix[4]arenes.[3] One interesting point regarding the yields of the nitration reactions is that the nitration of the diester calix[4]-arene (**4**) proceeds only in very low yield (17% in our case and 24% in the literature[3]). The conclusion that can be drawn is that the ester group, and in particular the carbonyl group, is playing some unexpected role in the reaction, thereby causing the yield to decrease. Reinhoudt et al.[3] suggest that the presence of electron donating groups on the narrow rim should enhance the nitration reaction but offer no explanation as to the low yield for this particular compound.

The dinitro compounds then underwent reduction with $Sn(II)Cl_2$ in ethanol to give the diamino-diprotected-calix-[4]arenes **8**, **9** and **10**, in a similar manner to that reported in the literature.[4] These compounds are easily identified by the large upfield shift of the aromatic protons from, for example, δ 8.03 and 6.89 in compound **5** (the dinitro-di-benzyl compound) to δ 6.84 and 6.42 in compound **8** (the diamino-di-benzyl compound). This type of shift has been observed previously in various wide-rim amino-calix[4]arenes.[4] Again, the presence of two doublets in the 4.5–3.0 ppm region indicates cone conformation retention. The diamino-calix[4]arenes (**8–10**) were not particularly air or moisture-stable but all decomposed to a sticky material when exposed to air, as a solid, for several hours. The ^{1}H NMR spectrum of the sticky material indicated that breakdown of the calix[4]-arene was occurring. For this reason, all samples were only made prior to proceeding with the next reaction in Scheme 1.

Compounds **11**, **12** and **13** were synthesised by reaction of the appropriate diamino-calix[4]arene with 4-methyl-4′-carboxylic acid-2,2′-bipyridine[5] using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride[6] (DMT-MM) as condensing agent. The successful condensation of carboxylic acids and amines by DMT-MM in THF to give the corresponding amides in good yields was reported by Kunishima et al.[6] The selective formation of carboxamides (–CONH–) in alcohol or water by a convenient one-step procedure, in which the condensing agent (DMT-MM) is simply added to a mixture of acids and amines, was also achieved successfully by the same group.[7] The choice of DMT-MM as the base for this reaction was based on the fact that the workup in these cases was a simple

filtration. DMT-MM also has the added advantage that the reaction conditions are very mild, that is, a 3-h stir in methanol. In all cases, the presence of the amide carbonyl group in the IR spectra was clearly seen at approximately 1670 cm^{-1} for the bipyridyl compounds (**11**–**13**). The ^1H NMR spectra again showed that the cone conformation was retained in all cases. The 9.0–6.5 ppm region of each spectrum contained many signals but in all cases there were no overlapping signals and all the signals were sharp and well-defined, making assignment straightforward. The use of an ^1H–^1H COSY spectrum further simplified the process, together with a COSY spectrum previously published by Hesek et al.[8] The presence of a sharp singlet at δ 2.49, due to the methyl group on the bipyridyl group, was a useful reference signal to indicate that attachment had taken place.

These bipyridyl calixarenes are potential building blocks for supramolecular structures as they should be able to bind transition metal centres at the wide rim. To test this theory, we decided to carry out an initial study of the reaction between *cis*-bis(2,2′-bipyridine)dichloro-ruthenium(II) (Ru(bipy)$_2$Cl$_2$) and the calix[4]arene derivatives **11**, **12** and **13**. This consisted of carrying out the reaction, in each case, in ethanol at reflux temperature for 3 h followed by the addition of tetrabutylammonium hexafluorophosphate in order to precipitate a solid material. In all cases, orange/brown coloured solids were obtained. TLC analysis on these complexes, using $CHCl_3$/MeOH (9/1) as the solvent system, showed no sign of the starting calix[4]arene compounds. Preliminary characterisation of the ruthenium(II) complexes was carried out using only ^1H NMR spectroscopy. A more in-depth characterisation will be reported for all the complexes at a later date. The ^1H NMR spectra of the three ruthenium complexes were obtained and all showed a more complicated spectrum, particularly in the aromatic region, than that obtained for the starting calix[4]arene derivative. Figure 2 shows the ^1H NMR spectra of **13** prior to and after complexation with the ruthenium compound.

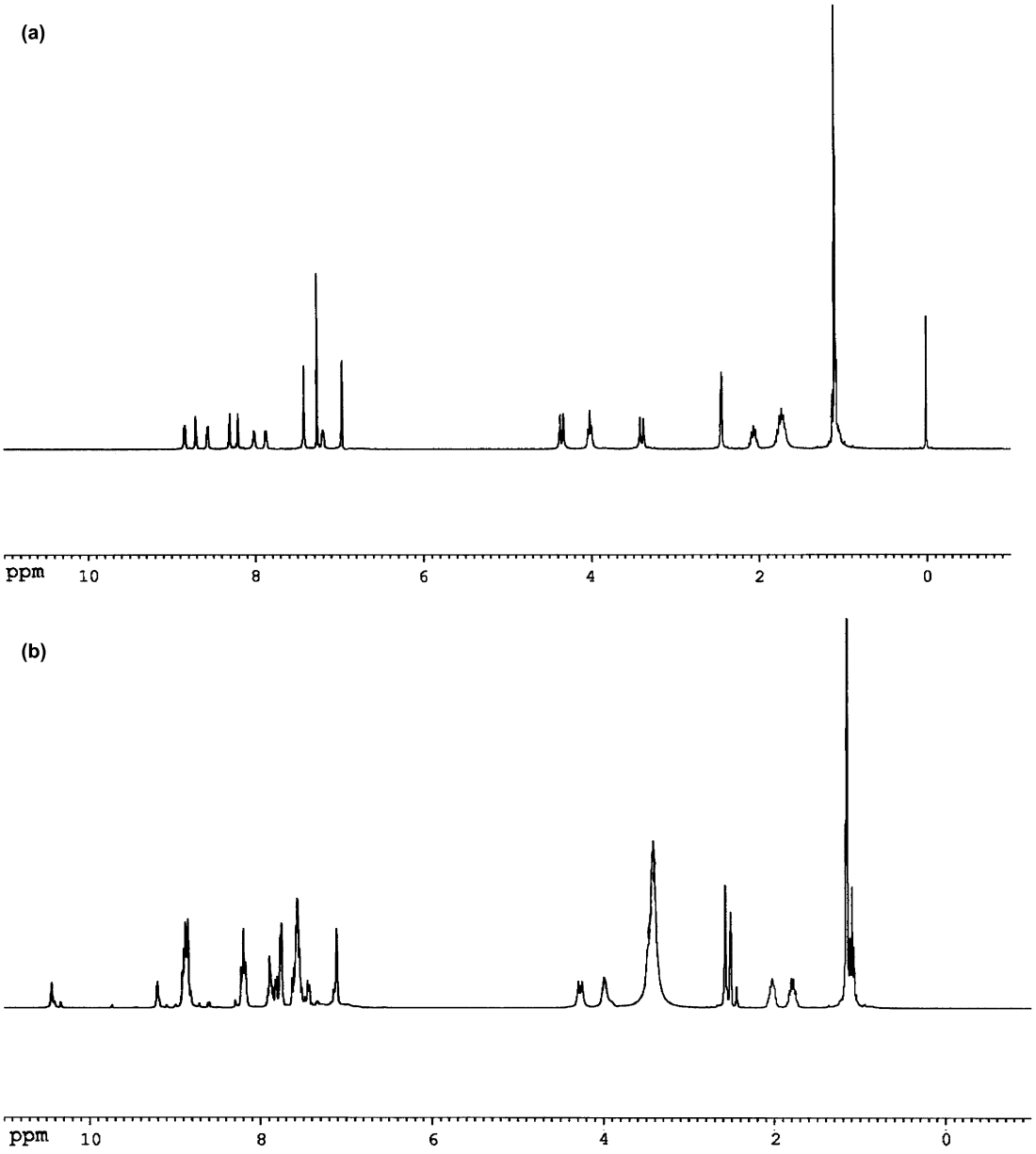


Figure 2. ^1H NMR spectra in $CDCl_3$ of (a) **13** and (b) [**13**·(Ru)$_2$]$^{4+}$ complex.

The resonance signals for the *tert*-butyl, ester/butyl/benzyl groups and the bipyridyl methyl group were clearly seen. Only one set of doublets was seen for the methylene bridges in all cases; the second set was covered by the DMSO signal. Because of the additional signals for the $[Ru(bipy)_3]^{2+}$ moiety, only one aromatic signal at 7.10 ppm was distinguished for the calixarene in the case of the butyl derivative (**12**); the second signal was under the signals for the $[Ru(bipy)_3]^{2+}$ moiety itself. The 3-H and 3′-H signals for the bipyridyl group attached to the calix[4]arene were easily distinguished in the proton spectrum, as they were singlet peaks; the rest of the spectra relating to the $[Ru(bipy)_3]^{2+}$ was complicated. Therefore, the attachment of this ruthenium moiety to the functionalised calix[4]arenes **11**, **12** and **13** produced the desired $[Ru(bipy)_3]^{2+}$ moiety on the upper rim of the modified calix[4]arenes. The di-ruthenium complexes were all isolated as their hexafluorophosphate salts in good yields (78, 64 and 90% using compounds **11**, **12** and **13**, respectively). From these preliminary reactions it can be seen that the di-ruthenium calix[4]arenes were easily isolated in acceptable yields.

3. Conclusions

The syntheses of calix[4]arenes, which are derivatised at both the wide (bipyridyl) and narrow rims (benzyl, butyl and ester groups), were carried out and the compounds were characterised by NMR and IR spectroscopies. Following 1,3-difunctionalisation of the narrow rim, the wide rim was nitrated, followed by reduction to the amine before condensation with the bipyridyl acid to form an amide group took place. All yields were moderate to good, except in the case of the dinitro-diester calix[4]arene (**6**) where the yield was very low. These bipyridyl calixarenes are potential building blocks for supramolecular structures. We have carried out some initial complexation reactions with $Ru(bipy)_2Cl_2$ and we are currently investigating further transition metal reactions based on these initial findings.

4. Experimental

4.1. General

^1H and ^{13}C NMR (δ ppm, J Hz) spectra were recorded on a JOEL JNM-LA300 FTNMR spectrometer using saturated $CDCl_3$ solutions with Me_4Si reference, unless indicated otherwise, with resolutions of 0.18 Hz and 0.01 ppm. Infrared spectra (cm^{-1}) were recorded as KBr discs or liquid films between KBr plates using a Nicolet Impact 410 FT-IR. All UV–vis spectra were recorded on a Shimadzu UV-160A spectrometer. Melting point analysis was carried out using a Stewart Scientific SMP 1 melting point apparatus and is uncorrected. Mass spectra were obtained using a Bruker-Esquire-LC_00050 electrospray ionisation mass spectrometer at positive polarity with cap-exit voltage of 167 V. Spectra were recorded in the scan range of 50–2200 *m*/*z* with a potential between 30 and 70 V. Microanalysis was carried out at the Microanalytical Laboratory of either University College, Dublin or the National University of Ireland Cork. Standard Schlenk techniques were used throughout. Starting materials were commercially obtained and used without further purification. The syntheses of compounds 4-*tert*-butyl-calix[4]arene, **1**,[9] 5,11,17,23-tetra-*tert*-butyl-25,27-dibenzyloxy-calix[4]arene, **2**,[10] 5,11,17,23-tetra-*tert*-butyl-25,27-dibutoxycalix[4]-arene, **3**,[2] 5,11,17,23-tetra-*tert*-butyl-25,27-diethoxycarbonylmethoxycalix[4]arene, **4**[11] and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride[6] (DMT-MM) have been described in the literature previously.

4.2. General synthesis of 2, 3 and 4

To a stirring suspension of 4-*tert*-butylcalix[4]arene (**1**, 3.1 mmol) and potassium carbonate (7.7 mmol) in acetonitrile (60 ml), under nitrogen, was added the appropriate halo-compound (6.8 mmol) in acetonitrile (10 ml), and the mixture was heated to reflux for 18 h. After being cooled to room temperature, the suspension was filtered to remove inorganic salts and the filtrate was concentrated on a rotary evaporator to yield the appropriate compound.

4.2.1. 5,11,17,23-Tetra-*tert*-butyl-25,27-dibenzyloxycalix[4]arene, 2.[10] White solid, yield=72%; mp 216–218 °C (lit. 216–220 °C); ν_{max} (KBr) 3395 (OH) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.64 (4H, t, *J* 6.5 Hz, Ph-*H*), 7.42 (4H, d, *J* 6.5 Hz, Ph-*H*), 7.35 (2H, m, Ph-*H*), 7.03 (4H, s, Ar-*H*), 6.83 (4H, s, Ar-*H*), 5.05 (4H, s, OCH_2Ph), 4.25 (4H, d, *J* 13.0 Hz, Ar-CH_aH_b-Ar), 3.29 (4H, d, *J* 13.0 Hz, Ar-CH_aH_b-Ar), 1.27 (18H, s, *t-Bu*), 0.98 (18H, s, *t-Bu*).

4.2.2. 5,11,17,23-Tetra-*tert*-butyl-25,27-dibutoxycalix[4]-arene, 3.[2] White solid, yield=45%; mp 262–265 °C (lit. 264–266 °C); ν_{max} (KBr) 3395 (OH) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 8.00 (2H, s, O*H*), 7.03 (4H, s, Ar-*H*), 6.84 (4H, s, Ar-*H*), 4.31 (4H, d, *J* 12.8 Hz, Ar-CH_aH_b-Ar), 3.97 (4H, t, *J* 6.5 Hz, OCH_2CH_2), 3.28 (4H, d, *J* 12.8 Hz, Ar-CH_aH_b-Ar), 2.02 (4H, m, CH_2), 1.70 (4H, m, CH_2), 1.26 (18H, s, *t-Bu*), 1.08 (6H, t, *J* 7.4 Hz, CH_2CH_3), 1.00 (18H, s, *t-Bu*).

4.2.3. 5,11,17,23-Tetra-*tert*-butyl-25,27-diethoxycarbonylmethoxycalix[4]arene, 4.[11] White solid, yield=64%; mp 184–186 °C (lit. 182–184 °C); ν_{max} (KBr) 3442 (OH), 1747 (ester C=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.15 (2H, s, O*H*), 7.02 (4H, s, Ar-*H*), 6.85 (4H, s, Ar-*H*), 4.73 (4H, s, OCH_2CO), 4.43 (4H, d, *J* 12.8 Hz, Ar-CH_aH_b-Ar), 4.29 (4H, q, *J* 6.5 Hz, $COCH_2CH_3$), 3.30 (4H, d, *J* 12.8 Hz, Ar-CH_aH_b-Ar), 1.33 (6H, t, *J* 7.3 Hz, CH_3), 1.25 (18H, s, *t-Bu*), 1.00 (18H, s, *t-Bu*).

4.3. General synthesis of 5, 6 and 7

Diprotected calix[4]arene **2**, **3** or **4** (9 mmol) was dissolved in a mixture of acetic acid (40 ml) and dichloromethane (40 ml). Concentrated nitric acid (8 ml, 90 mmol) was added dropwise over 10 min at 0 °C. The reaction was kept at 0 °C for a further 15 min before being warmed to room temperature for 3 h. The mixture was quenched by the addition of ice-water (100 ml) and the organic layer was separated. The aqueous layer was then extracted with dichloromethane (3×30 ml). The organic layers were combined, dried with $MgSO_4$ and then filtered. Removal of the solvent followed by recrystallisation from methanol yielded **5**, **6** or **7**, respectively.

4.3.1. 5,17-Di-*tert*-butyl-11,23-dinitro-25,27-dibenzyloxycalix[4]arene, 5. Yellow solid, yield=57%. Found: C, 74.24; H, 6.35; N, 3.58. Calcd for $C_{50}H_{50}N_2O_8$: C, 74.42; H, 6.25; N, 3.47; mp 220 °C dec; ν_{max} (KBr) 3340 (OH), 1520 (NO_2), 1320 (NO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 8.86 (2H, s, OH), 8.03 (4H, s, Ar-H), 7.61 (4H, m, Ph-H), 7.46 (4H, m, Ph-*H*), 7.39 (2H, m, Ph-*H*), 6.89 (4H, s, Ar-*H*), 5.07 (4H, s, OCH_2Ph), 4.23 (4H, d, *J* 13.0 Hz, Ar-CH$_a$$H_b$-Ar), 3.40 (4H, d, *J* 12.8 Hz, Ar-CH_aH$_b$-Ar), 1.01 (18H, s, *t-Bu*).

4.3.2. 5,17-Di-*tert*-butyl-11,23-dinitro-25,27-dibutoxycalix[4]arene, 6. Yellow solid, yield=70%. Found: C, 71.59; H, 7.37; N, 3.79. Calcd for $C_{44}H_{54}N_2O_8$: C, 71.52; H, 7.37; N, 3.79; mp 280 °C dec; ν_{max} (KBr) 3285 (OH), 1510 (NO_2), 1330 (NO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 9.44 (2H, s, O*H*), 8.03 (4H, s, Ar-*H*), 6.96 (4H, s, Ar-*H*), 4.30 (4H, d, *J* 12.8 Hz, Ar-CH$_a$$H_b$-Ar), 4.00 (4H, t, *J* 6.5 Hz, OCH_2CH$_2$), 3.49 (4H, d, *J* 12.8 Hz, Ar-CH_aH$_b$-Ar), 2.05 (4H, m, CH_2), 1.68 (4H, m, CH_2), 1.13 (6H, t, *J* 7.4 Hz, CH$_2$$CH_3$), 1.06 (18H, s, *t*-Bu).

4.3.3. 5,17-Di-*tert*-butyl-11,23-dinitro-25,27-diethoxycarbonylmethoxycalix[4]arene, 7.[3] Yellow solid, yield=17%; mp 190–192 °C; ν_{max} (KBr) 3360 (OH), 1752 (ester C=O), 1516 (NO_2), 1332 (NO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 8.94 (2H, s, O*H*), 8.02 (4H, s, Ar-*H*), 7.07 (4H, s, Ar-*H*), 4.84 (4H, s, OCH_2CO), 4.54 (4H, d, *J* 12.8 Hz, Ar-CH$_a$$H_b$-Ar), 4.29 (4H, q, *J* 6.8 Hz, COCH_2CH$_3$), 3.50 (4H, d, *J* 12.8 Hz, Ar-CH_aH$_b$-Ar), 1.37 (6H, t, *J* 7.4 Hz, CH_3), 1.11 (18H, s, *t-Bu*).

4.4. General synthesis of 8, 9 and 10

To a stirred solution of the appropriate dinitro-calix[4]arene **8**, **9** or **10** (1.4 mmol) in 25 ml ethanol was added $SnCl_2$ (14 mmol). The reaction mixture was heated under nitrogen for 24 h and then quenched by pouring into ice-water (100 ml). The pH was adjusted to 9–10 using 5 M KOH. The aqueous phase was then extracted with dichloromethane (3×30 ml) and the combined organic phases were dried over $MgSO_4$. After filtration, the evaporation of the solvent under reduced pressure yielded the diamino-calix[4]arene, which was used immediately without further purification. No elemental analyses were obtained for either **8**, **9** or **10**, as the samples decomposed while being sent for microanalysis.

4.4.1. 5,17-Di-*tert*-butyl-11,23-diamino-25,27-dibenzyloxycalix[4]arene, 8. Dark pink solid, yield=55%; mp 200 °C dec; ν_{max} (KBr) 3360 (OH), 1615 (NH_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.60 (4H, m, Ph-*H*), 7.38 (4H, d, *J* 6.8 Hz, Ph-*H*), 7.37 (2H, m, Ph-*H*), 6.87 (2H, s, O*H*), 6.84 (4H, s, Ar-*H*), 6.42 (4H, s, Ar-*H*), 4.98 (4H, s, OCH_2Ph), 4.25 (4H, d, *J* 12.8 Hz, Ar-CH$_a$$H_b$-Ar), 3.18 (4H, d, *J* 12.8 Hz, Ar-CH$_a$H$_b$-Ar), 1.04 (18H, s, *t*-Bu).

4.4.2. 5,17-Di-*tert*-butyl-11,23-diamino-25,27-dibutoxycalix[4]arene, 9. Dark pink solid, yield=81%; mp 140–142 °C; ν_{max} (KBr) 3365 (OH), 1619 (NH_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.68 (2H, s, O*H*), 6.90 (4H, s, Ar-*H*), 6.45 (4H, s, Ar-*H*), 4.25 (4H, d, *J* 12.8 Hz, Ar-CH$_a$$H_b$-Ar), 3.89 (4H, t, *J* 6.5 Hz, OCH_2CH$_2$), 3.20 (4H, d, *J* 12.8 Hz, Ar-CH_aH$_b$-Ar), 2.08 (4H, m, CH_2), 1.64 (4H, m, CH_2), 1.15 (18H, s, *t-Bu*), 1.09 (6H, t, *J* 7.4 Hz, CH$_2$$CH_3$).

4.4.3. 5,17-Di-*tert*-butyl-11,23-diamino-25,27-diethoxycarbonylmethoxycalix[4]arene, 10. Pink solid, yield=88%; mp 200 °C dec; ν_{max} (KBr) 3345 (OH), 1618 (NH_2), 1752 (ester C=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.04 (2H, s, O*H*), 6.97 (4H, s, Ar-*H*), 6.32 (4H, s, Ar-*H*), 4.83 (4H, s, OCH_2CO), 4.50 (4H, d, *J* 12.8 Hz, Ar-CH$_a$$H_b$-Ar), 4.30 (4H, q, *J* 6.8 Hz, COCH_2CH$_3$), 3.24 (4H, d, *J* 12.8 Hz, Ar-CH_aH$_b$-Ar), 1.23 (6H, t, *J* 7.4 Hz, CH_3), 1.16 (18H, s, *t-Bu*).

4.5. General synthesis of 11, 12 and 13

To a methanol solution (20 ml) of diamino-calix[4]arene **8**, **9** or **10** (0.15 mmol) and 4-methyl-4′-carboxylic acid-2,2′-bipyridine (0.31 mmol) was added DMT-MM (0.33 mmol). The mixture was stirred under nitrogen for 3 h. Over the course of the reaction, a solid, which is the product, precipitated. On cooling, the solid was filtered and dried.

4.5.1. 5,17-Di-*tert*-butyl-11,23-bis(2,2′-bipyridine-4-methyl-4′-carboxyamido)-25,27-dibenzyloxy-calix[4]-arene, 11. Red/pink solid, yield=32%. Found: C, 77.85; H, 6.05; N, 7.24. Calcd for $C_{74}H_{70}N_6O_6$: C, 78.01; H, 6.19; N, 7.38; mp 179–180 °C; ν_{max} (KBr) 3368 (OH), 1669 (amide C=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 8.85 (2H, d, *J* 6.8 Hz, 6-H), 8.73 (2H, s, 3-H), 8.58 (2H, d, *J* 7.8 Hz, 6′-H), 8.31 (2H, s, 3′-H), 8.06 (2H, s, OH), 7.89 (2H, t, *J* 7.6 Hz, 5-H), 7.61 (4H, m, Ph-*H*), 7.40 (4H, s, Ar-*H*), 7.38 (6H, m, Ph-*H*), 7.20 (2H, d, *J* 7.8 Hz, 5′-H), 6.90 (4H, s, Ar-*H*), 5.06 (4H, s, OCH_2Ph), 4.32 (4H, d, *J* 13.3 Hz, Ar-CH$_a$$H_b$-Ar), 3.34 (4H, d, *J* 13.3 Hz, Ar-CH_aH$_b$-Ar), 2.46 (6H, s, CH_3), 1.03 (18H, s, *t-Bu*); ESMS: *m*/*z* 1140.35 (**11**+H^+); $C_{74}H_{71}N_6O_6$ requires 1140.39; 1162.35 (**11**+Na^+); $C_{74}H_{70}NaN_6O_6$ requires 1162.37.

4.5.2. 5,17-Di-*tert*-butyl-11,23-bis(2,2′-bipyridine-4-methyl-4′-carboxyamido)-25,27-dibutoxy-calix[4]arene, 12. Cream solid, yield=53%. Found: C, 76.09; H, 6.82; N, 7.96. Calcd for $C_{68}H_{74}N_6O_6$: C, 76.23; H, 6.96; N, 7.84; mp 185–187 °C; ν_{max} (KBr) 3430 (OH), 1672 (amide C=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 8.85 (2H, d, *J* 6.8 Hz, 6-H), 8.71 (2H, s, 3-H), 8.56 (2H, d, *J* 5.8 Hz, 6′-H), 8.25 (2H, s, 3′-H), 8.10 (2H, s, OH), 7.86 (2H, t, *J* 7.6 Hz, 5-H), 7.40 (4H, s, Ar-*H*), 7.20 (2H, d, *J* 6.2 Hz, 5′-H), 6.96 (4H, s, Ar-*H*), 4.36 (4H, d, *J* 12.8 Hz, Ar-CH$_a$$H_b$-Ar), 4.01 (4H, t, *J* 6.5 Hz, OCH_2CH$_2$), 3.41 (4H, d, *J* 12.8 Hz, Ar-CH_aH$_b$-Ar), 2.42 (6H, s, CH_3), 2.06 (4H, m, CH_2), 1.68 (4H, m, CH_2), 1.09 (6H, t, *J* 7.4 Hz, CH$_2$$CH_3$), 1.06 (18H, s, *t-Bu*); ESMS: *m*/*z* 1071.35 (**12**+H^+); $C_{68}H_{75}N_6O_6$ requires 1071.36; 1093.34 (**12**+Na^+); $C_{68}H_{74}NaN_6O_6$ requires 1093.34.

4.5.3. 5,17-Di-*tert*-butyl-11,23-bis(2,2′-bipyridine-4-methyl-4′-carboxyamido)-25,27-diethoxycarbonyl-methoxycalix[4]arene, 13. Pale pink solid, yield=51%. Found: C, 72.44; H, 6.35; N, 7.65. Calcd for $C_{68}H_{70}N_6O_{10}$: C, 72.19; H, 6.24; N, 7.43; mp 218–221 °C; ν_{max} (KBr) 3416 (OH), 1742 (ester C=O), 1670 (amide C=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 8.81 (2H, d, *J* 7.2 Hz, 6-H), 8.52 (2H, d, *J* 7.2 Hz, 6′-H), 8.26 (2H, s, 3-H), 7.82 (2H, d, *J* 7.2 Hz, 5-H), 7.58 (2H, s, 3′-H), 7.57 (2H, s, O*H*), 7.39 (4H, s, Ar-*H*), 7.18 (2H, d, *J* 7.2 Hz, 5′-H), 7.01 (4H, s, Ar-*H*), 4.81 (4H, s, OCH_2CO), 4.55 (4H, d, *J* 12.8 Hz, Ar-CH$_a$$H_b$-Ar), 4.34 (4H, q, *J* 6.9 Hz, COCH_2CH$_3$), 3.39 (4H, d, *J* 12.8 Hz, Ar-CH_aH$_b$-Ar), 2.44 (6H, s, CH_3), 1.35 (6H, t, *J*

7.4 Hz, CH_2CH_3), 1.12 (18H, s, *t-Bu*); ESMS: *m/z* 1132.35 (**13**+H^+); $C_{68}H_{75}N_6O_6$ requires 1132.33; 1154.29 (**13**+Na^+); $C_{68}H_{74}NaN_6O_6$ requires 1154.31.

4.6. General synthesis of complexation reactions of 11, 12 and 13

A solution of the appropriate calix[4]arene derivative (0.078 mmol) and $[Ru(bipy)_2(Cl)_2]$ (0.156 mmol) in ethanol (20 ml) was heated to reflux for 3 h under nitrogen. After the reaction cooled to room temperature, 10 ml of a saturated tetrabutylammonium hexafluorophosphate ($TBAPF_6$) solution was added, resulting in precipitation of the product as an orange/brown powder. The product was filtered, air dried for 24 h and collected.

4.6.1. 11 + Ru(bipy)$_2$(PF$_6$)$_2$. Orange/brown solid, yield= 78%, δ_H (300 MHz, DMSO-d_6): 10.40 (2H, s, OH), 9.14 (2H, s, H-3), 8.96–8.88 (4H, m, bipy H-3), 8.20–8.17 (4H, m, bipy H-4), 7.91 (2H, s, H-3′), 7.84–7.77 (6H, m, bipy H-5), 7.62 (4H, m, Ph-*H*), 7.59–7.49 (6H, m, bipy H-6), 7.44 (6H, m, Ph-*H*), 7.09 (2H, s, Ar-*H*), 5.06 (4H, s, OCH_2Ph), 4.38 (4H, d, *J* 12.8 Hz, Ar-CH_aH_b-Ar), 2.48 (6H, s, CH_3), 1.03 (18H, s, *t-Bu*).

4.6.2. 12 + Ru(bipy)$_2$(PF$_6$)$_2$. Orange/brown solid, yield= 90%, δ_H (300 MHz, DMSO-d_6): 10.58 (2H, s, OH), 9.20 (2H, s, H-3), 8.99–8.84 (4H, m, bipy H-3), 8.22–8.17 (4H, m, bipy H-4), 7.88 (2H, s, H-3′), 7.82–7.75 (6H, m, bipy H-5), 7.63–7.47 (6H, m, bipy H-6), 7.11 (2H, s, Ar-H), 4.29 (4H, d, *J* 12.3 Hz, Ar-CH_aH_b-Ar), 3.99 (4H, m, OCH_2), 2.57 (6H, s, CH_3), 2.02 (4H, m, CH_2), 1.80 (4H, m, CH_2), 1.16 (18H, s, *t-Bu*), 1.09 (6H, t, *J* 7.3 Hz, CH_2CH_3).

4.6.3. 13 + Ru(bipy)$_2$(PF$_6$)$_2$. Orange/brown solid, yield= 64%, δ_H (300 MHz, DMSO-d_6): 10.30 (2H, s, OH), 9.10 (2H, s, H-3), 8.86–8.81 (4H, m, bipy H-3), 8.20–8.16 (4H, m, bipy H-4), 7.92 (2H, s, H-3′), 7.87–7.72 (6H, m, bipy H-5), 7.60–7.47 (6H, m, bipy H-6), 7.42 (2H, s, Ar-*H*), 7.10 (2H, s, Ar-*H*), 4.86 (4H, s, OCH_2CO), 4.47 (4H, d, *J* 12.8 Hz, Ar-CH_aH_b-Ar), 4.30 (4H, q, *J* 6.9 Hz, $COCH_2CH_3$), 2.52 (6H, s, CH_3), 1.34 (6H, t, *J* 6.9 Hz, CH_2CH_3), 1.13 (18H, s, *t-Bu*).

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Uroleuconaphins A_1 and B_1, two red pigments from the aphid *Uroleucon nigrotuberculatum* (Olive)

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Abstract—Two novel red pigments, uroleuconaphins A_1 (**1**) and B_1 (**2**) were isolated from the aphid *Uroleucon nigrotuberculatum* (Olive). The structures and the absolute configurations of **1** and **2** were determined by single-crystal X-ray analysis of their derivatives. These structures were constituted as dimeric compounds of two molecules of quinone A (**3**), which were linked via a dihydrofuran ring system.

1. Introduction

Aphids produce pigments such as rhododactynaphins,[1–5] xanthoaphins,[6–12] chrysoaphins,[6–14] erythroaphins,[1,6–10,15–27] protoaphins,[1,5–9,11,12,14,25,26,28–34] furanaphin,[35] and so on. It might be worthwhile to investigate these enchanting pigments, which were expected to possess interesting biological activities.[35] Unfortunately, however, the major and extraordinary works on aphids' pigments were discontinued in the early 1980s. Therefore, we started a chemical investigation on pigments in aphids', having an interest in biological activities and biological meaning of the aphids themselves. We recently isolated two red pigments, uroleuconaphins A_1 (**1**) and B_1 (**2**), from the red aphid *Uroleucon nigrotuberculatum* (Olive) (max. 4.0 mm long) (Fig. 1) feeding on *Solidago altissima* L. The structure of **2** (Fig. 2) was constituted as a dimeric compound of the C15 unit, quinone A (**3**) (Fig. 3).[2,3,14,29,32,36] Compound **1** was assigned as the dehydroxyl derivative of **2**. In this paper, we describe their structural elucidation in detail.

2. Results and discussion

The aphid *U. nigrotuberculatum* (Olive) was swept and collected with a soft paintbrush into a plastic Erlenmeyer flask equipped with a plastic funnel in Tokushima Prefecture, Japan in June. The aphid was squashed in ether, and then the ethereal supernatant solution was separated by decantation. The residue was washed with several portions of fresh ether. The combined ethereal solutions were evaporated and subjected to repeated silica-gel column chromatography to afford two yellowish pigments[37] and two red pigments **1** and **2** as major color components. The less polar compound **1** was obtained as red needles and its specific rotation was an extremely large value, $[\alpha]_D^{25}$ +2028.1 (*c* 0.01, $CHCl_3$). Its molecular formula was established as $C_{30}H_{28}O_{11}$ by HREIMS (*m/z* 564.1655).

Figure 1. *Uroleucon nigrotuberculatum* (Olive).

Keywords: Pigment; Structure determination; X-ray analysis; Aphid; *Uroleucon nigrotuberculatum* (Olive).
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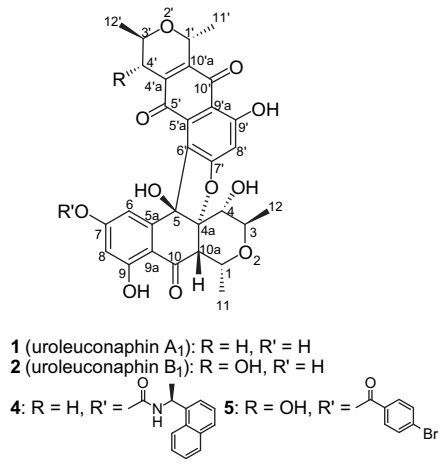

Figure 2. Structures of uroleuconaphins A_1, B_1 and their derivatives.

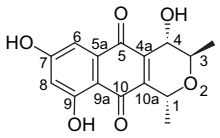

Figure 3. Structure of quinone A (**3**).

Detailed analyses of 1D and 2D NMR spectra involving ^1H–^1H COSY, NOESY, HMQC, and HMBC measurements revealed that **1** contained two component C15 unit (quinone A and dehydroxy quinone A). Unfortunately, however, the structure could not be elucidated clearly even by detailed analyses of the NMR spectra of **1** and its derivatives.

Finally, the structure and the absolute configuration of **1** could be established by a single-crystal X-ray diffraction analysis of the (*S*)-(+)-1-(1-naphthyl)ethyl carbamate **4** (Fig. 2), which was derived by carbamation employing (*S*)-(+)-1-(1-naphthyl)ethylisocyanate with 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in CH_2Cl_2. The IR and ^1H NMR spectra of **4** suggested that the skeleton of **1** did not change in this carbamation. Figure 4 illustrated the molecular structure of **4** with the atomic numbering. The X-ray analysis revealed that a dihydrofuran ring system connected the two component C15 unit. Furthermore, two planes consisting each of the two C15 units in **1** were oriented in almost perpendicular arrangement.

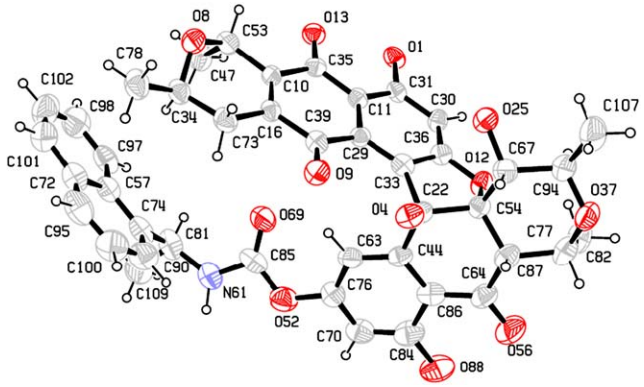

Figure 4. ORTEP drawing of **4** with 30% probability ellipsoids. Hydrogen atoms on hydroxy groups were not shown because of the difficulty to determine their positions.

The structure of compound **2** was confirmed as a hydroxy derivative at C4′ in **1** by detailed analyses of 1D and 2D NMR spectra. However, the stereochemistry of the additional hydroxyl group at C4′ could not be determined confidently even by NOE experiments of **2** and its monoacetate at C4′. Since compound **2** may simply consist of two units of quinone A (**3**), the hydroxy group at C4′ may be in α-orientation as illustrated. However, the extensive investigations of Todd, Cameron, and their colleagues revealed that quinone A′, the C4 hydroxy epimer of **3**, was also a component of aphids' pigments such as protoaphin-*sl* and erythroaphin-*sl*.[22] Therefore, the β-hydroxy epimer of **2** was also expected to be obtained from aphids.

The structural elucidation was accomplished again by a single-crystal X-ray diffraction analysis of the *p*-bromobenzoate **5** (Fig. 2), which was derived from **2** by esterification with *p*-bromobenzoyl chloride and DMAP in CH_2Cl_2. Disorder of the included AcOEt solvent molecules at the core of the benzoate **5** resulted in a loss of some resolution in the crystal structure, but the molecular structures and its stereochemistries were clearly refined from the diffraction data quickly obtained at 150 K. Figure 5 illustrates the molecular structure of **5** with the atomic numbering. The hydroxy group at C4′ was situated at trans position to the methyl group at C3′.

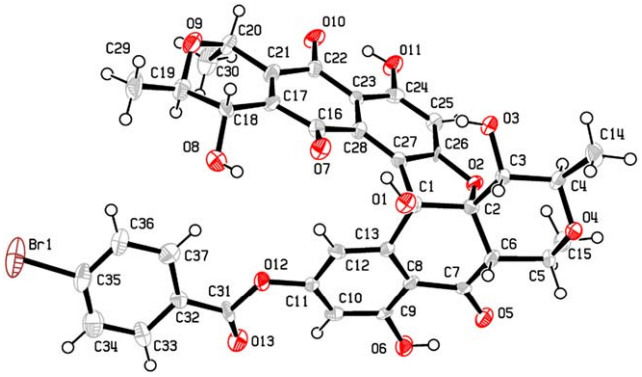

Figure 5. ORTEP drawing of **5** with 50% probability ellipsoids.

2.1. Cytotoxicity

Having an interest in biological activities of uroleuconaphins A_1 and B_1, we tested them for cytotoxicity against human promyelocytic leukemia HL-60 cells.[38] Compounds **1** and **2** were found to be active with ED_{50} of 45 μM and 20 μM, respectively. These results may suggest that the pigments are important for the aphids themselves in defense against viral infections. This finding encouraged us to continue the investigation of aphids' pigments.

3. Conclusion

Thus, the structures and absolute configurations of uroleuconaphins A_1 (**1**) and B_1 (**2**) were determined. Furthermore, they possessed cytotoxicity against HL-60 cells. Further work on the biological activities of **1** and **2**, and structure

determination of yellow pigments of the aphid *U. nigrotuberculatum* (Olive) is in progress.

4. Experimental

4.1. General

Melting points were determined on a Yanaco MP-3 apparatus and were uncorrected. IR spectra were measured on a JASCO FT/IR-410 spectrophotometer. UV–visible spectra were measured on a Shimadzu UV-1650pc spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Unity-600 (600 MHz) and a Varian Mercury-300 (300 MHz) with tetramethylsilane as an internal standard in acetone-d_6 and $CDCl_3$. ^{13}C NMR spectra were taken on a Varian Unity-600 (150 MHz) and a Varian Unity-200 (50 MHz), chemical shifts were referenced to the residual solvent signal (acetone-d_6: δ_C 29.8 ppm, $CDCl_3$: δ_C 77.0 ppm). Signal multiplicities were established by DEPT experiments. Mass spectra including high-resolution mass spectra were recorded on a JOEL JMX AX-500 spectrophotometer. Column chromatography was carried out with Silica gel 60N (Kanto Chemical Co. Inc., 63–210 μm). Acetyl chloride and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) were purchased from Nacalai Tesque Inc. (*S*)-(+)-1-(1-naphthyl)ethylisocyanate was purchased from Aldrich Chemical Co. Inc. *p*-Bromobenzoyl chloride was purchased from Acros Organics. They were used without any purification.

4.2. Material

The aphid *U. nigrotuberculatum* (Olive), which was feeding on *S. altissima* L. was collected in Tokushima Prefecture, Japan in June 1999.

4.3. Extraction and isolation

The aphid (200 g) was squashed in diethyl ether, and then the ethereal supernatant solution was separated by decantation. The residue was washed with several portions of fresh ether. The combined ethereal solutions were dried over Na_2SO_4 and were evaporated to give a crude extract (21.9 g). The reddish residue was subjected to silica-gel column chromatography (600 g) using hexane/AcOEt (3:1–1:3) as an eluent to afford two red pigments **1** (1.20 g) and **2** (755 mg), and two yellowish pigments (~780 mg).

4.3.1. Uroleuconaphin A_1 (1). Red needles (hexane/diethyl ether), mp 233 °C (dec). $[\alpha]_D^{25}$ +2028.1 (*c* 0.01, $CHCl_3$). UV (CH_3CN): λ_{max} 275 (log ε 4.38), 495 (log ε 3.68) nm. IR (KBr): ν_{max} 3436 (–OH), 1613 (C=O), 1442, 1406, 1282 cm^{-1}, NMR data: see Table 1, MS (EI) *m*/*z* 564

Table 1. ^{13}C (150 Hz) and ^{1}H (600 Hz) NMR data of **1** and **2**

Position	**1** In $CDCl_3$		**2** In acetone-d_6	
	δ_C	δ_H	δ_C	δ_H
1	68.5	4.74 (1H, qd, 6.9, 5.7)	68.5	4.66 (1H, qd, 7.0, 5.5)
3	64.3	4.00–4.08 (1H, overlap)	65.5	3.95–4.03 (1H, overlap)
4	73.9	4.00–4.08 (1H, overlap)	73.5	3.95–4.03 (1H, overlap)
4a	93.0		94.7	
5	79.5		80.1	
5a	146.8		148.2	
6	105.1	6.73 (1H, d, 2.3)	107.0	6.81 (1H, d, 2.4)
7	163.7		166.6	
8	103.7	6.26 (1H, d, 2.3)	103.6	6.21 (1H, d, 2.4)
9	164.3		165.1	
9a	108.0		108.0	
10	196.8		198.3	
10a	48.5	3.48 (1H, d, 5.7)	48.9	3.59 (1H, d, 5.5)
11	15.8	1.68 (3H, d, 6.9)	16.0	1.63 (3H, d, 7.0)
12	18.4	1.29 (3H, d, 5.8)	19.1	1.21 (3H, d, 6.2)
5-OH		8.20 (1H, s)		8.31 (1H, s)
9-OH		12.53 (1H, s)		12.55 (1H, s)
1′	67.1	4.96 (1H, qd, 6.9, 2.1)	66.9	4.86 (1H, br q, 7.0)
3′	62.5	4.00–4.08 (1H, overlap)	69.6	3.95–4.03 (1H, overlap)
4′	30.0	2.22 (1H, ddd, 19.2, 10.2, 2.1); 2.76 (1H, dd, 19.2, 3.3)	66.5	4.49 (1H, br d, 6.6)
4′a	141.8		142.9	
5′	188.8		187.3 or 190.6	
5′a	126.7		128.4	
6′	132.0		134.3	
7′	166.1		168.0	
8′	105.0	6.55 (1H, s)	104.7	6.60 (1H, s)
9′	166.8		167.3	
9′a	109.6		110.4	
10′	185.8		187.3 or 190.6	
10′a	148.8		150.4	
11′	19.8	1.56 (3H, d, 6.9)	19.4	1.60 (3H, d, 7.0)
12′	21.4	1.37 (3H, d, 6.0)	18.4	1.35 (3H, d, 6.2)
9′-OH		13.18 (1H, s)		13.13 (1H, s)
Other OH		4.23 (1H, br s)[a]; 9.64 (1H, br s)[a]		4.30 (1H, br d, 4.0); 5.04 (1H, br s); 9.69 (1H, br s)

[a] These signals were observed in acetone-d_6.

(M^+), HRMS (EI) calcd for $C_{30}H_{28}O_{11}$ 564.1632 (M^+), found 564.1655.

4.3.2. Uroleuconaphin B_1 (2). Red needles (hexane/$CHCl_3$), mp 223 °C (dec). $[\alpha]_D^{25}$ +2260.2 (*c* 0.01, $CHCl_3$). UV (CH_3CN): λ_{max} 276 (log ε 4.30), 497 (log ε 3.59) nm. IR (KBr): ν_{max} 3415 (–OH), 1613 (C=O), 1444, 1411, 1288 cm^{-1}. NMR data: see Table 1, MS (FAB) *m/z* 581 ([M+H]$^+$), HRMS (FAB) calcd for $C_{30}H_{29}O_{12}$ 581.1659 ([M+H]$^+$), found 581.1660.

4.3.3. (*S*)-(+)-1-(1-Naphthyl)ethyl carbamate of uroleuconaphin A_1 (4). To a suspension of **1** (20.5 mg) in CH_2Cl_2 (10 mL) were successively added (*S*)-(+)-1-(1-naphthyl)ethylisocyanate (22.3 mg) and DMAP (~5.0 mg). The resulting mixture was stirred at ambient temperature for 5.5 h and then was quenched with water (10 mL) and 1 N HCl (5 mL). The mixture was separated and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the crude residue was purified by silica-gel column chromatography (3.5 g, hexane/AcOEt=10:1–4:1) to give 17.8 mg of (*S*)-(+)-1-(1-naphthyl)ethyl carbamate **4** as red plates (AcOEt/hexane/$CHCl_3$), mp 166–168 °C (dec). $[\alpha]_D^{18}$ +2666.7 (*c* 0.01, $CHCl_3$). UV (CH_3CN): λ_{max} 271 (log ε 4.42), 493 (log ε 3.62) nm. IR (neat): ν_{max} 3310 (–OH), 1738 (C=O), 1638 (C=O), 1612 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 12 mg/mL): δ 0.82 (3H, d, *J*=6.2 Hz), 1.32 (3H, d, *J*=5.9 Hz), 1.37 (3H, d, *J*=6.6 Hz), 1.65 (3H, d, *J*=7.0 Hz), 1.69 (3H, d, *J*=7.0 Hz), 2.00 (1H, ddd, *J*=19.0, 10.3, 1.8 Hz), 2.37 (1H, d, *J*=5.1 Hz), 2.44 (1H, dd, *J*=19.0, 3.7 Hz), 3.37–3.41 (1H, m), 3.49 (1H, d, *J*=5.5 Hz), 4.05 (1H, dq, *J*=9.9, 5.9 Hz), 4.10 (1H, dd, *J*=9.9, 5.1 Hz), 4.67–4.73 (2H, overlapped), 5.41 (1H, d, *J*=7.7 Hz), 5.51 (1H, quint, *J*=7.0 Hz), 6.50 (1H, s), 6.51 (1H, d, *J*=2.2 Hz), 7.53 (1H, d, *J*=2.2 Hz), 7.50–7.57 (3H, m), 7.62 (1H, td, *J*=8.4, 1.5 Hz), 7.85 (1H, d, *J*=8.1 Hz), 7.93 (1H, d, *J*=8.1 Hz), 7.99 (1H, d, *J*=8.4 Hz), 8.54 (1H, s), 12.18 (1H, s), 13.04 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.8, 18.5, 19.7, 21.1, 21.8, 30.0, 47.5, 48.9, 62.3, 64.3, 66.6, 68.3, 73.5, 79.5, 92.6, 104.7, 108.8, 109.1, 109.8, 110.4, 122.0, 122.5, 125.4, 126.1, 126.8, 127.6, 128.6, 129.2, 130.4, 131.4, 134.1, 137.4, 142.2, 146.0, 147.5, 151.7, 157.9, 162.7, 165.8, 166.5, 185.8, 189.7, 198.2. MS (FAB) *m/z* 762 ([M+H]$^+$), HRMS (FAB) calcd for $C_{43}H_{40}NO_{12}$ 762.2550 ([M+H]$^+$), found 762.2564.

4.3.4. *p*-Bromobenzoate of uroleuconaphin B_1 (5). To a suspension of **2** (14.2 mg) in CH_2Cl_2 (6 mL) with *p*-bromobenzoyl chloride (16.5 mg) was added DMAP (~10.0 mg) in small portions over a period of 3 h with stirring at ambient temperature and then the resulting mixture was quenched with water (3 mL). The mixture was separated and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the crude residue was purified by silica-gel column chromatography (2.5 g, hexane/AcOEt=2:1–1:2) to give 17.0 mg of *p*-bromobenzoate **5** as red plates (hexane/AcOEt), mp 205 °C (dec). $[\alpha]_D^{20}$ +1345.0 (*c* 0.02, $CHCl_3$). UV (CH_3CN): λ_{max} 259 (log ε 4.53), 489 (log ε 3.63) nm. IR (ATR): ν_{max} 3425 (–OH), 1744 (C=O), 1608 (C=O), 1588 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 9.6 mg/mL): δ 1.31 (3H, d, *J*=5.4 Hz), 1.35 (3H, d, *J*=6.3 Hz), 1.59 (3H, d, *J*=6.9 Hz), 1.70 (3H, d, *J*=6.9 Hz), 2.35 (1H, br s), 3.43 (1H, d, *J*=5.7 Hz), 3.72–3.91 (2H, overlapped), 4.01–4.16 (2H, overlapped), 4.43 (1H, d, *J*=7.2 Hz), 4.70 (1H, qd, *J*=6.9, 5.7 Hz), 4.85 (1H, q, *J*=6.9 Hz), 6.59 (1H, s), 6.84 (1H, d, *J*=2.3 Hz), 7.34 (1H, d, *J*=2.3 Hz), 7.61 (2H, d, *J*=6.8 Hz), 7.90 (2H, d, *J*=6.8 Hz), 8.59 (1H, s), 12.13 (1H, s), 12.91 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.8, 18.4, 19.3, 48.9, 64.3, 66.3, 66.8, 67.8, 68.2, 73.5, 79.6, 92.8, 105.2, 109.6, 110.0, 110.3, 110.9, 127.5, 128.0, 129.5, 131.6, 131.7, 131.9, 142.2, 145.4, 149.8, 157.5, 162.9, 163.1, 166.1, 166.7, 185.7, 191.5, 197.7. MS (FAB) *m/z* 763 ([M+H]$^+$), 765 ([M+H]$^+$), HRMS (FAB) calcd for $C_{37}H_{32}{}^{79}BrO_{13}$ 763.1027 ([M+H]$^+$), found 763.1027.

4.4. X-ray analysis of 4 and 5

The structures of **4** and **5** were solved by direct methods with the program SHELXS97 (Sheldric, 1997). The crystal data and the experimental details are summarized in Tables 2 and 3. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 275214 for **4** and 275656 for **5**. Copies of the data can be obtained, free of charge, on

Table 2. Crystal data and experimental conditions of **4**

Chemical formula/formula weight	$C_{43}H_{35}NO_{12}$/757.72
Crystal system/space group	Orthorhombic/$C222_1$
Z	16
a, *b*, *c*(Å)	22.8600(8), 39.620(2), 18.3180(6)
V/Å^3	16590.9(11)
D_x/Mgm^{-3}	1.213
Diffractometer	MXC18
Radiation	Mo Kα
λ/Å	0.71073
μ(Mo Kα)/mm^{-1}	0.11
Crystal description/crystal dimensions (mm^3)	Plate/0.35×0.3×0.2
T/K	298
θ_{max}/°	25.86
Range of *h*, *k*, and *l*	$0\le h\le 27$, $0\le k\le 48$, $0\le l\le 22$
Reflections: independent/observed	8917/4843
$R(F)(I>3\sigma(I))/wR(F^2)(I>3\sigma(I))$	0.072/0.238
S	1.434
$(\Delta/\sigma)^{max}$	0.021
Δρ/eÅ^{-3}	−0.45, 1.69

Table 3. Crystal data and experimental conditions of **5**

Chemical formula/formula weight	$C_{37}H_{31}BrO_{13}\cdot 1/3C_4H_4O_2$/791.55
Crystal system/space group	Triclinic/*P*1
Z	6
a, *b*, *c*(Å)	13.2293(14), 15.5101(16), 29.022(3)
α(°)	94.808(2)
β(°)	93.165(2)
γ(°)	107.985(2)
V/Å^3	5623.4(10)
D_x/Mgm^{-3}	1.402
Diffractometer	Bruker Smart1000 CCD
Radiation	Mo Kα
λ/Å	0.71073
μ(Mo Kα)/mm^{-1}	1.164
Crystal description/crystal dimensions (mm^3)	Plate/0.40×0.40×0.15
T/K	150
θ_{max}/°	27.54
Range of *h*, *k*, and *l*	$-16\le h\le 17$, $-20\le k\le 12$, $-33\le l\le 37$
Reflections: independent/observed	28889/16706
$R(F)(I>2\sigma(I))/wR(F^2)(I>2\sigma(I))$	0.0720/0.1986
S	0.907
Δρ/eÅ^{-3}	−0.751, 1.982

application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.5. Cytotoxic activities

HL-60 (human promyelocytic leukemia-60) cells were grown in suspension culture and incubated at 37 °C in RPMI-1640 medium supplemented with 10% FBS and glutamine (2 mM). The cytotoxicity of **1** and **2** in HL-60 cells was analyzed by colorimetric 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay with some modification.[38] HL-60 (1×10^4 cells) were plated on 96-well plates and allowed to adhere at 37 °C in 5% CO_2/95% air for 1 h. Then 50 μL of serial concentration of test compound **1** and **2** were added and the cells incubated for 24 h. After 24 h, 10 μL of MTT (5 mg/mL: stock solution) was added and the cells were incubated for an additional 4 h. Following this time the cells were lysed and the dark blue crystals solubilized with 100 μL of 20% sodium dodecyl sulfate in 0.01 N HCl. The optical density (OD) of each well was measured with a microplate spectrophotometer equipped with a 570 nm filter. The results of cytotoxic activity are expressed as ED_{50} (the concentration of compound that inhibited cell line replication by 50%). The ED_{50} of **1** and **2** were 45 and 20 μM, respectively.

Acknowledgements

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